issue of the *B.M.J.* illustrates the dramatic effects of one variety of infection. In a recent influenza epidemic in Birmingham 29 patients were admitted to hospital with ketoacidosis. Three died apparently from loss of potassium. Seven were not hitherto known to be diabetic. Though it is not uncommon for ketoacidosis to be the presenting feature of diabetes, it usually occurs in young, insulin-dependent patients.

While infection is a fairly common cause of diabetic ketoacidosis and should always be sought, it is not the most common cause. In the series of 100 cases described by J. Sheldon and D. A. Pyke[3] and in the 72 cases of P. Taft and colleagues[4] the single most common cause was mismanagement of the diabetes, usually by the patient, occasionally by the doctor. This mismanagement included apparent disregard of warning symptoms or signs, deliberate omission or reduction of insulin by the patient, and inappropriate change from insulin to one of the oral drugs. Though better education of doctor and patient could help to prevent some of these misadventures, in many cases the patient stops taking insulin for emotional reasons. Adolescents are specially prone to do this as a means of escape from a difficult situation or as a protest or an appeal for help. Emotional stress in itself may provoke ketoacidosis in some patients, and they may be aware of the relationship and present themselves promptly for treatment.[4 5] Of the other known aetiological factors, vomiting from any cause and undiagnosed diabetes are the most common.[3] In many cases there is no obvious precipitant. In women it is worth considering a relationship with menstruation if no other cause can be found.[6]

Though ketoacidosis is now an uncommon cause of death in diabetics, it carries an appreciable mortality and should be treated as a medical emergency. Treatment of the established condition requires all the refinements of the well-equipped hospital and laboratory. Lesser degrees of ketosis may safely be treated at home so long as the patient is seen frequently and the situation kept under review. Vomiting or impairment of consciousness are indications for admission to hospital, which should also be promptly sought for children and for insulin-dependent diabetics known to be unstable.

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Jet Vaccination

Jet injection of drugs was first described in 1947[1] and was said at the time[2] to be pain-free and speedy; its main drawback was thought to be cost. Since then injectors have been improved, and it has been shown that a given volume of killed vaccine can be more antigenic when delivered subcutaneously by jet injector than when given by syringe.[3 4] An apparatus which injects 0·5 ml. subcutaneously may be too expensive for most purposes, but a considerably cheaper hand-cocked injector, which delivers 0·1 ml. either subcutaneously or intradermally, is available. An intradermal injection of 0·1 ml. of killed vaccine usually evokes an antibody response approximately equal to that produced by 0·5 ml. given subcutaneously.[5 6]

Primary vaccination with killed vaccines using intradermal jet injection cannot be recommended, because all vaccinators may not always be able to implant the entire 0·1 ml. dose of vaccine in the skin. The intradermal jet may, however, be suitable for vaccination if a satisfactory immune response occurs when most but not necessarily all of the 0·1 ml. dose of vaccine is deposited in the skin. Hence jet injection is satisfactory for booster doses of killed vaccines.

There is greater interest in intradermal jet injection of those live vaccines which necessarily have to be administered into the skin. Live vaccines are not as dose dependent as killed vaccines, because the live organisms produce their immunizing effect as a result of multiplication in the tissues. B.C.G. vaccination by jet injection has already been proved effective[7 8] and is widely practised in British schools. Though smallpox vaccination by jet injection is accepted in the U.S.A.[9] it is rarely carried out in Britain, partly because of problems associated with the dilution of vaccine lymph to volumes which can be used by jet injectors, and partly because lymph is not necessarily bacteriologically sterile and has, therefore, been regarded as unsuitable for intradermal inoculation.

A team of investigators from the Smallpox Eradication Program, National Communicable Diseases Center, Georgia, recently reported on their experiences of smallpox vaccination by jet injection.[10–12] They found that the cutaneous and serological responses to smallpox vaccine diluted twenty-fold to a titre of $10^{7.0}$ T.C.I.D. $_{50}$/ml. and administered by intradermal jet injection were as good as those obtained with undiluted vaccine titre $10^{8.3}$ T.C.I.D. $_{50}$/ml. inoculated by standard multiple pressure technique. The patients concerned included 140 adults who had been vaccinated more than five years previously, 625 Jamaican children who had not been previously vaccinated, and 140 well-immunized adults. Indeed, the primary-take rates in children vaccinated by jet injection of 0·1 ml. vaccine diluted two hundred-fold to $10^{6.3}$ T.C.I.D. $_{50}$/ml. were as good as those obtained by the multiple puncture method using undiluted vaccine. In the previously unvaccinated children the vesicle and scar sizes were generally smaller after jet vaccination than after vaccination by multiple pressure.

These studies confirm the results of others[13 14] and

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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.

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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-

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