Pulmonary embolism

Samuel Goldhaber's Seminar on pulmonary embolism (Apr 17, p 1295)[1] made interesting reading, and raises a few issues worth discussing. The first involves the imaging techniques used to study pulmonary embolism.

Although chest CT has been used increasingly to diagnose pulmonary embolism, one of the problems with it is that it is technology-dependent and operator-dependent, especially with respect to imaging of the subsegmental pulmonary vessels. Ruiz and colleagues[2] found that, after exclusion of unreadable scans caused by motion artifacts, assessment of half the subsegmental vessels were thought to be difficult by one of two readers. Chest CT might be the preferred method of assessing patients in large centres with experience in reading CT pulmonary angiography, but ventilation-perfusion scanning probably provides better interoperator consistency in the interpretation. Chest CT is therefore a very good test to diagnose pulmonary embolism, but its safety as a test to rule out the disorder is debatable, especially in smaller centres.

Goldhaber states that high-probability or low-probability ventilation-perfusion scans can diagnose or exclude pulmonary embolism. The PIOPED study[3] he quotes, however, found that in the presence of high clinical pretest probability, the post-test probability of a low probability ventilation-perfusion scan is 56%. This is hardly sufficient to exclude pulmonary embolism purely on the basis of a low-probability ventilation-perfusion scan if the clinical pretest probability is high.

I therefore believe that the key factor in the diagnosis of pulmonary embolism is clinical assessment with clinical pretest probability. In patients with high clinical pretest probability and signs and symptoms consistent with a large pulmonary embolus, a chest CT should be the diagnostic imaging technique of choice, with a view to doing venous ultrasonography if the chest CT is non-diagnostic. On the other hand, in patients with clinical signs and symptoms consistent with a possible peripheral embolus, then a ventilation-perfusion scan should probably be the technique of choice.

The second issue worth commenting on is our failure to provide adequate prophylaxis, especially in the medical wards. Although a large randomised controlled trial has shown the benefits of 40 mg enoxaparin in reducing venous thrombosis in inpatients,[4] a brief wander through our medical wards proves that we as physicians are far behind our surgical colleagues in providing routine prophylaxis for pulmonary embolism. Furthermore, despite the convincing evidence for out-of-hospital 3–4 week prophylaxis after high-risk orthopaedic surgery,[5] it has not been widely adopted in our hospital, since the conventional view that prophylaxis should be stopped once a patient can mobilise prevails.

Goldhaber's Seminar serves as a timely reminder to reassess our practice against best evidence. Perhaps it is also time for a widespread education campaign to inform practitioners about the use and adequacy of prophylaxis for pulmonary embolism among hospital inpatients.

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In his Seminar on pulmonary embolism,[1] Samuel Goldhaber covers nearly all aspects of treatment for this often life-threatening disease. However, he does not mention a controversial aspect of treatment. Volume loading is used to treat haemodynamically compromised patients with acute pulmonary embolism despite experimental data which suggest that volume loading after embolism might cause a leftward shift of the ventricular septum with subsequent decrease in left-ventricular end-diastolic volume and stroke work.[2] Could Goldhaber give a statement on the correct amount of fluid challenge?

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Congratulations to Samuel Goldhaber[1] on his excellent Seminar on pulmonary embolism. There is one important omission. Goldhaber makes no mention of the value of continuing heparin for at least 48 h after the achievement of therapeutic international normalised ratio (INR).

During the first 36 h of warfarin treatment, precipitous decreases in concentrations of protein C result in a transient hypercoagulable state. In-vivo prothrombin activation is a function of the balance between factor II and protein C concentrations and is not prevented until nadir concentrations of factor II are obtained, which can take 40–192 h.[2] During this time, patients are paradoxically at increased risk of thromboembolic disease and it is therefore important to overlap heparin and warfarin treatment for at least 48 h after therapeutic INR values have been achieved.

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Samuel Goldhaber's otherwise excellent Seminar on pulmonary embolism[1] includes in the risk factors a discussion of hormonal factors that must be challenged.

Pregnancy, hormone replacement therapy (HRT), and oestrogen-containing oral contraceptives are known to increase the incidence of venous thromboembolism (VTE).[2,3] However there is no evidence that progestogen-only methods of contraception, which include pills, implants, injectables, and intrauterine devices, significantly alter haemostatic variables or increase the risk of VTE.[4] Indeed, these preparations are often recommended to women with a past history of VTE or with an inherited or acquired prothrombotic state.

I would agree that a past history of VTE is an absolute contraindication to the oestrogen-containing contraceptive and would also suggest that a strong family history of VTE and an inherited prothrombotic state constitute absolute contraindications rather than the relative described in the article. Other oestrogen-containing contraceptives such as the vaginal ring or patch are also likely to increase the incidence of VTE; however, whether this increase will be lower than that seen with comparable oral preparations, as it is with HRT,[5] remains to be established.

The use of the term "generations" in the description of oestrogen-containing oral contraceptives relates solely to the progestogen content of the preparation and has nothing to do with the dose of oestrogen. It has recently been suggested that the term be abandoned owing to the introduction of newer progestogens and to avoid the confusion the term caused. There is evidence that reducing the dose of ethinyl oestradiol in the oestrogen-containing oral contraceptives to 50 μg resulted in a lowering in the incidence of VTE; however, in users of oestrogen-containing oral contraceptives containing less than 50 μg of ethinyl oestradiol, the risk of VTE is unrelated to the dose.

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Author's reply

Multidetector-row spiral CT technology has overcome the past limitations of CT and has emerged as the preferred imaging technique for patients suspected of having acute pulmonary embolism. Tiny, peripheral subsegmental emboli are well visualised. New-generation scanners seem to be virtually as accurate as catheter pulmonary angiography for detection of pulmonary embolism.[1]

The problem with clinical assessment and scoring of "clinical pretest probability" is that the scoring system is heavily weighted towards one subjective question: "Is an alternative diagnosis more likely than pulmonary embolism?" Despite valiant efforts to create a reliable formula and scorecard, the assessment of clinical pretest probability remains best achieved through gestalt, intuition, and experience.

As Sandra Fortunat and Georg Röggla state, volume loading is controversial and potentially dangerous in haemodynamically compromised patients with acute pulmonary embolism. When right heart pressures are elevated on physical examination or doppler echocardiography, fluid administration can precipitate further deterioration of cardiac function. These patients will benefit from the early use of vasopressors.[2] The optimum vasopressor is uncertain, but my three favourites are dopamine, phenylephrine, and vasopressin. They are selected and administered empirically.

Kwang Yee reminds us to be vigilant and insist on venous thromboembolism prophylaxis in our hospital inpatients. In a prospective registry of 5451 patients with ultrasound-confirmed deep-vein thrombosis, only 1147 (42%) of the 2726 who had deep-vein thrombosis diagnosed while in hospital had received prophylaxis within the previous 30 days.[3]

Habib-ur-Rehman makes the excellent point that heparin should be administered for at least 5 days after starting warfarin to prevent paradoxical hypercoagulability due to depletion of protein C.

The risk of fatal pulmonary embolism from oral contraceptives is small, perhaps as low as 1 per 10 million woman-years.[4] However, this risk does seem to be higher for women taking birth control pills that contain the third-generation progestogens desogestrel or gestodene. A meta-analysis indicates that third-generation oral contraceptives could triple the risk of venous thromboembolism compared with second-generation oral contraceptives.[5]

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Samuel Goldhaber's impressive Seminar[1] omits sickle-cell haemoglobin C disease from the list of risk factors.

The strong reaction between haemoglobins S and C explains why several patients with the disease have more thromboinfarctive events than patients

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with sickle-cell anaemia of the same age and sex.[2] The high haematocrit (packed cell volume) that SC patients often attain is another reason why such patients are prone to pulmonary embolism. Of 377 consecutive patients with SC disease, the mean haemoglobin concentration was 112 g/L; concentrations were above 135 g/L in 69 patients, and reached 165 g/L in two.[2]

One in three west Africans are heterozygous for the gene for haemoglobin S or C, resulting in 1% of all west African babies being born with sickle-cell anaemia (SS genotype), and another 1% with sickle-cell haemoglobin C disease (SC genotype).[3] Thousands of heterozygous individuals emigrate to Europe and elsewhere, and 2% of all their offspring will have sickle-cell disease (SS or SC). Those with sickle-cell anaemia will attract medical attention early, but those with sickle-cell haemoglobin C disease grow up to present diagnostic problems. For every adult SS patient seen in the UK, there are two or more with SC disease that have remained unrecognised. Doctors should suspect SC disease whenever an African woman with normal haemoglobin concentration presents with unresolved pneumonia or severe breathlessness, and should connect her illness with multiple pulmonary emboli.

It is not difficult to distinguish clinically a predominant pulmonary infarct from a predominant pneumonic consolidation, realising that pulmonary infarction can precede or succeed pneumonia, and vice versa.[2] I recommend the simple smear test that shows the poikilocytotic "blister" cells first described by Diggs and Barreras[4] in the blood of patients with sickle-cell disease and pulmonary embolism.

Hyperviscosity features of SC disease that distinguish it from other phenotypes include bilateral hip necrosis (seven times more common in SC than SS), intermittent claudication in patients older than 50 years, sudden monocular blindness from vitreous haemorrhage (10 times more frequent in SC than SS), and greater morbidity from dehydration.[2] My "numb lower lip sign" of sickle-cell crisis was first described in this phenotype,[5] and indicates how widespread thromboinfarctive areas can be, including sites associated with acute retention of urine.[2] Management of pulmonary embolism in sickle-cell disease starts with partial exchange blood transfusion, which can be done quickly at the bedside.[2]

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Rotavirus vaccines

Roger Glass and colleagues (May 8, p 1547)[1] write that the introduction of rotavirus vaccination in developing countries is politically difficult in light of its withdrawal from use in the USA. The issue goes beyond one of political correctness. The article glosses over the moral and ethical issues involved in the trial of this vaccine in poor countries.

The question of how many serious side-effects are acceptable to save a life has been discussed by us elsewhere.[2] The risk-benefit equation answers the question "Is the cure (prevention) worse than the disease?" It is true that developing countries, in which the risk of death from disease is greater than in developed countries, are more tolerant of preventive measures with side-effects.[1] We here seek to ask a more fundamental question: is it ethically justifiable to conduct trials of expensive vaccines such as that for rotavirus in developing countries?

Glass and colleagues note that, traditionally, vaccines are tested by multinational manufacturers in the USA and Europe and only later in developing countries as supply and competition increase and the cost of the vaccine decreases. We argue that ethically, too, this is the right way to go about it. The Helsinki Declaration suggests that trials be done in populations who are directly to use the drug, and that particular attention must be paid when trials involve vulnerable sectors such as prisoners and those of low socioeconomic status. It has been reported that it is easy to recruit participants for trials in developing countries, and that the cost of research is halved.[3] A major saving, we dare say, is in the provision of compensation for adverse effects, which is less likely to be claimed by the indigent population in poor countries. This is what makes drug companies press countries such as India to change their law and allow unfettered research by foreign manufacturers.[3]

We suggest that if a vaccine is not affordable to the population at its current price, trials of the vaccine in that population run counter to the Helsinki Declaration. The rotavirus vaccine costs US$38 per dose and is administered in three doses. For India's yearly birth cohort of 25 million, these three doses will cost $2850 million. According to Health Information of India 2000 and 2001, the Ministry of Health, and the Family Welfare Government of India, the health and family welfare budget outlay for the year 2002–03 was $1440 million. Rotavirus vaccination, which costs two times the entire health budget, prevents just 1·5% of the deaths that occur in children younger than 5 years (see below). The expenditure is thus difficult to justify.

It could be argued that the health budget needs to be enlarged. However, a more absolute measure of affordability comes from looking at the intervention against the per-capita gross national product of the country.[4] Under-five mortality in India is 98 per 1000 livebirths, and neonatal death is responsible for 49 deaths. Since rotavirus vaccine given at 3 months of age is unlikely to prevent neonatal deaths, we are potentially looking at the remaining 49 deaths per 1000 livebirths. 15% of deaths in under-

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fives in developing countries are due to diarrhoea, and 20% of them could be due to rotavirus.[5]

In effect, rotavirus vaccine can prevent 1·5 deaths per 1000 livebirths. Given the life expectancy of about 60 years in India, we can assume that this intervention results in 90 life-years saved. The cost of the vaccine itself (not counting the cost of administering the three doses) comes to $1266 per life-year saved (cost of vaccines for 1000 infants divided by 90); the yearly per capita income in India is only $450. The vaccine cannot therefore be recommended as cost-effective or affordable[4] and so it is unjustifiable to test the drug in this population. The stipulations of the Helsinki Declaration will permit the research only after its price has come down drastically. To do otherwise is to exploit the economic vulnerability of the population and to use them as guineapigs.

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In a Viewpoint, Roger Glass and colleagues (May 8, p 1547)[1] describe how, despite the setback to children of the developing world, withdrawal of the Rotashield vaccine (Wyerth-Ayerst, USA) from the US market ultimately created opportunities to consolidate efforts to tackle this important public-health problem.

This situation was certainly the case with the Pan American Health Organization and several of its partners, including the Centers for Disease Control and Prevention, the Gates Foundation, the National Institutes of Health, and the Albert B Sabin Vaccine Institute. This partnership is dedicated to the reduction of morbidity and mortality from diarrhoea caused by rotavirus infection,[1,2] which is accountable for about 75 000 admissions and 15 000 deaths every year in the Americas alone.

Much work has been done in Latin America; however, several challenges remain. As noted in a meeting held in Lima, Peru, in September, 2003,[2] surveillance systems, similar to those developed for polio and measles, should be strengthened. More economic studies are needed to accurately define the cost-effectiveness of vaccine interventions. This information will be critical for future decisions among national policy makers. Since the Lima meeting, substantial inroads have been made.

To that end, the Pan American Health Organization and its partners held a global meeting in Mexico City on July 7–9, 2004, to review progress towards the development of a rotavirus vaccine and its introduction in developing countries. Several ministers of health from Latin America and the Caribbean attended the meeting. Leading global experts will address a broad range of issues concerning: rotavirus pathogenesis, epidemiology, surveillance, vaccine adverse events, intussusception background rates in developing countries, vaccine cost-effectiveness, the results of new rotavirus vaccines being developed, finances, and partnerships.

The aim of this meeting was not just to share technical information, but to put forward a call to action that will ultimately benefit children in developing countries. Therefore, a Mexico City declaration was launched at the end of the meeting that will certainly go a long way to galvanise the political support and commitment to do exactly that. The declaration and proceedings of the meeting will be published in the near future.

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Alcohol intake, serum uric acid concentrations, and risk of gout

In their Article, Hyun Choi and colleagues (Apr 17, p 1277)[1] clearly show that alcohol intake is strongly associated with heightened risk of gout in men. Although serum uric acid concentrations were not measured, the authors proposed alcohol-induced hyperuricaemia due to raised urate production and diminished renal excretion as a main mechanism for this reported association.

This mechanism, however, might not be the case in heavy alcohol drinkers. In fact, reduced concentrations of serum uric acid have been reported in patients with alcoholic liver cirrhosis, due to loss of hepatic xanthine oxidase activity, resulting in decreased urate production.[2] Furthermore, De Marchi and co-workers[3] have shown that serum urate concentrations were slightly, although not significantly, reduced in alcoholic patients without liver disease compared with the control population (297·5 μmol/L [SD 71·4] *vs* 321·3 μmol/L [107·1]). Serum uric acid concentrations as low as 95·2 μmol/L, with profound renal urate, potassium, phosphate, and magnesium wasting, have been described in such patients.[4] On alcohol withdrawal, serum urate concentrations significantly increased to 321·3 μmol/L [71·4] ($p<0·05$),[3] and 178·5 μmol/L,[4] respectively, in the previously mentioned studies.

Ethanol misuse might result in reversible generalised proximal renal tubular dysfunction leading to uricosuria and various acid-base and electrolyte disorders.[3-5] This hypothesis is supported by studies reporting that ethanol interferes

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with the carrier function of these cells by decreasing Na^+-K^+-ATPase activity.[4,5] Furthermore, acetaldehyde produced after the oxidation of ethanol by alcohol dehydrogenase could possibly inhibit activity of several enzymes in the renal tubules, whereas oxidation of acetaldehyde, by acetaldehyde dehydrogenase, generates species of oxygen free radicals, which are capable of damaging cell membranes.[4,5]

We conclude that high alcohol intake could be associated with reduced serum uric acid concentrations in some heavy alcohol drinkers. Therefore, as Choi and colleagues state,[1] factors not related to serum uric acid concentrations might be implicated in the pathogenesis of alcohol-induced gout in these individuals.

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Authors' reply

We agree with Evagelos Liberopoulos and colleagues that alcoholic liver cirrhosis or renal tubular wasting can lower serum urate concentrations in some heavy alcohol drinkers. However, the potential significance of these findings in population-based studies seems minimal, since many studies, including those cited in our paper, have indicated consistently that alcohol increases serum urate concentrations. It is also conceivable that a cumulative hyperuricaemic effect of alcohol, especially before developing such organ involvement among heavy drinkers, or other mechanisms not directly related to serum urate might contribute to the development of gout.

Our *Lancet* paper and another[1] have also been discussed on the American College of Rheumatology hotline (www.rheumatology.org/publications/hotline), where five potential limitations were raised. The first was that our assessments were mainly restricted to middle-aged male health professionals. However, our study population (men aged 40 years and older) represents the most gout-prevalent population, and therefore the most relevant.

The second proposed limitation was lack of assessment of serum urate concentrations. But our study outcome was incident cases of gout (the final disease outcome), not serum urate as in previous studies. Although serum urate concentration would serve as an intermediate outcome,[2] adjustment for it in the same model would require careful consideration to accurately assess the effect of alcohol or dietary intake, since it is a strong causal intermediate. Inappropriate adjustment for this variable would lead to an underestimation of the effect of alcohol or dietary intake.

The fact that we did not require confirmation of gout diagnosis by synovial fluid crystal analysis was seen to be a limitation. However, one of our secondary endpoints was gout defined by the presence of a tophus or the detection of uric acid crystals on arthrocentesis (n=118). As reported, our findings persisted when we restricted the cases to those with tophus or crystal-proven gout. In fact, the magnitudes of association tended to increase substantially when this specific definition was used.

The fourth criticism was of our sole reliance on questionnaires for data on diet and hypertension. Food and alcohol intakes assessed by food frequency questionnaire have been validated against 1-week diet records specifically in this cohort and were found to be valid and reliable.[3,4] The validity of self-reported hypertension assessed in a validation study among randomly selected participants was also found to be accurate in this cohort.[5]

Finally, lack of data for metabolic syndrome was seen to be a limitation. We are not sure why such data would be needed in investigating the relation between alcohol intake or diet and incident gout. Although gout or hyperuricaemia might be a part of the syndrome, that does not mean the syndrome itself should be incorporated into this specific investigation. Our study adjusted for body-mass index and hypertension, which are both purported risk factors for gout and major components of the syndrome.

The hotline article also implied that dairy products would reduce the risk of gout by promoting weight loss. However, our analyses were adjusted for updated body-mass index, so all our results were independent of current adiposity.

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Developmental dyslexia and zinc deficiency

Jean-Francois Demonet and colleagues' extensive Seminar on developmental dyslexia (May 1, p 1451)[1] omits any reference to the nutrients essential for normal brain development and function. In 1989, we reported that dyslexic children were severely zinc-deficient in their

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sweat and had higher concentrations of toxic metals in their sweat and hair. The difference between the zinc concentrations in passive sweat of dyslexic children and their matched controls was highly significant (p<0·0001).

Animal studies show that zinc deficiency in offspring causes impaired learning which can be corrected by zinc supplementation. However, maternal zinc deficiency during early fetal development causes permanent impaired learning and impairs the offspring's stress-coping mechanisms, which can increase urinary loss of zinc throughout life in response to stress.

Good nutritional care involves correction of common deficiencies in both parents before conception, and maintenance of an adequate zinc status during pregnancy, lactation, and growth. This strategy seems to prevent troublesome dyslexia, even in families with a genetic susceptibility to the disorder. The deleterious effects of numerous genetic disorders could possibly be remedied by feeding high-dose B vitamins and by ensuring adequate levels of zinc, folic acid, and other essential nutrients.[3] Zinc deficiency, which can also be diagnosed from measurements of concentrations of zinc in white cells, impairs the function of B vitamins and blocks essential phospholipid pathways. In dyslexia there is evidence for reduced incorporation of docosahexaenoic acid and arachidonic acid into cell membranes, by contrast with schizophrenia in which there is an increased rate of loss of these omega-3 essential fatty acids.[4]

The fact that children and adults with developmental dyslexia are likely to continue to have important nutritional deficiencies throughout their lives, which further impair their already permanently impaired brain function, is too important to be ignored by dyslexia experts. Doctors who practise nutritional medicine, which includes monitored nutritional supplementation for individuals, find that the younger a child is repleted, the more rapid is the improvement in learning and behaviour. It is particularly important for children with developmental dyslexia that any treatable nutritional deficiencies should be diagnosed. Controlled trials find that vitamin and mineral supplements improve intelligence scores and brain-function tests, and reduce brain-wave abnormalities.[5]

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Political neglect in India's health

We admire your robust Editorial (May 15, p 1565)[1] regarding India's health; its message is consistent with what we have been trying to convey over the past many years. Despite repeated warnings about the deterioration of public health by medical, social, and international health authorities, health has never been a significant issue politically.[2]

India is the world's largest democratic country, but this democracy is in jeopardy owing to the rampant corruption that affects India's poor. In Indian politics, money and caste have a vital role. 80% of voters are villagers and most of them are illiterate and below the poverty line. During the grampanchayat (head of village) and parliamentary election campaign, politicians took advantage of their own caste and even paid cash to voters in their constituency in order to secure votes. Repeated victories by the same people result in heavy debts, which elected candidates try to reimburse by any means while in power, resulting in heavy corruption. Politicians are not interested in promising to provide long-term benefits to the public in the form of education, hospitals, irrigation, and industries, because they know that they can purchase their victory with cash.

Because of such corruption, medical professionals are not interested in politics. There should be a law that the Health Minister and his Chief Secretary should be medical graduates, since non-medically-qualified individuals do not seem to understand the importance of health problems. To give an example, in 1996 the barrister A R Antuley was elected from Raigad district and became Health Minister of India. We from Raigad district approached him and the Indian Council of Medical Research and requested the formation of a task force for the rational management of scorpion stings.[3] The task force was formed, but only three meetings were held, and soon afterwards the Health Minister portfolio was changed, the new Health Minister was not interested, and the project was abandoned.

In India, defence spending is inversely proportional to health investment. We must establish long-term peace with neighbouring countries such as Pakistan, and the problem of Kashmir has to be solved once and for all.

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Department of Error

Aaron R, Joseph A, Abraham S, et al. Suicides in young people in rural southern India. Lancet *2004;* **363:** 1117–18—In this Research letter (Apr 3), the seventh sentence of the Summary on page 1117 should be, "The average suicide rate for young women was 152 per 100 000, and for young men 69 per 100 000."

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