even in volunteers. We have not found it useful, either in ourselves or in our patients, to attempt to disguise the feeds. Enthusiasm on the part of the staff is nearly always enough to enable a tube or oral supplement of this kind to be consumed provided it does not produce side-effects such as gastric distension, borborygmi, or diarrhoea. If needed, additional sodium and/or potassium may be added to the feed, thus adjusting the electrolyte content to the needs of the individual patient. Table IV gives instructions for varying the electrolyte content of the 3,000-calorie 3-litre feed. It is to be noted that progressive hypertonicity

TABLE IV.—Effect of Adding Potassium, as Potassium Chloride, or Sodium, as sodium chloride, to Basic 3,000-Calorie Feed

Potassium			Sodium		
Na (mEq)	K (mEq)	Osmolality (mMol/kg.)	Na (mEq)	K (mEq)	Osmolality (mMol/kg.)
25 (0)	40 (0)	325	25 (0)	40 (0)	325
25 (0)	80 (3)	350	50 (1.5)	40 (0)	340
25 (0)	100 (4.5)	360	100 (4.4)	40 (0)	370
			150 (7.3)	40 (0)	400

Figures in parentheses are the approximate weights in grammes of potassium or sodium chloride which must be added to produce the required daily ration of milliequivalents.

Note the corresponding rise in osmolal concentration.

results and if large additions of electrolyte are needed the volume of the feed should, if possible, be increased.

In clinical practice we have not yet encountered diarrhoea although our experience of intrajeunal feeding is still small. These feeds have in our hands proved their worth and we are using them with increasing frequency in the management of our patients. The cost of each 1,000-calorie unit is a little less than half a crown.

Summary

The characteristics of tube feeds that can also be used by mouth have been re-examined. The most important single factor in a feed, whether it be used as a supplement or for total feeding, is that it should contain adequate calories. High protein intakes without sufficient total calories will not lead to positive nitrogen balance and are not recommended as a basis of tube feeds. In fact, a high protein content can be harmful, since it will produce a solute diuresis due to increased urea production, and in the absence of a high fluid intake this diuresis leads to loss of water in excess of intake. It is stressed that, in addition to calorie content, tube feeds should be sufficiently palatable to be taken by mouth and to prevent any regurgitant taste even when given by tube. The electrolyte

and osmolal concentrations of feeds must be carefully controlled, as a lack of attention to these may lead to diarrhoea and relative water deficiency as well as to serum electrolyte imbalance. The use of fine-particle fat emulsion as the major source of calories is advised, since a feed can then be made with a high calorie value but relatively low volume. A series of recommendations are made to facilitate ease of preparation and administration and to increase the flexibility and efficiency of liquid feeding.

One of us (H. A. F. D.) is in receipt of a personal grant from the Medical Research Council. We could not have carried out these studies without the unfailing help of the chief pharmacist Mr. H. N. F. Kinniburgh, Aberdeen General Hospitals Group, whose department weighed many samples of constituents during these trials. Dr. J. Crooks and, more recently, Professor S. C. Frazer have kindly carried out the faecal-fat estimations. We thank Drs. Calloway and Spector and the *American Journal of Clinical Nutrition* for permission to draw Fig. 1.

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TWO CASES OF UNTOWARD REACTION AFTER "ILOSONE"

BY

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The antibiotic "ilosone" (propionyl erythromycin lauryl sulphate or, as it is now called, erythromycin estolate) was first introduced in September, 1958. Since then more than twenty million "courses" have been dispensed, according to prescription surveys conducted by the manufacturers (Dolman, 1963).

During the past two years 59 cases of hepatitis following the use of this drug have been reported to the manufacturers (Dolman, 1963). The exact nature of the disease in some of these reports has been questioned (Dolman, 1963). But 20 cases which have been described in detail (Robinson, 1961, 1962a; Kohlstaedt, 1961; Johnson and Hall, 1961; Havens, 1962; Masel, 1962; Reed and Ritchie, 1962; Riley, 1962; Gilbert, 1962) all presented a syndrome

suggestive of cholestatic hepatitis, and most of them developed jaundice. In only two cases was the liver biopsied (Johnson and Hall, 1961; Robinson, 1962a), but in both cases the jaundice had subsided prior to biopsy.

This communication reports two cases of untoward reaction that occurred after the administration of ilosone. In one case a liver biopsy was done while jaundice was present.

Case 1

A man aged 25 was admitted to Wakari Hospital, Dunedin, on September 17, 1962, with a history of jaundice of seven weeks' duration.

In April, 1962, boils had developed on his right arm, for which he was given one 250-mg. capsule of ilosone q.i.d. for

three days. These boils cleared and he was well until July 14, when boils occurred on his right buttock. He was again given ilosone, in the same daily dosage, for five days. On the second day of this second course he developed a fever; he felt nauseated and generally unwell. In the evening he was seized with a severe constricting upper-abdominal pain. This was relieved by the injection of 100 mg. of pethidine. His doctor noted tenderness in the right hypochondrium, the right iliac fossa, and the right groin, where there were some swollen lymph nodes. Ilosone was continued for the next three days. The boils and associated lymphadenopathy subsided and he had no further abdominal pain. Ten days later jaundice appeared, together with a severe itch, but he felt otherwise well. He noticed that his faeces were pale and that his urine was dark. He then recalled that his urine had been a similar colour during his second course of ilosone. His doctor noted that he was again tender in the right hypochondrium. His serum bilirubin was 2.8 mg./100 ml. and his serum glutamic oxaloacetic transaminase (S.G.O.T.) 184 units/ml. (normal 8-40 units/ml.). He was diagnosed as suffering from acute viral hepatitis, put to bed, and given promethazine 10 mg. t.d.s. for the pruritus, which soon settled. After one week his S.G.O.T. level fell to 43 units/ml. and remained at this level. His serum bilirubin level, however, continued to rise, to 6.8 mg./100 ml., after which it too began to fall (see Chart). Three weeks later it rose again to 7.5 mg./100 ml. and he was admitted to hospital.

On examination the patient was seen to be a well-built man with obvious jaundice. His liver was just palpable and slightly tender, but his spleen was not palpable. The faeces were pale; the urine was dark and contained bilirubin.

Laboratory Investigations.—Serum bilirubin, 7 mg./100 ml.; S.G.O.T., 46 units/ml.; serum alkaline phosphatase, 10.2 K.A. units/100 ml.; serum cholesterol, 356 mg./100 ml.; serum proteins and zinc sulphate turbidity were normal. Haematocrit 44%; E.S.R. 15 mm. fall in 1 hour (Westergren); W.B.C. 5,200/c.mm. with a normal differential count.

The patient was kept in bed and given a low-fat diet, since fatty foods caused nausea. His serum bilirubin level fell in three weeks to 4.8 mg./100 ml., but then started to rise again (see Chart).

By this time the jaundice—apparently obstructive in type—had been present for 10 weeks, and so a laparotomy was performed by Mr. J. H. Heslop on October 5 to exclude any extrahepatic cause for the jaundice. The liver was slightly enlarged and uniformly greenish in appearance. No other abnormality was found. The liver was biopsied.

The jaundice settled over the next three weeks and he was discharged on October 25. His serum bilirubin level on October 19 had been 2.8 mg./100 ml. A bromsulphthalein-retention test on October 25 showed 9% retention of the dye at 45 minutes (normal 0-5%) and no retention at 210 minutes. Laboratory investigations three weeks later showed serum bilirubin, 0.5 mg./100 ml.; S.G.O.T., 34 units/ml.; serum

Case 1. Serum bilirubin levels.

alkaline phosphatase, 4.2 K.A. units/100 ml.; serum cholesterol, 205 mg./100 ml.; serum proteins and zinc sulphate turbidity normal. Blood picture normal.

Biopsy Report (Dr. T. P. Casey, Pathology Department, Otago University Medical School): "The specimen consists of a green fragment of liver tissue 1 cm. long. Histologically the normal lobular architecture is preserved. Many of the intrahepatic biliary canaliculi, particularly in the centrilobular zone, are distended with bile. Bile is also present in some hepatic cells and Kupffer cells. Many binucleate hepatic cells are seen in the periphery of the lobules, indicating cellular activity in these areas. The portal tracts contain a moderate number of chronic inflammatory cells and a few eosinophils. There is no bile-duct proliferation. The appearances are those of an intrahepatic cholestasis."

Case 2

A woman aged 51 was admitted to Wakari Hospital on November 29, 1962, suffering from an attack of pain resembling biliary colic. No jaundice developed, and a cholecystogram performed after the pain had settled was normal. An E.C.G. done on admission was also normal. The patient had taken one 250-mg. ilosone capsule on the previous day, and one capsule that morning, for an acute exacerbation of chronic bronchitis. She could recall two other occasions when she had developed a similar pain after taking ilosone. Liver-function tests done at the time of her admission were normal, but three days later they showed a serum alkaline phosphatase level of 23 K.A. units/100 ml. and an S.G.O.T. level of 95 units/ml. Her condition soon settled after withholding the drug.

Her serum alkaline phosphatase and S.G.O.T. levels were both normal three weeks later. Her serum bilirubin level was never raised.

Discussion

Fever, nausea, malaise, and an abdominal pain simulating biliary colic have all been described in association with reactions to ilosone (Johnson and Hall, 1961; Gilbert, 1962; Havens, 1962; Masel, 1962; Reed and Ritchie, 1962; Robinson, 1962a; Dolman, 1963). In those cases in which jaundice has been a feature it has usually developed while the patients were still receiving the drug and has closely followed the onset of other symptoms. In Case 1 the jaundice was not noticed until 10 days after the drug had been stopped, but in retrospect it would seem likely that the dark urine noted by the patient during his second course of ilosone contained bilirubin, and that he had subclinical jaundice for the next 10 days. A severe itch accompanying the jaundice has been reported in other cases (Havens, 1962).

Case 1 differs from all but one of the reported cases (Havens, 1962) in the long duration of jaundice after withdrawal of the drug. A diagnosis of viral hepatitis was rejected on account of (1) the mild constitutional disturbance, (2) the absence of splenomegaly, (3) the laboratory findings, and (4) the histology of the liver.

It is now generally accepted that cholestatic hepatitis may be a manifestation of an unusual idiosyncrasy to ilosone. Robinson (1962b) challenged three sensitive patients with test doses of the drug. All three patients promptly developed the same symptoms of hepatic dysfunction as they had shown originally. This finding suggests that hypersensitivity rather than direct toxicity is the aetiological mechanism. This contention is further supported by (1) the observation that patients do not always react adversely to their first course of the drug (Gilbert, 1962; Reed and Ritchie, 1962), which presumably acts as the sensitizing dose; (2) the relative rarity of untoward reactions; and (3) the varying amounts of ilosone which have precipitated symptoms.

The clinical picture and liver histology in ilosone hepatitis are similar to those which may occur with a hyper-

sensitivity to chlorpromazine (Popper and Schaffner, 1959). A delay in onset of jaundice, such as occurred in Case 1, has also been noted with chlorpromazine jaundice (Sherlock, 1962).

Prior to the introduction of this estolate of erythromycin there had been no reports of hepatic dysfunction associated with the drug. It is not known which fraction of the estolate is responsible for stimulating the immunological reaction. The drug appears in the blood as erythromycin-free base (40–50%) and erythromycin propionate (50–60%), but the fate of the lauryl sulphate, which is dissociated in the bowel, is uncertain (Griffith, 1960). Gilbert (1961) has suggested that the esterification of the free OH grouping on the desosamine side-chain of the erythromycin molecule confers the properties of a haptene on the molecule.

In view of the likelihood of this being a hypersensitivity type of reaction, it would seem advisable to avoid the use of repeated courses of the drug, particularly with patients who have a history of allergies (Havens, 1962).

Summary

Two cases of untoward reaction after treatment with "ilosone" (erythromycin estolate) are reported. The first patient developed prolonged jaundice, and occasioned sufficient diagnostic doubt to necessitate a laparotomy.

The liver was biopsied and the histological findings were those of an intrahepatic cholestasis.

The second patient presented with a pain simulating biliary colic after taking two capsules of ilosone. This was the third occasion on which she had reacted in this way. Jaundice did not develop on any of these occasions.

The findings in these and other reported cases suggest that the hepatic dysfunction is due to a hypersensitivity reaction.

I am indebted to Professor E. G. Sayers and Mr. S. L. Wilson for permission to publish these cases. I am also grateful for the co-operation of the staff of Eli Lilly and Co.

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Preliminary Communications

Effect of Cooling on Pre-mixed Gas Mixtures for Obstetric Analgesia

The term pre-mixed is used here to denote a gas mixture which has been formed by placing two or more non-reacting gases together in the same storage cylinder. A mixture of nitrous oxide and oxygen (in equal volumes when measured at atmospheric pressure) compressed in the same cylinder to 2,000 lb./sq. in. (kg./sq. cm. 140.6) at room temperature remains in a single gas phase. Such a pre-mixed mixture was first used for self-administered inhalational analgesia by women in labour in 1961 (Tunstall).

The only problem with regard to safety which has appeared in the clinical use of pre-mixed gases is that due to exposure of full cylinders to temperatures in the region of 0° C. or below. Cole (1962, personal communication) was the first to point out that if a full cylinder of pre-mixed 50% nitrous oxide and 50% oxygen, v/v, was cooled to –8° C. (the point at which nitrous oxide begins to form a liquid in the most dependent portion of the cylinder) the reversion to a single gas phase in even mixture, identical to that before cooling, was not immediate after rewarming. This implied that if a cylinder were brought into the labour ward from out-of-doors in freezing weather it would not, even after the elapse of some hours to allow for rewarming, be safe to use. It suggested, for example, that if the cylinder were used upright a mixture containing a weak concentration of nitrous oxide would at first be inhaled and then, when the cylinder was nearly empty, perhaps a dangerously high concentration. This paper summarizes the work done to assess the nature of this problem and to discover whether it could be overcome by simple means.

METHOD

Twenty-one different cooling experiments were performed with full cylinders containing various percentage mixtures

of pre-mixed nitrous oxide and oxygen. The changes induced in the physical state of the contents of the cylinder were studied by measuring the percentage of the oxygen in the gas mixture which issued from the cylinder outlet under stated conditions and after stated manœuvres. Measurements were made with a Beckman paramagnetic oxygen analyser. After cooling to –25° C., to 0° C. or above, and after stated manœuvres, measurements were made within 15, 5, and 2 minutes respectively. Where applicable stated manœuvres were performed immediately after the last preceding measurement.

If the oxygen percentage of the sample of the mixture taken from the outlet of the cylinder was the same as before cooling or the same for various positions of the outlet valve relative to the cylinder (for example, upright and inverted), it was assumed that the contents were in a single gas phase in even mixture. If the oxygen percentage measured just before the cylinder became empty was the same as at the beginning of the experiment, it was assumed that the cylinder would have been safe to use under the circumstances set.

RESULTS

The results of 14 of the experiments are tabulated. In the seven others the results provided neither new nor contradictory information and are therefore not included.

The column marked oxygen % gives the percentage content of oxygen in the sample of gas mixture obtained from the cylinder outlet valve. The position of the cylinder at the time of sampling is of course vital and is recorded. (When the cylinder is upright the outlet valve is at the top.) The pressure shown on the cylinder contents gauge at the time of sampling is an indication of the temperature of the contents of the full cylinders. Each sample resulted in about two litres of gas at atmospheric pressure being expended. Readings taken on day 0 were those at the beginning of the experiment and before any cooling had taken place.

In experiment 1 the oxygen content on sampling rose from 40% at the original reading to 68% after cooling. This meant that some of the original (60%) nitrous oxide content, which was at the beginning entirely gaseous and