emerged from large studies in Texas⁹ and South Africa.¹⁰⁻¹² Altogether it seems unlikely that enteroviruses or adenoviruses are significant causes of uncomplicated diarrhoeal disease. Routine virological investigation by present techniques of stools from diarrhoeal patients is an unrewarding diversion of effort. Perhaps when the technical trick of demonstrating hepatitis virus has been discovered a new group of agents may be found responsible for that large majority of diarrhoeal illnesses in which neither virological nor bacteriological tests are currently successful.—We are, etc.,

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Withdrawal of Heroin

SIR,—The biochemical mechanisms of physical dependence on drugs remain obscure. We wish to record a phenomenon in which marked manifestations of withdrawal followed a change from intravenous to intramuscular administration of a fixed dose of heroin in a long-standing addict, with recovery on returning to the intravenous route.

A 52-year-old woman was admitted to St. Stephen's Hospital, Chelsea, on 11 December 1966 with bronchial asthma. She had become addicted to morphine given for postoperative pain following accidental ligation of the right ureter at ovariectomy in 1936. She changed to heroin several years later, and at the time of admission was receiving 2 gr. (120 mg.) of heroin with 12.5 mg. cocaine intravenously five times daily.

She was treated with tetracycline, bronchodilators, and later A.C.T.H., with marked improvement in her bronchospasm.

Her general condition, nevertheless, did not improve, and though her chest was no longer troublesome she became confused, restless, and agitated. She became increasingly disorientated and developed a coarse tremor of the upper and lower limbs. During her asthmatic attack she had been experiencing difficulty in "fixing" herself, and had been receiving her heroin and cocaine intramuscularly. It was felt, therefore, that though she was in fact having her normal dosage she was suffering from withdrawal symptoms due to a change in the method of administration. At this time her condition was critical, and though heart action, lungs, and blood

pressure appeared to be normal she was moribund. A Gordh's needle was therefore inserted and intravenous administration of heroin and cocaine begun at the same dosage. She improved rapidly and was soon able to resume her own intravenous injections.

The practical problems of opiate addiction appear to be related mainly to the psyche of the addict; withdrawal, if desired, is usually easy in the early stages at least, but relapse is very frequent. Experience in prison suggests that withdrawal symptoms may be of psychic origin. Nellans and Massee¹ reported from the Atlanta State Penitentiary in 1929 that complete withdrawal could be accomplished with only minor symptoms, and suggested that the most powerful therapeutic agent was the absolute certainty that no further drug would be given. On the other hand, withdrawal can be reproduced in animals, and, though differences in route of administration do not influence effectiveness, monkeys given morphine for two months become moribund following withdrawal, and recover when the drug is given.²

It is striking that death from withdrawal does not seem to be a hazard for the present-day addict, though he is at risk for many other reasons. Helpern and Rho³ reported 1,561 deaths in addicts, none related to withdrawal. It is said that "exhaustion" may occur; treatment, with insulin for instance, may contribute.⁴ We felt that our patient would have died from withdrawal symptoms if she had not been returned to intravenous from intramuscular therapy. This, however, remains speculative.

This case emphasizes the physical aspect of withdrawal. If drugs of dependence become essential to some metabolic process, it may be that a certain concentration is required which would explain the effectiveness of intravenous heroin. This may have therapeutic implications, though such a severe reaction to withdrawal appears to be very rare.—We are, etc.,

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Carcinogenic Properties of Ortho-dianisidine

SIR,—In his letter (21 October, p. 172) Dr. D. G. Illingworth states that Occultest and Hematest reagent tablets (Ames) contain ortho-tolidine, but doubts whether, if used according to the manufacturer's instructions, any risk is incurred in their use. The manufacturer's leaflets which accompany the tablets confirm that both preparations contain ortho-tolidine. In view of the fact that they state "hands, droppers, and working area must be clean and free from any traces of blood," it is clear that a technique which involves the tablets coming in contact with the skin is envisaged.

Ortho-tolidine (dimethylbenzidine) is listed in the *Prescribed Industrial Diseases Regulations No. 39*¹ as a carcinogen in man, and is

also listed in the *Carcinogenic Substances Regulations*, which become law on 9 December.² It is known that the aromatic amines as a class can be absorbed through the skin.³ These tablets may be handled occasionally (for example, by doctors) or up to several times each working day (for example, by certain nurses or laboratory technicians).

According to the *British Medical Journal* (22 July, p. 189), "although it is not possible to say that there is a level of exposure to the carcinogenic aromatic amines below which there is no risk, the hazard to trained laboratory workers must be small." It may be that all that is necessary to obviate the risk is that a no-touch technique be employed. If so, clear instructions to this effect are necessary on the leaflet. Those interested are referred to *Precautions for Laboratory Workers who Handle Carcinogenic Aromatic Amines* published by the Chester Beatty Research Institute. However, the moral argument seems irrefutable that the persons concerned should have an opportunity of knowing that the tablets may contain a carcinogen (for example, by means of a label on the container), so that they may choose whether or not to use them.

The analogy which Dr. Illingworth makes with cigarette-smoking is a poor one. There may or may not be merits in having their carcinogenic action marked on the packet as he suggests. But employees are rarely instructed by employers to smoke as part of their duties, and in any case this hazard is already public knowledge.—I am, etc.,

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Streptomycin, I.N.H., and Thiacetazone

SIR,—We have read with interest the letter by Dr. S. N. Dutta and colleagues (7 October, p. 55) on streptomycin, I.N.H., and thiacetazone. We are concerned lest this should deter others from using thiacetazone in the treatment of tuberculosis in developing countries. The cheapness of the drug has made it possible for people to have effective treatment, whereas before the expense of streptomycin and P.A.S. often led to inadequate courses of treatment. We are convinced of the value of thiacetazone and isonicotinic acid hydrazide (I.N.H.) alone in the majority of cases.

In 1965-6 we conducted a trial on 90 patients in order to investigate the development of drug resistance in the treatment of pulmonary tuberculosis with thiacetazone and I.N.H. During this trial there were six patients who had a rash, one having exfoliative dermatitis. One patient had jaundice, thought to be due to the drugs.¹ The rash was mostly of the maculopapular type; it left behind a black pigmented area which persisted for many months. The case of exfoliative dermatitis was of a very severe type. The rash appeared usually about the end of the third week. It did not regress quickly with the cessation of the drug. There was some relief of severe skin irritation when treated with antihistamine drugs and corticosteroids. It is now thought advisable to stop the drug immediately²