Saturday 22 August 1998

BMJ

Cerebral sinus thrombosis and oral contraceptives

There are limits to predictability

Clinical review
p 520

In short succession two recently published papers have shown not only a very high relative risk of cerebral sinus thrombosis in users of oral contraceptives but an even stronger effect of contraceptives among women who carry hereditary prothrombotic conditions.[1 2] This raises several questions: Why this sudden wave of publications? Why the very high relative risks? What are the lessons for clinical practice and prevention?

The field of investigation into oral contraceptive use and the occurrence of venous thrombosis has been undergoing a rapid paradigm shift over the past couple of years. That oral contraceptives may cause venous thrombosis has been known since the 1960s, but ever since there have been controversies about the size of the risk, the role of bias in observational research, the role of hormonal dosage, the type of hormones implicated, and—particularly—the glaring absence of any biochemical explanation. Some have even doubted the reality of the association. The discovery of first the factor V Leiden mutation and then the factor II mutation has changed the picture.

These prothrombotic mutations strongly enhance the risk of oral contraceptives causing venous thrombosis, which, firstly, proves that the association is real and, secondly, offers the beginning of an explanation. For instance, different coagulation tests have shown that oral contraceptive use leads to "acquired activated protein C resistance" of the same nature as the factor V Leiden mutation.[3–6] For studying the mechanisms of coagulation underlying venous thrombosis by epidemiological and clinical means, the rare cerebral sinus thrombosis is a purer model than deep venous thrombosis of the legs or pulmonary embolism. In these two conditions several other chronic risk factors (obesity, trauma, surgery, immobilisation, etc) may confuse the picture, whereas these are not risk factors for cerebral sinus thrombosis. Thus cerebral sinus thrombosis might be caused almost entirely by general "circulating" factors in the blood, possibly aided by factors affecting the vascular wall. This may explain why about 90% of previously healthy young women with cerebral sinus thrombosis in the recent case-control series from the Netherlands and from Italy used oral contraceptives, compared with a population use of about 45% in the Netherlands and 30% in Italy.

These differences give rise to surprisingly high relative risks: 10-fold to 20-fold increases. These increases in risk are much higher than one would have expected from older series of patients. This is puzzling, since the recent studies reflect the era of modern low dose contraception. Part of the reason might be that the newer studies are methodologically more rigorous: for the first time we now have sizeable patient series limited to women who were previously healthy, were premenopausal, and were not pregnant, in the postpartum, or using other hormones.

Although cerebral venous thrombosis is rare, it seems almost entirely associated with hormone use in healthy non-pregnant premenopausal women,[7] with women with hereditary prothrombotic conditions at especially high risk. Given its poor prognosis, in terms not only of mortality but also of permanent neurological deficits, we should ask again whether screening for prothrombotic defects might be useful in women considering taking contraceptive hormones. Earlier, when discussing venous thrombosis of the legs and pulmonary embolism, we urged caution: widespread screening of asymptomatic people with no family history would necessitate biochemical investigations in hundreds of thousands of young women, and advice against the use of oral contraceptives in tens of thousands, to prevent a single death.[8] Nevertheless, a cost benefit analysis in Germany has shown that if the price of the screening test could be lowered to under 18 DM (£6) widespread screening would be completely cost effective from the point of view of a health insurer: the cost of the test would be balanced by the cost of days in hospital, anticoagulation treatment, post thrombotic complications, etc.[9] Such analysis does not take into account, however, the "cost" of less desirable or less effective modes of contraception to the individual (although the advent of newer modes of contraception may change that picture) or the burden of knowing that one carries a potentially deleterious gene. Given the rarity of cerebral venous thrombosis, it is unlikely to sway any cost benefit calculations on screening for prothrombotic conditions dramatically.

On p 520 Laffan and Tuddenham argue that it is now clear that venous thrombosis is a polygenetic condition and that this might change our view about screening: we should investigate a whole array of risk factors, not only coagulation factor V and II, but also factor VIII, etc, and arrive at a risk profile for an individual, possibly by a computer model mimicking the coagulation cascade.[10] Such a risk profile might more specifically pinpoint the individual at greatest risk. This proposal puts venous thrombosis due to oral contraceptive use in the brave new world of predictive

BMJ 1998;317:483–4

genetics. In one way it is a good working case to think about since the issues might be less emotionally charged than with screening for "cancer genes" and much more is known about genetic and coagulation mechanisms. Nevertheless, putting aside the practicalities, costs, and ethics, we might still wonder whether there is a limit to predictability. For weather forecasts it is accepted that no useful day to day predictions can be made beyond seven days since the meteorological system is too complex. May not the system of coagulation, anticoagulation, fibrinolysis, vascular wall factors, and other circulating factors such as cytokines be like meteorology? In risk factor epidemiology, as in the prediction of coronary heart disease, we know that the combination of several strong risk factors yields beautifully smooth risk functions but in the end poor specificity for the individual.[11] Would it be too hazardous a prediction to suggest that a complex coagulation model will face similar problems?

Jan P Vandenbroucke *Professor of clinical epidemiology*
Leiden University Medical Centre, 2300 RC Leiden, Netherlands

1 De Bruijn SF, Stam J, Koopman MM, Vandenbroucke JP. Case-control study of risk of cerebral sinus thrombosis in oral contraceptive users and in carriers of hereditary prothrombotic conditions. The Cerebral Venous Sinus Thrombosis Study Group. *BMJ* 1998;316:589-92.
2 Martinelli I, Sacchi E, Landi G, Taioli E, Duca F, Mannucci PM. High risk of cerebral-vein thrombosis in carriers of a prothrombin-gene mutation and in users of oral contraceptives. *N Engl J Med* 1998;338:1793-7.
3 Østerud B, Robertsen R, Åsvang GB, Thijssen F. Resistance to activated protein C is reduced in women using oral contraceptives. *Blood Coagul Fibrinolysis* 1994;5:853-4.
4 Meinardi JR, Henkens CMA, Heringa MP, van der Meer J. Acquired APC resistance related to oral contraceptives and pregnancy and its possible implications for clinical practice. *Blood Coagul Fibrinolysis* 1997;8:152-4.
5 Lowe GDO, Rumley A, Woodward M, Reid E. Re: Oral contraceptives and venous thromboembolism. *Lancet* 1997;349:1623.
6 Rosing J, Tans G, Nicolaes GAF, Thomassen MCLGD, van Oerle R, van der Ploeg PMEN, et al. Oral contraceptives and venous thrombosis: different sensitivities to activated protein C in women using second- and third generation oral contraceptive. *Br J Haematol* 1997;97:233-8.
7 Bertina RM, Rosendaal FR. Venous thrombosis—the interaction of genes and the environment. *N Engl J Med* 1998;338:1840-1.
8 Vandenbroucke JP, van der Meer FJM, Helmerhorst FM, Rosendaal FR. Factor V Leiden: should we screen oral contraceptive users and pregnant women? *BMJ* 1997;313,1127-30.
9 Szucs T, Osterkorn D, Schramm W. Gesundheitsökomische Evaluation des Screenings auf APC-Resistenz (Mutation Leiden) bei Neuanwenderinnen von Ovulationshemmern. *Med Klin* 1996;91:317-9.
10 Laffan M. Tuddenham E. Assessing thrombotic risk. *BMJ* 1998;317:520-3.
11 Wald N, Law M, Watt HC, Bailey A, Johnson AM, Craig WY, et al. Apolipoproteins and ischaemic heart disease: implications for screening. *Lancet* 1994;343:75-9.

Diagnosing and responding to serious child abuse

Confronting deceit and denial is vital if children are to be protected

Publishing recently in *Pediatrics*, Southall et al described their experience of using covert video recordings to diagnose life threatening abuse.[1] Of 39 children (median age 9 months) referred to two UK hospitals for investigation of suspicion of induced illness, including 36 with apparent life threatening events, the authors filmed evidence of abuse in 33. This included suffocation in 30, poisoning in two, and the breaking of an arm. The transcripts of the recordings make distressing, yet essential, reading. Risk of abuse extended to other children within these families: 12 out of 41 siblings had died suddenly and unexpectedly (suffocation was subsequently admitted for 8, and re-investigation of another revealed salt poisoning), and abuse was documented in a further 15.

Southall et al have revealed the grim world which has been intermittently explored over the past 100 or so years.[2–4] Now, however, the filmed evidence concretely exposes what was previously available only to professional imagination. These children were not damaged during bouts of anger but harmed coolly and callously by parents who appeared concerned and caring, yet when left alone with their children seriously harmed them. The added deception of the health professional increases the feeling of betrayal, not just on behalf of the child but also in relation to the trust doctors and nurses are accustomed to placing in the parent as the child's representative. What are the lessons from these disturbing data?

A crucial issue for doctors is the ability to distinguish cases of abuse from other causes of an acute life threatening event. Compared with controls, Southall et al found that the abused children were less likely to be prematurely born, more likely to present with bleeding from the nose or mouth, and more likely to have a history of sudden and unexpected death or abuse in siblings. In addition, 23 of the abusive parents were diagnosed as having personality disorders.

Intrafamilial child maltreatment is not a unitary, or easily definable, phenomenon but covers a wide range of ways in which parents harm their children. It ranges from neglect (the most common) through physical and emotional harm, to life threatening assault and rape of children. Most cases identified are not life threatening, and death from abuse is unusual. Professionals concerned with the majority can therefore be lulled into a sense of false optimism and assume circumstances will improve, even for the more problematic cases. Additionally, our training and professional calling to help the sick can encourage professional denial of such acts of harm.[3] By contrast, those working in specialised units have to appreciate that milder, non-life threatening forms of maltreatment comprise most cases. Systems of child protection must be able to cope with the full range of child maltreatment.

The variety of child abuse that is factitious illness by proxy also incorporates a range of seriousness.[5] In an epidemiological study in the United Kingdom McClure et al identified 128 cases.[6] In 23 the perpetrator gave only a false history of illness and in a further 21, although both history and signs were fabricated, the parents did not inflict direct physical harm on the child. Thus, for a third of children harm resulted from the subsequent medical investigations. Of the remaining 84 children, 44 were poisoned and 32 suffered deliberate suffocation (3 children experienced both); 8 children died.

Southall et al suggest that "partnership" may not be feasible in cases of life threatening or serious harm. The term partnership has acquired a range of meaning, including professional style (mutual respect, communicative openness), sharing of power, as well as

BMJ 1998;317:484–5

parental involvement in planning and decision making.[7] Partnership as avoiding confrontation, or mere togetherness, is always dangerous in serious abuse. However, partnership is still possible, provided it is made explicit that the focus of all work is the child's welfare.[8] A joint acknowledgment of maltreatment is mandatory, not merely desirable, and family reunification is not automatic. Indeed, partnership can exist around relinquishment of parental care—this being just as legitimate a therapeutic goal as reunification.[8] Professional style should be mutually respectful and as inclusive of parents as possible while still maintaining the child's safety. Some interprofessional discussion must, however, remain confidential when parents are devious or seriously harmful.

What implications are there from this work for practitioners? Firstly, all professionals must remain alert to the possibility of serious, life threatening abuse. Secondly, the nature of the working partnership with abusive parents needs to be moulded by the requirements of child safety and welfare. Thirdly, child protection systems must encompass a range of responses, from family support to an ability to respond vigorously to prevent fatal abuse. One way of ensuring deaths from abuse are not overlooked would be the universal introduction of local child death reviews.[9 10] Covert video surveillance needs to be available as a tool for diagnosing some forms of factitious illness, though it must not replace a full child and family assessment, on which intervention should be based. Southall et al's work reveals important clues which may help to distinguish cases of acute life threatening events caused by abuse. Finally, the work which follows recognition is all important, for herein lies the potential for preventing further harm to children, and stopping escalation in less serious cases.

David P H Jones *Consultant child and family psychiatrist*

Park Hospital for Children, Oxford OX3 7LQ

Margaret A Lynch *Reader in community paediatrics*

United Medical and Dental Schools of Guys and St Thomas's Hospitals, Guy's Hospital, London SE1 9RT

1 Southall DP, Plunkett MCB, Banks MW, Falkov AF, Samuels MP. Covert video recordings of life-threatening child abuse: lessons for child protection. *Pediatrics* 1997;100:735-60.
2 Tardieu A. Étude médico-legal sur les sérvices et mauvais traitments exercés sur des enfants. *Annales d'hygiene publique et de medicine legal* 1860;13:361-98.
3 Kempe CH, Silverman FN, Steele BF, Droegemuelleur W, Silver HK. The battered child syndrome. *JAMA* 1962;181:17-24.
4 Oliver JE. Successive generations of child maltreatment. *Br J Psychiatry* 1985;147:484-90.
5 Meadow R. What is and what is not Munchausen syndrome by proxy. *Arch Dis Child* 1995;72:534-8.
6 McClure RJ, Davis PM, Meadow SR, Sibert JR. Epidemiology of Munchausen syndrome by proxy, non-accidental poisoning, and non-accidental suffocation. *Arch Dis Child* 1996;75:57-61.
7 Department of Health. *Child protection, messages from research.* London: HMSO, 1995.
8 Jones DPH. Treatment of the child and the family where child abuse or neglect has occurred. In: Helfer R, Kempe R, Krugman R eds. *The battered child.* Chicago: University of Chicago Press, 1997.
9 Special issue on fatal child abuse. *Child Abuse Review* 1995;4:309-92.
10 Spotlight on practice on child maltreatment fatalities. *Child Abuse and Neglect* 1995;19:843-83.

Crisis in cremation

Positive action by the Home Office is urgently needed

Disposal of bodies by cremation in the United Kingdom gathered pace in the last 25 years of the last century, following the establishment of the Cremation Society in 1874. It is now the commonest form of disposal, accounting for 73% of disposals in 1996. The legislative framework for cremation was established in 1902: its centenary seems likely to be marked by a system in crisis, on the verge of collapse.

The legislation requires the signature of a medical referee before a cremation can take place. A recent survey of medical referees conducted by the BMA showed that less than 20% are aged under 50. Over half are over 60 and more than a third over 65. No arrangements seem to have been made for replacing this elderly group of doctors. Individual medical referees reported themselves trapped in a system from which there was no escape—required to attend virtually every day, for a fee which does not even pay their travelling costs. They are finding it impossible to recruit deputies or successors.

Several factors may be responsible for this worrying situation. Conspiracy theorists may blame the Home Office, which, having failed to secure the implementation of the recommendation by the Brodrick committee that medical referees should be abolished,[1] is now just allowing time to resolve the issue.

A more plausible explanation is the nature of the cohort itself. Almost 60% of referees above retirement age were previously employed in the public health service. Once local authorities (who own the overwhelming majority of crematoriums) could require their own medical staff to undertake the task of medical refereeing. Since 1974, and the transfer of these doctors to the NHS, the use of their successors can take place only by negotiation. Younger practitioners, dazzled by the attraction of quality issues in the secondary care services, dismiss such duties as "not proper public health medicine." It is, however, difficult to imagine a more effective form of medical audit in an area than every single working day to examine a random sample of the care given to dying patients.

General practitioners may be deterred by the fact that the work, if done properly, requires challenging colleagues about their standards of care from time to time. Most mention the derisory fee. Over half the current medical referees think that the fee is a significant deterrent to recruitment. Another factor is the apparently declining interest of doctors in the establishment of a reliable cause of death, which the medical referee must certify to be "definitely ascertained." The decline in hospital necropsies has long been documented. [2] A more recent survey found that

BMJ 1998;317:485–6

only 41% of forms presented to a northern crematorium were completed sufficiently for the cremation to proceed without further inquiry.[3]

The Home Office has been reluctant to give the subject the attention it deserves. Despite frequent rumours that changes to the cremation regulations are imminent, written evidence confirms that no such plans exist at present. Yet change is needed: much of the language of the documentation that doctors have to complete is antiquated. A hundred years ago it may have been possible to deduce from the mode of death that the patient may have been poisoned: it is no longer so. Coroners' certificates now account for about a third of the disposals, yet the coroner is under no obligation to record on the disposal form the cause of death, which the medical referee must "definitely ascertain." A reference to radioactive implants is now included, but its completion is not a statutory requirement.

The one major recent change to the regulations has been positively unhelpful. Astonishingly, it is designed to exclude senior hospital pathologists from any involvement in the cremation process, even though the results of a necropsy are the most satisfactory objective evidence on the confirmatory medical certificate. No confirmatory certificate is required in such cases. Instead a new single question on the initial medical certificate inquiring whether a necropsy has been done incorporates five qualifying clauses which the junior doctors who usually complete it find unusually difficult to understand.

What can be done? In the BMA survey medical referees themselves emphasised the need for induction and continuing training to promote common standards. A requirement to meet the costs of any necropsy requested by the medical referee would help to resolve the occasional problem when the cause of death is disputed, or when none of the doctors eligible to sign the requisite certificates is available. More effective supervision by the Home Office is urgently required, including random inspectorial visits to crematoriums. Differing necropsy rates and quality standards need identification and explanation. Thirteen crematoriums dispose of fewer than 1000 bodies a year; one as few as 219. The choice is simple: either the system should be made effective or it should be abandoned. The latter is an extremely hazardous option, but to do nothing is even worse. Despite the claims of cremation authorities that they expect no difficulty in recruiting medical referees, the present system is about to collapse under the impending manpower crisis.

Stuart Horner *Professor in medical ethics*

Centre for Professional Ethics, University of Central Lancashire, Preston PR1 2HE (j.s.horner@uclan.ac.uk)

1 Home Office. *Report of the committee on death certification and coroners*. London: HMSO, 1971. (Cmnd 4810.)
2 Cameron HM, McGoogan E, Clarke J, Wilson BA. Trends in necropsy rates: Scotland 1961-74. *BMJ* 1977;ii:1577-80.
3 Horner JS, Horner JW. Do doctors read forms? *J R Soc Med* 1998;91: 98-106.

Role of the ataxia-telangiectasia gene (ATM) in breast cancer

A-T heterozygotes seem to have an increased risk but its size is unknown

Genetic predisposition accounts for 5-10% of breast cancer, and two genes—BRCA1 and BRCA2—have attracted most attention as high risk factors.[1] However, these two genes probably account for only a small proportion of the genetic risk while other more common but less penetrant genes may explain the remainder of genetically predisposed breast cancers.[2] One such candidate is the gene, ATM, mutated in the human genetic disorder ataxia-telangiectasia (A-T).[3] A-T heterozygotes (estimated to be 1% of the population) do not show any of the major symptoms of the disease, though there is good evidence that they have an underlying cellular radiosensitivity, but to a lesser extent than observed in A-T homozygotes.[4] These observations, together with earlier epidemiological studies, reveal a raised incidence of mortality from cancer among blood relations of patients with ataxia-telangiectasia, with the greatest relative risk for breast cancer (5.1) in female relatives of patients.[5]

An association between the incidence of breast cancer and A-T heterozygosity was also revealed in two separate but smaller studies.[6 7] Based on an independent assessment of all these data the relative risk of breast cancer in A-T heterozygotes was estimated to be 3.9, with A-T carriers representing 3.8% of all cases.[8]

With knowledge of the sequence of the ATM gene, Fitzgerald et al detected heterozygous mutations in 2/202 (1%) healthy women with no personal history of cancer.[9] The frequency of 1% is consistent with that predicted from epidemiological studies.[5] When patients with early onset breast cancer (<40 years) were screened 2/410 (0.5%) showed mutations in the ATM gene. Fitzgerald et al therefore concluded that "heterozygous ATM mutations do not confer genetic predisposition to early onset breast cancer." On the other hand, a recent study by Athma et al using molecular genotyping suggested that A-T heterozygotes are predisposed to breast cancer.[10] Among 33 women with breast cancer 25 were A-T heterozygotes compared with an expected 15. For patients with earlier onset disease (<60 years) the odds ratio was 2.9 (21 cases), while for older patients it was 6.4 (12 cases) Based on these relative risks the authors calculated that 6.6% of all cases of breast cancer in America occur in A-T heterozygotes.

Clearly these two studies appear to be in conflict. In an analysis of these data Bishop and Hoppe pointed out that precise estimates were difficult since the study

BMJ 1998;317:486–7

of Fitzgerald et al relied on a small number of mutations while that of Athma et al analysed only a small number of breast cancers.[11] Larger scale studies are required with emphasis on age of onset of breast cancer to address conclusively the potential association between mutations in ATM and risk of developing breast cancer. In a workshop last November in Clermont-Ferrand results were presented from studies in several countries, but the connection between A-T heterozygosity and breast cancer remains unresolved.

If a link between breast cancer and A-T heterozygosity is established, what are the clinical implications? As for any gene that increases the risk of breast cancer, A-T carriers should ideally be identified, but given the size of the ATM cDNA (9.168 kb) and the known distribution of mutations over the entire length of the cDNA it would be difficult and expensive to conduct general population screening. Relying on identifying carriers in A-T families would narrow the scope and usefulness of such screening. A-T carriers would need to be identified by some other characteristic. One such feature does exist—cellular radiosensitivity—but it is not amenable to a widespread screening assay.

This intermediate radiosensitivity does, however, raise another issue which is pertinent to the development of breast cancer. Swift et al concluded that diagnostic or occupational exposure to ionising radiation probably increases the risk of breast cancer in women heterozygous for A-T.[5] High doses of ionising radiation, particularly before puberty, are known to increase the risk of breast cancer. What has emerged as a contentious issue is whether mammography screening leads to an increased risk for A-T carriers. A well conducted mammographic examination involves an absorbed dose of about 0.3 cGy/breast, which if applied annually over 35 years (40-75 years) would give rise to a lifetime radiation dose of 10.5 cGy—approximately the same as background radiation.[12] Exposures of this order, at the age of 40, are estimated to increase the number of deaths from breast cancer by about 1/2000 women, which is insignificant compared with the natural lifetime risk of 1/9 for breast cancer.

What then of carriers of the A-T gene? A-T heterozygotes are intermediate in cellular sensitivity to radiation between controls and A-T patients—that is, at best 1.5-fold to twofold more sensitive than controls. Thus a total dose of 10.5 cGy would not be expected to increase significantly the lifetime risk for breast cancer in A-T carriers.

For A-T carriers the picture that emerges is that while epidemiological studies point to a threefold to fourfold increased risk for breast cancer there remains uncertainty whether this is supported by mutation analysis of the ATM gene. Screening of increased numbers of patients with breast cancer is required to support a small moderate increased relative risk for A-T heterozygotes. It seems unlikely that the intermediate cellular radiosensitivity in A-T carriers increases the risk of breast cancer during mammographic screening, at least when this procedure is restricted to women aged over 40.

Martin Lavin *Professor of molecular oncology*

Queensland Institute of Medical Research/Department of Surgery, University of Queensland, Brisbane, Queensland 4029, Australia

1 Brugarolas J, Tyler J. Double indemnity: p53, BRCA and cancer. *Nature Med* 1997;3:721.
2 Easton DF, Ford D. The genetics of breast and ovarian cancer. *Br J Cancer* 1995;72:805-12.
3 Savitsky K, Bar-Shira A, Gilad S, Rotman G, Ziv Y, Vanagaite L, et al. A single ataxia-telangiectasia gene with a product similar to Pl-3 kinase. *Science* 1995;268:1749-53.
4 Chen P, Farrell A, Hobson K, Girjes A, Lavin M. Comparative study of radiation-induced G2 phase delay and chromatin damage in families with ataxia-telangiectasia. *Cancer Genet Cytogenet* 1994;76:43-6.
5 Swift M, Morrell D, Massey RB, Chase CL. Incidence of cancer in 161 families affected by ataxia-telangiectasia. *New Engl J Med* 1991; 325:1831-6.
6 Pippard EC, Hall AJ, Barker DJ, Bridges BA. Cancer in homozygotes and heterozygotes of ataxia-telangiectasia and xeroderma pigmentosum in Britain. *Cancer Res* 1988;48:2929-32.
7 Borresen AL, Anderson TI, Tretli S, Heiberg A, Moller P. Breast cancer and other cancers in Norwegian families with ataxia-telangiectasia. *Genes Chrom Cancer* 1990;2:339-40.
8 Easton D. Cancer risks in A-T heterozygotes. *Int J Radiat Biol* 1994;66:S177-82.
9 Fitzgerald MG, Bean JM, Hegde SR, Unsal H, MacDonald DJ, Harkin DP, et al. Heterozygous ATM mutations do not contribute to early onset of breast cancer. *Nature Genet* 1997;15:307-10.
10 Athma P, Rappaport R, Swift M. Molecular genotyping shows that ataxia-telangiectasia heterozygotes are predisposed to breast cancer. *Cancer Genet Cytogenet* 1996;92:130-4.
11 Bishop DT, Hopper J. AT-tributable risks? *Nature Genet* 1997;15:226.
12 Norman A, Withers HR. Mammography screening for A-T heterozygotes. In: Gatti RA, Painter RB, eds. *Ataxia-telangiectasia*. Berlin: Springer: 1993:137-40.

Prescription charges: change overdue?

Britain can learn from systems of copayments based on drugs' effectiveness

The NHS prescription charge, currently £5.80, is not related to the cost of the medicine but is a tax for the use of NHS services, intended partly to deter excessive demand for prescriptions. Its deterrent value is currently limited: about half the population are exempt, and only 14% of prescriptions are charged for.[1] The charge itself is criticised as a tax on the sick for its rate of rise and high level.[2] About 60% of prescriptions cost less than the charge, and many doctors now offer private prescriptions to non-exempt patients, where this will cost less than the charge,[3] or advise patients to buy some medicines over the counter.[4] Non-exempt patients are less likely to get a prescription dispensed than exempt patients.[5] Many anomalies exist: patients with some diseases, such as hypothyroidism, pay no charges even for unrelated medicines, while some groups, such as elderly people, are entirely exempt, irrespective of their financial circumstances.

A recent review concluded that while patient copayments do reduce medicine use, they reduce the use of both desirable and less desirable medicines.[6]

BMJ 1998;317:487–8

Experience in Australia suggests that any such detrimental effect is short lived,[7] and in the United Kingdom increases in prescription charges lead to only a slight decrease in prescriptions dispensed to non-exempt patients[8]—in part because the doctor, less sensitive to the charge than the patient, is often the decision maker.

What are the options for reforming the system? In 1994 the House of Commons Health Committee suggested a lower charge but with fewer exemptions.[9] Another, less crude, approach is to adopt a more selective policy targeted against medicines that are only marginally effective or cost ineffective.[10] Several countries run such systems. In France patient copayments range from 0% for essential medicines to 100% for so called "comfort medicines," but the potential deterrent is often negated by private health insurance.[6] In Italy medicines are classified by an expert committee as A (essential for the treatment of chronic illnesses and fully reimbursed), B (effective, but either not essential or poorly cost effective, and reimbursed at only 50%), or C (effective and inexpensive but used only for short periods, or ineffective, and not reimbursed). This policy reduced annual spending on medicines by a third over two years while apparently improving the quality of prescribing.[11]

Under a similar scheme in the United Kingdom effective treatment for all major illnesses and conditions could be free while less effective or cost effective medicines[12] attracted a payment from the patient. Medicines could be categorised (a job perhaps for the new National Institute for Clinical Excellence) as follows.

The A list would contain a selection of effective medicines, no more than 200-300, but sufficiently comprehensive to allow treatment of all major conditions, and free of charge to all.

B list medicines are either no more effective than A list medicines, or offer minor benefits at a disproportionate cost. These might require a low copayment, perhaps related to the cost of the prescription, to a preset maximum. A maximum cumulative annual copayment per patient should also be set.

C list medicines are those for which effective alternatives are already listed—for example, branded preparations where a generic equivalent is available or which are largely directed at patient convenience, such as many modified release preparations. Patients might pay perhaps 50% of the cost of these medicines.

D list medicines would not be funded by the NHS at all, as in the current selected list.

This system might disadvantage some patients for whom a list B drug was essential. For example, some patients with severe reflux oesophagitis might need a proton pump inhibitor (on the B list) because it is effective to an extent to which an H_2 antagonist (on the A list) is not. To avoid this a general practitioner might be allowed to endorse a prescription for exceptional patients, so that a list B medicine would be exempt from the copayment: the criteria for such endorsement would be carefully defined, such as intolerance to or failure of the list A medicine used as part of a therapeutic ladder. Such prescriptions would be audited and if the criteria had not been met the doctor could be held to account. Alternatively prior approval of such prescriptions, as in Australia,[13] could be used. The lists should be constructed so as to make any such use relatively rare.

The lists would not be static. Most new medicines would be listed as B or C initially, but a few might reach list A immediately. Medicines could move up or down the lists, as either new evidence or less expensive alternatives became available. The lists could be included in the *British National Formulary* and in general practice and pharmacy computer systems and updated every six months.

Patient selection need not be abandoned entirely: patients currently exempt might be allowed B list as well as A list medicines without charge in the short term. This would leave much current prescribing unaffected and allow a phased entry of this system, with time for assessment.

How might the various stakeholders react? This scheme should be attractive to the government: all patients would be guaranteed necessary medicines free of charge, but by helping to manage expenditure on medicines the scheme would also maintain patient options for other forms of treatment. But a secretary of state would need to prevent the categorisation being hijacked by vested interests. The BMA has repeatedly called for an overhaul of the prescription charge, and a discussion document suggested that general practitioners might accept limitations to their freedom to prescribe in return for reform of the prescription charge.[14] Some limitation of patient choice would occur if the patient were unable or unwilling to pay for a list B or C medicine, but where such medicines were necessary by objective criteria they would be available without charge. The pharmaceutical industry is used to operating in countries with copayment systems. Indeed, the proposal would reward companies for developing innovative medicines of true value and discourage the development of minor variations on existing medicines.

No one system is ever likely to allow complete management of the medicines bill, and a range of policies will be required. There would, for instance, still be a need to encourage high quality of prescribing and for capped medicine budgets. Prescription charges can be part of these options.

T Walley *Professor of clinical pharmacology*

Department of Pharmacology and Therapeutics, University of Liverpool, Liverpool L69 3GF

1 Department of Health. Statistics of prescriptions dispensed in the community: England 1986-96. *Statistical Bulletin* 1997;15.
2 Dean M. Prescription charges in the NHS. *Lancet* 1994;343:531.
3 Heath I. The creeping privatisation of NHS prescribing. *BMJ* 1994;309:623-4.
4 Medicines cheaper over the counter. *Drug and Therapeutics Bulletin* 1997;35(suppl).
5 Beardon P, McGilchrist M, McFendrick A, McDevitt S, McDonald T. Primary noncompliance with prescribed medication in primary care. *BMJ* 1993;307:846-8.
6 Freemantle N, Bloor K. Lessons from international experience in controlling pharmaceutical expenditure. I: influencing patients. *BMJ* 1996;312:1469-71.
7 McManus P, Donnelly N, Henry D, Hall W, Primrose J, Lindner J. Prescription medicine utilisation following patient co-payment changes in Australia. *Pharmacoepidemiology and Drug Safety* 1996;5:385-92.
8 Ryan M, Birch S. Charging for health care: evidence on the utilisation of NHS prescribed medicines. *Soc Sci Med* 1991;33:681-7.
9 House of Commons Health Committee. *Priority setting in the NHS: the NHS medicines budget*. Vol 1. London: HMSO, 1994.
10 Huttin C. The use of prescription charges. *Health Policy* 1994;27:53-73.
11 Garattini S.Cultural shift in Italy's medicine policy. *Lancet* 1995;346:5-6.
12 Maynard A, Bloor K. Regulating the pharmaceutical industry. *BMJ* 1997;315:200-1.
13 Commonwealth Department of Human Services and Health. *Schedule of pharmaceutical benefits*. Canberra: Australian Government Publishing Service, 1990.
14 Fellows P. *A national formulary linked to a prescription charge policy*. London: British Medical Association, 1995 (GMSC discussion document 25/95).