The clinical evidence shows, therefore, that metronidazole is effective in non-specific vaginitis, but these results pose a difficult question: Does the drug achieve clinical success by virtue of its antianaerobic activity, by its (much less good) activity against *G vaginalis*, or by both mechanisms? Further possible evidence for the part played by anaerobes, particularly *Bacteroides* spp (but not *B fragilis*) and peptococci in non-specific vaginitis, has been produced by Spiegel *et al*,[11] who suggest that non-specific vaginitis may be caused by anaerobes in conjunction with *G vaginalis*. Such a hypothesis would be compatible with many other so-called anaerobic infections, notably those in the gastrointestinal tract, where mixed infections including aerobes are so common and pure anaerobic infection so rare. Not only is treatment of these mixed infections with metronidazole alone frequently very effective[12 13] but prophylaxis with metronidazole alone also successfully prevents postoperative wound infection after elective colorectal surgery.[14] The therapeutic success of metronidazole is more difficult to evaluate in non-specific vaginitis than in the mixed infections of the gastrointestinal tract, since it is active in vitro against both the aerobic and the anaerobic components of the infection in the vagina but only against the anaerobes in the gut. If it were possible to use a drug highly active against anaerobes but inactive against *G vaginalis* their relative contributions to pathogenesis might become clear.

In practical terms, however, these studies suggest that non-specific vaginitis is yet another infection which comes into the anaerobic category currently so fashionable; and they offer some cause for real optimism to those concerned with treatment of this recalcitrant condition. Nevertheless, this optimism should be tempered with caution: before metronidazole becomes widely used in an uncritical fashion some more carefully controlled studies are needed.

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How does acupuncture work?

Acupuncture is a potentially cheap and safe form of treatment for relieving some types of pain, yet many doctors in the West remain sceptical of its value. They find the ancient Chinese concepts of traditional acupuncture and its claim to be a treatment for all ills unacceptable, but these concepts may be largely irrelevant to the practice of effective analgesic acupuncture. Sceptics suggest that acupuncture may be nothing more than a powerful placebo. If, however, acupuncture exerts some specific analgesic effect like other physical treatments, this is not amenable to proof by formal clinical trial. Acupuncture may be performed in several ways, including manual rotation of the needles and low-frequency or high-frequency electrical stimulation through them. No truly double-blind comparison can be made with alternative treatments since the needles must be inserted in the conscious patient. Despite the scepticism, however, evidence is accumulating about its mechanisms of action.

The possibility that acupuncture analgesia is mediated by a humoral factor was first suggested by a report that transfer of cerebrospinal fluid from rabbits having acupuncture produces analgesia in recipient rabbits.[1] The time course of analgesia is similar whether induced by acupuncture or by stimulation of the brainstem periaqueductal grey matter, both forms of stimulation producing effects with a delayed beginning and end.[2] Analgesia induced by stimulating neurones of the periaqueductal grey matter appears to be mediated by endogenous opiate-like peptides,[3] so perhaps analgesia after acupuncture is produced by the release of similar endogenous substances.

The endogenous peptides with opiate-like analgesic effects are broadly classed as enkephalins and endorphins. Research into the role of these opioids in acupuncture analgesia falls into into two main categories: firstly, the use of drugs modifying opiate action and, secondly, the measurement of opioid peptide concentrations in blood and cerebrospinal fluid. The specific opiate-receptor-blocking drug naloxone reduces or abolishes low-frequency (2-6 Hz) electroacupuncture analgesia in various animals subjected to pain.[4-7] Naloxone has no effect, however, on the analgesia induced by high-frequency (200 Hz) electroacupuncture in mice.[4] The degree of analgesia in these studies was assessed by behavioural measurements,[4 5] by the depression of the firing rate of pain-transmitting (nociceptive) spinal neurones,[6] or by changes in pain-induced cortical evoked potentials.[7] In human subjects with chronic or experimental pain all but one group of workers report that naloxone reduces the analgesia produced by manual acupuncture or low-frequency electroacupuncture via needles or surface electrodes.[2 8-10]

Certain D-amino-acids inhibit the peptidases that otherwise rapidly degrade the endorphins, thus limiting the duration of their effects. These D-amino-acids enhance the effect of low-frequency electroacupuncture in mice, the resulting analgesia being reversible by naloxone.[11] Mice of the inbred strain CXBK have a low density of opiate receptors in the brain and achieve little analgesia after morphine or acupuncture.[12] In contrast, the related group of C57BL mice, which have a normal density of brain opiate receptors, respond to acupuncture and morphine with normal analgesia. This evidence further supports a role for endogenous opioid peptides in acupuncture analgesia.

Some recent evidence points to the release of opioid pep-

tides in cerebrospinal fluid during acupuncture analgesia. Several workers have shown an increase in opiate-like activity in the cerebrospinal fluid of animals and man during acupuncture,[13-15] but this was measured by a radioreceptor assay that lacked specificity and did not identify structurally discrete peptides. Clement-Jones *et al*[16-18] measured cerebrospinal concentrations of beta-endorphin and met-enkephalin by radioimmunoassay in two groups of patients before and after 30 minutes of electroacupuncture. They used a highly specific met-enkephalin assay that had insignificant cross-reaction with other peptides.[16] A group of patients with recurrent pain received low-frequency electroacupuncture. Concentrations of met-enkephalin in the cerebrospinal fluid were unchanged but those of beta-endorphin rose after electroacupuncture.[17] In a second study, in heroin addicts who were being withdrawn from their drugs, high-frequency electroacupuncture was given to suppress the symptoms and signs of withdrawal. Clinically the treatment was highly effective and it was associated with a rise in met-enkephalin concentrations, which had been low before treatment; beta-endorphin concentrations, which were raised initially, did not change after electroacupuncture.[18] The difference between the effects on beta-endorphin and met-enkephalin may be due to the different conditions being treated, but more probably relate simply to the frequencies of the stimuli. Thus low-frequency electroacupuncture releases beta-endorphin, whose effects can be blocked, at least in part, by naloxone; whereas high-frequency electroacupuncture may release met-enkephalin, whose effects are not blocked by conventional doses of naloxone.

Information about changes in opioids in blood during acupuncture is more confused. The results of two studies suggest that circulating immunoreactive beta-endorphin rises during electroacupuncture,[19 20] but stress was not excluded as a cause of the changes. Beta-endorphin is released from the pituitary in parallel with adrenocorticotrophic hormone and the lipotrophins during stress and indeed all other known stimuli. Other workers have reported a fall in plasma adrenocorticotrophic hormone as well as beta-endorphin and cortisol concentrations during electroacupuncture,[18 21] an effect compatible with the central release of enkephalins.[22 23] In any event, beta-endorphin released into the blood is unlikely to mediate the central analgesia induced by acupuncture, since this peptide penetrates poorly into the central nervous system. Pomeranz *et al* found that hypophysectomy blunted the analgesic response to low-frequency electroacupuncture,[24] but this has not been confirmed.[5] In man the pituitary is probably not an important source of cerebral beta-endorphin, since the concentrations in the cerebrospinal fluid are normal in patients with panhypopituitarism, who have undetectable plasma concentrations of beta-endorphin.[25]

5-Hydroxytryptamine (serotonin) probably plays an important part in mediating the analgesic effect of acupuncture.[26-28] The tryptophan hydroxylase inhibitor parachlorphenylalanine decreases concentrations in the brain of 5-hydroxytryptamine but works in the opposite way to naloxone, reducing the analgesic effect of high-frequency electroacupuncture in mice but having no effect on low-frequency electroacupuncture analgesia.[4] Other neurotransmitter systems may mediate some effects of acupuncture but so far their role is uncertain.[28 29]

The effects of low-frequency electroacupuncture and manual acupuncture may be mediated, at least in part, by stimulation of beta-endorphin-containing neurones of the periaqueductal grey matter, thereby activating endogenous pain-control pathways. An important 5-hydroxytryptamine-containing pathway that inhibits pain arises in the nucleus raphe magnus in the medulla and projects to the spinal dorsal horns. Stimulation of this serotoninergic system activates inhibitory enkephalinergic interneurones situated in the spinal dorsal horns, which in turn inhibit the activity of nociceptive neurones in the dorsal horns.[30] Possibly high-frequency electroacupuncture has an effect in activating this serotoninergic-enkephalinergic system.

Can we now assert that acupuncture is more than a placebo? This question seems no longer relevant, since the relief of pain associated with placebos is probably also mediated by release of endogenous opioids and can be blocked by naloxone.[31] Perhaps the evidence that different forms of acupuncture elicit specific neurohumoral effects to produce analgesia in animals and man gives acupuncture some physiological respectability. In any event, if acupuncture provides effective and safe pain relief then its mechanism of action is of secondary importance. The most fruitful result of research into the neurochemical basis of acupuncture may be the discovery of a means of increasing cerebral release of specific opiate-like peptides and other neurotransmitters. This may be useful for investigating and treating pain and perhaps also some neurological, psychiatric, and neuroendocrine diseases.

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Pathological fractures due to bone metastases

The observation that cancerous tumours may spread to bone and destroy it was first made by clinicians in the late eighteenth and early nineteenth centuries.[1] With increased understanding of the "carious" condition of the bone they became aware of the need to treat this secondary problem in an active way despite the patient's poor overall prognosis.

The surgeon today has several techniques for dealing with bone metastases, as well as modern anaesthesia and chemotherapy to help him in his task. Indeed, the problem is often technically simple; but it raises profound ethical problems about the welfare of a patient who has only a short time to live. Surgery, however, may produce the considerable benefits of pain relief and increased mobility, and should not be withheld from any patient if even brief improvement is likely.

Skeletal scintigraphy[2] is now established for early diagnosis of skeletal metastases. This poses the problem of whether prophylactic internal fixation should be carried out, as not all metastases in bone are likely to cause a fracture. But prophylactic fixation prevents stress and pain, and is technically much easier than fixation of a comminuted displaced fracture in soft bone. In long bones increasing pain and destruction of more than half the cortex as seen on an *x*-ray film are indications for prophylactic internal fixation[3 4]; local irradiation of the lesion is a further indication, since this increases the risk of fracture.[4] In patients with advanced disease any risk of local or general spread of the tumour is outweighed by the benefits of the procedure.[3–5]

Most pathological fractures of the long bones will be treated by internal fixation with a plate or nail plate or with an intramedullary rod. In all cases a biopsy specimen should be taken at the time of operation to confirm the nature of the lesion and help in planning radiotherapy or chemotherapy after operation. Fractures of the femoral neck are best treated by replacement arthroplasty.[4] When a large part of the upper femur is destroyed special femoral prostheses designed for extensive replacement of bone may be required. Problems may arise with large lesions that destroy much bone, and here metal plates may be combined with high-density polyethylene plates[6] or nylon plates and straps.[7]

During the last 10 years methyl methacrylate cement has been used to supplement internal fixation, the material being used to replace the tumour and restore the mechanical continuity of the bone. By moulding methyl methacrylate round a metal device the shape of the bone can be restored.[8] Yablon and Paul[9] reported the use of methyl methacrylate in 73 patients with 81 pathological fractures. They concluded that although methyl methacrylate probably had an adverse effect on fracture healing fixation was adequate, there being no failure of fixation in their series. Twelve of their patients had survived over five years, and only four failed to regain function in the limb that had been operated on. Harrington *et al*[10] achieved similar success in a smaller series of patients. More recently Harrington[11] has used methyl methacrylate for replacement and stabilisation of vertebral bodies in pathological fracture-dislocations of the spine. In a series of 14 patients followed up for 13-45 months there was only one failure of fixation. Of 12 patients with major neural lesions before operation, nine had complete neurological recovery after surgery. Two others were improved and one was unchanged. None deteriorated neurologically.

Pathological fractures occur in under 1% of patients with advanced carcinoma.[12] When a fracture does occur, however, it inflicts a dismal burden on a patient, often at the end of life. As the number of elderly people in the population increases the incidence of these fractures is likely to rise. Improved surgical, radiological, and chemotherapeutic techniques have given patients with advanced cancer a longer life span. The resources for dealing with disabling secondary disease will need to be correspondingly increased if these patients are to live the end of their lives in dignity and without pain.

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