The patient is put back to bed with the foot of the bed raised in order to lessen pelvic congestion. A follow-up CO_2 test is done in six to eight weeks' time. A lipiodologram is not recommended.

After using the above technique 6 patients out of 17 have conceived and gone to term. Four were confined naturally and two by caesarean section. There was one ectopic pregnancy. It is perhaps worth recording that in one of these patients, a nurse, the distal block on both sides extended almost to the ampulla and was less than 5 cm. from the fimbrial end. With an 11-mm. Silcock punch I was able to implant the wider portion of the tube with ease, the end appearance of the uterus being somewhat like that of a penguin. She conceived, however, within a few months and went to term.

Discussion

One-conception infertility is very often seen to-day. Close and scientific investigation of such cases shows that in a great majority (82%) the tubes are only blocked at the internal ostia or isthmus. The increased skill that results from experience has greatly added to our success rate in recent years—indeed, rising from 8% to more than 30%—and there can be no question that when larger numbers of gynaecologists throughout the world undertake these operations the end-results will be greatly improved and, we hope, reach that of 50% from the point of view of full-term pregnancies; for close observation and study of a number of previous failures revealed the fact, now so obvious, that it was the coning out of a jagged wedge from the cornu of the uterus with a knife that so often spelt strangulation of the tube, or later resulted in constriction by muscle scar tissue. The smooth clean-cut tunnel made by the 9 mm. modification of the Silcock punch (Fig. 3) obviates this.

Salpingostomy

As already indicated, it is a common finding that a cuff or spoon operation on the tubes, or for that matter simple salpingolysis, does not give the results one would expect, even though, in some, CO_2 tests repeated month after month are positive, with excellent oscillations.

The lessened incidence of pregnancy and the increased occurrence of ectopics in these cases would seem to point to a failure of the endosalpinx and its cilia to transmit the ovum. In others, however, although at the time of operation there is perfect bubbling rippling CO_2 patency, it has been found, on tests being made one, two, or three weeks afterwards, that no gas passes. Moreover, the area of gas-distension pain is referred right out to both iliac fossae, indicating recurrent closure at the spoon aperture or fimbrial end. To counter this it is suggested that in a suitable case the operation should be performed on the sixth to the eighth day of the cycle, and that on the first day of verified ovulation we should give a saline-and-dextrose douche and then do as Hunter did with success in 1799—namely, hornspoon into the vagina a fresh specimen of the husband's semen.

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According to the census commissioner in Delhi the population of India was 356,829,485 on March 1, 1951 (*The Times*, June 2). The ratio of females to males was 947 to 1,000. Since 1941 the population has increased by 12.5%. Over two-thirds of the population depend on agriculture for a livelihood, and nearly 83% of the people live in rural areas. Seventy-three cities have more than 100,000 inhabitants.

SULPHONE AND STREPTOMYCIN IN PULMONARY TUBERCULOSIS

BY

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Diaminodiphenylsulphone (D.D.S.) was the first sulphone to be synthesized by Fromm and Wittman (1908), but it was not until the work of Buttle *et al.* (1937) that its remarkable pharmacological and therapeutic properties in streptococcal infections in mice became known. Rist *et al.* (1940) demonstrated the action of sulphone in experimental tuberculosis in animals, and soluble derivatives—"promin" ("promanide" in Great Britain) and "diasone"—were used extensively in America and elsewhere in the treatment of animal and human tuberculosis.

Feldman *et al.* (1944) thought that D.D.S. itself was too toxic for use in man. From 1940 onwards the use of sulphones was largely confined to the soluble derivatives, promanide, diasone, and "sulphetrone," which could be tolerated in much larger doses. It was some time before it was generally realized that the efficacy of a compound was not wholly decided by the magnitude of the dose tolerated. Hinshaw and Feldman (1941) found that considerably larger doses of promanide could be given parenterally than orally without producing cyanosis. Francis and Spinks (1950) reviewed earlier work, and presented their own results, indicating that the activity of the soluble sulphones depended on the amount of free sulphone (D.D.S.) which was liberated in the body, the breakdown occurring mainly in the stomach and in the intestinal tract. The therapeutic ratio of D.D.S. proved just as good as any of its soluble derivatives.

Lowe (1950) concluded that, contrary to general belief, D.D.S. is not too toxic for use in man, and in the treatment of leprosy he established a regime of oral administration of small doses, rising from 100 to 500 mg. a day, over a period of five weeks. These small doses could be maintained for long periods, and proved at least as effective as the much larger doses of the complex soluble sulphones. Lowe (1951) now recommends a regime of 400 mg. of D.D.S. twice a week.

The small observed effects of D.D.S. on tuberculosis have been overshadowed by the discovery of streptomycin, which has a much greater demonstrable influence on the disease. The great drawback to streptomycin is the rapidity with which the tubercle bacillus acquires resistance to the drug. The possible preventive effect of sulphone administered with the streptomycin on the emergence of resistant strains was investigated by Bernard *et al.* (1950), and they showed that sulphone retarded the emergence of resistant strains, though the clinical success was not great. Francis (1952) showed that small doses of sulphone, when administered with streptomycin to guinea-pigs infected with tuberculosis, gave better results than streptomycin given alone.

Laboratory Control and Technique

In the present investigation streptomycin sensitivity was determined every two weeks; positive and negative sputa were cultured, and any growth of tubercle bacilli was tested for sensitivity by a surface diffusion method, using Loewenstein–Jensen medium. Controls of H37Rv were included in each batch of tests, and the results recorded as "sensitive," "reduced sensitivity," and "resistant." The resistant strains indicated resistance to at least 100 μg. of streptomycin per ml. Sulphone estimations were made weekly, and haemoglobin, blood counts, blood sedimentation rates, reticulocyte counts, icterus determinations, and any other examinations which were indicated were made at the same time. Sulphone (D.D.S.) estimations were made by the method of Bratton and Marshall (1939), and the extraction method of the free D.D.S. in the cases receiving the soluble 2196 followed the procedure of Francis and Spinks (1950).

The aim of the pilot trial was to determine if sulphone prevented or delayed the emergence of streptomycin-resistant strains of the tubercle bacillus, and, if a sufficient number of cases were treated, to compare the results with a similar series treated with streptomycin and P.A.S. As the M.R.C. type of case is rare in sanatoria, it was decided to use all the streptomycin-treated material.

D.D.S. was administered instead of P.A.S. in one-half of the sanatorium in every case in which streptomycin was prescribed, while continuing to use P.A.S. in the other half. In the 22 cases under test the indication for streptomycin was as follows:

Bronchial tuberculosis	6
Recent spread of disease	6
Tension cavity	4
Persistent positive sputum (collapse cases)	2
Slipping chronic	2
Tuberculous peritonitis	1
Indefinite indication	1

Plan of Treatment

At the initial conference it was decided to give 50 mg. of D.D.S. twice daily for two weeks before beginning streptomycin. From the third week 1 g. of streptomycin daily was given by intramuscular injection, and the sulphone dosage was increased to 100 mg. twice daily. After another two weeks the sulphone was increased to 100 mg. thrice daily. Streptomycin was to be given for a minimum of eight weeks, and sulphone for a minimum of 12 weeks. After the appearance of haemolytic anaemia in three of the early cases, sulphone treatment was suspended. It was then decided to administer a much smaller dose, beginning with 25 mg. daily and increasing to 50 mg. daily after two weeks. This scheme was applied to the patients already in the trial and to new entrants. Thereafter, blood changes were not alarming. Four of the 22 cases received an equivalent dosage of a soluble sulphone, "2196" (Francis and Spinks, 1950), by subcutaneous injection, instead of D.D.S.

TABLE I.—*Detailed Results*

Case No.	Sex	Age	Sputum Before Treatment	Indication	Duration of Course (Weeks)	Max. Daily Dose	Blood Sulphone Average (mg./100 ml.)	Haemoglobin		Sputum After Treatment	
								Start	Finish		
1	F	25	S	Endobronchial tuberculosis	16	Reduced 200 mg.	0·4	83 74%	70%	RS, then:	Neg. Dose reduced after 8th week. Hb drop and serious icterus
2	F	43	RS	Recent spread	14	300 mg.	0·4	92 85%	71%	R	Sulphone reduced after 7th week. Icterus and anaemia
3	F	30	RS	Endobronchial	12	200 mg.	0·15	76%	68%	R	Reduced because of drop and change of scheme
4	M	38	S	Persistent pos. sputum	12	200 mg.	0·1	82%	74%	Neg.	Sharp drop in Hb on large dosage
5	M	39	S	Recent spread	12	200 mg.	0·1	79%	71%	RS, then:	Sharp drop in R.B.C. with icterus (spherocytosis)
6	F	17	RS	Recent acute	11	200 mg.	0·35	78 69%	66%	R	Spread of disease
7	F	27	Neg.	Endobronchial	12	100 mg.	0·2	73%	72%	Neg.	Soluble sulphone
8	M	32	S	Tension cavity	13	100 mg.	0·15	93%	87%	S	
9	F	16	S	Early acute	16	50 mg.	0·35	72%	62%	R	Methaemoglobinaemia
10	F	29	Neg.	Slipping chronic	12	50 mg.	0·15	78%	73%	Neg.	Positive sputum. Not cultured after course
11	F	30	S	Recent spread	12	50 mg.	0·15	85%	75%	R	Soluble sulphone
12	M	41	S	Tension cavity	12	50 mg.	0·1	91%	80%	Neg.	Later positive. S.S. not tested
13	M	39	S	,, ,,	12	50 mg.	0·1	91%	82%	RS, then:	Neg.
14	F	49	S	Recent spread	12	50 mg.	0·2	85%	70%	Neg.	Soluble sulphone
15	F	26	NT	Endobronchial	9	50 mg.	0·35	86%	75%	,,	Sulphone stopped. Poor clinical response
16	M	22	Neg.	Slipping chronic	12	M. 2196	0·05	96%	80%	,,	Sol. sulphone. Blood estimations not reliable
17	F	37	,,	Tuberculous peritonitis	5	50 mg.	0·3	70%	59%	,,	Change to P.A.S. because of other poor results
18	F	25	S	Endobronchial	12	M. 2196	0·16	90%	78%	R	Soluble sulphone
19	F	18	NT	Endobronchial and spread	12	50 mg.	0·15	86%	73%	Neg.	,, ,,
20	M	27	RS	Indefinite	12	M. 2196	0·25	97%	88%	R	,, ,,
21	M	20	NT	Persistent pos. sputum	13	M. 2196	0·30	103%	93%	Neg.	Marked icterus
22	F	29	S	Tension cavities	12	50 mg.	0·3	85%	76%	R	

S = sensitive. RS = reduced sensitivity. R = resistant. NT = not tested.

Results

The detailed results are shown in Table I. In 15 out of the 22 cases the organism was isolated from the sputum and tested for streptomycin sensitivity before treatment was started. Eleven strains were fully sensitive, and four showed some reduction in sensitivity; none were resistant. The remaining seven cases were either negative at the time or an organism seen on direct smear failed to grow on culture, and therefore could not be tested for sensitivity. Twelve strains were isolated either during treatment or after its completion. Of these, one was fully sensitive, three showed reduced sensitivity before disappearing from the sputum, and eight were completely resistant to streptomycin. The fate of the strains is shown in Table II.

TABLE II

Before Treatment	After Treatment
11 Sensitive	1 Sensitive 3 Reduced sensitivity (negative later) 4 Resistant 3 Negative
4 Reduced sensitivity	4 Resistant
7 Negative	7 Negative

Because of the rapid emergence of resistant strains the trial was stopped after it had been made in 22 cases. This small number does not lend itself to analysis of the therapeutic effectiveness of the streptomycin–sulphone combination, but the results were not encouraging. Streptomycin

and P.A.S. gave very good results in a large number of cases of endobronchial tuberculosis. The six cases of this condition treated with streptomycin and sulphone, however, produced only one satisfactory result; two showed considerable improvement and two slight improvement; and one patient, whose strain showed reduced sensitivity before treatment, was unimproved.

Complications.—The only serious complication encountered was haemolytic anaemia, which was present in three of the six patients who received a daily dose of 200 mg. or more of D.D.S. One of these showed a drop of over two million red cells per c.mm. in a fortnight. After a short interval (two weeks) treatment was resumed on the reduced dosage scheme, and the haemoglobin slowly improved. In spite of iron administration throughout there was an average drop of 10% haemoglobin in the 22 patients. Methaemalbumin was present in the blood in three of the high-dosage cases, and the violet coloration of the skin associated with this substance was observed in two further cases.

Discussion

The African leper and the European tuberculous patient appear to differ greatly in their tolerance to sulphone. Lowe's cases (Lowe, 1950) received up to 300 mg. of D.D.S. a day, giving blood levels from 0.8 to 1.4 mg. per 100 ml. without showing haemolysis, whereas a smaller dosage scheme in our cases caused severe haemolysis with a much lower blood sulphone level of from 0.2 to 0.6 mg. per 100 ml. It certainly seemed inadvisable to proceed with our original dosage scheme, which was based on the leprosy work, when serious drops in erythrocyte counts occurred with great rapidity.

There is no apparent trend suggesting a correlation between blood sulphone levels and emergence of resistant strains. The only surviving sensitive strain was in a patient whose blood sulphone never exceeded 0.15 mg. per 100 ml.

The emergence of eight resistant strains and only one fully sensitive strain after eight weeks' streptomycin treatment compares very unfavourably with the findings in the streptomycin and P.A.S. group of the M.R.C. (1950) trial, in which 97% showed a resistance ratio of less than 9 at the same stage of treatment. Bernard *et al.* (1950) found 51% resistant strains after 70 days of combined streptomycin and sulphone treatment, compared with 91% in the control group treated with streptomycin alone. This result also is much worse than the M.R.C. streptomycin and P.A.S. group.

Conclusions

D.D.S. is not tolerated in doses of 200 mg. daily by European tuberculous patients.

In the tolerated dosage it does not prevent or delay the emergence of streptomycin-resistant strains of *Myco. tuberculosis*.

The clinical results with combined streptomycin and D.D.S. were not encouraging.

Our thanks are due to Messrs. I.C.I. (Pharmaceuticals) Limited for the supply of D.D.S., and to Drs. L. B. Wevill and A. S. R. Stewart and Professor J. Francis, with whose collaboration the trial was planned, for their invaluable criticism and advice.

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MEGALOBLASTIC ANAEMIA OF INFANCY

BY

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Megaloblastic anaemia of infancy was first recognized as a distinct clinical syndrome by Zuelzer and Ogden (1946). The disease occurs predominantly within the first year of life, is characterized by a fairly distinctive clinical pattern, and responds to folic-acid therapy. The response to folic acid is often complete and permanent. Since its original description the disease has often been reported from America, though the only case recorded by British authors is that by Hutchison and MacArthur (1949). A further case is here described and the literature on the subject is briefly reviewed.

Case History

A baby girl aged 8 months was referred by her practitioner for a blood count on August 8, 1951. She was the youngest of a family of three children, her sister and brother being healthy and never having suffered from anaemia. The mother is in good health and has never suffered from anaemia either before or during her recent pregnancy. For the first three months of life the child had been breast-fed, and during this time she was well and there were no feeding difficulties. After the third month she was weaned and put on National dried milk, her diet being supplemented by daily orange juice and cod-liver oil. After about one month on dried milk she first started to show symptoms of feeding difficulty characterized by frequent attacks of diarrhoea and vomiting coupled with a marked reluctance to take her feeds. During the three months before admission increasing pallor had become evident.

Clinical examination revealed a very pale infant weighing 15 lb. (6.8 kg.)—about 3 lb. (1.4 kg.) under her expected weight—with a temperature of 99° F. (37.2° C.), but no other physical abnormality. A blood count at this time showed: Hb, 46% (6.8 g. per 100 ml.); red cells, 1,900,000 per c.mm.; reticulocytes, 0.8%; white cells, 16,000 per c.mm.; the differential count showed one nucleated red cell for every 100 white cells counted, and 63% lymphocytes.

The infant was admitted to hospital during the course of the next few days. A blood count on admission showed little change except for one important feature: nucleated red cells were still present, and a few of these showed a quite distinctive megaloblastic pattern. A diagnosis of megaloblastic anaemia of infancy was suggested on this finding and a tibial puncture was performed. The marrow showed a typical megaloblastic reaction. Not only were the erythroblasts of megaloblastic type, but hypersegmentation of polymorphs and ballooning of metamyelocytes were evident.

Other investigations included a fractional test meal, which showed free acid after histamine stimulation. The faeces were examined for evidence of steatorrhoea, but analysis revealed normal fat content. Tests for occult blood were negative, and no parasites were found in the faeces. The Wassermann reaction and Coombs test were negative. Radiographs of the long bones showed no abnormal features.

Treatment consisted of only one 10-mg. dose of folic acid and one 10-μg. dose of vitamin B_{12}. Within a very short time there was a dramatic clinical and haematological response. On the fifth day the reticulocyte count reached a peak of 26%. The haemoglobin showed a steady rise, and 15 days after treatment it had risen from 46% to 84%. Within 36 hours of treatment bone-marrow films showed a complete reversion to normoblastic erythropoiesis. Marrow