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- Collinge J. Variant Creutzfeldt-Jakob disease. *Lancet* 1999;354:317-23.
- Schreuder BEC, van Keulen LJM, Vromans MEW, Langeveld JPM, Smits MA. Preclinical test for prion diseases. *Nature* 1996;381:563.

- Hill AF, Butterworth RJ, Joiner S, Jackson G, Rosser MN, Thomas DJ, et al. Investigation of variant Creutzfeldt-Jakob disease and other human prion disease with tonsil biopsy samples. *Lancet* 1999;353:183-9.
- Hilton DA, Fathers E, Edwards P, Ironside JW, Zajicek J. Prion immunoreactivity in appendix before clinical onset of variant Creutzfeldt-Jakob disease. *Lancet* 1998;352:703-4.
- O'Rourke KI, Baszler TV, Besser TE, Miller JM, Cutlip RC, Wells GAH, et al. Preclinical diagnosis of scrapie by immunohistochemistry of third eyelid lymphoid tissue. *J Clin Microbiol* 2000;38:3254-9. (Accepted 30 July 2002)

## Informed consent for genetic research on blood stored for more than a decade: a population based study

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With recent advances in molecular genetics, there has been a surge in interest in using stored blood samples for genetic research, even though informed consent at the time of blood sampling did not include this possibility. One of the cornerstones of the World Medical Association's Declaration of Helsinki on ethical principles for medical research is the need for informed consent and the right of any participant in a research project to withdraw at any time.<sup>1</sup> We report here our experiences of seeking informed consent for academic and commercial genetic research on blood samples collected more than a decade earlier.

### Methods and results

A total of 1583 out of 2000 (79.2%) randomly selected men and women in the age group 25-64 years participated in the 1990 risk factor survey in the World Health Organization's MONICA project.<sup>2,3</sup> Participants were given written information and asked to donate blood for "future research on cardiovascular disorders and diabetes." A total of 1494 blood samples were taken (in 89 participants, consent was not given or technical problems arose in obtaining a blood sample). The blood samples were fractionated and stored at  $-80^{\circ}\text{C}$ .

In 2001, 11 years later, 85 of the 1494 individuals had died, moved abroad, or had an unknown address (figure). We sent a letter to the remaining 1409 participants with information about ongoing genetic studies and seeking consent at three different levels (figure). Of the 1409 subjects, 1342 (95.2%) responded.

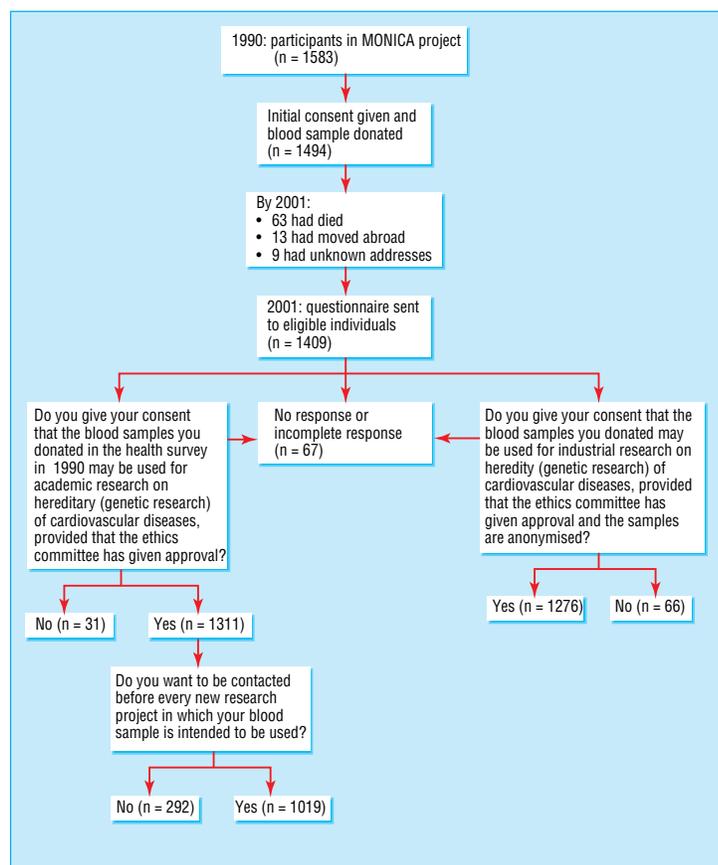
A total of 1311 out of 1409 (93.0%) eligible participants gave their consent for their blood samples to be used for academic genetic research, provided that the ethics committee had approved the research. Thirty one (2.2%) participants did not give their consent; 64 participants did not reply and three provided incomplete answers (4.8% together).

Of the 1311 participants who gave their consent, 292 (22.3%) wanted to be informed about, and give new consent for, each new genetic project (figure). The rest gave general consent to genetic research, as long as an ethics committee had approved the research. However, a further 35 (2.5%) participants did not give consent for their blood to be used for industrial genetic research (figure).

### Comment

Eleven years after donation of samples, only a very small proportion of participants did not give consent for their blood to be used in academic or industrial genetic research.

To our knowledge, this report is the first to provide empirical data from a "real life" situation—that is, people's willingness to give consent to genetic research on their own blood donated more than a decade previously, when genetic research was not an issue. Participation in risk factor screening is, in itself, an expression of willingness to contribute to research. The participants in the original survey in 1990 were randomly selected, with a participation rate as high as 79%, thus suggesting that



Follow up in 2001 of participants in 1990 MONICA survey, showing numbers of participants lost to follow up and responses to questionnaire about consent for blood to be used in genetic research

our results are representative. The MONICA project is well known and well regarded among the people in this part of Sweden, where it has been running since 1985, and the great willingness to give consent to genetic research emphasises the importance of close researcher-participant interaction.

We conclude that (a) it is feasible to obtain individual consent for genetic research many years after blood was donated; (b) people's readiness to contribute to genetic research is high, at least in the framework of a carefully conducted study that is well known to the population; and (c) consent is given nearly as often for industrial genetic research as for academic genetic research, provided that the blood samples are anonymised and an ethics committee has approved the research.

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- 1 World Medical Association. Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA* 2000;284:3043-5.
- 2 Huhtasaari F, Asplund K, Stegmayr B, Lundberg V, Wester PO. Trends in cardiovascular risk factors in the northern Sweden MONICA study. Who are the winners? *Cardiovasc Risk Factors* 1993;3:215-21.
- 3 Tunstall-Pedoe H. The World Health Organization MONICA project (monitoring of trends and determinants in cardiovascular diseases): a major international collaboration. *J Clin Epidemiol* 1988;41:105-14.

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## Drug points

### Gabapentin induced cholestasis

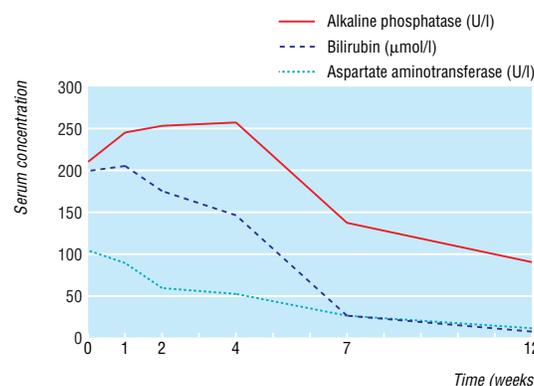
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The treatment of painful diabetic peripheral neuropathy is troublesome and limited by the range of effective treatments available. Optimal control of diabetes is important, and simple analgesics such as aspirin and paracetamol may be beneficial. Further relief of symptoms may be achieved with tricyclic antidepressants and anticonvulsants.<sup>1,2</sup> Unfortunately, despite these treatments many patients still have symptoms and the search for more effective therapy continues. Preliminary studies have shown that the anticonvulsant gabapentin is beneficial in the management of this condition, but this remains an unlicensed indication. We report a case of serious hepatotoxicity associated with gabapentin.<sup>3,4</sup>

During a routine visit to a diabetes clinic, a 50 year old man complained of symptoms attributable to his peripheral diabetic neuropathy. He was subsequently treated with an escalating dose of gabapentin (day 1, 300 mg once daily; day 2, 300 mg twice daily; day 3 and thereafter, 300 mg three times a day). Three years previously he had been diagnosed as having maturity onset diabetes, at which time evidence of retinopathy and neuropathy was noted. He was initially treated with gliclazide, which was discontinued one year later and Human Mixtard 30 started. His other drugs consisted of metformin 1 g twice daily, amitriptyline 50 mg nightly, dihydrocodeine 30 mg as required, and ramipril 5 mg once daily—he had been taking all these for more than 12 months.

After taking the gabapentin for two weeks he developed the clinical characteristics of cholestasis—namely, jaundice, dark urine, pale stool in association with fatigue, and epigastric tenderness. Physical examination confirmed jaundice and the previously noted retinopathy and neuropathy. Liver function tests at this stage showed aspartate transaminase 104 U/l (reference range 10-40 U/l), bilirubin 199 µmol/l (5-20 µmol/l), alkaline phosphatase 210 U/l (25-115 U/l), and  $\gamma$ -glutamyltransferase 839 U/l (<85 U/l). Other serological investigations excluded viral hepatitis (negative IgM anti-hepatitis A, hepatitis B surface antigen, antibody to hepatitis B core and antibody to hepatitis C) and autoimmune hepatitis (negative antinuclear antibody and anti-smooth muscle antibody). A full blood count, renal profile, and liver ultrasound scan were also normal.

Gabapentin induced cholestasis was thought likely and the drug was stopped. After this, clinical symptoms



Liver function tests after withdrawal of gabapentin

and liver function tests improved gradually (figure). A liver biopsy showed normal liver architecture with evidence of portal tract expansion by a chronic inflammatory cell infiltrate that incorporated eosinophils and neutrophils. Patchy steatosis, cholestasis, and some foci of chronic inflammation were evident within the lobules. We thought that these features were consistent with a drug induced aetiology. The temporal relation between ingestion of gabapentin and the development of a reversible cholestasis on its withdrawal strongly support causality.

We submitted a yellow card to the Committee on Safety of Medicines and discussed the case with the drug manufacturers. There have been four reports of jaundice (one cholestatic) associated with the use of gabapentin and, as far as we know, none of these have been published. To the best of our knowledge this is the first reported case of gabapentin induced cholestatic jaundice. Gabapentin should be added to the list of drugs capable of producing this adverse reaction.

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- 1 Max MB, Culnane M, Schafer SC, Gracely RH, Walther DJ, Smoller B, et al. Amitriptyline relieves diabetic neuropathy pain in patients with normal or depressed mood. *Neurology* 1987;37:589-96.
- 2 Tremont-Lukats IW, Megeff C, Backonja M. Anticonvulsants for neuropathic pain syndromes. *Drugs* 2000;60:1029-52.
- 3 Backonja M, Beydoun A, Edwards KR, Schwartz SL, Fonseca V, Markday Hes BS, et al. Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus. *JAMA* 1998;280:1831-6.
- 4 Morello CM, Leckband SG, Stoner CP, Moorhouse DF, Sahagian GA. Randomized double-blind study comparing the efficacy of gabapentin with amitriptyline on diabetic peripheral neuropathy pain. *Arch Int Med* 2000;160:1040-1.