make sure that rats which were supposedly vitamin A-deficient really were so—for vitamin A is stored in the liver and its presence there can protect animals during even relatively prolonged low vitamin A intake. Other experimentalists have been less painstaking, and this may partly or wholly account for the minority of reports of vitamin A showing no protective effect against carcinogenesis by PAH.[9-10] It would, however, be imprudent to ignore well-conducted experimental studies in which hypervitaminosis A seems to have enhanced cancer induction by PAH.[11 12] As to the mechanism, Genta *et al*[13] showed that vitamin A deficiency enhanced the binding of benzpyrene—another carcinogen of the PAH-type—to DNA, providing a plausible explanation for the vitamin's protective effect. On the other hand, studies by Lasnitzki *et al*[5] on the response of mouse prostate in organ culture to methylcholanthrene suggested that the effect of vitamin A was more complex and that various analogues of the vitamin might act differently. With this mass of experimental data it was not surprising that in 1975 Bjelke[14] reported an association between lung cancer and low intake of vitamin A, which suggested that smokers might to some extent be protected from the consequences of inhaling the PAH in cigarette smoke by increasing their vitamin A intake. Bjelke's failure to obtain information about the consumption of vitamin pills and liver—an important source of vitamin A—cast some doubt on his findings; nevertheless, they appear to have stimulated further work and to have helped to spark off the new clinical trial[1] in the United States.

Vitamin A occurs naturally in different forms. In a typical Western diet the most important sources are carrots, liver, milk, butter, margarine, certain green vegetables—and vitamin pills. According to nutritionists, vitamin A deficiency hardly occurs in Britain, yet possibly subgroups of the population, such as smokers, may need more than the average intake and giving them more of the vitamin[8] might have a useful cancer-protective effect. One real difficulty is that excessive doses of vitamin A are toxic,[15] so that to increase everyone's intake of vitamin A irrespective of their requirement for the vitamin might do more harm than good. The American study[1] is based on the controlled administration of a vitamin A analogue, 13-*cis*-retinoic acid,[16] to individuals deemed to be at relatively high risk of developing cancer. Like another analogue which has been extensively studied in Europe,[17-19] it differs from vitamin A palmitate and vitamin A acetate in that it does not accumulate in the liver. The distribution of other forms of the vitamin to the tissues tends to be limited by the availability of a specific serum carrier protein to which it binds, but 13-*cis*-retinoic acid binds freely to serum albumin and in this form can be readily distributed to body tissues by the bloodstream. The hope is that this study will show that it is possible to protect certain high-risk individuals—perhaps everyone—against the development of certain forms of cancer of epithelial origin. A wealth of experimental evidence suggests that this hope is not as unreasonable as it might appear, and we may therefore await the outcome of the trial with cautious optimism.

[1] *Journal of the American Medical Association*, 1976, **235,** 1409.
[2] Fell, H, and Rinaldini, L M, in *Cells and Tissues in Culture*, ed E N Willmer, vol 1, p 659. New York, Academic Press, 1965.
[3] Aydelotte, M B, *Journal of Embryology and Experimental Morphology*, 1963, **11,** 279.
[4] Lawrence, D J, and Bern, H A, *Experimental Cell Research*, 1960, **21,** 443.
[5] Lasnitzki, I, and Goodman, D S, *Cancer Research*, 1974, **34,** 1564.
[6] Chu, E W, and Malmgren, R A, *Cancer Research*, 1965, **25,** 884.
[7] Saffiotti, U, *et al*, *Cancer*, 1967, **20,** 857.
[8] Cone, M V, and Nettesheim, P, *Journal of the National Cancer Institute*, 1973, **50,** 1599.
[9] Polliack, A, and Levij, I S, *Cancer Research*, 1969, **29,** 327.
[10] Prutkin, L, *Cancer Research*, 1968, **28,** 1021.
[11] Smith, D M, *et al*, *Cancer Research*, 1975, **35,** 11.
[12] Smith, D M, Rogers, A E, and Newberne, P M, *Cancer Research*, 1975, **35,** 1485.
[13] Genta, V M, *et al*, *Nature*, 1974, **247,** 48.
[14] Bjelke, E, *International Journal of Cancer*, 1975, **15,** 561.
[15] Maugh, T H, *Science*, 1974, **186,** 1198.
[16] Sporn M B, *et al*, *Federation Procedings*, 1976, **35,** 1332.
[17] Bollag, W, *European Journal of Cancer*, 1972, **8,** 689.
[18] Bollag, W, *Chemotherapy*, 1975, **21,** 236.
[19] Bollag, W, *European Journal of Cancer*, 1975, **11,** 721.

Other tunnels, other nerves

The common problem of damage to the median nerve in the carpal tunnel still provokes interest (see *BMJ*, 12 June, p 1439). Even so, it is by no means the only peripheral nerve compression syndrome. Some nerves are exposed to damage by outside pressure. The patient anaesthetised on the operating table[1] or the convalescent propped on his elbow may lie upon the ulnar nerve in its groove behind the medial humeral epicondyle and cause unpleasant paraesthesiae in the ulnar side of the hand and fingers. When persistent, damage to the ulnar nerve may cause paresis of the small muscles of the hand and serious loss of dexterity. A tight knee bandage or splint or an improperly applied tourniquet may all too easily cause foot drop by damage to the common peroneal nerve as it winds around the neck of the fibula. The median nerve may be damaged by habitual heavy pressure from an unpadded handle of a walking stick. Similar damage to the deep branch of the ulnar nerve has been reported from repetitive occupational injury from using wire-cutting shears.[2]

A nerve trunk, and especially one running in a relatively confined space, may be compressed by a lesion that itself may produce few symptoms. Thus a ganglion, a lipoma, or an anomalous muscle mass deep in the palm may cause a median or ulnar palsy. The swelling and deformity of a fracture or of arthritis may cause mechanical irritation of a related nerve. The diffuse tissue thickening of myxoedema or acromegaly may lead to presenting symptoms of peripheral nerve compression. The possibility of pressure on the lowest trunk of the brachial plexus by a cervical rib or other anatomical anomaly has recently been reviewed.[3]

Such gross causes of nerve compression are usually, and tantalisingly, absent in carpal tunnel median neuritis. Nerve damage appears to arise by pressure from normal anatomical structures. This possibility of spontaneous nerve compression has stimulated speculation to the extent that almost any peripheral nerve diving under the sharp edge of a ligament or aponeurosis has become liable to surgical exploration. Several syndromes are now widely recognised. In general these nerve lesions develop near a joint, where movement may add friction to compression. Pain, paraesthesiae, and paresis occur in the distribution of the nerve. The sensory effects may be reproduced by local pressure or percussion or by the tourniquet test.[4] Nerve conduction across the lesion may be shown to be delayed. Local injection of steroids may help for a time, while surgical decompression permanently relieves the pain and is usually followed by useful recovery of nerve function.

The ulnar nerve emerges from behind the medial epicondyle to plunge between the two heads of origin of flexor carpi ulnaris. Ulnar neuritis will often be relieved by division of the aponeurotic arch over this muscle: anterior transposition should be reserved for patients with evidence of damage to the nerve in the bony groove.[5 6] Similarly, the common peroneal

nerve may be compressed by the tendinous arch of origin of peroneus longus, when nocturnal cramps and burning paraesthesiae may be felt down the outer side of the leg to the dorsum of the foot. The paresis of the dorsiflexors and evertors may present with recurrent inversion strains of the ankle.[7] Squatting cross-legged may initiate the syndrome.[8] Irritation of the lateral cutaneous nerve of the thigh where it passes through the outer end of the inguinal ligament is known as meralgia paraesthetica.[9] The symptoms, on the anterolateral aspect of the thigh, are worse with walking and standing and are eased by hip flexion. The syndrome is not uncommon in pregnancy, though it is rarely severe or persistent enough to require treatment by dividing the deep fibres of the inguinal ligament.

Many examples of tarsal tunnel nerve compression are now on record.[10 11] The posterior tibial nerve is compressed under a fibrous band behind and below the medial malleolus, causing nocturnal burning pain and paraesthesiae in the sole and toes. Sensory loss may be demonstrable, but muscle weakness is inconspicuous. The syndrome is important in the differential diagnosis of the paraesthesiae of peripheral artery disease. It is, indeed, worth considering the possibility of a mechanical cause for any isolated peripheral nerve lesion. Forearm pain with paralysis of flexor pollicis longus and the long flexor to the index finger has been relieved by division of a fibrous band compressing the anterior interosseus nerve as it passes between the heads of pronator teres.[12 13] Mechanical compression of the posterior interosseus nerve in its course on the front and outer side of the elbow has been blamed for pain along the radial side of the elbow and forearm, weakened grip, and sometimes paraesthesiae—a possible variant of tennis elbow.[14]

1 Wadsworth, T G, *Anesthesia and Analgesia*, 1974, **53,** 303.
2 Seddon, H J S, *Surgical Disorders of the Peripheral Nerves*. Edinburgh, Churchill Livingstone, 1972.
3 *British Medical Journal*, 1976, **1,** 1033.
4 Gilliatt, R W, and Wilson, T G, *Lancet*, 1953, **2,** 595.
5 Osborne, G V, *Journal of Bone and Joint Surgery*, 1957, **39B,** 782.
6 Vanderpool, D W, *et al*, *Journal of Bone and Joint Surgery*, 1968, **50B,** 792.
7 Sidey, J D, *British Medical Journal*, 1969, **3,** 623.
8 Marwah, V, *Lancet*, 1964, **2,** 1367.
9 Stevens, H, *Archives of Neurology and Psychiatry*, 1957, **77,** 557.
10 Keck, C, *Journal of Bone and Joint Surgery*, 1962, **44A,** 180.
11 Lam, S J S, *Journal of Bone and Joint Surgery*, 1967, **49B,** 87.
12 Fearn, C B D'A, and Goodfellow, J W, *Journal of Bone and Joint Surgery*, 1965, **47B,** 91.
13 Mills, R H B, Mukherjee, K, and Bassett, I B, *British Medical Journal*, 1969, **2,** 555.
14 Roles, N C, and Maudsley, R H, *Journal of Bone and Joint Surgery*, 1972, **54B,** 499.

Cartilage and bone in osteoarthrosis

Osteoarthrosis is characterised by focal splitting and fragmentation (fibrillation) of the articular cartilage, which may lead eventually to exposure of the underlying bone. The nature of this process remains uncertain. Biochemical analyses of fibrillated cartilage show that the amount of collagen is normal but that there is a reduced content of proteoglycans, on which the compressive stiffness of the cartilage depends.[1-3] Since the synthesis of proteoglycans is normal[4] or increased[2] in the early stages of fibrillation this loss has been attributed to excessive catabolism. Chondrocytes contain proteolytic enzymes capable of degrading the proteoglycans of cartilage, and the activity of these enzymes is increased in fibrillated cartilage.[5-7] Given all these findings, it seemed likely that fibrillation was due to a chondrocyte-mediated depletion of the extrafibrillar matrix, which made the cartilage softer and more susceptible to stress.

Recent studies, however, have presented a somewhat different view. Experiments in vitro have shown that the collagen network of healthy cartilage in which the proteoglycans are enmeshed is prone to fatigue (at least in the superficial layers of the superior surface of the human femoral head) and that resistance to fatigue falls with age.[8] Furthermore, some apparently healthy human hip joints, tested in vitro, develop unusually high contact pressures over the zenith of the femoral head. This is more common in joints with a thin area of fibrocartilage in the zenith of the acetabulum.[9] On the basis of these experimental findings Freeman has suggested that fibrillation could be due to fatigue failure of the collagen network leading to simple leakage of proteoglycans, and this would be more likely to occur in hips in which the structure of the acetabulum predisposes the cartilage to high local pressures.[10]

Whether the collagen or the chondrocyte fails first will be difficult to determine in man if only because onset of the disease cannot be precisely determined. In dogs in which mechanical osteoarthrosis had been produced by severance of a cruciate ligament, and in which the early stages of the disease could be studied, McDevitt and Muir[11] found evidence of chondrocyte malfunction before the onset of fibrillation. A few weeks after the operation changes were observed suggesting that the chondrocytes were synthesing proteoglycans that contained more than the normal amount of chondroitin sulphate. There was also evidence that in the prefibrillation stage the cartilage contained excess water and that the aggregation of proteoglycans and their interaction with collagen was impaired. Whether the increased hydration, which is also a feature of fibrillated cartilage,[3] is due to defects in the collagen network, as Maroudas[12] suggests, or to the striking qualitative changes observed in the extrafibrillar components, or both, remains to be decided.

Alternatively,[13] fibrillation may be secondary to sclerosis of subchondral bone (produced by repetitive impulse loading) and not vice versa, as in the orthodox view. Subchondral bone acts as a shock absorber,[14] protecting the overlying cartilage, and the efficiency of this action is reduced by stiffening of the bone. Repetitive impulse loading of a rabbit knee joint in vivo causes both fibrillation and stiffening of subchondral bone.[15] Whether the changes in the bones precede those in the cartilage is still, however, uncertain.[16] Patients with osteoarthrosis of the hip tend to have a generalised increased bone density,[17 18] but the importance of this remarkable finding is still uncertain. The hypothesis that bone stiffening precedes the joint changes has not yet been adequately tested.[19]

In some forms of osteoarthrosis mechanical factors are clearly of primary importance. Some cases of so-called primary osteoarthrosis may well be based on abnormal joint mechanics resulting from occult anatomical defects. A mechanical explanation has also been offered for "primary generalised osteoarthrosis," [20] but since there is evidence for a genetic predisposition[21 22] in this syndrome some generalised abnormality may be concerned in addition to local mechanical factors.

1 Bollet, A J, and Nance, J L, *Journal of Clinical Investigation*, 1966, **45,** 1170.
2 Mankin, H J, *et al*, *Journal of Bone and Joint Surgery*, 1971, **53A,** 523.
3 Maroudas, A, Evans, H, and Almeida, L, *Annals of the Rheumatic Diseases*, 1973, **32,** 1.
4 Maroudas, A, *Philosophical Transactions of the Royal Society*, Series B, 1975, **271,** 293.
5 Ali, S Y, *Biochemical Journal*, 1964, **93,** 611.