Preliminary Communications

"1314" in Pulmonary Tuberculosis

We have been concerned in the early clinical trial of a new substance, alpha-ethylisonicotinic thioamide ("1314"), synthesized by Libermann *et al.* (1956). This compound is not a derivative of isoniazid, but, like isoniazid, a derivative of isonicotinic acid. Its use in tuberculosis is being explored because Rist *et al.* (1958) showed that it was active *in vitro* against isoniazid-resistant tubercle bacilli and that cross-resistance apparently did not occur.

Brouet (1958) treated with 1314 alone 18 patients who had minimal disease and a positive sputum. Organisms resistant to the drug emerged in three patients at the end of three months' treatment. Loss of sensitivity to 1314 was not recorded when it was combined with isoniazid, streptomycin, and other antibiotics, though detailed information is awaited.

In an attempt to delay the development of resistance we combined 1314, 1 g., with tetracycline, 4 g., both in two divided doses daily. Tetracycline was used because it has only very slight antituberculous activity but may delay the emergence of resistance to certain antituberculous drugs (Stewart *et al.*, 1954; Murdoch and Stewart, 1956). We were therefore able to assess the antituberculous activity of 1314 more accurately than if it had been given in combination with a more effective drug.

Seven patients with chronic advanced pulmonary tuberculosis whose bacilli were known to be resistant to streptomycin, para-aminosalicylic acid, and isoniazid were treated with the combination of 1314 and tetracycline. The trends of sputum positivity were studied by weekly viable counts. The sputum became negative on culture in one patient after five weeks' treatment, and has remained so during a subsequent 27 weeks' follow-up. This patient had had a positive sputum for at least seven years. A second patient showed a marked decrease in sputum positivity, but occasional positive cultures have been obtained up to 17 weeks; no resistance has yet been demonstrated. An initial reduction in sputum positivity occurred in a further four patients, but there was a subsequent rise in positivity while still on treatment. In all four cases organisms resistant to 1314 were detected after 5, 7, 8, and 18 weeks' treatment. The seventh patient showed a reduction in sputum positivity, but resistant organisms were detected at the third week and the patient died three weeks later.

Drug intolerance in the form of nausea and sometimes vomiting proved troublesome in six out of the seven patients. In several it necessitated reduction of dosage or even temporary cessation of treatment.

CONCLUSION

Our preliminary bacteriological evidence suggests that 1314 is an effective antituberculous drug but that tetracycline will prove relatively ineffective in preventing resistance to it. On present dosage nausea and vomiting are likely to prove troublesome in a number of patients.

We suggest that at this stage it would be inadvisable for physicians to hazard their patients' future by premature use of a potentially powerful drug. The

result may be a few weeks' improvement at the expense of permanent drug-resistance. Further studies, now being planned through the Clinical Trials Committee of the British Tuberculosis Association, may establish a better tolerated but effective dose and also indicate drug-combinations which will prevent resistance. A wider use of the drug in patients with bacilli resistant to standard chemotherapy may then be justifiable.

We are grateful to Dr. Noël Rist, of the Pasteur Institute, Paris for much information, and to Messrs. May and Baker Ltd. for supplies of 1314, which is known in France as "1314 T.H."

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Medical Memoranda

A Case of Twin Pregnancy in a Double Uterus

The patient, aged 39, presented herself at my antenatal clinic on September 19, 1956, with a history of amenorrhoea since May 23, 1956, and early morning sickness and enlargement of the breasts.

Previous Obstetric History.—1943: Spontaneous delivery of a 4-lb. (1,800-g.) boy of 36 weeks' gestation. Severe blue asphyxia due to the cord being round the neck. He responded to treatment and is alive and well. 1945: Spontaneous delivery of a 5-lb. (2,270-g.) boy of 40 weeks' gestation. Precipitate labour. Alive and well. 1949: Miscarriage at 4½ months. 1954: Miscarriage at 10 weeks.

Menstrual History.—Onset at 11, 5-6/25-26; regular.

On examination she was clinically anaemic. A soft systolic murmur was audible all over the praecordium. There was no cardiac enlargement. Her pulse was 76 a minute, blood pressure 120/80. The urine was normal. The uterus was enlarged to three fingerbreadths above the umbilicus. A distinct groove was felt down the anterior wall of the uterus. Movements had not been felt nor could they be heard. Vaginal examination revealed a roomy pelvis with an outlet of more than four knuckles and an internal conjugate of more than 4½ in. (11.4 cm.). Two cervixes were present lying side by side. Her blood was group O, rhesus positive. No antibodies were present. The Wassermann and Price reactions were negative. Her haemoglobin was 59% (8.76 g./100 ml.); R.B.C., 3 millions; M.C.H., 29 µµg.; P.C.V., 28%; M.C.H.C., 31%; M.C.V., 93 cubic microns. A diagnosis of twins in a double uterus and anaemia was made. She was treated with "ferromyn," one tablet three times a day after food, and rest in bed at home. On examination a month later it was obvious that the two foetuses were lying a long way apart; this was confirmed on subsequent x-ray examination.

The pregnancy continued normally, and by January 10, 1957 (33 weeks), her haemoglobin was 81%. The two foetuses were presenting by the vertex and two foetal hearts could be heard. On January 21 her blood pressure was 140/90; there was pitting oedema of both ankles but no albuminuria.

She was admitted next day and put to bed on a salt-free diet, phenobarbitone, and restricted fluid intake. By January 25 the blood pressure had risen to 160/100, oedema had increased still further, and albumin had appeared in the urine. In view of this, "puroverine," half a tablet four-hourly, was given, and within 12 hours the blood pressure had fallen to 110/70 and the urine became free from albumin. Oedema was still marked, and this, combined with the distended abdomen, made it very difficult for her to rest.

Labour began at 12.5 a.m. on January 27. A vaginal examination at 4 a.m. showed that the cervix was dilated two to three fingerbreadths and irregular in outline. She was given 100 mg. of pethidine and 50 mg. of promethazine hydrochloride intramuscularly, and she slept until 10 a.m. Her pains became much stronger at this stage and by 11.30 a.m. she was fully dilated. Throughout the first and second stages both uteri contracted simultaneously.

At 12.10 p.m. she was delivered of a male child face to pubes. The child was in a state of blue asphyxia and his hands and feet were oedematous. The asphyxia responded to clearing of the air passages and oxygen. His colour never became normal, however, and two hours after delivery he began to have blue attacks and pass large quantities of a clear fluid from his mouth. A fine catheter could not be passed into his stomach, and a diagnosis of oesophageal atresia was made. The baby died at 7.10 p.m.

After delivery, the right side of the abdomen was seen to be empty and all uterine contractions had ceased. It was not possible to make out the usual signs of placenta separation, but, since there was no bleeding, no action was necessary. An hour after delivery the cord lengthened by 4 in. (10 cm.) and there was a slight loss of blood. A vaginal examination showed that the placenta was lying half in and half out of the cervix. It was gently removed and there was no further bleeding. The placenta was small and almost a solid mass of infarcts.

Examination of the abdomen showed that the remaining foetus was lying obliquely with the vertex presenting, but high over the pelvic basin. The foetal heartbeat was quite normal and regular, and the sounds were of good quality. The blood pressure was 148/78.

In view of this and the small size of the first foetus—5 lb. 14 oz. (2,665 g.)—I decided to await the onset of labour

in the hope that the second foetus would grow a little bigger, and that the toxæmia would improve now that an infarcted placenta had been expelled.

Twelve hours after delivery she began a profuse diuresis, and within a week her oedema had gone and a central stream of urine showed no albumin. There was no evidence of lactation. By February 15 her blood pressure was steady at 130/80, her oedema had gone, and the head was beginning to engage in the pelvis. On the right-hand side of the uterus an irregularity could be felt, which was the retracted part of the uterus that had contained the first twin.

At 3 a.m. on February 18 her membranes ruptured and at 6 a.m. labour pains began. By 7.40 a.m. she was fully dilated, and at 7.50 a.m. had a normal delivery of a female child weighing 6 lb. 4 oz. (2,835 g.). Ten minutes later the placenta and membranes were expelled complete. The loss was 4 oz. (114 ml.). This placenta appeared quite normal.

The baby cried well and was a good colour from birth. Examination showed no congenital abnormalities.

The puerperium was normal apart from a mild urinary infection which responded to sulphonamides, and she was discharged fully breast-feeding on March 1. Six weeks later the uterus was well involuted and anteverted. Both cervixes were healthy and just admitted the tip of the index finger. A hysterosalpingogram showed that there were two uteri with separate cervixes, and that the left one was slightly bigger than the right.

COMMENT

Several points arise from this case that merit discussion. (1) What is the mechanism of the onset of labour, bearing in mind that in this case one uterus went into labour whilst the other did not? (2) What causes the uterine muscle to change from contraction and relaxation to retraction? In this case the right uterus was retracting during the expulsion of the first twin whilst the left uterus was undergoing first-stage contractions. (3) What is the cause of toxæmia? This case suggests that placenta infarcts are the cause rather than the result of the toxæmia. (4) What causes lactation to begin?

A review of the literature shows that the only similar case reported is that by Williams and Cumming (1953), where twins were born alive 56 days apart in a patient with a completely double uterus.

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Hysterosalpingogram taken in April, 1957, showing two uteri with separate cervixes.

The 1959 volume of the *Modern Treatment Yearbook* (published for the Medical Press by Baillière, Tindall and Cox, Ltd., London; price 30s.) is the twenty-fifth in the series. Sir Cecil Wakeley is the editor, and not unnaturally he sees to it that the surgeon's point of view is given proper prominence. The aim of the book is to provide practical information, and among the subjects chosen for discussion are some of the foremost therapeutic topics of the day—hypertension, intervertebral disk protrusion, treatment of cardiac infarction in the home, chronic bronchitis, mental disorders in old age, painful feet, "the cough that kills," tranquilizers, and the treatment of non-vital teeth. The book includes a special section of illustrations on art paper.