are illustrated by the 1996 NEJM editorial by JoAnn Manson and Gerald Faich. The NEJM policy is to refuse to publish editorials and reviews if authors have “any financial connection with a company that benefits from a drug or device discussed.” Angell and Kasriss, for the NEJM, claimed that they “did not appreciate until it was too late . . . that Dr Manson and Dr Faich had both been paid consultants for companies that stood to gain” from an anti-obesity drug that they were writing about. The editors argued that this “violation” of their editorial policy was “disturbing” and raised “troubling questions.” Manson and Faich replied that the events under scrutiny were due simply to “a series of misunderstandings” between authors and editors. Manson describes her ordeal further in the current issue of Epidemiology, where she notes that in the NEJM editorial, “we were pilloried over what were, in essence, misunderstandings. During the last several months, my colleagues have railed behind me and shown me tremendous support. Literally hundreds have expressed disappointment and outrage at how this situation was handled by editors at NEJM and by the media.”

In an accompanying commentary, Rothman and Cannel point out that the NEJM’s policy “actually compromises rather than enhances objectivity, by infringing on the openness of scientific dialogue.” The only way to minimise bias among interpretations is to allow maximum dialogue from all parties, irrespective of their interests. The Lancet also prefers a pluralistic solution to one based on censorship. Similarly, Manson goes on to ask whether, “Given the premise that science-industry collaborations are beneficial to the public and the advancement of knowledge”, scientific discussion can ever proceed fully and fairly if journals disqualify researchers from writing editorials and reviews because of their “associations” with industry. Here, it seems to me, our obsession with conflicts of interest may harm free discussion in science.

Perhaps part of the difficulty with conflict of interest lies in the phrase itself, which has disparaging connotations. The Annals of Internal Medicine uses the term “dual commitment” and asks authors to disclose these to editors. The Lancet’s policy is much the same.

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End of the line for "third-generation-pill" controversy?

By an ingenious transformation of an old in-vitro test for thrombin conversion, a research group from Maastricht, the Netherlands, has proved three things: one, third-generation oral contraceptives induce a resistance to the blood’s natural anticoagulation system (APC-resistance) of almost the same magnitude as the resistance induced by a mutation in coagulation factor V (factor V Leiden); two, second-generation contraceptives show only part of this effect—in that users of second-generation pills can be clearly demarcated both from women not on oral contraceptives and from women on third-generation pills; three, in women heterozygous for the factor V Leiden mutation who take oral contraceptives, APC-resistance is as high as that among homozygotes for the mutation.

These results fit admirably with the epidemiological data. The relative risk of deep venous thrombosis conferred by the factor V Leiden mutation is between 5 and 10, and centres around 8. The increased risk of using third-generation contraceptives compared with no oral contraception is of the same order: 6 to 9-fold (a baseline relative risk of 3 to 4 for second-generation pills that is multiplied two-fold for third-generation pills). The presence of the mutation combined with oral-contraceptive use has been estimated to raise the risk of venous thrombosis 30-fold, and perhaps more—up to 50-fold—when the contraceptives are of the third generation. In keeping with this finding, the risk of venous thrombosis for a homozygote of the mutation is at least 50-fold and probably more.

For over a year the epidemiological findings pointing at an increased risk with some third-generation oral contraceptives have either been ignored or downplayed (“small effects”), or have been denied (“bias, confounding”). These objections were extremely tenuous. The objection that the third-generation effect was merely a matter of “starters” and “healthy users” had been completely countered by several data analyses restricted to first-time or recent users. Prescription bias had been countered by the fact that all risk factors that can predict a first venous thrombosis in healthy young women had been accounted for. Nevertheless, “experts” continued to sow confusion, at their best with data and analyses restricted, to first-time or recent users. Prescriptions bias had been countered by the fact that all risk factors that can predict a first venous thrombosis in healthy young women had been accounted for. Nevertheless, “experts” continued to sow confusion, at their best with data and analyses restricted, to first-time or recent users. Prescriptions bias had been countered by the fact that all risk factors that can predict a first venous thrombosis in healthy young women had been accounted for. Nevertheless, “experts” continued to sow confusion, at their best with data and analyses restricted, to first-time or recent users. Prescriptions bias had been countered by the fact that all risk factors that can predict a first venous thrombosis in healthy young women had been accounted for.
"coagulation guesswork": it involved developing a pill that showed the least possible alteration of known haemostatic variables; however, as has become clear, not all were known. Now we have the beginning of a test system for discriminating between the thrombogenic potential of different pills. The public will demand that such a test will be used in the development of safe contraceptives. Of course, there are loose ends to be tied up and issues to explore—eg, what exactly is the molecular mechanism behind the thrombogenic potential.

Women who have lost out are those who have, in the meantime, developed severe venous thrombosis on highly thrombogenic pills—especially since the warning about third-generation contraceptives containing gestodene or desogestrel by the British Committee on Safety of Medicines of October 18, 1995, did not lead to sufficiently similar regulatory action in all European countries. In particular, the European Agency for the Evaluation of Medicinal Products (CPMP) has been too willing to postpone action by demanding "more evidence" in the face of a rather complete epidemiological file. For the future, greater involvement of independent consumer boards or patient platforms in drug-safety regulation will be used in the development of safe contraceptives. Of the British Committee on Safety of Medicines of October 18, 1995, did not lead to sufficient harassment regulatory action in all European countries. In particular, the European Agency for the Evaluation of Medicinal Products (CPMP) has been too willing to postpone action by demanding "more evidence" in the face of a rather complete epidemiological file. For the future, greater involvement of independent consumer boards or patient platforms in drug-safety regulation will be used in the development of safe contraceptives. Of the British Committee on Safety of Medicines of October 18, 1995, did not lead to sufficiently similar regulatory action in all European countries. In particular, the European Agency for the Evaluation of Medicinal Products (CPMP) has been too willing to postpone action by demanding "more evidence" in the face of a rather complete epidemiological file. For the future, greater involvement of independent consumer boards or patient platforms in drug-safety regulation will be used in the development of safe contraceptives. Of

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Endoscopic balloon dilatation of biliary sphincter for removing bileduct stones
See page 1124
The introduction of endoscopic sphincterotomy (to destroy the sphincter of Oddi) in the mid 1970s facilitated therapeutic intervention for common bililaduct stones. Since then there have been modifications to the indications for this technique, especially with the introduction of laparoscopic cholecystectomy. The endoscopic approach remains the treatment of choice for choledocholithiasis both following previous cholecystectomy as well as in the presence of gallstone-related cholangitis (and probable pancreatitis). Despite the technical ability to explore and clear the common bileduct at the time of laparoscopic cholecystectomy, many surgeons prefer to have the duct cleared endoscopically either before or after the cholecystectomy.

In experienced hands the success rate for endoscopic sphincterotomy exceeds 90%, although the ability to clear the duct of stones is somewhat lower. However, the therapeutic efficacy of endoscopic sphincterotomy is balanced by a significant complication rate (8-12%), with mortality of 0-5-1%. The commonest complications are pancreatitis, bleeding, and duodenal perforation. The complication rate is no better than that seen with open surgical exploration of the common bileduct. It is only in an elderly and infirmed population that the endoscopic approach may show significant advantage.

There has also been some concern about late complications of endoscopic sphincterotomy, especially in the younger age-group, who may be exposed to biliary complications secondary to duodenobiliary reflux. Bacterial contamination and chronic inflammation of the common bileduct have been recognised after sphincterotomy.

This sizeable risk of complications has led to evaluation of balloon dilatation of the sphincter of Oddi as an alternative technique for gaining access to the common bileduct. Several small reports published in the early 1980s prompted concerns about the risks of pancreatitis following this technique. However, more recently, a high success rate for completion of the technique, with an encouragingly low incidence of complications, has been obtained in a large uncontrolled series. Also, there is now evidence that function of the sphincter of Oddi may recover after balloon dilatation. Sphincterotomy permanently destroys the sphincter. The size of the lumen created by balloon dilatation is limited by existing balloon diameters (8-10 mm). With sphincterotomy, it may extend to 1-5 cm, depending upon the length of the intramural segment of the distal common bileduct. The small orifice obtained with balloon dilatation limits the size of stone that can be removed from the common bileduct without resort to mechanical lithotripsy, the need for which can be a disadvantage in that the procedure time is lengthened and there is an increased risk of papillary trauma.

In today's Lancet Bergman et al report a controlled trial comparing balloon dilatation with sphincterotomy for the removal of bililaduct stones. This is an extremely well-designed study with adequate power. The known experience of the endoscopists may account for the high success rate for bililaduct clearance, which was almost identical in both groups at approximately 90%. There were slightly fewer early complications with balloon dilatation than with sphincterotomy, although this difference was not statistically significant. The level of complications at 17% and 24%, respectively, was higher than reported elsewhere but may reflect the strict recording of the events in this trial. There was no evidence that balloon dilatation was associated with an increased risk of procedural pancreatitis. With respect to long-term complications there were significantly fewer episodes of acute cholecystitis among patients undergoing balloon dilatation. The authors speculate that duodenal biliary reflux may precipitate gallbladder infection in patients following sphincterotomy, whereas sphincter function may have recovered after the balloon dilatation.

The use of an 8 mm balloon inevitably restricted the size of calculus extractable. Mechanical lithotripsy was required in 31% of the dilatation group patients,