similar to those from 1971 are important. It looks as if unemployment is still associated with a substantially increased mortality despite being a common experience.

Unemployment probably disables more often than it kills, and Arber (p 1069) shows from the General Household Survey 1981-2 that unemployed men report chronic ill health much more often than employed men. She shows, too, that the unemployed are concentrated in lower social classes, which explains some of the class inequalities in health that are so much in the news. Indeed, one of the most important aspects of Arber's paper is the way it brings together the debates on unemployment and health and inequalities and health—for the class differences in chronic ill health are greater among those without jobs than among those who have them. Another important aspect is the way her paper broadens the issue by showing that unemployment is associated with more chronic ill health among women when classified by their own occupations as well as when they are classified by their husbands' occupations. Further, it is not only those who describe themselves as unemployed but also those who describe themselves as housewives who have poorer health. Many women may describe themselves as housewives not because they do not want employment but because they think they will never get it. The "early retired" must also be considered among the unemployed, and the important work from Beale and Nethercott in Wiltshire has shown that far from being a protected group those older workers who take "early retirement" may be especially vulnerable.⁴

New evidence is also presented this week on unemployment and child abuse. These twin modern evils have been assumed to go together, but Taitz *et al* show how complex the relation may be (p 1074). They compared the rates of unemployed men living in homes in Sheffield where children

had been abused in 1974-9, when unemployment was relatively low, and 1980-5, when it was high. They found that, although the proportion of men without work increased, the increase could not be ascribed to an increase in those who had had jobs and lost them. Rather there was an increase in men who had never had jobs. I draw two lessons from this study: firstly, it reminds me of the dangers of talking of the unemployed as if they were one homogeneous group; and, secondly, it provides more evidence of the creation of an "underclass" such as already exists in America.

But not all the news is bad. A medical student, Christiane Harris, and I have surveyed all the regional and district health authorities in England, the health boards of Wales, Scotland, and Northern Ireland, and the family practitioner committees of England and Wales to see whether they were responding to unemployment and health (p 1077). My impression when researching the series of articles on unemployment and health published in the *BMJ* in late 1985 was that only a few doctors and other health workers were interested in the issue. We were surprised therefore both by our high response rate (77%) and by the high percentage of respondents (50%) who were taking some action.

We suggest in our report that a conference might be called to consider what action is being taken so that authorities can learn from each other. The same conference could consider the new evidence that is appearing all the time.

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Regular Review

Treating Paget's disease

D A HEATH

In the past five years published reports have advocated treating Paget's disease with one of three different calcitonins (either injected or by nasal spray), three different diphosphonate drugs (either orally or injected and in high or low dosage for short or long periods), mithramycin, calcium and thiazides, fluoride, colchicine, and the antiviral agent inosiplex. In addition, various combinations have been proposed either as simultaneous or as sequential treatments. To add to the confusion the recommended nomenclature has been changed so that the diphosphonates are now called bisphosphonates, although all current abbreviations are based on the diphosphonate terminology and use the letter D rather than B. Apart from having to decide which patients to treat, then, doctors are faced with a bewildering choice of treatments.

Whom to treat?

Paget's disease is common in Britain, increasing with age and affecting 5% of those over 55.¹ In most cases the disease is asymptomatic. The main indication for treatment is bone pain that cannot be controlled with simple analgesics. Another indication is spinal cord compression secondary to Paget's disease,² for which medical treatment rapidly improves the abnormal neurological signs. Such cases are uncommon and best handled in specialised centres, and I will not discuss their management further.

Little or no evidence supports using drugs to prevent or treat established nerve deafness, facilitate orthopaedic operations, prevent or treat deformities, or prevent malignant bone tumours. Heart failure is rarely caused by

Paget's disease and should be treated along conventional lines. Hypercalcuria does not warrant treatment, and hypercalcaemia usually has other causes. Paget's disease is often associated with osteoarthritis, and the cause of the pain may not be clear. Even when the arthritis is serious a trial of treatment for Paget's disease may be rewarding. The almost exclusive indication for treatment therefore is bone pain.

Treatment with calcitonin

Only two drugs are generally available for treatment—calcitonin, either salmon or porcine, and the bisphosphonate disodium etidronate. Many other bisphosphonate drugs have been synthesised, and two have been subjected to extensive studies but are available only on a named patient basis. Of the other drugs advocated for Paget's disease, only mithramycin has been studied extensively. Although highly effective, concern about its hepatic, haematological, and renal toxicity has prevented its widespread use. Rare indications for its use remain, but it is best restricted to specialised units.

Calcitonin treatment, usually with the synthetic salmon form, has been shown over 12 years to be effective and safe.³ The main advantage is its safety: few if any serious side effects have emerged. The disadvantages are that it has to be injected; that non-dangerous but uncomfortable side effects, such as nausea, flushing, or faintness, are common shortly after injection; and that after successful initial treatment about a third of patients develop a biochemical relapse that may be followed by a clinical relapse with the return of bone pain, despite continued treatment.³ Finally, calcitonin is expensive—a 50 unit dose of salmon calcitonin costs £4.15.

If calcitonin is used a common starting dose is 50-100 IU subcutaneously daily, reducing to 50 IU two or three times a week once a symptomatic response has been achieved. Patients usually notice a reduction of pain within four weeks of starting treatment, and if they have no relief within three months then the Paget's disease is probably not responsible for the pain. Treatment should then be stopped and other causes of the pain sought; osteoarthritis may well be the culprit. The patient who responds to treatment usually relapses shortly after treatment is stopped so that it has to be continued indefinitely. The patient who relapses clinically while having one form of calcitonin may respond to a different species.⁴ Effective treatment has been claimed to halt or reverse the progression of the disease, especially the osteolytic form, and to improve the histological⁵ and radiological⁶ appearance of the affected bone.

Treatment with disodium etidronate

The bisphosphonate disodium etidronate (1-hydroxy-ethylidene-1,1-diphosphonate; EHDP; Didronel) has been used in Paget's disease for nearly 10 years and both relieves pain and causes a biochemical improvement.^{7,8} The main advantages over calcitonin are that it can be taken by mouth; six months' treatment causes a few patients to go into a prolonged remission⁸; relapse while on treatment is less common; and it is cheaper—a 400 mg dose costs £1.11. The main disadvantage is that it may lead to osteomalacia and so an increased fracture rate.⁹ The development of osteomalacia is related to the duration of treatment and the dose and was seen particularly in patients taking 10-20 mg/kg/day. The drug has a low and very variable absorption from the gut that is further depressed if it is taken with food. No reliable

method has been found for measuring drug concentrations in the blood.

Can disodium etidronate be given in a way that will not cause osteomalacia and increased fractures? Non-traumatic fractures have been particularly associated with prolonged high dose treatment—that is, doses of 10-20 mg/kg/day for six or more months. Two regimens are currently being recommended—5 mg/kg/day for six months or 20 mg/kg/day for one month. (In fact as only 200 mg tablets are available a standard dose of 400 mg or 1600 mg is given daily to adult patients.) A review of 737 patients treated with varying doses of disodium etidronate for prolonged periods found that fractures occurred in 11%, within the range reported for untreated patients.¹⁰ A possible increased fracture rate was found in patients who had had prolonged treatment but was mainly associated with a greater severity of the disease. No evidence was found that short term low or high dose treatment increased the fracture rate. Other authors have come to a similar conclusion,⁷ though a case report of a patient who had a spontaneous fracture of the patella and severe osteomalacia during short term treatment with 5 mg/kg/day has been described.¹¹

Undoubtedly treatment with disodium etidronate may lead to focal osteomalacia and reduced bone formation even when given at the recommended doses for the requisite period of time,¹² but the frequency and severity of these changes vary considerably from centre to centre.¹³ This variability has been ascribed to variable drug absorption. With increasing doses of disodium etidronate the serum phosphorus concentration rises progressively because of enhanced renal tubular reabsorption of phosphorus. A correlation has been suggested between osteomalacia and a raised serum phosphorus concentration, and the presumption is that those who absorb most taking the same dose of the drug will have a higher serum phosphorus concentration than those who absorb less and so be at greater risk of osteomalacia and fractures. Whether measurements of the serum phosphorus concentration can be used to predict those at greater risk and hence those whose dose needs adjusting requires formal evaluation.

The generally available bisphosphonate, disodium etidronate, thus seems to be effective in Paget's disease, is well tolerated, and when used in low dose for not more than six months is unlikely to lead to an increased fracture rate, although microscopic focal osteomalacia may be seen. Such a treatment is much cheaper than calcitonin but like that agent rarely produces complete biochemical control of the disorder. Are other regimens of disodium etidronate more effective, are there any advantages of combining calcitonin with disodium etidronate, and are there any subgroups of patients with Paget's disease who should not receive the drug?

Recent studies have shown that disodium etidronate 20 mg/kg/day for one month is as effective as a six month course and better than six months' continuous treatment with 5 mg/kg/day in suppressing the biochemical markers of the disease.¹⁴ The authors claimed that such treatment gave more consistent results than longer duration low dose treatment. As only 12 patients were treated further studies are clearly needed before such a regimen replaces the low dose one, particularly as another study claimed that one month's treatment was less effective than three months' treatment.¹⁵ Even short high dose treatment is associated with transient histological evidence of osteomalacia.^{14,16}

Although using calcitonin and disodium etidronate together has been advocated¹⁷ and claimed to have a greater

effect on the biochemical markers of the disease and to prevent mineralisation defects, such a combination is hard to justify on the grounds of cost, particularly if an adequate symptomatic response can be achieved with a single drug.

Some workers have considered that the osteolytic form of Paget's disease is a specific indication for calcitonin; they claim that disodium etidronate does not prevent the disease progressing and may increase the risk of fracture.¹⁸ The evidence of this is not clear as these adverse effects have not been seen by other groups.⁷

Present "best buy" for treatment

The doctor has two treatments for symptomatic Paget's disease—subcutaneous calcitonin and disodium etidronate. I favour disodium etidronate at a dose of 400 mg/day for not more than six months. My treatment would be directed at producing pain relief without trying to bring the serum alkaline phosphatase concentration to normal. If after 3 months the patient was symptomatically no better but there had been a reduction in serum alkaline phosphatase concentration, I would stop treatment and look for other causes of the pain. The main danger of such a regimen is that patients are often inadvertently left having treatment for more than six months. This can be avoided by restricting the drug only to those doctors familiar with its use. Patients who relapse after stopping successful treatment can be given further intermittent six month courses of treatment.

The future

Is this recommended treatment likely to change? Although a second calcitonin gene has been identified, raising the possibility of different calcitonins of differing bioactivity within the same species, there will probably not be any important advance in treatment with calcitonin for Paget's disease. Other bisphosphonates are, however, being evaluated, and a whole series of newer ones with varying effects on bone formation and resorption are being synthesised. The two other drugs being used but unavailable for general use are aminohydroxypropylidene diphosphonate (APD) and dichloromethylene diphosphonate (Cl₂MDP, clodronate). Although both seem highly effective, perhaps more so than disodium etidronate their safety has been questioned and the development of each drug abandoned by two major pharmaceutical companies. Aminohydroxypropylidene diphosphonate caused pulmonary damage when given in large doses to dogs, and clodronate was linked with several cases of leukaemia. Subsequent studies have questioned the causal relation of these side effects, and both drugs are now being developed by other companies.

Clodronate may be given orally or intravenously, and an oral dose of 1600 mg daily for as short a period as one month is highly effective in relieving symptoms and suppressing biochemical indices of the disease for up to one year after stopping treatment.¹⁹ Alternatively, 300 mg given intravenously for five days seems equally effective.²⁰ Limited studies have not shown any histological evidence of osteomalacia after treatment.

Aminohydroxypropylidene diphosphonate has also been shown to be highly effective when given either orally or intravenously. A recent study of oral treatment with a daily average dose of 500 mg found that the drug was clinically effective in 87% of cases and caused a complete biochemical

remission in 88% of previously untreated cases.²¹ Intravenous treatment using 15 mg daily for five days or 15-30 mg once a week for 12 weeks gives excellent symptomatic and dramatic biochemical improvement.²² Again, to date, osteomalacia does not appear to be a problem.

Whether either or both of these newer bisphosphonates will replace disodium etidronate is not clear, and much will depend on whether the pharmaceutical companies promote the drugs for Paget's disease. Currently there seems little prospect that either drug will become generally available in the near future. Even should they do so more studies are needed to decide on the best route of administration, dose, length of treatment and whether focal osteomalacia can occur. But even if these two drugs are not marketed newer bisphosphonates will almost certainly be introduced in the coming years.

Should this happen I hope that the initial studies will clearly define the optimum dose and route of administration and whether or not osteomalacia and fractures are induced by treatment. To achieve this larger groups of patients will be needed than have been used in current studies, and they will need to be followed up for longer periods of time. Detailed studies to show whether complete suppression of disease activity is more advantageous than mere symptom relief will also be needed.

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