We will be increasingly invited to play up the risks of the diseases against which hormone replacement offers effective and downplay the increased risks. As is already the case, we are invited to believe that the women's health initiative study[10] and the million women study are less relevant than is currently thought or flawed with biases. Subgroups will be cited for which the bad effects are not observed—the latest results on coronary heart disease from the women's health initiative study provide (unsafe) opportunities to cite subgroups for which the bad effects are not observed.[11] This is a predictable bandwagon effect, not to be ignored—but such claims are often not plausible, never mind adequate. Reputations (and money) are at stake. Where is the scientific evidence for alternative inferences, more reliable than we now have? That the simple message above, intuitive to public health a while ago, has had to wait to achieve credibility is pitiable.

At least two further developments are now indicated. One is providing hormone therapy with which it is easier to cut the dose gradually. Women can test their individual metabolic balances with progressively lower doses and presumably thereby lower their risk of breast cancer and cerebrovascular disease. As it is, patches and pills can often be cut—but what is required is a product for achieving the lowest doses that can be found to combat symptoms with fewest side effects.

Further, the increased availability of natural remedies that do not need licences requires care with efficacy and safety. If they work for some, fine, but evidence from trials would be essential for women to be assured that they pose no greater risks than hormone replacement therapy. Safety data are vital for products whose constituents are not necessarily entirely known and that may contain, for example, phytoestrogens in large doses. What are the long term effects of these preparations, taken on the assumption that being natural they are safe? Will adequate research be done to ensure that we avoid another half century of uncontrolled experimentation on menopausal women? Women have greater expectations of menopausal remedies now—given the false promise of the hormone replacement therapy bandwagon.

It can take decades to detect important and unanticipated side effects of medications reliably. Do the current regulatory provisions adequately provide for the sensible avoidance of more, tragic episodes? Tucker conservatively estimates an extra 1400 cases of breast cancer, 1200 cases of heart disease, and 1400 cases of stroke—against 860 fewer hip fractures and 1000 fewer cases of colorectal cancer per year in the United States alone.[12] Regulators and legislators will be contemplating the implications, as they did after thalidomide, and hopefully we will not get the marketing so wrong again. Severe menopausal symptoms are rated as having worse effects on quality of life than having any of the diseases—pills for symptoms and prevention pose complicated public health problems. Hormone replacement therapy may be a mere example of what is to come—the opportunities remain enormous.

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Competing interests: KM is a member of the Committee on the Safety of Medicines and its expert working group on hormone replacement therapy.

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Thalassaemia major: the murky story of deferiprone

Conducting life saving research properly and quickly is a moral imperative

Every year over 200 000 babies are born with thalassaemia major. They have a life expectancy of less than 30 years and are dependent on blood transfusions. Repeated transfusions result in cirrhosis of the liver, cardiomyopathy, endocrinopathies, and death due to haemosiderosis. Desferoxamine, an iron chelator, has been used for more than 30 years to treat haemosiderosis. It is given by daily, subcutaneous, slow injection, with inconvenience and local reactions resulting in suboptimal compliance in about half the patients.[1] Despite desferoxamine, cardiac disease is still responsible for 70% of all deaths in these patients. Developing an orally administered chelating agent has therefore been a major objective in the care of patients with thalassaemia. Unfortunately the development of such a drug (deferiprone) has resulted in one of the most acrimonious and destructive of conflicts between a clinical researcher (Nancy Olivieri) and a drug com-

Additional references w1-w4 are on bmj.com

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pany (Apotex).[2 w1-w4] This dispute raises several ethical issues, which are discussed in a symposium in the *Journal of Medical Ethics*[3] and in part here.

Dr Olivieri began to study deferiprone in 1989. In 1993 Apotex began to provide financial support for her trials. By March 1996 Dr Olivieri believed that her data showed that participants had iron concentrations in the liver that were above clinically desirable levels. Apotex disagreed with her interpretation and terminated these trials 72 hours after she attempted to amend consent forms to warn patients of alleged reduced efficacy. The company also invoked a non-disclosure clause in its contract to prevent Dr Olivieri from publishing her results. In 1998 Dr Olivieri and her colleagues published their findings.[4] The resulting conflict spread to involve eminent individuals at the University of Toronto, the Hospital for Sick Children, the academic community, and even the prime minister of Canada.

Ethical issues relating to compromise of patients' safety, suppression of academic freedom, conflict of interest in commercially sponsored research, undue influence, constructive dismissal, and professional misconduct are discussed in the *Journal of Medical Ethics*.[3] One ethical issue has, however, received little attention. The first trials of deferiprone were carried out 15 years ago. We still do not know whether deferiprone harms or benefits people with thalassaemia compared with deferoxamine. Deferiprone was licensed for use by the European Committee for Proprietary and Medicinal Products in 1999. In December 2003 the European Court of Justice rejected Dr Olivieri's attempt to intervene in this decision. However, deferiprone is not currently licensed for use in the United States and Canada. Thousands of patients in Europe and Asia are using deferiprone, whereas patients in the United States and Canada do not have access to it. This has grave ethical consequences.

Dr Olivieri has argued that deferiprone is less effective and harmful. If this is true then thousands of patients in Europe and Asia are being harmed by being exposed to a risk of premature death. However, several studies have not supported Dr Olivieri's claims. The main side effect that she attributed to deferiprone was fibrosis of the liver. A large study failed to support this.[5] Another recent trial also showed that deferiprone is safe and effective.[6] Some evidence supports the protective effect on the heart of deferiprone compared with deferoxamine,[1 7] which would be important as cardiac disease accounts for 70% of deaths in thalassaemia. If deferiprone is more effective than deferoxamine (or more tolerable), then thousands of patients with thalassaemia in the United States and Canada are being harmed by being exposed to an increased risk of premature death by being denied deferiprone. Either way, depending on whether deferiprone is or is not more effective than deferoxamine, thousands of people are being harmed. Yet after 15 years we still do not know the answer.[7 8] How could this happen?

A moral imperative exists to conduct potentially life saving research properly and as quickly as possible. All parties—drug companies, researchers, governments and ethics committees—have a moral obligation to expedite this research. Anything that delays the delivery of good evidence harms people because during that unnecessary delay some people are denied an effective treatment. This principle—the moral urgency of scientific research—applies to all research.

The welfare of patients with thalassaemia has been compromised by an inability of all parties to resolve these disputes. Apotex, Dr Olivieri, officials of the Hospital for Sick Children and the University of Toronto, perhaps even other pharmaceutical companies, ethicists, and others could have helped to resolve these issues and facilitate research much sooner.

One problem is that no one group has the responsibility of representing the interests of all people affected by thalassaemia. The closest advocate of patients is the research ethics committee, which has the responsibility to protect people while they participate in research. In March 1996 Apotex submitted data to the Hospital for Sick Children's research ethics committee. The chair responded to Apotex, informing the company that the ethics committee did not act as an intermediary between researchers and sponsors. He instructed Apotex to direct further communications to Dr Olivieri for resolution of disagreements.[9]

Some people believe that ethics committees should not review the science of research, but I believe that this view is mistaken. Bad science and slow science both harm patients. In a recent controversy, a healthy volunteer died partly as a result of a failure of the ethics committee to require researchers to conduct a systematic review of the literature.[10 11]

One can only speculate that this whole affair may never have happened if the ethics committee in Toronto had taken a proactive and independent role in attempting to resolve the scientific dispute between Apotex and Dr Olivieri in 1996. Although one cannot expect ethics committees to have the expertise to resolve complex scientific issues, it is reasonable to expect them to manage a process, including setting up external expert review, to expedite their fair resolution. Now we all need to encourage the research that will necessarily save many lives.

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