Thirty seven of 40 cases in one series combining types III and IV showed striking radiological femoral changes.[9]

Estimates of the incidence of osteogenesis imperfecta range from 1 in 15 000 births to 1 in 60 000. One in 20 000 is the figure I will use,[10] and type I could thus be assumed to occur in about 1 in 30 000 births.[2]

Neither type II osteogenesis imperfecta nor type III should be confused with non-accidental injury. In both there are recurrent multiple fractures with severe skeletal deformity. Nor should type I pose any serious problems as blue sclerae are almost universal: in one study they were noted in 370 out of 392 subjects in a pedigree of 60 families.[11] Osteogenesis imperfecta type IV is not, however, associated with blue sclerae.[12]

Other clinical and radiological features would be expected in both types I and IV of osteogenesis imperfecta. These include radiological evidence of wormian bones and osteopenia in the child and hyermobility of the joints, deafness, and dentinogenesis imperfecta in relatives. Not all these features will always be present, but their absence reduces the possibility of the diagnosis. For example, dentinogenesis imperfecta was seen in two thirds of families with type IV osteogenesis imperfecta,[12] and more than 10 wormian bones arranged in a mosaic pattern were found in all patients with osteogenesis imperfecta after the neonatal period.[13] In doubtful cases of suspected non-accidental fractures careful radiological examination of the skull with both lateral and Townes views may be advisable with repeat examination of neonates in later infancy. The absence of wormian bones is strong evidence against osteogenesis imperfecta.

All children with fractures and their parents should be examined for blue sclerae. A glance at a parent's bulbar conjunctivae may save an awkward moment in the witness box. Other clinical stigmata of osteogenesis imperfecta—such as joint laxity and a triangular facial appearance—should be noted but are in themselves too non-specific to allow a diagnosis of osteogenesis imperfecta. Detailed family histories should be obtained, and when they suggest osteogenesis imperfecta they should be verified by checking past medical records—it is all too easy to claim a history of multiple fractures. Radiographs should be scrutinised by a radiologist experienced in examining the bones of young children.

The problem that most often leads to doubt and medicolegal confusion is a young infant with one or more fractures. How likely is it that such a child could have osteogenesis imperfecta if neither child nor parent has blue sclerae, radiographs are normal, fractures do not recur after the child is removed from home, and there is no family history of deafness, osteogenesis imperfecta, or dentinogenesis imperfecta? Only sporadic cases of the very uncommon type IV should give rise to real difficulty.[14]

An estimate of the likelihood of encountering such a case can be made from a large population study.[15] Of 180 patients with osteogenesis imperfecta nine were classified as having type IV, and only one had no family history. Thus at most 5% of cases of osteogenesis imperfecta would have neither blue sclerae nor progressive deformity, and only 0·6% would in addition have no family history. If we accept an overall prevalence of 1 in 20 000 for osteogenesis imperfecta, the concurrence of this disease with the absence of blue sclerae, progressive deformity, and family history would occur in about 1 in 3 000 000 births. Since, however, at least some cases of type IV osteogenesis imperfecta do have deforming disease this is an overestimate. In another study the ratio of type I osteogenesis imperfecta to IV was between 1 in 4 and 1 in 5.[12] If the incidence of type I osteogenesis imperfecta is 1 in 30 000 the incidence of type IV would be 1 in 120 000. The absence of a family history of either osteogenesis or dentinogenesis imperfecta would increase these odds to about 1 in 1 000 000. The additional absence of appreciable wormian bones after the neonatal period would probably exclude the diagnosis.

Thus in a city of 500 000 people with 6000 births a year the chance of encountering a child under 1 year old with osteogenesis imperfecta who shows no other features or family findings of the disease would be between 1 in 1 000 000 and 1 in 3 000 000. This would produce an incidence of 1 case every 100 to 300 years. The annual incidence of fractures caused by non-accidental injury would be about 15 cases.

Medical witnesses need to formulate their opinion in the light of such odds. Provided care is taken osteogenesis imperfecta does not provide a satisfactory reason for unexplained fractures in otherwise healthy babies.

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Community acquired pneumonia

Pneumonia is the commonest fatal community acquired infection in Britain. Although not all deaths can be prevented, any guidance on the best immediate treatment and on those features which indicate a poor prognosis is welcome. A recent multicentre study coordinated by the British Thoracic Society has shed a new and authoritative light on these problems of clinical management.[1]

In a prospective study of 453 adults (aged 15-74) admitted to 25 British hospitals with pneumonia strenuous efforts were made to reach an aetiological diagnosis by microbiological and serological means (including tests for pneumococcal antigen in sputum, blood, and urine). For each case the relation of the causative organism and other features to the outcome were subjected to exhaustive multivariate analysis, which had been designed to avoid any preconceived bias.

Reassuringly the results endorse the principles that have

guided most physicians. Most cases of community acquired pneumonia requiring hospital admission are caused by *Streptococcus pneumoniae* (34%); *Mycoplasma pneumoniae* is the next and most frequent cause (18%); legionnaires' disease as a sporadic condition is uncommon (2%); and the combination of influenza and *Staphylococcus aureus* is rare but disastrous (three cases, all fatal). A microbiological diagnosis was made in two thirds of cases, but this proportion would have been much lower if countercurrent immunoelectrophoresis for pneumococcal antigen had not been performed. The most valuable of the widely available and rapid aetiological investigations were Gram's stain of sputum (insensitive but with a high positive predictive value in pneumococcal infection), blood culture, sputum culture, and cold agglutinin detection (present in 56% of mycoplasma infections with a specificity of 96%).

A fatal outcome was associated with hypotension and tachypnoea on admission and with a rise of the blood urea concentration during admission. Additionally statistical associations between death and increasing age, confusion, leucopenia, and excessive leucocytosis could be shown but only when they were given preference in the order of analysis. The overall mortality was almost 6%. No patient died who had been treated before admission with an antibiotic to which the causative organism was sensitive. Of those who had been treated only a fifth had pneumococcal pneumonia compared with almost half of those who had not received antibiotics. Almost all antibiotics prescribed at home would have been effective against *S pneumoniae* and hence early treatment selected on the basis of clinical probability is effective in saving lives. The survey's unexpected finding that no fewer than four out of 81 patients with mycoplasmal pneumonia died must surely be a fluke, but it emphasises that these infections must be taken seriously and not dismissed as trivial.

The British Thoracic Society's paper has two important messages. Firstly, the statistical analysis of complex data may not always be as objective as an untutored reader might imagine. Secondly, the management of patients with community acquired pneumonia can be improved. As soon as clinical features of pneumonia are evident in an adult treatment with an antibiotic effective against *S pneumoniae* should be started and if *Mycoplasma* infections are prevalent at the time, or there are other suggestive clinical features, erythromycin or tetracycline should also be given. During influenza outbreaks at least one (and, in view of the lethal effect of staphylococcal superinfection, perhaps two) antistaphylococcal antibiotics should be prescribed. Patients should be referred to hospital if they fail to improve with treatment at home, if their diastolic blood pressure is less than 60 mm Hg, if their respiratory rate is over 30 per minute, or if they are confused or elderly. If the patient is critically ill or if epidemiological evidence suggests legionella infection treatment for that condition should be added. Thus, though we may rightly condemn the indiscriminate prescription of antibiotics, their timely and informed use in patients with pneumonia is vital.

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Gonadotrophin hormone releasing analogues open new doors in cancer treatment

Agonist analogues of gonadotrophin releasing hormone cause intense stimulation in the pituitary if given once but then become inhibitory if given repeatedly. This occurs because they are resistant to degradation by pituitary enzymes: they thus block the gonadotroph receptors in the pituitary and make it unresponsive after initial supraphysiological stimulation.[1] There are many different such analogues, and they have been used to inhibit the production of gonadal hormones and treat hormone responsive cancers.

Hormonal treatments were introduced for prostatic cancer in the 1940s, but only in 1967 did it become apparent that treatment with oestrogen caused excess deaths from cardiovascular disease.[2] Moreover, neither orchidectomy nor oestrogens confer a significant survival advantage over no treatment,[3] so other specific treatments were needed that had minimal side effects and were not so mutilating as orchidectomy. Gonadotrophin hormone releasing analogues were discovered to be effective against prostatic cancer in 1980,[4] and the first studies showed response rates equivalent to those achieved with orchidectomy or treatment with oestrogens.[5-8] Randomised prospective trials confirmed these initial results. One group randomised 199 patients with metastatic prostatic cancer to receive either 3 mg diethylstilboestrol or 1 mg daily of the gonadotrophin releasing hormone analogue leuprorelin (leuprolide): 46% of those treated with diethylstilboestrol and 38% of those treated with leuprorelin responded. Only 10 of the 98 patients treated with leuprorelin had cardiovascular side effects compared with 33 of the 101 treated with diethylstilboestrol.[9] In another randomised study 41% of 70 patients treated by orchidectomy responded compared with 50% of those treated with the gonadotrophin releasing hormone analogue decapeptyl.[10] The duration of the response seems to be the same with conventional treatments and with the analogues. In the leuprorelin study the time to treatment failure was identical in the two groups (46 weeks), and median survival was 146 weeks in those treated with leuprorelin and 136 weeks in those treated with diethylstilboestrol.[11] In the decapeptyl study median survival was 16 months in those failing treatment with decapeptyl and 13 months in those treated by orchidectomy.[12]

The analogues are thus just as effective as conventional treatments, but are they safer? The fact that the analogues are stimulatory in the first few days of treatment may mean that they exacerbate the disease at first: about a third of patients had minor transient exacerbations and 1% had appreciable complications.[13] Analogues are thus contraindicated if the patient has neurological dysfunction or obstructive uropathy. Antiandrogens such as cyproterone acetate or flutamide may reduce these initial problems, but the best antiandrogen regimen has not been established. Giving antiandrogens and analogues together has been suggested as a way of increasing the number of patients responding and the length of response,[14] and randomised trials to test this hypothesis are in progress. A preliminary report has shown a median time to progression of 14·5 months in 307 patients randomised to receive leuprorelin and flutamide and 12·8 months in 303 patients treated with leuprorelin and placebo (E Crawford *et al*, American Urology Association, Anäheim, 1987).

Gonadotrophin hormone releasing analogues may now be given as monthly depot injections, which improve com-