antibodies to HIV should soon become available. Negative results should ease concerns about AIDS, but systematic research will be needed to distinguish illnesses in people incidentally infected with HIV from those in people with HIV induced immunosuppression. The distinction is crucial since it is the progressive immunodeficiency, not simply having antibodies to HIV, that is associated with a poor short term prognosis.

What is critically important about AIDS in Africa, however, is the enormity of the problem. Already many central and east Africans are infected with HIV, and if these people develop AIDS at the same rate as elsewhere a huge increase in the number of cases of AIDS will occur in the next few years. Even if effective treatments are developed for HIV infection and immunodeficiency, applying these in Africa to many thousands of cases will be difficult if not impossible. Only prevention holds any promise of limiting the tragedy, and education about sexual transmission and programmes to eliminate parenteral exposure from infected blood or contaminated needles are essential—but ultimately a vaccine will be needed.

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A limited role for manipulation

Whatever treatment is offered 80-90% of patients with backache will be free of symptoms within about two weeks. Many patients, however, suffer frequent attacks, and some have persistent pain with occasional exacerbations. Against this background it is difficult to assess the value of any treatment—including manipulation. Two previous leading articles in the *BMJ* have considered the uncertainties over manipulation and called for controlled trials.[1,2] In this issue two manipulators—one medically qualified, the other an osteopath—give their views on the value of manipulation (pp 1481 and 1482).

Manipulation might be viewed as an art rather than a science as each therapist has an individual approach and modulates treatment techniques in a personal way for each patient.[3] This might seem to make scientific assessment of its value hopeless, but scientists believe that such an assessment should be possible given sufficient commitment and resources.

Manipulation includes manual methods of diagnosis as well as of treatment, and the system of diagnosis is not that of conventional medicine. Manipulators observe, feel, and describe spinal lesions such as subluxation and vertebral fixation and blockage. They find malposition of vertebrae with abnormal vertebral motion and joint play, soft tissue abnormalities, and muscle contractures. A pathological basis for these lesions has not been shown, but that does not mean that any abnormalities are not there—because pathological examination is obviously almost impossible in such circumstances.

The treatment that the manipulator offers a patient depends on his physical findings and is modulated according to the patient's progress. In "non-specific long lever manipulation" rotational forces are applied to the spine through the shoulder, pelvic girdle, or even limbs. In "specific short lever manipulation," in contrast, small amplitude high velocity adjustments are applied manually to individual segments of the spine through the spinous or transverse processes. These manipulative techniques may be supplemented by a wide range of treatments such as mobilisation, muscle traction, and soft tissue massage. Assessing whether manipulation works is complicated not only by the wide range of treatments, but also by the fact that surgeons, physicians, physiotherapists, osteopaths, chiropractors, and others all manipulate in different ways. Furthermore, some are much more skilful than others.

How manipulation might work is uncertain. It may mobilise stiff joints and free adhesions, but it may also produce neurophysiological stimulation with afferent impulses that suppress pain. In addition, the "hands-on" attention of the manipulator must produce powerful psychological effects.[4]

A control group is thus essential for any adequate trial of manipulation, and such trials are rare.[5-13] Some suggest that manipulation may hasten the recovery of those who are going to recover anyway. In the first adequately controlled trial those who were manipulated had significantly better relief 15 minutes after manipulation, but after three days this benefit was lost.[5] Another study in general practice also showed that patients were significantly better than controls immediately after treatment, but again the advantage had been lost after about two months.[6] The study referred to by Dr Grayson[7] suggested that recovery was more rapid over the first two weeks following manipulation but thereafter there was no difference between treated patients and controls. A comparison of manipulation and soft tissue massage showed significantly better immediate relief in those manipulated, but again three weeks later—when both groups had improved substantially—the difference had disappeared.[8]

Other studies, however, have failed to show significant differences between patients manipulated and controls,[9-12] although in two studies there were minor indications that the manipulated patients might have improved more quickly.[9,10] Any benefit may relate to the total amount of physical therapy rather than to any specific form of treatment.[10] Whatever benefits there might be from manipulation seem to be confined to those with acute pain of recent onset. There is no evidence that manipulation helps those with severe or

chronic back problems[13]; nor does it reduce long term complications or prevent recurrences.

Manipulation may thus speed recovery of a few of those with acute backache, which is valuable as it will get some people back to work more quickly. Alternative approaches will be needed to prevent recurrences and help those with chronic backache.

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Adenosine: an importance beyond ATP

Adenosine is familiar as a component of the ubiquitous intracellular energy store adenosine triphosphate (ATP) and the intracellular second messenger 3′,5′-adenosine monophosphate (cyclic AMP), but the extensive biological activity of the free nucleoside is less widely recognised and was the subject of a recent international symposium in Munich.[1]

Newby has emphasised that many effects of adenosine may be viewed as controlling the balance between local energy (or oxygen) supply and demand.[2] When energy supply and demand are out of balance ATP breakdown is increased, and some of the metabolites reach the extracellular space as adenosine.[3 4] Adenosine released in this manner tends to increase energy supply (often through vasodilatation) or reduce energy demand, or both—and so tends to restore the tissue energy balance.

Adenosine exerts such a homoeostatic role in the metabolic control of coronary blood flow.[5 6] Its release is augmented by increased myocardial work[7] or impaired blood supply,[8 9] and it then increases coronary blood flow and the energy supply. Such feedback mechanisms allow the heart to adjust coronary blood flow to constantly varying demands; the importance of this process is shown when stenoses of the coronary arteries override metabolic control of coronary flow and produce angina and myocardial infarction. The precise circumstances in which, and to what degree, adenosine controls coronary flow are debated,[10-12] but the coronary vasodilator effect of adenosine has been confirmed in man.[13 14]

Adenosine also slows cardiac rate and impairs conduction through the atrioventricular node,[15 16] and adenosine release during myocardial ischaemia[17] may explain the bradyarrhythmias commonly seen in the early phases of myocardial infarction.[18] These cardiac electrophysical effects of adenosine have been used in the acute treatment of supraventricular tachycardia[16 19 20]: it restores sinus rhythm by interrupting re-entrant circuits involving the atrioventricular node.[16] Its extremely short half life (about 10 seconds[21]) makes it particularly useful when intravenous verapamil is contraindicated—for example, in patients with poor left ventricular function or those treated with β blockers. Adenosine is of little use, however, in preventing these arrhythmias.

Adenosine is also a peripheral vasodilator and has been used to produce controlled hypotension during cerebral artery surgery.[22] It produces hypotension smoothly, and the infusion rate can be titrated to give a stable blood pressure; normal blood pressure is rapidly restored after the infusion is stopped, without rebound hypertension.[23 24] The lack of rebound may be to do with adenosine inhibiting renin release.[25] An autoregulatory role for adenosine in controlling blood flow in the brain[26] and the skeletal muscle[27] has also been proposed, but the evidence is less extensive than that relating to coronary flow.

Renal blood flow, glomerular filtration rate, and salt and water clearance are all reduced by adenosine.[25 28] Renal energy demand depends largely on the volume of glomerular filtrate,[29] and so the vasoconstrictor effect of adenosine released in response to increased renal metabolic work reduces glomerular filtrate and hence energy demand.

By interacting with release of other neurotransmitters in the peripheral and central nervous system and by other presynaptic and postsynaptic actions adenosine (and the nucleotide ATP) modulate neural activity in the peripheral and central nervous system.[30 31] These effects are complex and subtle, but overall adenosine is a central nervous system depressant. Caffeine and other methylxanthines, which are antagonists at cell surface adenosine receptors, probably achieve their stimulant effect by reversing the central sedative actions of adenosine.[32] Adenosine may participate in the spontaneous termination of epileptic fits[33] and in the action of certain anticonvulsant drugs—for example, phenytoin[34]—but further work is needed on these mechanisms.

Adenosine reduces platelet aggregation in vitro,[35] but its part in platelet function in vivo is uncertain. It has, however, been used to reduce platelet consumption during cardiopulmonary bypass.[36] Adenosine appears to be an important substrate for ATP synthesis in red cells; these have a circulating life of about 120 days, but the half life of ATP in erythrocytes (which cannot synthesise ATP de novo) is only about nine hours.[37] Adenosine released by the liver appears to play a significant part in replenishing erythrocyte ATP and so keeps red cells alive.[37 38]

As well as having a local effect on oxygen balance adenosine is a respiratory stimulant in man.[39-42] This action is achieved through the carotid body in animals[43 44] and also, it seems, in man.[40] Adenosine release is intimately linked to control of local oxygen balance in other tissues, but the suggestion that adenosine may help to initiate the ventilatory response to hypoxia in the carotid body remains to be proved.[39]

Adenosine may also be important in pathophysiological states. It is a bronchoconstrictor in asthmatic but not normal subjects.[45] The efficacy of aminophylline and other methylxanthines, which are antagonists at cell surface adenosine receptors, may be attributable to them antagonising adenosine in asthmatic subjects.[46]

The physiological importance of endogenous adenosine