

interacting factors through clinical and epidemiological investigations.

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## Patient package inserts

To be successful, drug treatment needs co-operation from the patient, who must therefore have certain information about the drugs he is taking. The minimum information<sup>1</sup> includes dosage, frequency of dose, and duration of treatment; whether the drug or drugs should be taken before, during, or after meals; whether alcohol, driving, or operating heavy machinery should be avoided; and whether there are any adverse effects requiring prompt action. Moreover, in an age when unquestioning acceptance of professional advice is being eroded (and doctors who dispute—or deprecate—this tendency should recall their own attitudes to accountants, solicitors, and their children's teachers) younger patients in particular may wish to know how their drugs work, how they will help their disease, why it is necessary to take them, and what adverse reactions might occur.

Traditionally, responsibility for telling patients about their drugs has rested primarily with the prescribing doctor, who has given the patient a verbal explanation and instructed the dispensing pharmacist to label the medicine bottle appropriately. This system, however, has drawbacks. Consultation times in general practice are little enough for an adequate history and physical examination. Patients remember only about half the information they are given during a consultation,<sup>2,3</sup> and most of the forgetting takes place immediately. And, even if that unenlightening phrase "Take as directed" is excluded, patients' interpretations of apparently unambiguous labelling instructions (for example, "every six hours," "three times a day," "with meals") are erroneous in up to two-thirds of cases.<sup>4</sup>

In Britain patients receive written instructions about a few categories of drug. These include warning cards for those taking monoamine-oxidase inhibitors, systemic corticosteroids, and anticoagulants. Other cards have been produced by bodies such as the British Diabetic Association and the British Epileptic Association, and some drug manufacturers

supply leaflets for patients with their products. In the United States of America the Food and Drugs Administration (FDA) requires printed material ("patient package inserts" or PPIs) to be provided for patients receiving oral contraceptives, intrauterine contraceptive devices, and oestrogens. The FDA is now under pressure from professional<sup>5</sup> and consumer<sup>6</sup> organisations to extend PPIs to other (and ultimately nearly all) prescribed drugs. According to the present plan,<sup>7,8</sup> the FDA would draw up PPIs (after consultation with interested parties), which would be issued to patients by the dispensing pharmacist at the same time as the prescribed drug. Doctors would retain the right, however, to prevent the patient from receiving a PPI by annotating the prescription accordingly. The information contained in the PPI would answer questions about why the drug is used, how it can help the patient, why it should be taken as directed, what adverse effects may develop, and what to do if these occur.

Inevitably, the PPI proposals have met with resistance. Critics argue, for example, that they would interfere with doctor-patient relationships, increase the tendency towards malpractice suits, pose considerable problems of production and distribution,<sup>9,10</sup> and also possibly diminish, rather than enhance, patients' compliance by making them afraid of adverse reactions. Moreover, PPIs are likely to benefit a small minority of younger educated patients. Most of these doubts could be investigated by controlled trials, and the FDA is indeed conducting a study of PPIs for thiazides and methyl dopa among hypertensive patients.<sup>7</sup>

In Britain there are no immediate plans for introducing PPIs, but the health professions are increasingly aware that patients need more information. Last month some 160 doctors, pharmacists, nurses, and health education officers took part in a symposium at Sheffield University on "Medicines, Information and the Patient"; and the DHSS and Medicines Commission are exploring ways of providing patients with information about drugs. These might include a more subtle approach to the medical consultation,<sup>11</sup> counselling by the dispensing pharmacist, and better labelling of medicine bottles. A British equivalent of the PPI might well supplement these more traditional approaches, but which individuals taking which drugs would benefit? This is a problem needing carefully constructed randomised trials.

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## The gate control theory of pain

The gate control theory of pain sounds complex, but its principle is simple and has had wide practical consequences. Its essence is that signals which reach the spinal cord and are transmitted upwards to conscious sensation are modulated by

other afferent impulses and by control from higher centres. From these concepts has come the impetus for the development of pain clinics and for the growth of interest in acupuncture and transcutaneous electrical stimulation. Yet, despite the high status of the theory, its mechanisms, originally presented diagrammatically by Melzack and Wall,<sup>1</sup> need re-examination. The gate control theory is, after all, only a hypothesis based on uncertain predictions of microelectrode studies on the spinal cords of animals. In a penetrating reappraisal one of its originators, Professor Wall,<sup>2</sup> has admitted that some of the initial data were frankly misleading.

Peripheral pain receptors relay impulses to the dorsal horn cells via unmyelinated (C) fibres and small myelinated (delta) fibres.<sup>3</sup> The gate theory requires that the passage of these impulses should be slowed or abolished by any simultaneous input in the larger myelinated nerve fibres, but this antagonism cannot always be shown.<sup>4</sup> Delta and unmyelinated fibres are not a homogeneous group, and the presence or absence of pain in any particular neuropathy cannot be forecast from preferential loss of large or small fibres or from the acuteness or severity of the degenerative change.<sup>2-4</sup> For example, the loss of large fibres in alcoholic neuropathy and myelomatosis and of small fibres in Fabry's disease causes pain; but a similar loss of large fibres in Friedreich's ataxia and the polyneuropathy of renal failure or of small fibres in familial amyloidosis and Tangier disease does not.

We are still uncertain about the location of the modulating mechanisms within the spinal cord, and about the identity of the cord cells which respond to injury and transmit the impulses onward (T, or transmission, cells). Any role for the substantia gelatinosa in pain is conjectural; and the relative importance of presynaptic and postsynaptic inhibition in determining the input of the T cells from the periphery is unknown. Understanding the function of the cell groups of the dorsal horns of grey matter is helped by their division into laminae.<sup>5</sup> Lamina V is the most likely site for adjustment by the modulating mechanism, for its numerous cells respond to both myelinated and unmyelinated nociceptive afferents. There is an inhibitory surround; but low-threshold afferents evoke an excitation from the centre followed by a prolonged period of inhibition. The cells in lamina V may also be influenced chemically, and are related electrically to activity along the spinothalamic tract. The cells of the substantia gelatinosa (laminae II and III) also respond to low-threshold afferents but project only over very short distances. Their axo-axonic synapses may provide a system of local segmental modulation through multiple synaptic chains,<sup>6</sup> and this modulation may be transmitted from one segment to another via Lissauer's tract. A few cells in lamina I, overlying the dorsal horn, respond at high threshold to cutaneous receptors via delta afferents, but the stimulus specificity they show is carried over to more central cells without obvious modification.

Neurophysiologists have criticised the emphasis Melzack and Wall placed on presynaptic inhibition of afferent impulses. The role of postsynaptic inhibition is widely accepted, but Wall conceived presynaptic inhibition of cutaneous fibres as a mechanism for switching an input from one pathway to another. Through changes in the membrane potential of the terminals of afferent fibres, an identical input on one occasion may, he suggests, cause a sensation of touch and on another a sensation of pain. To histological criticisms—that axo-axonic contacts in the substantia gelatinosa are "almost without exception" the wrong way round for presynaptic control of the afferent terminals<sup>7</sup>—Wall contends that the mammalian dorsal horn contains synaptic interconnections too small and

too intricately interwoven to allow definite causal mechanisms to be demonstrated. No easy answer has been found to this problem of electrical alterations. Presynaptic depolarisation undoubtedly occurs; its origin is unknown, and it roughly coincides with inhibition. We know little on the subject of facilitation as distinct from excitation. The role of presynaptic inhibition in accentuating or filtering afferent inputs is not clear, and there is a variability of electrical response: the shape and duration of positive and negative waves do not coincide nor is there a clear duality of effect, with depolarisation and hyperpolarisation.

In 1976 Nathan<sup>4</sup> concluded his critique of the gate control theory with the statement "Ideas need to be fruitful; they do not have to be right." Melzack and Wall's theory has enshrined a major concept and it has had a powerful impact on research, theory, and treatment. Yet we still have to label the precise mechanisms, and the duality of function necessary for triggering the hypothetical gate remains far from proved.

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## Ticks, tourists, and encephalitis

Tick-borne encephalitis occurs throughout Russia, eastern and central Europe, and as far west as Alsace. The Far Eastern form, occurring particularly in Siberia and transmitted by *Ixodes persulcatus*, causes severe paralytic encephalitis, with a 30-38% mortality rate.<sup>1</sup> The European type, transmitted by *Ixodes ricinus*, causes an encephalitis with less paralysis, which generally follows a biphasic course with a mortality rate of about 1 to 2%. After an incubation period of 4 to 14 days, most patients develop a mild febrile illness, often unrecognised, during which viraemia occurs. In a relatively few cases the febrile stage may be followed by a more severe illness, at which time viraemia may have ceased and immunological responses, including the formation of antibodies, may have taken place.

The European form of tick-borne encephalitis virus is widely distributed in western USSR, Czechoslovakia, Hungary, Poland, Bulgaria, Romania, Yugoslavia, Austria, Germany, Switzerland, Finland, Sweden, and France—and possibly also Greece, Turkey, and northern Italy.<sup>1</sup> Most human infections are acquired through the bite of an infected *I. ricinus*, but in some areas tick-borne encephalitis can also be transmitted by drinking goats' milk. (Goats are infected by a tick bite and some human cases occurring early in the season are due to drinking raw goats' milk.<sup>2</sup>) The virus is found in various wild mammals and birds as well as in the tick vector *I. ricinus*. Its natural habitat is in and around forest and woodland areas, and traditionally those most at risk have been forestry and agricultural workers. Nevertheless, with radical changes such as the development of forest clearings as camping and picnic sites and clearing the forest edges to increase grazing for cattle and sheep, the possibility of