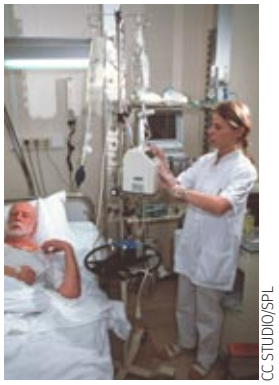
Antithrombin III in critically ill patients

Evidence shows that it does not improve outcomes and increases the risk of bleeding



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RESEARCH, p 1248

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Competing interests: None declared.
Provenance and peer review: Commissioned; not externally peer reviewed.

BMJ 2007;335:1219-20
doi:10.1136/bmj.39399.552245.80

This article was published on bmj.com on 23 November 2007

Antithrombin III, first described in 1939 as a cofactor of heparin, is one of the most important physiological inhibitors of coagulation.[1] Absence of this cofactor is regarded as incompatible with life, and acquired deficiency—for example, in sepsis—is associated with a high risk of venous thrombosis. In the 1960s researchers found a link between coagulation abnormalities and infection,[2] and the anti-inflammatory characteristics of antithrombin III were reported more recently.[3] These discoveries have helped us understand how sepsis develops. In the past 15 years, several clinical trials have investigated whether giving antithrombin III to patients who are deficient in this factor—such as those with sepsis, pre-eclampsia, and traumatic brain injury—improves outcomes. Overall, it had no effect on mortality, although it did improve secondary end points in some trials.

In their systematic review in this week's *BMJ*, Afshari and colleagues assess the effects of giving antithrombin III to critically ill patients.[4] They reviewed 20 randomised controlled trials and found no significant difference in mortality between people given antithrombin III and those given placebo or no intervention (relative risk 0.96, 95% confidence interval 0.89 to 1.03). Antithrombin III significantly increased the risk of bleeding events (1.52, 1.30 to 1.78).

Unfortunately, the authors did not define "critically ill" in detail (for example, by the amount of intensive care needed); patients were loosely defined as critically ill in the included trials. This may have led to a heterogeneous group of trials with mortality ranging from zero—for example, in women with pre-eclampsia—to almost 50% in patients with sepsis. Interestingly, trials of patients with myocardial infarction receiving antithrombin III were not included for unspecified reasons. Therefore, the biological plausibility of some of the included trials and the generalisability of the meta-analysis is uncertain.[5] Even though statistical heterogeneity between trials may be negligible, confidence intervals of the I^2 value of 0%, which are essential to assess the extent of heterogeneity, were not reported.[6]

Pooling trials of poor methodological quality in meta-analyses may introduce bias. Consequently, the authors classified the methodological quality of included trials into whether they had a low or high risk of bias. Although they accounted for important factors—how the allocation sequence was generated, whether allocation was concealed, whether the trial was blinded, and whether an intent to treat analysis was used—a validated measure such as the Jadad scale would have been helpful.[7]

The largest trial (2314 patients) contributed a relative weight of 80% to the meta-analysis, dominating the results of the meta-analysis. None of the forest plots deviated from the findings of this single large trial.[8] Afshari and colleagues applied the method of trial sequential analysis to extrapolate the sample size needed to demonstrate or reject an a priori effect of the intervention on mortality. Thus, they calculated that 14294 patients would be needed to detect a 5% relative risk reduction (mortality and relative risk reduction in trials with low bias risk), but the meta-analysis included only 3458 patients. Their calculation may be inaccurate, however, because of heterogeneity in the definition of critically ill.

Subgroup analysis in Afshari and colleagues' review indicated that survival was better when antithrombin III was given without concomitant heparin. Other retrospective analyses have indicated that antithrombin III given without heparin may reduce mortality in patients with severe disseminated intravascular coagulation.[9] A randomised controlled trial in patients with severe sepsis and disseminated intravascular coagulation that has adequate power to compare antithrombin III with and without heparin would therefore be useful.

The interaction between antithrombin III and heparin is poorly understood. Although heparin increases anticoagulatory activity when bound to antithrombin III, we know little about the modulation of its anti-inflammatory properties under these circumstances. Before a large clinical trial is started, a more in-depth analysis of the pharmacokinetics of antithrombin III in critically ill patients is needed; this should include an assessment of the dose-response relation between antithrombin III and heparin.[10] Unfractionated heparin on its own reduced mortality in sepsis under experimental conditions,[11] and it is being evaluated as a single immunomodulatory anticoagulant in ongoing clinical trials.[12]

Why has antithrombin III failed in clinical trials so far? Its lack of effect may be a true finding. Alternatively, it may be the result of interactions with other drugs, such as heparin, or the result of methodological limitations in terms of patient selection or classification.

Afshari and colleagues' review[4] is currently the most comprehensive summary of the use of antithrombin III in critically ill patients. Despite some minor limitations,

the conclusion that antithrombin III cannot be recommended in critically ill patients is sound.

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Treatment of displaced intracapsular hip fractures in elderly patients

Arthroplasty improves function and has a lower reoperation rate than internal fixation

RESEARCH, p 1251

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Competing interests: MJP has been reimbursed for expenses when attending symposiums and product design meetings organised by manufacturers of implants for internal fixation and for arthroplasty.

Provenance and peer review: Commissioned; not externally peer reviewed.

BMJ 2007;335:1220-1
doi:10.1136/bmj.39392.353090.80

Displaced fracture of the intracapsular proximal femur has been termed the "unsolved fracture" because it is unclear whether it should be treated by internal fixation or by replacement of the femoral head with an artificial hip (arthroplasty).[1] More than a third of fixed fractures will require revision surgery for either redisplacement (a complication of fracture healing), fracture non-union, or avascular necrosis of the femoral head. Arthroplasty, however, is a more extensive surgical procedure and may cause dislocation, loosening, and peri-prosthetic fracture, which together have an overall incidence of 5-15%. In their randomised controlled trial in this week's *BMJ*, Frihagen and colleagues compare the effects of internal fixation or bipolar hemiarthroplasty after displaced fracture of the femoral neck.

Numerous reports of case series and some methodologically weak randomised controlled trials have failed to resolve the question of which treatment is best, and different surgeons tend to favour one or the other. The Scandinavian countries have generally advocated retaining the femoral head, whereas surgeons in other parts of Europe and North America have favoured arthroplasty. As the quality of randomised controlled trials in orthopaedics has improved and such trials have been evaluated in systematic reviews the mystery of the unsolved fracture is being resolved.

Frihagen and colleagues' study was designed and carried out well.[2] All potential participants were reported fully, those assessing the outcome were blinded to the type of surgery, and all relevant outcomes were clearly reported. Both treatments tested—a modern method of reduction and internal fixation and a cemented bipolar hemiarthroplasty—were appropriate. People who had hemiarthroplasty had significantly better hip function (at four and 12 months), better health related quality of life (at four months), and better scores of activities of daily living (at 12 and 24 months) than those who had internal fixation. Significantly more complications occurred in the internal fixation group, but no significant difference was seen in mortality at 24 months.

The results agree with other recent randomised controlled trials on this topic,[3-5] which have been summarised in a Cochrane systematic review.[6] The results indicate that cemented arthroplasty is better than internal fixation in most patients.

The matter is not clear cut though. Internal fixation is still appropriate for younger people, who have fewer complications of fracture healing. Also, these people have a longer life expectancy, and arthroplasty may need to be revised at a later date because of wear or loosening of the implant. At present, the age at which fixation should be replaced by arthroplasty is somewhere between 55 and 75 years. And for the very frail elderly, the lesser surgical assault of internal fixation compared with arthroplasty may enable a few more patients to survive the trauma of hip fracture.

The value of the second articulating joint within the hemiarthroplasty (bipolar joint) is questionable. The few randomised trials to date have shown no benefit for this additional joint compared with a traditional unipolar hemiarthroplasty.[7] Other randomised controlled trials have suggested that total hip replacement—in which the acetabular surface is replaced—is superior to hemiarthroplasty, with less residual pain, lower revision rates, and better regain of function.[3 8] Many of these studies included elderly people with hip fracture who were "fitter," so whether these improved outcomes will apply to less fit people is unclear.

Clinicians should be wary that, along with most other clinical studies, Frihagen and colleagues' study reports relatively short term outcomes (two years). Avascular necrosis of the femoral head after internal

This article was published on bmj.com on 4 December 2007

fixation may occasionally occur more than two years after surgery. Late complications after arthroplasty, such as loosening of the implant, can be expected in about 1% of cases each year.

In conclusion, the evidence so far suggests that a cemented arthroplasty for a displaced intracapsular fracture in elderly patients is better than reduction and fixation—it has a lower rate of reoperation and results in better function. As about one million of these fractures occur worldwide each year, we must continue to define the optimum surgical procedure for this potentially disabling condition.[9]

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Regulation of drugs for children in Europe

New legislation encourages the drug industry to produce high quality transparent research

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Competing interests: None declared.
Provenance and peer review: Commissioned; not externally peer reviewed.

BMJ 2007;335:1221-2
doi:10.1136/bmj.39400.376424.BE

Over the past 10 years, studies have shown widespread use of unlicensed and off-label drugs to treat children in hospital and in the community.[1 2] A prospective European study showed that two thirds of children in hospital received at least one unlicensed or off-label drug, and almost half of all drug prescriptions for these children were either unlicensed or off label.[1] Subsequent studies confirmed that the use of unlicensed and off-label drugs is more likely to be associated with drug toxicity.[3]

In 1999, concerns were raised about children in Europe receiving unlicensed or off-label drugs instead of ones that have been scientifically evaluated and licensed.[4] In December 2006, after extensive consultation, the European parliament approved legislation that should improve the regulation of drug treatment for children (regulation number 1901/2006 on medicinal products for paediatric use).

The legislation aims to ensure that drugs used for children are subject to high quality research that is ethical and appropriately authorised. It will also provide better data on the benefits and harms of drugs used in infants and children. This will hopefully be achieved without subjecting children to unnecessary clinical trials and—as authorisation for medicines in children can take longer than in adults—will not slow down the introduction of new drugs for adults.[5]

It is more expensive to develop drugs for children than for adults. Children need tailored formulations; for example, suspensions for young children and infants and ampoules containing appropriate drug doses for children of different weights.[6] The importance of appropriate formulations for children has been recognised by the World Health Organization, which launched a new initiative last week to improve children's access to safe and effective medicines.[7]

The European legislation provides financial incentives for the drug industry to study drugs in children. Drug companies will have to develop and agree a paediatric investigation plan for an individual drug with the European Medicines Agency. On completion of the study, the patent will be protected for an extra six months through an extension of the supplementary protection certificate. For older medicines not covered by a patent, a paediatric investigation plan can still be agreed. On completion of the study, the company can apply for a "paediatric use marketing authorisation," which would allow 10 years of data protection by a patent.[5]

The financial incentives are considerable, but experience in the United States has shown that the drug industry is more likely to study drugs that are prescribed extensively in adults and generate the most profit than those that infants and children require clinically.[8] The European Medicines Agency and its paediatric committee will be responsible for ensuring that the drugs studied will benefit children and will not just provide the most profit to drug companies.

A European register of clinical trials of drugs for children will be established, and the results submitted to the regulatory agency will be made public. This transparency is essential, as a database of paediatric clinical trials only accessible to the European Medicines Agency would not benefit children in Europe.

The legislation is aimed primarily at the drug industry. To ensure that clinical trials in children of all ages are designed and performed with safety as a priority, the industry will need to work closely with paediatric health professionals. National networks are being set up to facilitate the development of clinical trials; the French network of paediatric clinical investigation centres is the most well established of these and has been involved in more than 200 clinical trials in the past three years.[9]

Clinical trials of drugs are needed in many areas where

the drug industry has no interest. In the United Kingdom, the National Health Service has invested heavily in funding clinical trials in these areas through the health technology assessment programme. This funding has had the additional benefit of involving more academic units and hospitals in paediatric clinical trials. It is anticipated that funding on a European level will be available through framework programme 7—the current programme for funding scientific research within the European Union.

The scientific study of drugs in children is the basis for a new subspecialty of paediatrics—paediatric clinical pharmacology—which has a recognised training programme in the UK.[10] Paediatric clinical pharmacologists have played a key role in documenting the use of unlicensed and off-label drugs in children and the risk of drug toxicity.[1 11] They have been involved in the design of clinical trials in children, which usually require different approaches to trials carried out in adults.[12] A recent survey, however, identified only 18 paediatric clinical pharmacologists in Europe.[13] Only four countries (Finland, France, Germany, and the UK) had more than one paediatric clinical pharmacologist. Hopefully, the new legislation will stimulate scientific interest in the study of drugs in children and increase the number of paediatric clinical pharmacologists in Europe.

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The future for trainee doctors

The Tooke report has identified the challenges, now the profession must respond

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Competing interests: MM was deputy chief medical officer in the Department of Health, England, until November 2007, and he was the lead for the MMC programme from March 2007.

Provenance and peer review: Commissioned; not externally peer reviewed.

BMJ 2007;335:1222-3
doi:10.1136/bmj.39421.672523.BE

Medicine has always been a highly competitive career option, attracting some of the brightest and best of each generation. For those who succeed, the rewards go beyond job satisfaction and social standing. Few careers guarantee the same level of income and security of employment. Fewer still offer the same high odds of getting to the top of the professional ladder by becoming a consultant or principal in general practice. After years of good fortune, these benefits are seen by most doctors almost as a right. Other professions must look on with envy.

The fallout from the current reforms of postgraduate medical training, Modernising Medical Careers (MMC), is shaking these expectations to the core. The tacit understanding that some specialty training programmes were more popular than others has now been turned into the hard reality of competition ratios.[1] In 2007, there were 53.2 applicants for each post in the third year of specialist training in cardiothoracic surgery, whereas fewer than one person applied per post for a similar number of jobs in clinical immunology. Next year is likely to be even more competitive, with an overall competition ratio of three applicants for each post, compared with two this year. As a result of these high levels of competition and the intent of MMC to eliminate the "lost tribe" of junior doctors,[2] applicants are starting to recognise that they may have to choose less popular specialties at an earlier stage. A substantial number of graduates in the United Kingdom may fail to get into an approved training post in any specialty.

The respective roles of junior doctors and consultants are also changing, as the European Working Time Directive dictates a shorter working week, and the focus on protected learning time reduces the time that trainees spend seeing patients. This has led to consultants doing much of the work that was traditionally done by their juniors. To cap it all, the dream of reaching the top of the profession after years of self sacrifice is now being challenged with talk of a "sub-consultant grade" refusing to go away, despite the best efforts of the BMA.

These threats to traditional expectations have resulted in demoralisation and anger, not just among junior doctors but across the profession. This response is understandable but not helpful. However damaging the events of the past year for all concerned, Sir John Tooke's independent inquiry into the MMC provides an opportunity for the profession and the Department of Health to accept some stark realities, to demonstrate far sighted leadership, and to act.[3]

The interests of patients, the service, and the profession will be met only if several deficiencies in policy are sorted out swiftly. Chief among these is the need for more effective workforce planning,[4] in particular tackling the disconnect between the policy of self sufficiency in the medical workforce and the open door policy that allows international medical graduates to apply for training posts on the same terms as UK graduates. In 2007, this resulted in 3687 UK

graduates failing to get training posts. The choices are stark—either home grown graduates should be given preference, as is the case for most other developed countries, or the UK needs to reverse the 60% expansion of medical school places that has taken place over the past decade.

No less challenging is the need for greater clarity about the shape of future careers for doctors, as this should influence the structure and the content of specialist training. More specialists are likely to work in the community alongside generalists. This will require a different set of knowledge, skills, and attitudes, not just a change of location.

As unpopular as it may be in some quarters, the profession needs to accept that post-training career progression should take the form of a pyramid—rather than the current square, which allows most doctors to progress to the top. If no consensus is reached at a national level over this matter, then increasingly independent employers will inevitably drive change at a local level, particularly in the hospital sector. Enough flexibility exists within the current consultant contract to allow them to do so without the need to renegotiate terms and conditions. More flexible models are likely to prove popular with doctors who want to concentrate on clinical practice rather than extended professional roles or who want greater career flexibility.

Most junior doctors accept that medicine is competitive and see this as a good thing. However, they want to be confident that the criteria on which they are competing are fair, valid, and reliable. The perception that this was not the case in 2007 was the trigger for the MMC crisis, though emerging evidence suggests that the recruitment process was more discriminating than many critics have claimed.[5] Having established a fair process, junior doctors deserve better careers advice and mentorship than many have previously received. Medical schools and professional bodies need to rise to this challenge, and urgent work is needed to match career choices not only to individual aspirations but also more closely to aptitudes and the needs of the service.

Few in the medical profession have wanted to see a silver lining to the medical training application service cloud, but one does exist. Postgraduate medical education is now firmly on the agenda of ministers, policy makers, and National Health Service managers. We are now starting to see a real debate about matters that were previously ignored, notably the purpose, size, and shape of the medical workforce. The Tooke report provides a window of opportunity; the profession must respond.

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Assuring the confidentiality of shared electronic health records

Sharing data between multiple institutions offers better regulation and public protection

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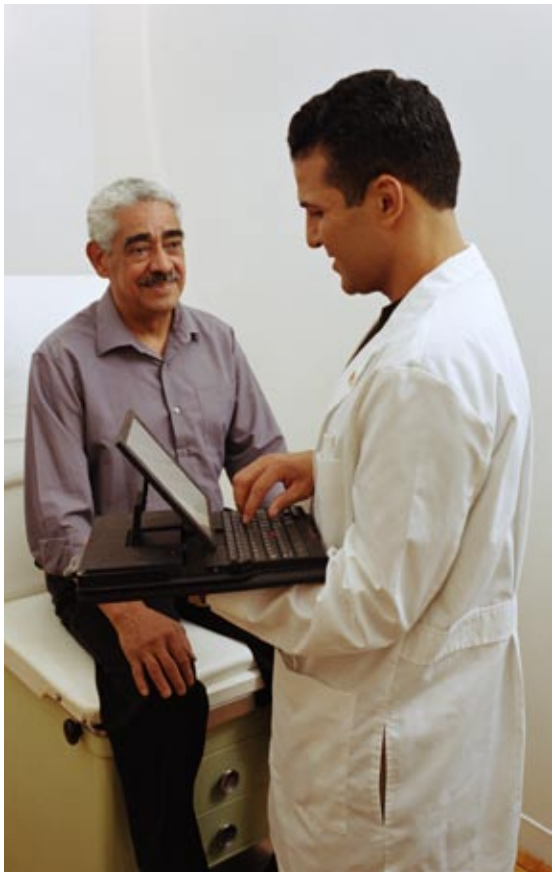
Competing interests: None declared.
Provenance and peer review: Commissioned based on an idea from the author; not externally peer reviewed.

BMJ 2007;335:1223-4
doi:10.1136/bmj.39421.544063.BE

The recent loss of sensitive data on 25 million people by the government of the United Kingdom is just the latest in a series of events covering a wide variety of institutions in different countries.[1 2] Media coverage has tended to focus on obvious aspects of the unintended release of personal data, such as the disks that were lost and omissions in procedure, such as encryption.[3] The most important question in all of these scandals, however, is how a single failure or lapse in procedure could result in a catastrophic disclosure.

The consequences of these security failures are exacerbated by our increasing tendency to centralise large and detailed data from multiple sources, and the existence of policies and legislation that enable the sharing of data between organisations. In health care, the collection and storage of sensitive personal data is essential for delivering a high quality clinical service and for research.[4] Indeed, the future function of the National Health Service (NHS) depends on it.[5]

The fundamental problem is the simplistic approach often taken to define and regulate the access of users to data. Privilege management and access control refer to the policies and systems in place to specify what users are allowed to do, including what modifications, exports, or onward communications may be performed.[6] Once the system has given a user access to certain data, the only protection against misuse is usually a set of documented procedures that specify how users should behave in given circumstances. The same rules apply whether the data come from a single system, a data warehouse, or a group of systems logically connected to appear as one (database federation). These written documents, often called standard operating procedures (SOPs), can prevent inadvertent disclosure of data only if staff are trained to use them consistently; if users do not have malicious intent, are competent, and don't make mistakes; and if the author of the SOP has planned for all scenarios relating to data access and sharing. Unfortunately, evidence



shows that it is difficult for all of these conditions to be fulfilled.[7]

Access control is one of a range of security measures; other examples are encryption and authentication. Authentication confirms the identity of the user as opposed to determining what he or she is permitted to do, whereas encryption prevents eavesdropping. Neither improves the quality of access control.

A common feature of the methods used to allow the legitimate release of data is that usually only one authorised user extracts and communicates the requested information, without supervision or cross checking. This is why SOPs are important but also insufficient, because they form a closed opaque system. Many features of an SOP can be computerised, and we urgently need better technical measures to enforce and verify procedures that represent good practice. When properly implemented, this can provide transparency, counter conflicts of interest, and enforce agreed procedures.

The dispersal of identifiable data between institutions has advantages—ranging from improved security to local control—but it does require a multi-institutional policy and a mechanism for the construction of combined datasets.[8] General practitioners concerned about the NHS Care Record Service might be more comfortable with the concept of local record systems, which need additional authorisation before aggregation at a national level.[9]

Providing such additional authorisation has logistic and workload implications, but it is possible. Transparency can be provided by multiple intermediaries who are independent from those who hold and receive the data.[10] Under such a framework, a single failure or lapse in procedure cannot result in release of data.

The use of unique individual identifiers is essential when sharing bulk data. Different institutions often use different identifiers and this contributes to the problem of sharing data. To share person specific data—for example, in a post-genomic research project that links drug prescribing to genetic data—we must either share unique identifiers or understand the relation between the different sets of identifiers used.[11] This process is known as linkage, and the purpose of the new NHS number and the proposed national ID card is to make this accurate and efficient. The best way of achieving linkage is for an independent intermediary to anonymise the data and provide a new common identifier that links the different records for the same person, but which is not the same as any "real" identifier used in the NHS. This process, known as pseudonymisation, permits authorised users to combine the anonymised data on individuals that they have been given. It does not permit linkage to any other (identifiable) clinical data that they might gain access to.

The ID card is the subject of much debate, and whether it protects or harms depends on the environment into which it is introduced.[12] In a world of many institutions sharing data behind closed doors it could be harmful. But in a world in which data are shared in an open, transparent, and well regulated environment it is an essential way to preserve privacy. In a multi-institutional mechanism, the dispersal of data provides safeguards for both privacy and security, while combining these data offers independent regulation and technical safeguards to control who receives such data and to limit the ability to identify such data.

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