What has been said regarding persons working overseas but whose long-standing home is the United Kingdom applies to this third group of patients. Rapid air travel enables such persons to reach this country during the incubation period of some serious infective disorders of which typhoid fever, smallpox, and malaria are the most common, and many of the patients seen suffering from these disorders have recently left their country of origin.

Acute illness should be managed as for group 1 patients; in those suffering less acute illness it is probably advisable to obtain further opinion either from a general hospital or from one specializing in tropical disorders. It is understandable that general hospitals should like to keep an "interesting patient," though this is not always in the best interest of the individual; they too might do better by obtaining expert opinion and by obtaining it early rather than as a last resort when all other investigations have proved negative. As there are good and bad ways of handling an acute abdomen, a spontaneous pneumothorax, and a placenta praevia so there are good and bad ways of handling an amoebic liver abscess or an infection with *P. falciparum*.

Conclusions

Clearly the greatest hurdle to overcome is to discover that the patient has been overseas, information which is not always volunteered. Acute illness should be managed as outlined in this article and failure to make a diagnosis calls for early assistance from one of the specialized hospitals. Less acute illness should be investigated as for permanent residents of this country, but failure to make a satisfactory diagnosis should suggest an expert opinion, again early rather than late; this might be sought more often by general hospitals as well as by general practitioners.

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TODAY'S DRUGS

With the help of expert contributors we print in this section notes on drugs in common use.

Non-steroid Anti-inflammatory Agents

In the 1920s and even later it was fashionable to treat fevers with analgesic-antipyretic substances. As there were then no effective bactericidal or bacteriostatic agents all one could do was to attempt to reduce pain, fever, and other unpleasant symptoms. Today, in spite of a vast selection of antibiotics, many inflammatory diseases cannot be rapidly cured but can be symptomatically relieved; examples are virus pneumonias, connective tissue disorders such as rheumatoid arthritis, rheumatic fever and systemic lupus erythematosus, glandular fever, sarcoidosis, and gout. Patients with such disorders are often glad of symptomatic relief. Since the anti-inflammatory agents have also analgesic and antipyretic properties they are extremely useful in this widely scattered group of inflammatory disorders.

Anti-inflammatory agents available are: the *salicylates*—particularly aspirin in all its different forms; the *pyrazolones*—phenylbutazone and oxyphenbutazone; indomethacin; the *anthranilates*—mefenamic and flufenamic acids; and ibuprofen.

Though gold salts, chloroquine, and immunosuppressive agents can be legitimately considered to be anti-inflammatory long-term agents, they are not discussed here.

Salicylates

Aspirin in its various forms is usually first choice in the treatment of any inflammatory disorder, whether it be a common cold, rheumatoid arthritis, or glandular fever. Sodium salicylate has been largely given up in favour of aspirin as the latter drug relieves symptoms more effectively. Aspirin is rapidly absorbed from stomach and small intestine and begins to ease pain within 15 minutes of ingestion. Used in low dosage it is essentially an analgesic agent only; in larger dosage, such as 5 g. or more daily, it has a measurable anti-inflammatory effect also, as has been shown in patients with rheumatoid arthritis.[1] Similarly, it has different effects at different dose levels in gout, small doses (1-2 g. daily) lessening uric acid output and causing elevation of serum uric acid levels, larger dosage (5-6 g.) having the opposite effect. It should be said in passing that aspirin has little part to play in the treatment of acute gout.

In larger dosage aspirin has a definite anti-inflammatory effect, and for this reason it is usually the first choice in the treatment of rheumatoid arthritis. Soluble aspirin is generally the most popular, but all preparations may cause gastrointestinal complications and bleeding. Popular proprietary preparations are Paynocil (glycinated aspirin), each tablet containing 0·6 g. which dissolves on the tongue, Palaprin forte (aloxiprin) each tablet containing 0·6 g. which may be chewed, sucked, swallowed, or dispersed in water, Bufferin (aspirin buffered with magnesium carbonate and aluminium glycinate), enteric coated preparations, and several others. This anti-inflammatory analgesic action has been shown by Lim[2] to be at least in part peripheral. Unfortunately, the high dosage necessary to achieve the effect is often poorly tolerated, and dosage has to be reduced or the drug changed to something better tolerated. At high dose levels compound preparations containing phenacetin, caffeine, or codeine are never used.

Pyrazolones

Phenylbutazone and its metabolite oxyphenbutazone are effective long-acting, slowly metabolized, anti-inflammatory, antipyretic, analgesic agents. They are only slowly broken down and are excreted in the urine largely as a number of water-soluble metabolites. They are firmly bound to plasma protein, largely to albumin and alpha globulin, and for this reason they exert an even, prolonged action, which is particularly effective in the chronic arthropathies and in acute gout (total daily dosage being 200-400 mg. in the former and 600 mg. in the latter condition). When treating acute gout the dosage should be gradually reduced by 100 mg. daily as the attack comes under control. Though oedema, rashes, and gastrointestinal complications are known to occur, the much rarer, though more dangerous, toxic effects are haematological—neutropenia, thrombocytopenia, or aplastic

anaemia.[3] For this reason blood counts should be done every few weeks if the patient is on regular therapy, and immediately if suggestive symptoms arise, such as buccal ulceration, unexplained pyrexia, sore throats, stomatitis, or odd ill feelings which cannot be accurately described. Buccal ulceration commonly occurs, however, without any changes in the blood and is in most cases of nuisance value only.

Its even therapeutic action makes phenylbutazone particularly effective in disorders such as ankylosing spondylitis, where frequent aches and pains and constant stiffness is the rule throughout the 24 hours, but the pyrazolones are also useful in the treatment of osteoarthritis, rheumatoid arthritis, Reiter's (Brodie's) disease, and a number of other rheumatic afflictions. In non-arthritic conditions, such as thrombophlebitis, where pain and swelling play a part in the disease the pyrazolones may also prove useful, and in non-inflammatory conditions of bone such as metastatic malignant and Paget's disease symptoms may be at least partly relieved in some cases. Both phenylbutazone and oxyphenbutazone may be given in suppository form (250 mg.) and the former by intramuscular injections (600 mg.), but the oral route usually proves the most satisfactory. Nifenazone has not proved to be as effective as its predecessors.[4]

A few more rare side effects may be noted. Thyroid enlargement may very rarely occur, with clinical features of hypothyroidism, owing to blocking of iodine uptake by the thyroid gland. Enlargement of the salivary glands with dryness of the mouth may be erroneously thought to be due to Sjögren's syndrome rather than to the drug. Salt and fluid retention may occasionally precipitate cardiac failure in patients with heart disease.

As these drugs are largely bound to serum proteins competition for binding may occur with other drugs. The sulpha group, for example, may be displaced and so have increased antibacterial action.[5] Similarly, the hypoglycaemic action of tolbutamide may be increased by concurrent administration of phenylbutazone; and the action of warfarin—98% bound to albumin with only 2% of the total drug in the plasma biologically active—may be greatly potentiated, with a very real risk of serious haemorrhagic complications.[6] For quite different reasons phenylbutazone enhances the hypoglycaemic action of acetohexamide.[7] Care should be taken, then, in giving phenylbutazone and oxyphenbutazone with other drugs. The whole question of drug interreaction has been reviewed recently by Prescott.[8]

The toxic effects of this useful group of drugs may have been over emphasized. In common with many new drugs, phenylbutazone was introduced at higher dose levels than was therapeutically necessary, with the inevitable flood of reports of toxic reactions in the world's literature. In a recent survey in the U.S.A.[9] 562 patients treated for 2-10 and averaging 4·1 years showed an incidence of 7·5% adverse reactions on an average daily dosage of 148 mg. phenylbutazone. In only 4 cases (0·7%) was it necessary to stop treatment, in one because of oedema, in three because of peptic ulceration.

Indomethacin

This is an effective anti-inflammatory, antipyretic, analgesic agent in much the same conditions as phenylbutazone proves useful : acute gout, ankylosing spondylitis, rheumatoid arthritis, osteoarthritis, Reiter's (Brodie's) disease, and also in febrile inflammatory disorders such as glandular fever, where unpleasant symptoms may be relieved. Unlike the pyrazolones it has a relatively short duration of action, roughly 4-12 hours or more depending on the dose given. It is rapidly absorbed when given by mouth or rectum and is rapidly eliminated, largely in the urine : for this reason it should be given very warily or not at all if there is any impairment of renal function, and it is wise to estimate the blood urea before starting therapy. The commonest and earliest side effect is a dose-related one, an unpleasant swimmy or muzzy sensation in the head or a true headache, sometimes severe.[10]

As with tinnitus in patients on salicylates and nausea with digitalis, this toxic effect is met by reduction of dosage. Dyspepsia, on the other hand, sometimes with gastrointestinal bleeding, is not dose related[11] and may occur at any stage of therapy on almost any dosage. Prepyloric ulceration may occur[12] which radiologically may closely resemble a malignant condition; but such ulcers diminish and disappear, usually within four weeks of stopping the drug.

Indomethacin is available in 25 mg. capsules taken by mouth with or after food, as an elixir 25 mg. per 5 ml. and in suppository form (100 mg.). In many rheumatic disorders more pain is experienced at night and in the early morning than in the day, and painful morning stiffness is characteristic of rheumatoid arthritis, ankylosing spondylitis, some cases of periarthritis of the shoulder, and a number of other conditions. A 100 mg. suppository inserted late at night or three to four capsules (75-100 mg.) by mouth taken with food on retiring may help the patient through the night very effectively,[13] the larger dose being tolerated since headaches rarely waken the patient from sleep. The usual total daily dosage is two, three, or four capsules (50-100 mg.) taken with food. There is great individual variation in tolerance, some patients experiencing headaches on 50 mg., others none on 200 mg. a day. Rashes are rare, purpura rarer still. Buccal ulceration may sometimes occur, but in almost all cases without any change in white cell count. Recently[14] there has been a report of corneal deposits, reversible on stopping the drug, and of decreased retinal sensitivity, as shown by decreased electroretinograms, altered thresholds of dark adaptation, and visual field changes : in clinical practice, however, ocular side effects appear to be very rare. Though the dose-related cerebral sensations referred to earlier may limit the usefulness of the drug, as many patients cannot tolerate it at effective dose levels, indomethacin continues to be a useful and widely used anti-inflammatory, analgesic agent in a large number of conditions.

Anthranilates

Mefenamic and flufenamic acids are relatively mild anti-inflammatory, analgesic, antipyretic agents used usually in the rheumatic disorders where other drugs prove ineffective or toxic. The recommended dosage of mefenamic acid is 500 mg. initially, then 250 mg. six-hourly by mouth. It causes diarrhoea in about 10-20% of patients on continued dosage, and occasionally haemolytic anaemia; rashes or dyspepsia may occur but are not common. In patients on anticoagulants the prothrombin time may be prolonged. Flufenamic acid is given orally in a dose of 100 mg. four to six times a day. It also causes diarrhoea and more rarely dyspepsia.

Ibuprofen

This is a newcomer which succeeded ibufenac from the same laboratories. Ibufenac was withdrawn because of hepatotoxicity; this complication has not been noted with ibuprofen. Opinions vary as to its clinical merit, some workers[15] finding it as effective as aspirin in full dosage, others[16] no better than placebo, some[17] half way between. General opinion seems to be that it is a weak, but non-toxic, analgesic agent : its anti-inflammatory action has not been as yet demonstrated in rheumatoid disease in man. The dosage advocated is 200 mg. three times daily.

Conclusions

Though the steroids remain the most effective anti-inflammatory agents available, their endocrine effects make long-term therapy too complicated and dangerous in any except

conservative dosage. Of the non-steroidal agents the salicylates, phenylbutazone, and indomethacin remain the most popular and probably the most effective.

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ANY QUESTIONS?

We publish below a selection of questions and answers of general interest.

Vitiligo

Q.—*Why do lesions of vitiligo fluoresce brilliantly in Wood's light? Can this be a clue to the aetiology of vitiligo?*

A.—This question is based on a false premise—patches of vitiligo do not fluoresce in Wood's light but the contrast between the unpigmented and adjacent pigmented skin is heightened and areas of slight hypopigmentation not obvious in daylight or conventional artificial light are easily identifiable in Wood's light. This is particularly helpful when examining the skin of patients suspected of epiloia.

Sclerodermatous Plaques

Q.—*Is it safe to try to remove small sclerodermatous plaques in the fingers with ring blocks, or are they contraindicated in this condition? Is the removal of plaques worth while, or are they more likely to recur?*

A.—It is not easy to answer this question without further information about the underlying condition. If the sclerodermatous plaques are due to fibrosis secondary to the ischaemic changes of systemic sclerosis on discoid lupus erythematosus the result of local surgery may be disastrous and lead to intractable ulceration requiring the amputation of the digit. Painful plaques of calcinosis cutis of fingers, whether due to systemic sclerosis, dermatomyositis, or of idiopathic origin, can be removed easily without dangerous trauma and with much symptomatic relief of the pain with which these lesions are usually associated. Sclerodermatous plaques due to other causes, including scars, can be softened or diminished in size by intralesional corticosteroids like triamcinolone injected with a pressure syringe.

Acute Torticollis

Q.—*What is the aetiology of acute torticollis (acute wryneck), and does being in a draught of cold air play any part?*

A.—Acute torticollis (wryneck) may be a psychogenic tic—a habit spasm—often in a tense, nervous, and sometimes hysterical subject. It was occasionally seen in the last war after unnerving incidents on active service. It may also result from disease of the nervous system as a limited form of torsion spasm, as a sequel to epidemic encephalitis with or without Parkinsonism, or some other extrapyramidal syndrome.

The commonest cause, however, appears to be a minor subluxation in an osteoarthrotic cervical spine or even in a normal one. It occurs when a fixed position has been held unnaturally for prolonged periods, as in driving a car. A cold draught through the open window seems to play an aggravating part. The condition usually responds to analgesics, warmth, and gentle manipulation and traction.

Notes and Comments

Generalized Oedema.—Dr. E. G. ROBERTSON (Department of Obstetrics and Gynaecology, Princess Mary Maternity Hospital, Newcastle upon Tyne) writes: With reference to the answer to this question ("Any Questions?" 25 July p. 212), I would like to add some further comments about the relationships between generalized oedema and changes in mucopolysaccharides.

Generalized oedema is found commonly in normal pregnancy[1] as well as in association with pre-eclampsia. The excess water stored in generalized oedema is no doubt mainly extracellular, but as suggested by Hytten and Thomson[2] it is not necessarily free fluid in the extracellular space. The ground substance of connective tissue may be responsible for the storage of water. There are widespread changes in the nature of connective tissue in pregnancy. In a recently completed study[3] evidence was found of progressive increases in skinfold compressibility with gestation which were greater in the presence of generalized oedema.

Gersh and Catchpole[4] and Langgård[5] have suggested that changes in skin associated with oedema may be caused by alterations in the component mucopolysaccharides of ground substance. Langgård and Hvidberg[6] showed that the administration of oestradiol could cause oedema in mice, there being an increase in the tissue hexosamine and hyaluronic acid content. The long chain mucopolysaccharide molecules appeared to undergo physical change (possibly polymerization) which was accompanied by a disproportionately large increase in the water content of the tissue. The water molecules seemed to be bound to the mucopolysaccharide molecules and to have been retained without a corresponding increase in electrolyte. Similar changes can be induced in the sex skin of monkeys by administering oestrogen.[7]

Thus the evidence from animal experiments suggests that, in some instances, generalized oedema may occur as part of the process of adjustment to increased steroid levels. It has already been suggested[8] that the ground substance of connective tissue may act as an "organ" for water storage in pregnancy, and that the function of the mucopolysaccharides may be to provide a buffer against a changing tissue water and electrolyte concentration in order to maintain the constancy of the internal environment. When the functional capacity of this "organ" is exceeded then generalized oedema can occur. In pregnancy these changes are also enhanced by the lowered oncotic pressure of the plasma proteins[8] thus enabling more rapid transfer of fluid to the extravascular space.

OUR EXPERT replies: Though oestrogen-induced changes in the mucopolysaccharides may provide the explanation for the oedema of pregnancy there are other factors operative which encourage the formation of oedema.[1] Exchangeable sodium values are increased in normal pregnancy, and, despite controversy over the relationship between sodium balance and pre-eclampsia, the balance of evidence lies in favour of the conventional view that excessive storage of sodium takes place. Thomson *et al.*[2] report d that whereas 35% of normotensive patients developed oedema in pregnancy 60% of hypertensive subjects and 85% of those with proteinuria were oedematous. Unless pre-eclampsia leads to increased levels of oestrogen or a change in tissue sensitivity sodium retention is probably the major cause of oedema in these patients. The diminished oncotic pressure of plasma proteins which Dr. Robertson has demonstrated also tends to favour the accumulation of extracellular fluid.

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