terms in an era of financial stringency, when all new developments must be considered carefully in terms of relative priorities. Zellweger and Antonik have done a useful service, however, in confirming with their preliminary observations the reliability of the method and in reopening debate upon this difficult problem.

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Influenza Prospects

Influenza vaccines have been studied and widely used for over 30 years, but influenza remains probably the most important uncontrolled infectious disease in Britain. The sickness and death that result from the almost inevitable winter epidemics, the effects on industry and health services, and the recollection of the impact of past pandemics have stimulated research in most temperate countries towards the aim of prevention of influenza. Of the possible means of prophylaxis only vaccination at present offers hope of control, and progress in the development and application of influenza vaccines formed the subject of an international symposium held in London last month.

The vaccines at present licensed in Britain are inactivated preparations. Their manufacture is difficult, because the vaccines have to be changed periodically—recently almost every year—to accommodate the shifts and drifts in the antigens of the natural virus, and the manufacturers have an excellent record in both keeping their vaccines up to date and at the same time improving their quality. The virus, grown in fertile hens' eggs, is inactivated and purified by centrifugation and often by treatment with detergents, which can split the protective haemagglutinin and neuraminidase antigens from the virus. An injection of a modern killed influenza vaccine will usually protect 70-80% of those vaccinated at the expense of only minor side effects such as the occasional sore arm. Inactivated vaccines given by nasal spray are available, but a convincing field trial has yet to be reported, so that the protection they offer is still uncertain.

To whom should vaccine be given? An annual injection is justifiable for persons in whom an attack of 'flu might be especially hazardous—those with chest disease, for example, and elderly persons in institutions. Some speakers at the symposium advocated vaccination for infants and children both because the incidence of influenza is often high in children and because they may be responsible for much of the spread of infection, so that vaccination of children might benefit the whole community. It might be difficult, however, to convince many doctors, parents, or children of the justification for annual revaccination against a disease which in children is rarely serious.

Vaccination in industry was also considered. Studies from the Public Health Laboratory Service in collaboration with industrial medical officers and general practitioners suggest that the effects of vaccination on sickness absence may be relatively small in the usual winter epidemics, probably because only about 30% of healthy people will usually accept an offer of vaccination and because the incidence of clinical influenza among adults in the moderate epidemics of recent years appears to have been only about 2%. Thus industrial vaccination programmes could probably not have prevented more than one illness per 100 employees during each of the last few winters; such an effect might go unnoticed against the background of other respiratory infections characteristic of the British winter. Until major outbreaks can be forecast reliably a more rational policy for industry may prove to be the vaccination of those key workers among whom even a small increase in absence may be critical.

Perhaps the greatest possibility of control lies in the use of live, attenuated vaccines given by nose-drops or spray. Live vaccines require only a small dose to stimulate serum antibodies, local immunity in the respiratory tract, and, possibly, cell-mediated immunity, which may also have some part to play in protection. As with inactivated vaccines it is necessary to prepare a new vaccine whenever the influenza virus undergoes a significant antigenic change. Attenuated strains with the protective antigens of a new virulent strain can be produced quickly in the laboratory nowadays by genetic recombination techniques, but the essential tests for safety and potency remain time-consuming; a major epidemic due to a new strain may be over before an appropriate live vaccine can be released. As experience with live vaccine is gained the time taken for safety and potency tests should become less.

One section of the symposium was given to discussion of plans for control of the next pandemic. The timing of the next pandemic can be forecast no more accurately than that of next winter's outbreak, and even short-term forecasting of influenza seems to be less reliable than forecasting the weather. But surveillance of influenza is improving in Britain and throughout the world, so that the emergence of new virus variants is likely to be spotted quickly; strains with obvious epidemic potential can then be adapted for vaccine production. We are fortunate in Britain that epidemics often affect the Far East or the Southern Hemisphere first, so that we can benefit from their experience. Once a new pandemic strain is recognized, with its complete shift in the structure of the virus haemagglutinin, we are bound to be seriously affected sooner or later. There is a real prospect of preventing the effects of such a pandemic if an acceptable and effective vaccine can be produced quickly enough and in sufficient quantity to be used on a very wide scale before the virus affects the country.

Polyarthritis and Yersinia enterocolitica Infection

Infection with *Yersinia* (*Pasteurella*) *enterocolitica*,[1] or pseudotuberculosis,[2] usually causes a mild gastrointestinal illness with abdominal pain, fever, and diarrhoea. It may also present like an acute appendicitis, owing to mesenteric adenitis, or like a terminal ileitis. The arthritis which may follow, usually within three weeks of onset, is sufficiently well known to have earned a page to itself in a recent textbook on the arthropathies.[3] It is generally considered to be a postinfective condition rather than a direct bacterial invasion of joint structures. This is a

polyarthritis, the lower limbs being predominantly affected, knees and ankles most commonly but fingers, toes, and wrists also, and occasionally the lumbar spine, hips, shoulders, jaw or sacroiliac joints, usually in an asymmetrical pattern. The joints are tender and swollen and effusions are not uncommon.

Until recently reports of such infections were mostly from Scandinavia and Central Europe, but Thomas, Solomon, and Rabson[4] state that over 100 cases have now been diagnosed at the South African Institute for Medical Research. Erythema nodosum, a not uncommon manifestation of the disease in other countries,[5] is a relatively rare finding in South Africa, but a septicaemic form of the disease with a 50% mortality rate is there relatively more common than elsewhere,[6] particularly in patients with hepatic cirrhosis or iron overload. The department of orthopaedic surgery in Witwatersrand University, Johannesburg has recently seen[4] 11 patients with infection attributed to *Y. enterocolitica*, 10 of whom presented with a polyarthritis and one with a backache. Of the ten patients with polyarthritis four had also an associated backache. Five were women, six men, ages ranging from 18 to 51 years. Abdominal pain or diarrhoea was present in five and absent in six. Sedimentation rates were raised in all but two patients; a leucocytosis was present in only four. Most were febrile. Stool cultures were negative, and the diagnosis was made on H-agglutination tests, titres varying from 1/100 to 1/6400. Blood cultures were negative in all cases. The polyarthritis tended to be flitting in nature, and though never disappearing from any joint fluctuated in intensity from one area to another. Some joints were hot, red, swollen and tender resembling an acute pyarthrosis, some were less acute, resembling rheumatoid arthritis. Articular erosions were seen in the *x*-ray films of only one patient, who had sacroiliitis. Treatment was essentially symptomatic and somewhat unsatisfactory, though combined antibiotic and anti-inflammatory therapy was associated with improvement in 10 of the 11 patients. But, as the authors state, this improvement may well have been due to the natural regression of the disorder.

This clinical picture of the arthropathy is very similar to that previously described by workers in Finland,[7] who found the duration of acute joint symptoms ranged usually from one to four months, fluid aspirated from the affected joints showing usually a polymorphonuclear pleocytosis. One point of difference is that though the Finnish workers noted slight radiological changes suggesting a mild left sacroiliitis in one case there is no mention of backache in the nine patients they reported. On the other hand they noted signs of carditis in 6 patients, whereas no mention is made of cardiac findings in the South African patients. These differences may well have been due to differences of observation and emphasis. In view, however, of the importance of the histocompatability antigen HL-A 27 (W 27) and its relation to disease, particularly the inflammatory spondylarthropathies, cases such as those reported from South Africa should be tissue-typed and followed for several years. Both in Britain[8] and the U.S.A.[9] patients with ankylosing spondylitis have been found in a large majority of cases to have the HL-A 27 (W 27) antigen, and this has also been shown to be true of spondylitis secondary to Reiter's disease,[10 12] psoriasis,[11 12] the enteropathic arthropathies associated with ulcerative colitis and Crohn's disease,[12 13] and some male cases of juvenile rheumatoid arthritis.[14] Indeed, it has been suggested[15] that these disorders be called collectively "W27 rheumatic disease." Of particular interest in relation to yersinia infection are the publications by Professor Aho and his colleagues in Helsinki.[16–18] They found the histocompatability antigen HL-A 27 in 43 of 49 patients with yersinia arthritis and 36 of 40 patients with Reiter's disease, compared with 3 of 20 patients with yersinia infection without arthritis and 14% of the normal Finnish population. They observe that instead of an orientation towards individual clinical syndromes there is now more emphasis "on the role of a host genetic factor in the mediation of common pathologic expressions of multiple aetiologic stimuli." The old saying that the soil is as important as the seed in development of disease would seem to be as true in rheumatology as in the rest of medicine.

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How Innocuous is the White Medicine?

Everyone is now aware that one drug may change the clinical effect of another when they are taken together, but some commonplace remedies have not been questioned because they seem to be harmless. Antacid preparations have seemed innocent in this respect, and this partly stems from some uncertainty about their efficacy in treating peptic ulcer and in neutralizing gastric acidity. They are, however, less innocuous than was thought; for it seems that some can alter drug elimination from the body by changing urinary acidity.[1]

The kidney is the most important route for the excretion of some drugs, and it is ideally suited for this role because it is an efficient filter, passing through the glomerulus a large volume of fluid and with it those molecules small enough to pass through the capillary pores. Most drug molecules are sufficiently small, and the fraction not bound to plasma proteins will come through into the filtrate. However, the tubular epithelium reabsorbs water and solutes, including drugs, and as with other membranes this may be an active or passive process. Furthermore some drugs, such as penicillin, are secreted into the tubular fluid. Non-ionized drug molecules cross membranes easily, but not ionized ones, and the dissociation constant (pK_a value) of the drug itself determines in part the degree of ionization. The other factor is the pH of the solvent; in this instance, the tubular fluid. Most drugs contain weak acidic and basic groups, and if the tubular fluid is acidic there will be more ionization of basic drugs, which will not be reabsorbed so readily, and their renal elimination will be enhanced. Alteration of pH towards alkalinity will have the opposite effect. The converse happens with acidic ones.