Blood Pressure.—In six of these cases there was hypertension (either a systolic pressure above 170 mm. Hg or a diastolic pressure above 100 mm. Hg).

Summary

Myxoedema is a much commoner cause of psychosis than is usually believed. Treatment with thyroid usually cures the psychosis dramatically. Fourteen cases are described—nine recovered completely, two recovered partially, one showed no change, and two were fatal. There is no specific psychosis, but paranoid ideas are common. A description of myxoedema is given and methods of diagnosing it are reviewed. Photographs before and after thyroid treatment give the best confirmation of the diagnosis.

I want to thank the visiting doctors and magistrates who left cases uncertified so that I could keep them for thyroid treatment rather than transfer them to a mental hospital. Also I must thank Miss Buckle and Mr. Booker for their excellent photographs. I am indebted to Dr. Barnes, of Hillingdon, for Case 10, to Mr. Iltydd James for Case 9, and to Dr. Pagel for the necropsy on Case 4. Dr. Leonard Simpson has given advice and criticism.

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OPTIMAL METHODS IN THE TREATMENT OF OPHTHALMIA NEONATORUM

BY

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The relative value of sulphanilamide, sulphapyridine, sulphamezathine, sulphathiazole, and sulphadiazine in the treatment of ophthalmia neonatorum has been discussed in a previous study (Sorsby, 1945). It was pointed out that, with the dose of 0.25 g. on admission and 0.125 g. four-hourly day and night until 48 hours after clinical cure, the results obtained by different sulphonamides were essentially the same, and that sulphanilamide itself and sulphapyridine were less desirable than sulphamezathine and sulphathiazole and sulphadiazine, as they tended to give toxic symptoms rather more frequently.

Sulphamezathine seemed to be at least as satisfactory as sulphathiazole and sulphadiazine, but, like the other drugs, still gave a residue of about 15% of cases that responded either poorly or showed relapse. In a series of 84 cases treated with sulphamezathine a clinical cure was obtained within one to three days in 39.3%, 44% required four to eight days' treatment, whilst 16.7% showed an unsatisfactory response or a relapse.

The different modes of using penicillin were found to give a high rate of adequate results only when penicillin locally was applied in high concentration and at frequent intervals (Sorsby, 1947). In a series of 104 cases treated

initially at intervals of one minute for half an hour (with drops in a concentration of 2,500 units per ml. in 71 cases, and a concentration of 10,000 units per ml. in 33 cases) the average total time of treatment was 38 hours. This, however, applied to only 77 of the 104 cases, while 27 showed a poor response or relapse. Likewise there were six unsatisfactory results in a total of 39 cases treated by systemic injections (800,000 units: four injections of 200,000 units each at four-hourly intervals).

Taking the whole series of 333 cases treated with sulphonamides and 143 cases treated intensively with penicillin, the percentage of failures—assessed by poor response or relapse—was considerable in both series: 16.3% with sulphonamides and 23.1% with penicillin. It was pointed out, however, that unsatisfactory response is to be understood in a relative sense only. In not a single instance was the response so poor as to cause anxiety for the state of the eye, and some of the cases classified as relapses were almost certainly cases of reinfection rather than relapse. The present study, covering 151 cases, was undertaken to determine whether better results could be obtained, particularly from the sulphonamides, by more intensive use of the agents employed.

A Series of 151 Cases

Table I sets out the 151 cases studied, classified according to causal organism and severity of the affection in relation to mode of treatment. It will be seen that *Staphylococcus albus* was responsible for the largest number of cases (33), *Staphylococcus aureus* for 22, various bacilli, including diphtheroids, for 21, and the gonococcus for 14 cases. There were 31 cases completely negative, showing neither organism nor inclusion bodies, whilst 18 cases showed no organisms but had inclusion bodies. In addition, inclusion bodies were seen in combination with causal organisms in 25 cases. The total incidence of inclusion bodies in this series was therefore 43. Of the whole series 48 cases were mild, 78 moderate, and 25 severe. The different grades of severity seemed to be fairly evenly distributed over the whole range of causal organisms. Several modes of treatment were tried out in this series.

Therapeutic Results

1. *Systemic Penicillin Therapy (30 Cases).*—In all 30 cases were treated by penicillin systemically. Four received 800,000 units of penicillin exclusively by mouth—200,000 units initially with a second dose one and a half to three hours later, and two further doses at three-hourly intervals. The response was slow and incomplete, and all four cases relapsed. This method was not tried further. Twenty-six cases received an initial intramuscular injection of 200,000 units, followed by the same dose orally one and a half to three hours later, and subsequently by two further doses by mouth at three-hourly intervals. All the 26 cases recovered, but 11 relapsed. As the method was obviously inferior to treatment by four intramuscular injections it was discontinued.

2. *Treatment by Oral Sulphamezathine with an Initial Dose of 0.5 g. and a Maintenance Dose of 0.25 g. at Six-hourly Intervals (57 Cases).*—In the previously reported series of 84 cases treated by sulphamezathine the initial dose was half that in the present series and the maintenance dose also half, but given at four-hourly instead of six-hourly intervals. The total dose of sulphamezathine was therefore increased on the first day from 0.875 g. to 1.25 g., and on subsequent days from 0.75 g. to 1 g. Table II sets out the comparative results in the two series. It will be seen

TABLE I.—Classification of Cases by Causal Organism and Severity in Relation to Mode of Treatment

	Penicillin Therapy		Sulphamezathine Therapy (Oral)			Sulphamerazine Therapy (Oral)	Total
	Oral Administration 200,000 Units $\times$ 4	One Intramuscular Administration 200,000 Units Followed by 3 Oral Administrations	0.5 g. Initially 0.25 g. 6-hourly	0.25 g. Initially 0.125 g. 4-hourly With Penicillin Locally	0.5 g. Initially 0.25 g. 6-hourly With Penicillin Locally	0.5 g. Initially 0.25 g. 8-hourly	
Gonococcus							
Mild		—	4	—	—	—	4
Moderate		2	1	1	1	2	5
Severe		2	—	—	—	—	2
Staphylococcus aureus							
Mild		1	—	2	—	3	6
Moderate		2	1	3	—	3	10
Severe		1	—	2	—	2	6
Staphylococcus albus							
Mild	1	3	3	2	—	1	10
Moderate	—	3	2	4	3	2	17
Severe	—	2	2	1	—	1	6
Staphylococcus albus with diphtheroids							
Mild	—	—	2	—	—	—	2
Moderate			1	—	—	—	1
Severe			—	—	—	—	—
Diphtheroids							
Mild	—	1	4	—	—	—	7
Moderate	1	—	—	2	—	—	3
Severe	—	—	—	—	—	—	—
Other bacilli							
Mild	—	1	—	1	—	—	2
Moderate	1	1	2	2	—	—	6
Severe	—	1	1	—	—	—	2
Streptococcus viridans							
Mild			2	—	—	—	2
Moderate			1	—	—	—	1
Severe			—	—	—	—	—
Other coccal organisms							
Mild		1	—	1	—	—	2
Moderate		2	—	—	—	—	2
Severe		—	—	—	—	—	—
Negative without inclusion bodies							
Mild		—	8	—	2	2	12
Moderate		2	6	3	—	6	18
Severe		—	1	—	—	—	1
Negative with inclusion bodies							
Mild		—	5	—	—	1	6
Moderate		1	2	3	1	—	10
Severe		—	—	—	—	—	—
Total	4	26	57	30	10	24	151

(a) Inclusion bodies present in 1 case.

(b) " " " " 2 cases.

(c) Inclusion bodies present in 3 cases.

(d) " " " " 4 "

(f) Inclusion bodies present in 6 cases.

(g) " " " " 10 "

that by increasing the dose a rapid cure is obtained in a greater percentage of cases, but that the incidence of unsatisfactory response is uninfluenced.

3. *Combined Use of Sulphamezathine Orally and Penicillin Locally (40 Cases).*—A series of 30 cases were treated with sulphamezathine orally in the smaller dose combined with penicillin drops 10,000 units per ml., initially instilled at one-minute intervals for 30 minutes. A further 10 cases were treated with the larger dose of sulphamezathine and the same mode of penicillin locally. As can be seen from Table III, in both these small series the percentage of cases with rapid response was high (29 out of 40). For this series of 40 cases as a whole, the proportion of unsatisfactory responses is, however, once more not diminished. This is clearly so for the 30 cases treated with the smaller dose of sulphamezathine, whilst the 10 cases treated with the larger dose of sulphamezathine in combination with penicillin are too few to allow any definite conclusions to be drawn.

4. *Sulphamerazine Orally in an Initial Dose of 0.5 g. and a Maintenance Dose of 0.25 g. at Eight-hourly Intervals (24 Cases).*—In a series of 24 cases so treated, no fewer

than 21 responded within one to three days, and the remaining three all cleared up within four to eight days, so that there was no case with an unsatisfactory response or relapse. Sulphamerazine had the further advantage that in none of these 24 cases was there any suggestion of intolerance, and the occasional cyanosis observed with sulphamezathine was entirely lacking.

5. *The Series as a Whole.*—Table IV brings out the salient features observed with the different modes of treatment in this series of 151 cases compared with the previously recorded result. If the small series of 24 cases treated by sulphamerazine is excluded it would seem that the methods recorded in the present study have failed to reduce the incidence of unsatisfactory responses and relapses. It is, however, clear that two conclusions can be confidently drawn regarding the use of penicillin and the sulphonamides. First, the intensive use of penicillin locally at one-minute intervals is still the best mode of applying

TABLE III.—Results Obtained by the Combined Use of Sulphamezathine Orally and Penicillin Locally

Mode of Treatment	Total No. of Cases	Cases Showing Clinical Cure in		Cases Showing Unsatisfactory Response
		1-3 Days	4-8 Days	
Sulphamezathine orally (a) 0.25 g. initial dose; 0.12 g. maintenance dose, 4-hourly	30	20	1	9
(b) 0.5 g. initial dose; 0.25 g. maintenance dose, 6-hourly	10	9	1	0

TABLE II.—Comparative Results with Two Different Dosages of Sulphamezathine

Dose		Total Cases	Clinical Cure in		Unsatisfactory Response or Relapse
Initial	Maintenance		1-3 Days	4-8 Days	
0.25 g.	0.125 g. 4-hourly	84	39.3%	44.0%	16.7%
0.5 g.	0.25 g. 6-hourly	57	68.4%	14.0%	17.6%

TABLE IV.—*Salient Features in the Present Series Set Against Main Results Previously Recorded*

	Total No. of Cases	Percentage of Cases Showing	
		Clinical Cure in 1-3 Days	Poor Responses or Relapses
<i>Previous series :</i>			
Sulphonamides orally (sulphapyridine, sulphamezathine, sulphadiazine, sulphathiazole, and sulphanilamide—0.25 g. initially and 0.125 g. 4-hourly) ..	333	32.4	16.3
Penicillin locally (drops, 2,500-10,000 units per ml., initially at 1-minute intervals) ..	104	74.0	26.0
Penicillin systemically (4 injections of 200,000 units at 3-hourly intervals) ..	39	84.4	15.6
<i>Present series :</i>			
Penicillin systemically (800,000 units)	4	0.0	100.0
Oral administration			
Combined intramuscular and oral administrations	26	57.7	42.3
Sulphamezathine orally:			
0.5 g. initially and 0.25 g. 6-hourly ..	57	68.4	17.6
0.25 g. initially and 0.125 g. 4-hourly, with penicillin locally ..	30	66.6	30.0
0.5 g. initially and 0.25 g. 6-hourly, with penicillin locally	10	90.0	0.0
Sulphamerazine:			
0.5 g. initially and 0.25 g. 8-hourly ..	24	87.5	0.0

penicillin in ophthalmia neonatorum. Secondly, the sulphonamides can with advantage be used in higher doses than those employed at present. A more rapid response is obtained if an initial dose of 0.5 g. is given, with a maintenance dose of 0.25 g. at six-hourly intervals with sulphamezathine and at eight-hourly intervals with sulphamerazine. As to the small series with sulphamerazine, the suggestion is that this drug may prove the sulphonamide of choice, possibly reducing the frequency of unsatisfactory responses and relapses as well as giving a high incidence of rapid results. The chance occurrence of a high proportion of these 24 cases being due to organisms readily susceptible to sulphonamides cannot, however, be excluded.

Therapeutic Failures

In the present series of 151 cases there were 34 which gave an unsatisfactory response or which relapsed; 15 of these were observed in the 30 cases treated with penicillin intramuscularly or orally. As this method of treatment was experimental and has proved unsatisfactory, these 15 cases need not be considered in any detail. It is enough to note that they did not contain an undue proportion of relatively resistant organisms.

Of the 121 cases treated by sulphamerazine or sulphamezathine with or without local penicillin 19 gave a poor response or relapsed. These 19 cases were observed in a series of 87 cases—the 57 treated by large doses of sulphamezathine orally and the 30 treated by sulphamezathine in smaller doses with penicillin locally. Seventeen of these 19 were relapses; in one case—completely negative bacteriologically—there was a persistent membranous cast of the conjunctiva, and in the remaining case diphtheroids, coliform bacteria, and inclusion bodies were present, leading to prolonged treatment but ending in a primary cure. Table V shows the clinical features of these 19 cases in comparison with the cases responding satisfactorily. It is

TABLE V.—*Degree of Severity in Cases with Satisfactory Response Compared with that seen in Cases with Relapse*

	Whole Series (121 Cases)	Series of 87 Cases	17 Cases with Relapse and 2 Cases with Slow Response
Mild	40	31	4
Moderate	62	41	10
Severe	19	15	5

clear that unsatisfactory response is not related to the degree of severity of the affection.

Table VI sets out the data concerning causal organisms. It will be seen that the cases with unsatisfactory response are not confined to any one aetiological group. In all groups the satisfactory responses considerably outnumber the cases with relapse or slow response. It should, however, be noted that 10 out of the 19 cases showed inclusion bodies either alone or in combination with organisms. In the whole series of 121 cases inclusion bodies occurred either alone or in combination with organisms in 33 cases. There are therefore 10 failures out of 33 cases showing inclusion bodies, and nine failures in 88 cases without inclusion bodies. This confirms the previously recorded observation that cases with inclusion bodies are the most resistant to treatment. As the

TABLE VI.—*Distribution of Organisms in Cases with Satisfactory Response Compared with that seen in Cases with Relapse or Slow Response*

	Whole Series (121 Cases)	Series of 87 Cases	17 Cases with Relapse and 2 Cases with Slow Response
Gonococcus	10	7	2
Staphylococcus aureus	18†	10†	2*
“ albus	23	16	3*
“ with diphtheroids	3	3	1
Diphtheroids	7§	7§	3†
Other bacilli	8‡	7‡	3†
Streptococcus viridans	4*	3	—
Other coccal organisms	2	2	—
Negative, without inclusion bodies ..	29	18	1
“ with “ “ “	17	14	4

* One case associated with inclusion bodies.

† Two cases “ “ “ “

‡ Three cases “ “ “ “

§ Four “ “ “ “

|| Five “ “ “ “

difficulty centres on relapse rather than on slow response, the question arises whether such cases should not be given a longer consolidation treatment than cases of ophthalmia neonatorum due to other exciting organisms.

Discussion

The present study suggests that the sulphonamides, used in larger doses than those advocated until now, tend to give results almost as rapid as those obtained by the intensive local use of penicillin. With larger doses of sulphonamides some 60 to 70% of cases of ophthalmia neonatorum give a clinical cure within one to three days. This is still less rapid than the results obtained with intensive local penicillin treatment, but not to any marked degree. Local penicillin therapy has the advantage that it can suppress pus formation within 20–30 minutes, whereas the sulphonamides take the better part of 24 hours to achieve this initial improvement. Sulphonamide therapy is, however, much simpler in application and is far less exacting on both the baby and the nurse.

When sulphonamides were first used in the treatment of ophthalmia neonatorum a dose of 0.125 g. initially and 0.062 g. at six-hourly intervals was given (Sorsby, Hoffa, and Smellie, 1942). Subsequently the maintenance dose was raised to 0.083 g. With these doses the incidence of unsatisfactory response and relapse was 38.1%. With the subsequent increase of the dose to 0.25 g. initially and 0.125 g. as a maintenance dose at four-hourly intervals this percentage fell to 16.3.

The higher dose suggested in the present study, whilst not influencing the relapse rate, has the merit of reducing the duration of treatment. This higher dose is innocuous and there is nothing to be gained by not adopting it as the standard dose for ophthalmia neonatorum. As between

sulphamezathine and sulphamerazine, the advantage seems to lie with sulphamerazine, though it has still to be proved that the frequency of relapses with this drug will be less than with sulphamezathine. Contrary to expectation, the combined use of penicillin locally and sulphonamide orally does not seem to reduce the relapse rate, but it should always be borne in mind that relapses are sometimes, possibly often, reinfections rather than relapses in the true sense.

Routine Procedure for Treatment

The steps in the two alternative methods of treating ophthalmia neonatorum available at present—sulphonamides orally and penicillin locally—may be thus summarized:

(a) *Steps in Common for the Two Methods.*—On admission a swab is taken for smear and culture and the eye is irrigated with half-normal saline at room temperature. A drop of adrenaline 1 in 1,000 is instilled and a scraping is taken from the palpebral conjunctiva for examination for the presence of inclusion bodies. Gutt. atropinae sulphas, 1%, are instilled if the cornea is affected. Any pus that may have accumulated is wiped away with moist pledgets of cotton-wool.

(b) *Procedure for Sulphonamide Treatment.*—(1) After the preliminary measures a tablet of sulphamerazine or sulphamezathine (0.5 g.) crushed into powder is given by mouth in a teaspoonful of water or milk. Alternatively a stock mixture can be used. (2) Sulphamerazine administration in doses of 0.25 g. is continued every eight hours. If sulphamezathine is used the administration has to be at six-hourly intervals. (3) Local treatment consists of three-hourly irrigation with saline solution during the first day in cases with profuse discharge; as a rule there is no need for further irrigation on the subsequent days. After irrigation medicinal paraffin is instilled as a precaution against the sticking together of the lids. (4) Atropine is instilled three times daily in cases with corneal haze or ulceration. (5) Sulphonamide administration is continued for 48 hours after clinical cure.

With this treatment swelling of the lids generally subsides within 12 hours after admission; purulent discharge disappears within 24 hours.

(c) *Procedure with Local Penicillin Therapy.*—(1) The preliminary measures are completed by the instillation of a drop of penicillin in a concentration of 10,000 units per ml. into the conjunctival sac. (2) The baby is now placed on the nurse's lap, while another nurse sitting near by instils one drop of penicillin solution, 10,000 units per ml., every minute for 30 minutes. Irrigation is not needed, as pus does not form to any extent; such thin mucoid discharge as is present can be ignored or, if it clings to the lid margin, wiped away with moist pledgets of cotton-wool. (3) At the end of this time there is invariably no pus and generally little or no discharge. The eye, however, is still moist, the lids are still swollen, and the lid margins tend to be sticky. The baby is returned to its cot, and instillation of penicillin drops is continued six times at five-minute intervals, followed by a similar number of instillations at half-hourly, hourly, and two-hourly intervals. This gives a total of 22 hours' treatment. Many cases require no further attention. (4) In some babies the lid margins still tend to remain sticky. It is advisable in such cases to continue with penicillin at two-hourly intervals until the eye is dry, when treatment is carried on for a further 12 hours.

Crystalline penicillin only should be used for making up the drops. Impure penicillin is likely to cause irritative reactions.

Summary

A series of 151 cases of ophthalmia neonatorum treated by several different methods is recorded.

Oral administration of doses of 200,000 units of penicillin, either exclusively or after an initial intramuscular injection, has proved disappointing.

Combined oral sulphonamide and local penicillin therapy proved effective in reducing the duration of treatment but ineffective in reducing the considerable frequency of relapses seen with either sulphonamide or penicillin therapy.

Duration of treatment was likewise reduced by increasing the dose of sulphonamide. With sulphamezathine, 0.5 g. initially and a maintenance dose of 0.25 g. six-hourly, some 70% of cases showed clinical cure within one to three days. Similar results were obtained with sulphamerazine, 0.5 g. initially and 0.25 g. at eight-hourly intervals. The use of these larger doses of sulphonamide does not apparently influence the relapse rate; it is, however, possible that sulphamerazine may prove to be a favourable exception.

For the present the best way of administering penicillin is still the instillation of drops of 10,000 units per ml. initially at intervals of a minute for half an hour and subsequently at less frequent intervals. For the best results with sulphonamide therapy higher doses than those used previously are necessary.

We are indebted to the matron of White Oak Hospital and Sister Condon, of the Ophthalmia Neonatorum Unit, for their loyal help in the treatment of the cases recorded here.

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BACTERIOPHAGE TYPES IN PENICILLIN-RESISTANT STAPHYLOCOCCAL INFECTION

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Many studies concerning the incidence of penicillin-resistant staphylococcal infection have been reported, and it is now generally agreed that this is increasing (Spink *et al.*, 1944, 1945; Bondi and Dietz, 1945; Gallardo, 1945; Plough, 1945; Harley *et al.*, 1946; Barber and Rozwadowska-Dowzenko, 1948). Results of investigations of a series of infections occurring in a single hospital, however, are difficult to assess, as such institutions often seem to be breeding-grounds of a particular strain of pathogenic staphylococcus. Thus in previous studies in a single hospital by one of us (Barber, 1947a, 1947b; Barber and Rozwadowska-Dowzenko, 1948) it was found that 59 of 100 cases of staphylococcal infection investigated in 1948 yielded penicillin-resistant staphylococci, whereas the incidence in a similar series was 38% in 1947 and 14.1% in 1946. Each year, however, it was found that a significantly high proportion of the penicillin-resistant strains when typed by the bacteriophage method fell into the 6/47 group, suggesting that most of the penicillin-resistant infections might have been caused by a single strain of staphylococci.

Recent experience, however, has led us to the conclusion that a large number of penicillin-resistant staphylococci isolated from infections in widely separated hospitals belong to the 6/47 phage group. In the present investigation, therefore, staphylococci isolated from a series of 100 cases of infection occurring in this hospital have all been tested for penicillin sensitivity and phage-typed to see if the two could be correlated.