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[15] 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.[1] This is because phenobarbitone stimulates the enzymes concerned in the metabolism and breakdown of the anticoagulants ("enzyme induction"). Conversely, when the barbiturates are stopped[2] increased anticoagulation effects may occur, since the enzymes responsible for their metabolism cease to be stimulated.[3] Similar effects have been described for barbiturates and diphenylhydantoin, and for griseofulvin and digitoxin.[1]

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.[4] These last two agents have been used to hasten the conjugation of cortisol in patients with Cushing's syndrome.[5]

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 6βhydrocortisol excreted in the urine[6] 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[7]—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.[8] The epidemiological ramifications of these findings have yet to be explored.

[1] Conney, A. H., *Pharmacological Reviews*, 1967, **19**, 317.
[2] Cucinell, S. A., Conney, A. H., Sansur, M., and Burns, J. J., *Clinical Pharmacology and Therapeutics*, 1965, **6**, 420.
[3] MacDonald, M. G., and Robinson, D. S., *Journal of the American Medical Association*, 1968, **204**, 97.
[4] Kupfer, D., and Peets, L., *Biochemical Pharmacology*, 1966, **15**, 573.
[5] Southren, A. L. *et al.*, *Journal of Clinical Endocrinology*, 1966, **26**, 268.
[6] Kuntzman, R., Jacobson, M., Levin, W., and Conney, A. H., *Biochemical Pharmacology*, 1968, **17**, 565.
[7] Thompson, R. P. H., and Williams, R., *Lancet*, 1967, **2**, 646.
[8] Kuntzman, R., *Annual Review of Pharmacology*, 1969, **9**, 21.

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.[1] 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.[2] Similar problems exist in the United Kingdom. Among patients in Gateshead 25% failed to take P.A.S. and isoniazid regularly.[3] In London 16% of patients were unable or unwilling to take P.A.S. because of side effects.[4]

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.[5] 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-

[1] Frimodt-Möller, J., *Tubercle*, 1968, **49**, Suppl., p. 22.
[2] Kent, P. W., *et al.*, *Tubercle*, 1970, **51**, 24.
[3] Pande, B. R., Martischnig, K. M., and Feinmann, L., *Tubercle*, 1970, **51**, 39.
[4] Poole, G., and Stradling, P., *British Medical Journal*, 1969, **1**, 82.
[5] Tuberculosis Chemotherapy Centre, Madras, *Bulletin of the World Health Organization*, 1964, **31**, 247.
[6] Tripathy, S. P., *Bulletin of the International Union Against Tuberculosis*, 1970, **43**, 276.
[7] Menon, N. K., *Bulletin of the International Union Against Tuberculosis*, 1970, **43**, 271.
[8] Stradling, P., and Poole, G. W., *Tubercle*, 1970, **51**, 44.
[9] Bignall, J. R., *Bulletin of the International Union Against Tuberculosis*, 1970, **43**, 253.
[10] Polansky, F., *Bulletin of the International Union Against Tuberculosis*, 1970, **43**, 295.

weekly regimen in rapid inactivators is due to the shorter duration of exposure to isoniazid than in slow inactivators.[6] The duration of exposure to isoniazid might be increased in rapid inactivators by increasing the dose of isoniazid. Little increase in dosage is possible, however, because of the risk of acute toxicity. The addition of P.A.S. slightly enhances isoniazid blood levels but does not appreciably improve the efficacy of the once-weekly regimen.[7] Slow-release preparations of isoniazid might prolong absorption, or alternatively derivatives of isoniazid might prolong high concentrations in the blood. These possibilities merit investigation.

P. Stradling and G. W. Poole[8] have treated outpatients in London with streptomycin, isoniazid, and P.A.S. daily for the first three months and thereafter continued therapy with the fully supervised administration of streptomycin 1 g. and isoniazid 600 mg. twice-weekly. Disease was satisfactorily controlled in all patients, and the authors considered that the results were better than were likely to have followed the self-administration of drugs on a conventional regimen.

Twice-weekly supervised therapy has been compared with daily self-administered therapy in two recent controlled studies. No important advantage for supervised therapy was detected in either. The International Union against Tuberculosis conducted a study in seven developing countries. Daily supervised streptomycin, isoniazid, and thiacetazone were given for the first month followed by twice-weekly streptomycin and isoniazid. This was compared with the same initial treatment followed by daily self-administered isoniazid and thiacetazone. The results of the two regimens were similarly good in respect of therapeutic efficacy, toxicity, and patient co-operation.[9]

In a study in Czechoslovakia initial daily supervised therapy with streptomycin, isoniazid, and P.A.S. for three months was followed by either twice-weekly streptomycin and isoniazid or self-administered daily isoniazid and P.A.S. Equally good results occurred in both groups.[10]

In well-organized treatment services it is possible to monitor self-administered regimens closely by means of urine tests, tablet counting, surprise home visits, and frequent interrogation of patients. In these circumstances they may have no advantage over supervised intermittent regimens. Where self-administered treatment gives poor results, an intermittent supervised regimen may improve them.

Recurrent Abdominal Pain in Children

Many medical parents, most family doctors, and all paediatricians have to take responsibility for the diagnosis and management of children with recurrent abdominal pain. J. Apley[1-3] in a survey in Bristol schools found that 1 in 7 children complained of recurrent headaches, 1 in 9 of recurrent abdominal pain, and 1 in 25 of recurrent limb pains. He sought a common denominator for these pains and found that there was a strong emotional element in most of them, often with a family history of the same complaint. The problem of the child with recurrent abdominal pain was admirably summarized in his classic book.[3]

Now R. T. Stone and G. J. Barbero in Philadelphia[4] have studied 102 children aged 2½ to 14 years with recurrent abdominal pain. The pain was central in 78, vaguely localized in a further 10, and on the right or left side in the remainder. It was described as cramp-like in 7%, dull aching in 18%, and acute spasmodic in the others. Associated symptoms included mainly headache, sickness, dizziness, poor appetite, and vomiting. The symptoms in two-thirds were related to stress. Previous diagnoses included appendicitis in 17%, duodenal ulcer in 14%, an emotional problem in 13%, and fibrocystic disease of the pancreas, allergy, regional ileitis, and constipation in others. Stone and Barbero performed a proctoscopy in 90 children and found a mixture of signs—rectal dilatation, hyperaemia, lymphoid hyperplasia, oedema, friability of the mucous membranes, and pellet stools. All laboratory investigations were negative. They thought that the symptoms were part of the irritable colon syndrome as described by M. Davidson and R. Wasserman.[5]

As there are no pathognomonic signs of the condition, the difficulty facing the family doctor and paediatrician is that of satisfying himself of the correctness of the diagnosis. It is always wrong to decide that a symptom is entirely emotional merely because one cannot detect organic disease. The diagnosis must be made on the basis of positive evidence of emotional disturbance and the exclusion of organic disease—not only at the time of the initial diagnosis but on follow-up examination. Apley found evidence of organic disease in about 6% of his cases. Microscopy and culture of a clean midstream specimen of urine are essential parts of the investigation. A good nonspecific test is the erythrocyte sedimentation rate. An abnormal figure points immediately to organic disease, but a normal figure does not exclude it. Sometimes a paediatrician will want to see an intravenous pyelogram in order to eliminate a hydronephrosis. He may ask for occult blood tests as a guide to the diagnosis of a peptic ulcer and rarely a barium meal examination for the same condition. In countries abroad it is wise to eliminate round-worm infestation by examining the stools and tuberculosis by a tuberculin test. It is psychologically unsound to carry out a series of investigations, week after week or month after month; it is better to satisfy oneself once and for all that there is no discoverable organic disease. The family doctor may feel that none of the tests mentioned would eliminate a "grumbling appendix," but such a diagnosis is extremely unlikely to be correct—though the removal of a normal appendix is common in these children. An allergic cause can be virtually excluded if there is no other indication of allergy. In some cases the diagnosis may be migraine, the so-called periodic syndrome, in which there is any combination of abdominal pain, vomiting, headache, and fever, nearly always with a family history of migraine. Some children with migraine lose their attacks when they avoid cheese, chocolate, and some related foodstuffs.[6]

If the family doctor concludes that the cause is entirely emotional, some understanding of the mechanism would be desirable. Unfortunately we do not fully understand how emotion and stress cause abdominal pain. It is clear that the pains may be related to imitation—for example, of a parent who is constantly complaining of his gastric discomfort—or fear in the child's mind that he will experience the same pain as his parent. The child may feel fear and anxiety about stress at school—bullying by a teacher or child, distaste for arithmetic or other subject. Or the pain may be due to suggestion

[1] Apley, J., *Lancet*, 1959, **1**, 641.
[2] Apley, J., *Proceedings of the Royal Society of Medicine*, 1958, **51**, 1023.
[3] Apley, J., *The Child with Abdominal Pains*. Oxford, Blackwell Scientific, 1959.
[4] Stone, R. T., and Barbero, G. J., *Pediatrics*, 1970, **45**, 732.
[5] Davidson, M., and Wasserman, R., *Journal of Pediatrics*, 1966, **69**, 1027.
[6] Hanington, E., in *Background to Migraine: 2nd Migraine Symposium*, ed. R. Smith, p. 10. London, Heinemann Medical, 1969.