STREPTOMYCIN TREATMENT OF SEPTICAEMIA AND MENINGITIS DUE TO INTESTINAL ORGANISMS IN INFANTS

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The effectiveness of streptomycin on Gram-negative organisms of the *Bact. coli* and *Salmonella* groups *in vitro* was quickly recognized by Waksman and others, and has led clinicians to make use of this property in the treatment of infection by intestinal organisms. Since 1945 encouraging results of the use of streptomycin have been reported in urinary infections (Helmolz, 1945) and miscellaneous conditions (Herrel and Nichols, 1945). Several authors have confirmed these results (Keefer *et al.*, 1946; Goettsch *et al.*, 1948), and we ourselves, struck with the frequency of septicaemia and meningitis of this type in the newborn and the infant, have reported our preliminary investigations (Debré, Mozziconacci, Grumbach, and Boulard, 1948).

We were able to collect 41 cases of infection due to organisms of the *Salmonella* groups and of the *Bact. coli* and similar groups—infection which previously was fatal but in which streptomycin has given appreciable results. We think, however, that our technique might be improved and we hope for still better results in the future.

The 41 cases include all infections, slight or severe, during the course of which bacteraemia was demonstrated either by blood culture or by the development of metastatic abscesses, or both. We have not included mild infections of the urinary tract in this series.

Clinical Picture

The clinical picture, no matter what the organism, presents the same general features. At the onset the infection may be subacute, with failure to gain weight (23 cases), or with diarrhoea and vomiting (sometimes severe) that often ceases after a few days. There may be a persistent irregular fever of about 38–39° C., anorexia, and progressive loss of weight. The stools may indicate faulty digestion. In 11 of our patients these features continued during the entire illness; in eight others a neurotoxic state was superimposed. In other cases the infants rapidly became dehydrated and critically ill. The onset may also be marked by signs suggesting acute meningitis (8 cases). In our series, cases with meningitis due to Friedländer's bacillus were the only ones giving rise to clear-cut signs of the condition. Cases complicated by meningitis should be considered separately, owing to their more grave prognosis. We have therefore divided our series into (a) 16 cases of septicaemia without meningitis, and (b) 25 cases of meningitis with or without septicaemia.

Alimentary symptoms dominate the clinical picture in the septicaemic forms of the disease. Diarrhoea occurred in 29 cases out of the 41. The stools often had a peculiar odour and were sometimes orange-coloured. Vomiting occurred in 30 cases, and in 16 of these it ushered in the disease. In four cases the stools contained fresh blood and mucus, as in the dysenteric colitis of older children.

Abdominal distension was a striking feature. In several cases oedema of the abdominal wall was present, particularly in the subumbilical region, and sometimes oedema of the genitalia as well. In one case there was a red periumbilical swelling. Purpura often occurred on the abdominal or thoracic walls. Usually no splenomegaly was present, but the liver was sometimes enlarged. In four cases there was hepatomegaly alone and in three cases jaundice, which was accompanied in two patients by abdominal distension and the appearance of a collateral circulation. In some cases there were areas of localized gangrene.

The temperature was always raised, often to 38–39° C.; sometimes it reached 40° C. Loss of weight accompanied the infection, and often a rapid loss preceded the rise in temperature by 24 to 48 hours. There were also loss of appetite, intense dehydration, and frequently cyanosis, even without pulmonary signs. Localized suppuration, for which systematic search should be made, may occur as otitis, pyelitis, or meningitis. Otitis and mastoiditis were found in 18 cases, and many authors have considered this route to be the means by which the meninges are infected. The organism obtained from blood culture is not invariably that recovered from the middle ear. Pyuria was found in 16 cases, in almost all of which the infective organism was *Bact. coli*. In every case the organisms in the urine were the same as those recovered from the blood and the meninges. Infection was, however, most often localized in the meninges, and it is necessary not only to search carefully for physical signs but to perform lumbar puncture in all cases.

It has recently been shown that in infections by intestinal organisms there is a raised white cell count in which polymorphs predominate (Debré, Grumbach, and Mozziconacci, 1948). All our cases except four had a leucocytosis of over 10,000 per c.mm., the count occasionally reaching 63,000–83,000. The average number of polymorphs was 72%; as the red blood count was not altered the condition was obviously a pure leucocytosis, and did not represent haemoconcentration or the marrow reaction of the acute infectious anaemias of infancy. Infections with *Pseudomonas pyocyanea* sometimes produce exceptions to this rule.

Blood cultures were positive in 27 cases out of 32. In many cases culture was performed aerobically and anaerobically. The organisms grew rapidly in a simple aerobic medium, and the only difficulty was their exact identification. Treatment with streptomycin should be started once a Gram-negative organism has been isolated. Without doubt final success depends on early treatment, and non-meningitic forms so treated are likely to be cured (12 cases out of 16 in our series).

Recovery is usually rapid. The alimentary disturbances disappear first, the temperature falls to normal, and there is a gain in weight. A relapse may occur, and there is always the risk that the second attack will involve the meninges. In fatal forms of the disease fatty degeneration of the liver or a subclinical meningitis may be discovered at necropsy.

Meningitic forms of the disease are the most serious and the most difficult to treat. Out of the 41 cases we had 25 cases of meningitis, of which only four have been definitely cured. In many instances the dominant feature of the meningitis was its extreme latency. In 12 out of 25 cases the condition was discovered by lumbar puncture, which was performed after either a positive blood culture or the appearance of slight signs suggesting meningeal irritation. In 13 cases, however, the meningitis was revealed

by the classical signs. In some cases it resembled pneumococcal meningitis. The cerebrospinal fluid was usually frankly purulent and the organism could be recovered from it. But the fluid may be clear, with only a lymphocytic reaction and a raised albumin to suggest the possibility of meningitis. In three cases the cerebrospinal fluid was normal in all respects, although severe suppurative meningitis was revealed at necropsy. Of the 25 cases only four were cured, and four became chronic.

Cure seems to be possible only in cases that are treated promptly: two who were eventually cured were treated when the cerebrospinal fluid was still clear and showed only an increase in lymphocytes and albumin. If treatment is insufficient or too late the patient may die or the disease may become chronic and hydrocephalus may appear. One of our patients, on whom we had decided to operate, developed hydrocephalus. A ventricular puncture revealed

in 24 hours for the first five days and once in 24 hours on the following days. When necessary a ventricular injection of 0.01 g. of streptomycin, similarly diluted, was given. This route is not without danger, and we have seen convulsions produced by its use. It should be employed only in cases of ventricular infection not affected by the subdural injection of streptomycin, or in cases of subdural obstruction. The dose injected must be small and well diluted; the injection must be made slowly and an equivalent amount of cerebrospinal fluid removed first. The results are shown in Table II.

We have used sulphonamides with streptomycin, and have favoured sulphadiazine in a dose of 0.3 to 0.4 g. per kg., given by the oral route.

Penicillin was given in cases of superadded infection. These cases of meningitis of mixed aetiology are not exceptional. Neurosurgical treatment is the only measure

TABLE I.—*Treatment of Septicaemia without Meningitis*

Case No.	Age	Organism	Previous Illness	Sensitivity <i>in vitro</i>	Treatment (Units of Streptomycin)	Clinical Progress	Result	Necropsy Findings
1	5 months	Bact. coli	—	—	300,000 I.M.	Slow improvement	Recovered	
2	7½ "	" "	—	—	600,000 I.M. and sulphonamides	Rapid improvement	"	
9	8 "	" "	—	Blood, 2,000 γ	300,000 I.M. and sulphonamides	" "	"	
11	1 year	Str. pneumoniae	—	—	1,000,000, later 500,000 I.M.	Improvement then rapid deterioration	Died	
12	2 months	Bact. coli	—	—	600,000 I.M.	Rapid improvement	Recovered	
15	2 "	" "	—	Blood, < 5 γ	250,000 I.M.; 100,000 orally; sulphonamides	Progressive deterioration	Died	Fatty degeneration of liver; no meningitis
20	1 year	" "	—	Blood, 1,000 γ	700,000 I.M.; 100,000 orally	Rapid improvement	Recovered	
25	6 months	S. typhi-murium	—	Blood, 30 γ	400,000 I.M.; 100,000 orally; sulphonamides	Two successive attacks	"	
26	3 "	S. enteritidis	—	Blood, 40 γ	400,000 I.M. and sulphonamides	Favourable	"	
27	3 "	Bact. coli	—	Blood, 2,000 γ	600,000 I.M.; 300,000 orally; sulphonamides	Slow, with relapses	"	
31	1 month	Ps. pyocyanea	—	—	300,000 I.M.	Very rapid improvement	"	
33	2½ months	" "	—	—	—	Rapid deterioration	Died	
34	2 "	Bact. coli	—	—	400,000 I.M.; 200,000 orally; sulphonamides	Slow; favourable	Recovered	
35	2½ "	Str. faecalis	—	Blood, 2,000 γ	600,000 I.M.; 200,000 orally; sulphonamides	Slow improvement	"	
40	4 "	Bact. coli	—	Pus from ear, 20 γ; Blood, 40 γ	400,000 I.M. and sulphonamides	Rapid deterioration, then slow improvement	"	
41	3 "	" "	Congenital syphilis	—	300,000 I.M. and 200,000 orally	Slow deterioration	Died	

I.M. = Intramuscular.

at first a clear fluid, which became opaque at the end of the aspiration and was found to contain *Bact. coli*. These findings precluded further intervention. These cases of hydrocephalus are rapidly progressive and call for operative treatment, but we have not yet seen a case in which this has been successful.

Treatment

Our experience is too limited to allow us to lay down definite rules for treatment. We can only indicate the measures that we have adopted.

General Infections.—From 0.05 to 0.1 g. (50,000 to 100,000 units) of streptomycin sulphate or hydrochloride per kg. body weight was given daily. For oral administration 0.1 to 0.3 g. (100,000 to 300,000 units) of streptomycin dissolved in 60 ml. of sugared water was divided into six doses of 10 ml. and given four-hourly. Medication by this route, which had previously given good results (Goettsch *et al.*, 1948), seemed efficacious in treating simple intestinal infections in small children, and therefore appeared to be indicated as an adjuvant in septicaemia. The results are shown in Table I.

Meningeal Infection.—This was treated by the intrathecal injection of 0.025 g. of streptomycin dissolved in 5 ml. of warm physiological serum. The injection was made twice

possible in chronic cases of meningitis with hydrocephalus. Lumbar puncture may be discontinued when the cerebrospinal fluid is sterile—usually after five to eight days. Treatment with intramuscular streptomycin should be continued for two to three weeks for fear of relapse.

Sensitivity of Organisms

The response of the organisms to streptomycin was assayed from time to time during treatment. The method used consisted in inoculating a series of tubes containing the same volume of peptonized water with an equal quantity of organisms, then adding to each of these tubes a progressively increasing amount of streptomycin. After 24 hours note was taken of the dilutions in which turbidity was absent. We have made similar studies with solid media, which is a more precise method and allows the colonies to be counted.

The sensitivity of organisms so far studied has often been considerable—of the order of 3 to 7 γ per ml.: that is, it required 3 to 7 units of streptomycin to inhibit growth in 1 ml. of the culture. We could expect treatment to be effective in the case of organisms sensitive to 20 to 30 γ per ml. But this method estimates only bacteriostasis and not bacteriolysis, which is an important cause of error and explains certain discrepancies between sensi-

TABLE II.—*Treatment of Meningitis with or without Septicaemia*

Case No.	Age	Organism	State on Admission	Delay in Treatment	Sensitivity <i>in vitro</i>	Treatment (Units of Streptomycin)	Bacteriological Progress	Clinical Progress	Result	Necropsy Findings
3	18 days	<i>Proteus vulgaris</i>	---	3 days	C.S.F. <5 γ	500,000 I.M. 100,000 I.V.	Good	Hyperpyrexia; convulsions	Died	Suppurative arachnoiditis
4	8 months	<i>Str. pneumoniae</i>	---	1 month (relapse after sulph.)		300,000 I.M. 100,000 I.V. 50,000 I.T.	"	Bad	Hydrocephalus; died	
5	1 year	" "	---	0		900,000 I.M. 50,000 I.T. 4,000 I.V. sulphadiazine	Improvement then relapse	Improvement then deterioration	Died	
6	10 days	<i>Str. pneumoniae</i> , <i>Proteus vulgaris</i>	---	4 days	C.S.F. 20 γ	300,000 I.M. 100,000 I.V. 50,000 I.T.	Good	Bad	"	Ventricular collapse; pus in two ventricles
7	1 month	<i>Str. pneumoniae</i>	---	1 month	C.S.F. 3-5 γ	300,000 I.M. 100,000 I.V. 50,000 I.T.	"	Bad; pneumococcal superinfection	Hydrocephalus; died	Purulent arachnoiditis
8	6 weeks	<i>N. meningitidis</i> , <i>Bact. coli</i>	---	0	C.S.F. 4 γ	800,000 I.M. 100,000 I.V. 100,000 I.T.	Rapid	Improvement then deterioration	Died	" "
10	1 month	<i>S.r. pneumoniae</i> , <i>Bact. coli</i>	---	5 days	Blood 1 γ C.S.F. 30 γ urine 50 γ	450,000 I.M. 50,000 I.T.	Rapid improvement then relapse	" "	"	
13	6 months	<i>Bact. coli</i>	---	0	Blood <5 γ stools and urine >2,000 γ	500,000 I.M., sulphonamides	Rapid	Bad	"	Meningitis found
14	10 days	<i>Proteus vulgaris</i>	---	10 days		200,000 I.M. 30,000 I.T., sulphonamides		Improvement then rapid deterioration	"	
16	2 months	<i>Bact. coli</i>	---	0	C.S.F. >2,000 γ blood 5 γ urine >2,000 γ	300,000 I.M. 30,000 I.T.	"	Slow improvement	Recovered	
17	17 days	<i>Bact. coli</i> , <i>Str. pneumoniae</i>	---	6 days		600,000 I.M.; penicillin 600,000 I.M., 25,000 I.T.	No improvement	Rapid deterioration	Died	Pus at base of skull
18	19 "	<i>Str. faecalis</i>	---	0	Blood 100 γ	200,000 I.M. 50,000 I.T.	Nil	Bad	"	
19	27 "	<i>Bact. coli</i>	---	2 days		300,000 I.M.		"	"	Meningitis found
21	7 weeks	" "	---	4 "		150,000 I.M.		Progressive deterioration	"	" "
22	17 days	<i>S. typhi-murium</i>	---	8 "	C.S.F. 80 γ	200,000 I.M. 50,000 I.T.	Nil	Bad	"	
23	5 months	<i>Ps. pyocyanea</i>	---	15 "	C.S.F. 40 γ	1,000,000 I.M. 100,000 I.V. 50,000 I.T.	Rapid	"	"	Purulent arachnoiditis
24	1 month	<i>Bact. coli</i>	---	1½ months	C.S.F. <50 γ stools 500 γ	300,000 I.M. 25,000 I.T., sulphonamides	"	Relapse, then deterioration	Hydrocephalus; died	
28	4 months	<i>Str. pneumoniae</i>	---	0	C.S.F. 7 γ	500,000 I.M. 25,000 I.T. 100,000 orally	Good	Toxic relapse	Recovered	
29	2 "	<i>Bact. coli</i>	---	15 days		400,000 I.M. 12,000 I.T. 12,000 I.V.	Rapid in C.S.F., slow in ventricular fluid	Cachexia; hydrocephalus	Died	Hydrocephalus; suppurative ependymitis of 4th ventricle
30	3 "	<i>Ps. pyocyanea</i>	---	15 "	C.S.F. 3 γ	800,000 I.M. 25,000 I.T., sulphonamides	Rapid, then reappearance of organisms	Improvement, then relapse	"	
32	27 days	" "	---	4 "		400,000 I.M. 15,000 I.T.		Rapid deterioration	"	
36	1½ months	<i>Bact. coli</i>	---	0		300,000 I.M. 15,000 I.T. 100,000 orally, sulphonamides	Rapid	Rapid improvement, then relapse	Recovered	
37	1 month	<i>Salmonella</i>	---	5 days	C.S.F. 150 γ	400,000 I.M. 25,000 I.T. 25,000 I.V.	Nil	Rapid deterioration	Died	Pus on vault, base, and spinal cord
38	15 months	<i>Ps. pyocyanea</i>	---	0	C.S.F. 2,000 γ	800,000 I.M. 200,000 orally 25,000 I.T. sulphonamides	Rapid	" "	Recovered	
39	4½ "	<i>Bact. coli</i>	---	6 days	Blood 50 γ urine 2,000 γ	500,000 I.M. 200,000 orally 20,000 I.T. sulphonamides		Progressive deterioration	Died	Brain congested; thin fibrinous film at the base

I.M. = Intramuscular. I.V. = Intraventricular. I.T. = Intrathecal.

tivity of the organism *in vitro* and the clinical progress of the disease. We have proved this by centrifuging in five cases the clear (and therefore apparently sterile) tubes and culturing the deposit on agar. Although the five cultures originally appeared to be sensitive to concentrations of streptomycin of 1 γ , 10 γ , 20 γ , 40 γ , and 200 γ , respectively, it was demonstrated that the newly cultured organisms were still living and could grow in media containing 10 γ , 50 γ , 20 γ , and 500 γ of streptomycin. The organisms had therefore not been destroyed, but their development had been inhibited. The sensitivity of the organisms varied greatly from case to case, according to whether they were recovered from the urine, the blood, or the cerebrospinal fluid. The sensitivity of those affecting the meninges is obviously the most important.

It was not possible to estimate the resistance of the organisms in all our cases, but our results show that there is no clear relation between the resistance of the organisms and the clinical progress of the case. The progress of the patient is determined not only by his response to streptomycin but also by anatomical lesions and the obstruction they present to the diffusion of antibiotics. This is, in our opinion, the reason for the difference between the relatively favourable prognosis in cases with septicaemia and the extreme gravity of those with meningitis. All the necropsies on cases of meningeal infection have shown a purulent arachnoiditis at the base of the skull which was almost always associated with marked ventricular distension whether there was clinical hydrocephalus or not. It does not seem to us that these lesions acted by the simple

mechanism of producing ventricular block, but it is certain that they affected the circulation of the cerebrospinal fluid and the diffusion of streptomycin injected subthecally.

Comment

We cannot close this paper without remarking on the relative frequency of infection by intestinal organisms in infants. In many circumstances saprophytic organisms in the digestive tract of the newborn become pathogenic and produce bacteraemia, septicaemia, and meningitis. It is significant that in 18 months we have been able to observe in the Clinique Médicale des Enfants 41 cases of this type of infection, 25 of which developed meningitis. The signs of these infections are often obscure at first sight, and many of the cases can be discovered only by the careful examination of infants suffering from toxæmia and subacute fever with alimentary disturbances.

A search must be made for the organism in blood, marrow, stools, urine, pus from the ear, cerebrospinal fluid, nasopharyngeal secretions, and pus from any metastatic supuration in the skin. Repeated blood culture is extremely important. The occurrence during a gastro-intestinal illness of an inexplicable alteration in the patient's general condition or, as we have shown, a polymorphonuclear leucocytosis, is a diagnostic sign of great importance. The possibility of meningeal infection must always be considered, and lumbar puncture, repeated if necessary, must be done as a routine measure. At the same time it must be remembered that the cerebrospinal fluid may be normal or be little changed.

Summary

An account is given of 41 cases of infection in the infant by intestinal organisms, seen over a period of 18 months. Of these cases 16 had septicaemia alone and 25 developed meningitis.

The clinical features of the condition are discussed, and an account is given of treatment with streptomycin given by the intramuscular, oral, intrathecal, and intraventricular routes.

A method of assaying the sensitivity of organisms to streptomycin *in vitro* is discussed.

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The family allowances scheme has now been in operation for three years. The Ministry of National Insurance states that about 2,941,000 families of two or more children are receiving allowances varying between 5s. and £3 5s. a week at a total cost of £60 million a year. Family allowances are a payment of 5s. a week for every child after the elder or eldest below the age limit, which is usually 15 (school-leaving age), but is extended to July 31 following the sixteenth birthday where full-time education is continued and in cases of apprenticeship. During the three years the Ministry has received nearly three and a half million claims to family allowances, of which fewer than 100,000 have had to be rejected. The 2,941,000 families receiving allowances contain children within the qualifying ages as follows: two children, 1,850,000; three children, 688,000; four children, 247,000; five or more children, 156,000. The family drawing the largest allowance of £3 5s. a week consists of 14 children within the age limits. In the last year over 290,000 new claims to allowances resulted in payments for over 300,000 children. In the same period the total number of allowances in payment and the number of children for whom allowances are paid increased in each case by over 100,000.

STREPTOMYCIN TREATMENT OF INFANTILE DIARRHOEA AND VOMITING

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Crowley *et al.* (1941), in a survey of the literature and from their own findings, concluded that no single specific aetiological agent could be incriminated in infantile diarrhoea and vomiting. A wealth of facts relating to the clinical and metabolic changes arising in that condition has been accumulated and has made treatment more rational and effective; none the less, modern medical science has not yet provided the answer to the challenge of this illness. It is therefore not surprising that almost every chemotherapeutic agent introduced during the last decade has been tried in the treatment of infantile diarrhoea and vomiting in the vain hope that it might offer a satisfactory solution to the problem.

Recently streptomycin has been used and a number of encouraging results have been published. James, Kramer, and Armitage (1948) treated 30 children aged from 6 days to 13 months with streptomycin by mouth, on the basis of their finding in the stools *Proteus vulgaris*, to which they attributed pathogenic significance. They pointed out that some of their cases not associated with *Pr. vulgaris* also improved on streptomycin. There were no deaths in their series, and convalescence was particularly rapid. In a control group of eight cases *Pr. vulgaris* was isolated from the stools of five infants; all recovered, though at a slower rate. The total dose of streptomycin was 2 g., given over a period of seven days. No toxic effects were noticed, and *Pr. vulgaris* was rapidly cleared from the gut as a result of treatment.

Pulaski and Amspacher (1947) reported an epidemic involving 13 infants, three of whom died; the successful outcome in the ten who recovered was attributed directly to streptomycin. The dosage used in all the cases was 0.1–0.2 g. of streptomycin per kilogram of body weight by mouth for two to ten days. Loeschke and Cochlovius (1949) attributed recovery from infantile gastro-enteritis to streptomycin in 9 of 13 cases. They gave 25–75 mg. five to eight times daily by mouth. Their bacteriological findings were *Bact. coli*, *Pr. vulgaris*, *Pseudomonas pyocyanea*, and *Streptococcus faecalis*. A reduction in the number of Gram-negative organisms isolated generally followed the oral administration of streptomycin. Leisti (1947) recorded his results in 46 infants suffering from diarrhoea; 38 were full-term babies, eight of whom died; 8 were premature infants, all of whom recovered. Streptomycin was given in a dosage of from 40,000 units (40 mg.) to 160,000 units (160 mg.) intramuscularly daily for one to eight days. Goettsch, Cobley, and Mulloy (1948) obtained excellent results in 44 cases of parenteral gastro-enteritis. There were three deaths in their group, which they felt could not be attributed to failure of streptomycin. Their dosage was 0.5 g. intramuscularly and 0.5 g. orally for seven to ten days.