show that patients, including infants, tolerate jet vaccination without difficulty. The procedure has been proved to be safe and effective, and patients may prefer a single jet injection method to the multiple pressure or scratch technique. The Smallpox Eradication Program team used the relatively expensive hydraulic jet apparatus with a special intradermal nozzle; a previous report indicates that there is no reason why similar results cannot be obtained with the much cheaper jet injector which injects a fixed volume of 0·1 ml. per shot.

Drugs and Enzymes

When patients being treated with anticoagulants are given phenobarbitone as well, they are found to need a higher dose of the anticoagulants to maintain the effect. This is because phenobarbitone stimulates the enzymes concerned in the metabolism and breakdown of the anticoagulants ("enzyme induction"). Conversely, when the barbiturates are stopped increased anticoagulation effects may occur, since the enzymes responsible for their metabolism cease to be stimulated. Similar effects have been described for barbiturates and diphenylhydantoin, and for griseofulvin and digitoxin. Liver microsomes contain enzyme systems which hydroxylate steroids, cutting short their biological activity. The administration of many drugs also increases the hydroxylation of steroids. They include diphenylhydantoin, chlorocyclizine, phenylbutazone, dicophane (D.D.T.), and o,p'-D.D.D. These last two agents have been used to hasten the conjugation of cortisol in patients with Cushings syndrome.

In two papers in this week's B.M.J. a team from University College Hospital in London show that epileptic patients receiving long-term anticonvulsant therapy may develop osteomalacia. This, they suggest, is a further example of possible enzyme induction, which this time produces a relative lack of vitamin D activity. Careful investigation of their patients ruled out dietary, absorptive, and hepatic causes for the osteomalacia. The close relationship between total drug dosage and the serum calcium concentration was particularly striking, while the results of studies in animals were highly suggestive that the metabolism of vitamin D in man may be seriously affected by barbiturates and phenytoin, primidone, and pheneturide. Tests of enzyme induction in man by measuring the amount of 6β-hydroxycortisol excreted in the urine would be particularly revealing in this group of patients.

The results reported this week by the U.C.H. workers point to three important clinical lessons. Firstly, every routine history should include a note of the drugs the patient has been taking. Secondly, the report shows the value of determining the site of origin of the raised alkaline phosphatase levels in the plasma. The third important point is the concept that diseases may be linked by therapy rather than by a common aetiology. Moreover, this work highlights the dangers of the long-term administration of barbiturates, and when they are being specifically used for enzyme induction—for example, in the treatment of hyperbilirubinaemia—osteomalacia must be expected to occur eventually.

We are now beginning to realize that a variety of substances may cause enzyme induction. Thus cigarette smoke contains 3,4 benzpyrene and certain cooked foods contain polycyclic hydrocarbons, both of which may also stimulate the metabolism of drugs. The epidemiological ramifications of these findings have yet to be explored.

Intermittent Chemotherapy for Tuberculosis

Chemotherapy for tuberculosis must be continued for about two years to ensure freedom from relapse. Patients are generally given preparations of isoniazid with para-aminosalicylic acid (P.A.S.) or thiacetazone and instructed to take them daily. In addition injections of streptomycin may be given during the first two or three months of treatment. Almost 100% success has attended these regimens in clinical trials on selected patients harbouring drug-sensitive organisms who take the medicaments as instructed. But the gap between the best results attained in controlled clinical trials and the results following the same regimens in routine practice is a matter of concern.

In a survey of routine treatment in India only about half the patients starting chemotherapy were known to have negative sputum after one year. In Kenya a comparison of results achieved in controlled clinical trials with those achieved by routine treatment services showed that the inferior results attained in the latter were due almost entirely to failure of patients to take their tablets. It was evident that with the passage of time patients became increasingly unreliable in attending clinics and in taking their medicaments.

Similar problems exist in the United Kingdom. Among patients in Gateshead 25% failed to take P.A.S. and isoniazid regularly. In London 16% of patients were unable or unwilling to take P.A.S. because of side effects.

Irregularity of drug consumption may be avoided if the administration of drugs is fully supervised. This becomes practicable only if treatment is given intermittently rather than daily. Twice-weekly fully supervised administration of streptomycin 1 g. together with isoniazid in the large dose of 14 mg./kg. body weight has been shown to be at least as effective as conventional self-administered daily isoniazid and P.A.S. in controlled studies by the tuberculosis chemotherapy centre at Madras. Once-weekly streptomycin and isoniazid was not as effective as twice-weekly except in patients who were slow inactivators of isoniazid. The failure of the once-

References