PENICILLIN THERAPY IN OPHTHALMIA NEONATORUM

BY

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In an earlier communication (Sorsby and Hoffa, 1945) it was shown that penicillin locally is highly efficacious in ophthalmia neonatorum. Consistent results could be obtained when drops in a concentration of 2,500 units per ml. were used, lower concentrations being rather erratic in their effect. The frequency of application was also shown to be of significance (Sorsby, 1945a, 1945b). Clinical cure was obtained more readily when drops were used at half-hourly instead of at hourly intervals, and readier still when the intervals were reduced to five minutes. Any tendency to pus formation was then generally suppressed within half an hour to three hours (by the instillation of six to 30 applications). When there was no longer any discharge, instillation of penicillin drops was continued at half-hourly intervals for six to 12 hours. At the end of this time a clinical cure was usually obtained, and penicillin was continued hourly for 12 hours and two-hourly for a further 24 hours. It was found that all the common causal organisms of ophthalmia neonatorum, including the virus of inclusion blennorrhoea, responded to penicillin, though there appeared to be a varying degree of susceptibility of the different exciting organisms.

The present series of 232 cases were observed at the ophthalmia neonatorum unit at White Oak Hospital from May 8, 1945, to March 10, 1947.

Local Treatment with Penicillin in Watery Solution

at Five-minute Intervals

To the 25 previously reported cases treated at five-minute intervals 30 more can now be added. Table I sets out

TABLE I.—*Commercial Penicillin* 2,500 *Units per ml. at Five-minute Intervals Initially. Time taken for Clinical Cure: in Relation to Severity and Distribution of the Affection*

		No. of Cases	Clinical Cure in Hours for Each Case
Mild	Unilateral ..	2	2, 1
	Bilateral ..	5	½*, 2, ¼, 7½, 17†
Moderate	Unilateral ..	6	2, 12, 35, 45, 21, 2½
	Bilateral ..	10	1, 68†, 2, 6½†, 68, 115, 6½*, 9, 6, X
Severe	Unilateral ..	4	45, 82†, 4½*, 44
	Bilateral ..	3	67, 6, 40

* Relapsed. Cured by sulphamezathine.
† Relapsed. Cured by a further course of penicillin.
X=Poor response. Cured by sulphamezathine.

these 30 cases in relation to severity and the time taken to obtain a clinical cure. It will be seen that four of the 30 failed to give a satisfactory response to penicillin, and treatment had to be completed by a course of oral sulphamezathine. Four other cases showed a mild relapse necessitating a further course of local penicillin therapy. A primary cure was thus obtained in 22 (73%) out of 30 cases, the time taken extending from 15 minutes to 115 hours, with an average of 24 hours for clinical cure and an additional 36 hours' treatment to consolidate the cure, or a total of 60 hours' treatment in all.

at One-minute Intervals

(*a*) *Penicillin in a Concentration of 2,500 Units per ml.*—As penicillin drops are rapidly washed out from the conjunctival sac a further series of cases were treated more intensively. Drops in the same concentration (2,500 units per ml.) were instilled at intervals of one minute. It became apparent that such intensive treatment gave a quick response and had to be maintained for only a relatively short time, as any tendency to pus formation was rapidly suppressed. In most cases there was no pus within 20 minutes, though the lids remained swollen and the eye was still moist. A series of 71 cases were treated by drops instilled at intervals of one minute for half an hour; subsequently six applications were made at five-minute, half-hourly, hourly, and, finally, two-hourly intervals. The time for clinical cure varied considerably in the different cases, but in no instance was there any anxiety about the state of the eye after the first 20 minutes of treatment. Some eyes became completely dry within a matter of two to three hours; others remained moist or showed stickiness of the lid margins for a much longer time. Table II

TABLE II.—*Commercial Penicillin* 2,500 *Units per ml. at One-minute Intervals Initially. Total Time of Treatment in Hours (for Clinical Cure and for the Subsequent Treatment to Consolidate the Cure): in Relation to Severity and Distribution of the Affection*

		No. of Cases	Total Time of Treatment in Hours for Each Case
Mild	Unilateral ..	9	35, 6, 21, 12, 21, 36, 36, 14, 62
	Bilateral ..	9	16, 29, 25, 12, X, 40, 16, 17, X
Moderate	Unilateral ..	12	22, X, 72, 31, X, 16, 21, 30, 24, X, X, 96
	Bilateral ..	23	21, 96, 21, 22, 36, 19, X, X, 29, X, 10, X, 22, 52, 31, 21, X, 21, 22, X, X, X, 53
Severe	Unilateral ..	5	39, 20, 44, 92, 47
	Bilateral ..	13	12, 24, 108, 40, X, X, 44, X, X, X, 20, 25, 29

X=Poor response. Cured by sulphamezathine.

sets out the total number of hours each case was actually treated. The time of treatment included at least 12 hours during which the eye was apparently normal. It will be seen that in 19 cases the response was not good, necessitating the use of sulphonamides to clear the condition. In the remaining 52 cases (73%) a primary cure was obtained, the total time of treatment ranging from six to 96 hours, with an average of 33 hours.

(*b*) *Penicillin in a Concentration of 10,000 Units per ml.*—As this work was proceeding pure (crystalline) penicillin became available. In view of the fact that the proportion of failures (27%) was still not insignificant, and that the eye tolerates pure penicillin in higher concentrations than previously employed (the highest tolerated concentration of commercial penicillin being 2,500 units per ml.), a further series of cases were treated at one-minute intervals with drops in a concentration of 10,000 units per ml., using white crystalline penicillin dissolved in sterile water. Table III shows the results obtained. It will be seen that

TABLE III.—*Pure Penicillin* 10,000 *Units per ml. at One-minute Intervals Initially. Total Time of Treatment in Hours: in Relation to Severity and Distribution of Affection*

		No. of Cases	Total Time of Treatment in Hours for Each Case
Mild	Unilateral ..	2	45, 72
	Bilateral ..	9	X, X, 46, 45, 48, 24, 45, X, 38
Moderate	Unilateral ..	8	48, 93, 48, 45, R, R, X, 72
	Bilateral ..	12	20, 46, 72, 48, 44, X, 48, X, 14, 50, 42, 54
Severe	Unilateral ..	—	—
	Bilateral ..	2	57, 34

X=Poor response. Cured by sulphamezathine.
R=Relapse. Cured by a second course of penicillin locally.

in this series of 33 cases six still required sulphonamide by mouth, and that two further cases showed a relapse, which necessitated a second course of penicillin therapy. The time taken over treatment in the 25 cases (76%) of primary cure ranged from 20 to 72 hours, with an average of 48 hours.

Considered in relation to the number of hours taken over treatment in those cases of primary cure, treatment with penicillin 10,000 units per ml. gave apparently less satisfactory results than treatment with drops of 2,500 units per ml., the comparative figures being 48 and 33 hours respectively. The significant fact is, however, that there were rather fewer poor responses or relapses in the series treated with the more concentrated drops—and this, as will be seen below, in spite of the high percentage of cases with inclusion bodies in this series (15 out of 33 treated with 10,000 units per ml. as against 16 out of 71 treated with 2,500 units per ml.).

Clinical Cure in Relation to Organism

The causal organisms seen in the 30 cases treated at five-minute intervals are shown in Table IV. Of the four

TABLE IV.—*Commercial Penicillin* 2,500 *Units per ml. at Five-minute Intervals Initially. Time Taken for Clinical Cure: in Relation to Causal Organism and Severity of the Affection*

	No. of Cases	Clinical Cure in Hours for Each Case
Gonococcus:		
Mild	1	½*
Moderate	4	1, 2, 68†, 2½
Staph. aureus:		
Mild	4	½, 7½, 17†, 1
Moderate	3	12, 2, 35
Severe	1	45
Staph. albus:		
Moderate	1	9
Str. viridans:		
Moderate	1	6
Diphtheroids:		
Moderate	1	6½†
Severe	1	82†
Morax–Axenfeld:		
Mild	2	2, 2
Virus presumed from presence of inclusion bodies:		
Moderate	6	68, 45§, 115§, X, 6½*‡, 21‡
Severe	5	67§, 6§, 40§, 4¼*‡, 44

* Relapsed. Cured by sulphamezathine.
† Relapsed. Cured by a further course of penicillin.
‡ *Staph. aureus* also present.
§ *Staph. albus* also present.
X = Poor response. Cured by sulphamezathine.

cases requiring sulphonamides to complete treatment three were cases of inclusion bodies, which numbered 11; the fourth case was one of the five cases due to the gonococcus. All the cases due to *Staph. aureus, Staph. albus,* diphtheroids, *Str. viridans,* and Morax–Axenfeld bacillus—the remaining causative organisms in this series—responded to penicillin, though three (out of a total of 14) required a second course of treatment. These results are not dissimilar to those observed in the 25 cases previously recorded. Here there was one failure in the gonococcal cases, and one in the diphtheroid group. Three relapses were noted in the eight cases due to *Staph. aureus,* and one relapse in the three diphtheroid cases. Taking this group as a whole there were 55 cases, which included 15 cases due to virus and five due to diphtheroids. Of the 15 virus cases three gave a poor response to penicillin, and of the five diphtheroid cases three relapsed and required a second course of penicillin.

The 104 cases treated intensively at intervals of one minute (71 cases with drops in a concentration of 2,500 units per ml. and 33 with drops of 10,000 units per ml.) show a total of 25 cases that required sulphonamide treatment because of a poor response to penicillin (Table V). The distribution of these 25 cases and of two further cases that relapsed is shown in Table VI. It will be seen that all cases due to *Staph. aureus* responded well, as did the three cases due to the Koch-Weeks bacillus. The two failures with gonococcus occurred with drops in the lower concentrations, as did three of the four failures with *Staph. albus.* Unsatisfactory response to diphtheroids appears to be

TABLE V.—*Commercial Penicillin* 2,500 *Units per ml., Pure Penicillin* 10,000 *Units per ml., at One-minute Intervals Initially: Total Time of Treatment in Hours in Each Case in Relation to Causal Organism and Severity of the Affection*

	No. of Cases	Commercial Penicillin 2,500 Units per ml.	No. of Cases	Pure Penicillin 10,000 Units per ml.
Gonococcus:				
Mild	1	X	—	—
Moderate	2	31, X	5	48§, 45§, 46, 72, 48
Severe	6	20, 25, 29, 39, 20, 40	1	57
Staph. aureus:				
Mild	5	29, 25, 6, 21, 12	—	
Moderate	5	72, 21, 22, 36, 19	2	48, 20
Severe	2	24, 108	—	
Staph. albus:				
Mild	4	12, 21, 36, 36	3	X, 46, 45
Moderate	5	X, X, 16, 29, X	1	93
Streptococcus:				
Mild	1	16	—	
Pneumococcus:				
Mild	—		1	X
Diphtheroids:				
Mild	3	40, 16, 62	1	45
Moderate	8	10, X, 22, 52, 31, 21, 21, 30	4	44, X, 48, X
Severe	6	44, 92, X, X, 44, X	—	
Koch-Weeks:				
Mild	1	35	—	
Moderate	2	21, 96	—	
No organisms or inclusion bodies present:				
Moderate	2	22, X	—	
Severe	2	12, 47	—	
Virus presumed from presence of inclusion bodies:				
Mild	3	17§, X‡, 14‡	6	48, 24, 45§, 72§, X, 38
Moderate	11	24, X‡, X‡, 96, X†§, 21‖, 22§, X‡, X‡, X†, 53	8	40*, 46*§, X, 72, 14, 50§, 42§, 54§
Severe	2	X, X	1	34

* Relapsed. Cured by a further course of penicillin.
† *Staph. aureus* also present.
‡ *Staph. albus* also present.
§ Diphtheroids also present.
‖ Gonococcus also present.
X = Poor response. Cured by sulphamezathine.

equally distributed in the two series, four of the six cases falling in the 2,500 units per ml. group and two in the 10,000 units per ml. group. The most suggestive finding refers to the inclusion bodies. Of the total of 13 unsatisfactory responses nine occurred in the 16 cases treated by

TABLE VI.—*Summary of Table V. Treatment at One-minute Intervals Initially: in Relation to Causal Organisms*

Organism	Total No.	Poor Response. Sulphonamides Needed	Relapse. Further Course of Penicillin Needed	Primary Cure by Local Penicillin	Average Total Time Treated (in 77 cases with primary cure)
Gonococcus	15	2	—	13	40 hours
Staph. aureus	14	—	—	14	33 ,,
Staph. albus	13	4	—	9	37 ,,
Streptococcus	1	—	—	1	—
Pneumococcus	1	1	—	—	—
Diphtheroids	22	6	—	16	39 ,,
Koch-Weeks	3	—	—	3	51 ,,
No organisms	4	1	—	3	27 ,,
Virus presumed from presence of inclusion bodies	31	11	2	18	41 ,,
	104	25	2	77	38 ,,

drops of a concentration of 2,500 units per ml., while only four were observed in the 15 cases treated with drops in a concentration of 10,000 units per ml.

Penicillin in Vehicles other than Water

In an attempt to overcome the tediousness of intensive penicillin therapy at one-minute intervals other vehicles than water were tried in the hope that the penicillin so instilled would not be washed out from the eye as rapidly as is watery solution. The detailed results are shown in Table VII.

Lamellae.—In 14 cases lamellae were used containing 400 to 1,000 units of commercial penicillin. The excipient employed

TABLE VII.—*Distribution of Causal Organisms and Incidence of Primary Cure in 51 Cases Treated with Penicillin Locally in a Vehicle Other than Water*

Organism	Lamellae of Commercial Penicillin (400-1,000 U./g.)	Ointment with Commercial Penicillin (800–2,000 U./g.)	Ointment with Pure Penicillin (8,000–25,000 U./g.)	Pure Penicillin in Oily Suspension (10,000 U./ml.)	Pure Penicillin in 2% Methyl Cellulose Solution (10,000 U./ml.)
Gonococcus ..		1‡		2	
Staph. aureus ..	3			3	
Staph. albus	3			2	1
Pneumococcus ..					1
Diphtheroids ..	1	4	2	1	1
No organisms ..	2				1
Virus presumed from presence of inclusion bodies ..	5		5*‡	5†‡	8§
Total	14	5	7	13	12
Primary cure:	0	0	0	7‖	6¶

* *Staph. aureus* also present in one case.
† *Staph. albus* also present in one case.
‡ Diphtheroids also present in one case.
§ *Staph. albus* also present in three cases, diphtheroids in one, and *Str. viridans* in one.
‖ Three cases of inclusion bodies, one of diphtheroids, two of *Staph. albus*, and one of gonococcus.
¶ Four cases of inclusion bodies, one with no organisms, and one with pneumococcus.

was either lactose or a base specially prepared by Parke, Davis and Co. It was found that the instillation of lamellae in a baby with swollen lids was not particularly easy. Moreover, the lamellae either proved so readily soluble as to have no advantage over watery drops or were rather insoluble. The insoluble lamellae were often extruded from the conjunctival sac by the constant squeezing of the lids. Not a single clinical cure was obtained, and these babies all had to be treated with sulphamezathine.

Ointment.—In five cases commercial penicillin in watery solution containing 800 to 2,000 units per gramme were incorporated in "eucerin L.M." ointment base and used at two-hourly intervals. Here again instillation proved difficult; the ointment was frequently extruded and not a single cure was obtained. In seven further cases pure penicillin in a concentration of 8,000 to 25,000 units per gramme was used at two-hourly intervals. Only one cure was obtained, and this patient relapsed and had to be readmitted for sulphonamide treatment.

Oily Suspension.—Thirteen cases were treated with pure pencillin, 10,000 units per ml. in suspension of castor oil or liquid paraffin, instilled at five-minute intervals. Seven of these cases responded to treatment. One of the cases that did not respond did well when watery drops were instilled. The high incidence of poor response and the protracted course in the seven cases that responded to treatment led to the discontinuance of this experimental method.

Methyl Cellulose.—In 12 cases 2% methyl cellulose solution was employed as a vehicle for pure penicillin 10,000 units per ml. instilled at five-minute intervals. Six of these cases gave a poor response, necessitating sulphonamide treatment in five and watery penicillin in the other. Two of the six successfully treated cases remained irritable and subsided only when all treatment was discontinued. It appeared that 2% methyl cellulose is not free from irritation, though it has advantages over watery solution and might conceivably be developed to modify the one-minute treatment by watery drops.

Systemic Injection of Penicillin

As no suitable substitute for watery penicillin which would diminish the frequency of instillation seems as yet to be available, a series of cases were treated by massive systemic injections of penicillin. An empirical dose of 200,000 units, dissolved in 0.5 ml. of water, was injected into the buttock, the dose being repeated three times at three-hourly intervals, giving a total of 12 hours' treatment by systemic injection. This was followed by the instillation of drops of pure penicillin 10,000 units per ml. in 1% methyl cellulose solution, instilled at two-hourly intervals as long as the eye remained sticky. In most of the 39 cases so treated a tangible improvement in the state of the eye was seen within 15 minutes, pus formation being suppressed exceptionally within half an hour, generally within two to three hours, and occasionally not for five to six hours or even longer. Table VIII shows

TABLE VIII.—*Systemic Injections of Penicillin 800,000 Units, Four Injections of 200,000 Units each at Three-hourly Intervals. Total Time taken over Systemic Treatment and Follow-up Local Treatment: in Relation to Severity of the Affection*

		No. of Cases	Total Time of Treatment in Hours for Each Case
Mild	Unilateral ..	4	36, 38*, 33, 24
	Bilateral ..	7	24, 23, 12*, 60, 18, 52, 21*
Moderate	Unilateral ..	7	12, 6, 12, 24, 24, 48, X
	Bilateral ..	5	40, X, 48, X, 120
Severe	Unilateral ..	6	24, 46, 48, 30, 12, 21
	Bilateral ..	10	58, 40, 22, 48, 52, 42, 30, 40, 30, 54

* Relapsed. Cured by a course of local penicillin.
X=Poor response. Cured by sulphamezathine.

the distribution of the cases according to severity. It will be seen that three cases in this series required sulphonamide treatment, and three more a course of local penicillin treatment—10,000 units per ml. instilled at intervals of one minute. The significant findings are: (1) the low incidence of cases giving a poor response and requiring sulphonamide—three (7.7%) out of 39; (2) the low incidence of cases showing relapses—three (7.7%); (3) primary cure in 33 (84.6%) out of 39 cases; (4) the excellent response in five cases in this series—the response being so good that treatment was completed within 12 hours of intramuscular injection, so that subsequent penicillin drops were unnecessary; (5) the total duration of treatment in the 33 cases with primary cure was from six to 120 hours, with an average of 46 hours.

As can be seen from Table IX this series of 39 cases contained 17 that showed inclusion bodies and only two of

TABLE IX.—*Systemic Injections of Penicillin 800,000 Units (Four Injections of 200,000 Units each at Three-hourly Intervals). Total Time taken over Systemic Treatment and Follow-up Local Treatment: in Relation to Causal Organism and Severity of the Affection*

	No. of Cases	Total Time of Treatment in Hours for Each Case
Gonococcus:		
Mild	1	24
Moderate	1	24
Severe	2	48, 30
Staph. aureus:		
Mild	1	23
Staph. albus:		
Mild	1	12*
Severe	1	58
Str. viridans:		
Mild	1	36
Moderate	1	40
Diphtheroids:		
Moderate	2	X, 12
Severe	3	46, 22, 48
Koch-Weeks:		
Mild	1	38*
Severe	1	24
Friedländer:		
Mild		24
No organisms:		
Mild	2	60, 33
Moderate	2	12, 6
Severe	1	40
Virus presumed from presence of inclusion bodies:		
Mild	3	18, 52, 21*
Moderate	6	24, 48, X, 48, X, 120
Severe	8	12, 21, 52, 42, 30, 40, 30, 54

* Relapsed. Cured by a course of local penicillin.
X=Poor response. Cured by sulphamezathine.

these 17 cases required sulphonamide treatment, while only one relapsed requiring local penicillin therapy. Likewise of the five cases due to diphtheroids only one required sulphonamide treatment and none relapsed.

Discussion

Course of Affection in Primary Cure

The course of the affection varies somewhat with the different modes of application. With commercial penicillin, 2,500 units per ml. instilled at five-minute intervals, pus may be suppressed within half an hour, but generally up to three hours is required. Subsequently the eye does not become completely dry for a variable number of hours, while stickiness of the lid margin may persist for one or two days. With instillations at one-minute intervals pus is invariably suppressed within half an hour, while the eye remains moist and the lid margins may remain sticky for as long as two days, though recovery generally is rapid. It would appear that persistence of moistness and of stickiness of the lid margin is not altogether due to the infection, for occasionally suspension of all treatment has led rapidly to the clearing of these residual reactions. In individual cases it is often difficult to decide whether these reactions are the remains of an infection or the result of irritation from commercial penicillin. One of the advantages of pure penicillin has been that fewer cases present these residual symptoms. When intramuscular injections are used suppression of pus is not so rapid, but substantially fewer moist and sticky eyes are seen at the end of 24 hours. In all probability commercial penicillin in a concentration of 2,500 units per ml. is not devoid of irritative reactions in some infants, and it is possible that irritative reactions seen with pure penicillin may well be due not to the penicillin itself but to the constant handling of the lids that local therapy involves.

Relapses and Unsatisfactory Response

When relapses occur it is only exceptionally that the condition is as severe as it was initially: generally an eye that had shown clinical cure becomes either moist or shows sticky lid margins. In such cases a further course of local penicillin usually clears the condition, suggesting an activated latent infection rather than a condition which is the result of mechanical handling. The possibility of reinfection also arises. In two cases with unilateral infection satisfactorily treated by systemic administration the second eye became involved on the second and third days after cessation of treatment. Both these infants were nursed by their mothers, so that extragenital infection is not unlikely.

In contrast to relapses there are the cases that have initially shown an unsatisfactory response. It must be understood that this does not mean that the condition is not brought under control. In no single instance was there any failure in that sense. An unsatisfactory response means little more than persistent moistness of the conjunctiva and sticky lid margins with occasionally some oedema of the fornices. In no case did any complications develop after admission, and occasional cases admitted with a hazy cornea rapidly returned to normal. There was, however, one exception which is not included in the tables:

A baby aged 6 weeks was admitted with an ophthalmia neonatorum of four weeks' standing with both corneae heavily involved. One cornea perforated within two hours after admission, with extrusion of the lens. Intensive penicillin therapy rapidly brought the conjunctival infection under control, but appeared to have little effect on either of the heavily infiltrated corneae. After a protracted course of combined carbolization, penicillin, sulphonamide, and Kiton fast green V treatment the baby was ultimately discharged with a shrinking right eye and an extensively opalescent left cornea. No causal organism could be found in this infant, nor were inclusion bodies obtained.

As can be seen from Table X if relapses and unsatisfactory responses are counted as failures there were 15 failures out of 55 cases treated at five-minute intervals with penicillin 2,500 units per ml.—that is, the 30 cases recorded here and the 25 cases recorded previously. When

TABLE X.—*Summary Table Showing Results Obtained with Commercial Penicillin and Pure Penicillin Locally, and Systemic Penicillin in Relation to Causal Organism*

Mode of Treatment:	Drops at 5-minute Intervals (2,500 U./ml.)		Drops at 1-minute Intervals (2,500 U./ml.)		Drops at 1-minute Intervals (10,000 U./ml.)		Systemic		Total	
Organism	+	−	+	−	+	−	+	−	+	−
Gonococcus	7	3	7	2	6	—	4	—	24	5
Staph. aureus	12	4	12	—	2	—	1	—	27	4
Staph. albus	1	—	7	2	3	1	1	1	12	4
Diphtheroids	1	4	13	4	3	2	4	1	21	11
Str. haemolyticus	1	—	1	—	—	—	—	—	2	—
Str. viridans	1	—	—	—	—	—	2	—	3	—
Pneumococcus	—	—	—	—	—	1	—	—	—	1
Gram-negative diplococci	—	1	—	—	—	—	—	—	—	1
Friedländer	1	—	—	—	—	—	1	—	2	—
Koch-Weeks	—	—	3	—	—	—	1	1	4	1
Morax-Axenfeld	3	—	—	—	—	—	—	—	3	—
No organisms	1	—	3	1	—	—	5	—	9	1
Virus presumed from presence of inclusion bodies	12	3	7	9	11	4	14	3	44	19
	40	15	53	18	25	8	33	6	151	47

+ = Successful treatment.
− = Unsatisfactory response or relapse necessitating sulphonamide or further penicillin treatment.

treatment was instituted at one-minute intervals there were 26 failures out of a total of 104. The number of failures declined somewhat to six out of 39 when intramuscular treatment was instituted. Taking the series as a whole there were 47 failures in a total of 198 cases.

Response in Relation to Causal Organism

From Table X it can be seen that the response with the less frequent exciting organisms, such as *Str. haemolyticus, Str. viridans,* Friedländer's bacillus, Koch-Weeks bacillus, and Morax–Axenfeld bacillus, was almost uniformly good, as was response in cases where no organisms could be established. In gonococcal infection response was distinctly better with drops of 10,000 units per ml. and with intramuscular injection than with drops of 2,500 units, whether instilled at five-minute or one-minute intervals. *Staph. aureus* gave uniformly good results with the one-minute treatment and intramuscular injection; there were four failures out of 16 treated at five-minute intervals. The most significant findings are with diphtheroids and virus infections. With each of the four different methods of treatment diphtheroids gave some failures: four out of five with the five-minute treatment; four out of 17 with one-minute treatment of 2,500 units per ml.; two out of five treated with drops 10,000 units per ml.; and one out of five with systemic treatment. Likewise there were 12 failures out of 31 cases of virus infection treated with penicillin in a concentration of 2,500 units per ml., but only four out of 15 when the concentration was 10,000 units per ml. and three out of 17 when systemic treatment was applied. It is clear from Table X that the two most resistant groups are infections due to diphtheroids and to virus, the incidence of failures for diphtheroids in the series as a whole being 11 out of 32 and for virus infections 19 out of 63. The failures were, however, largely concentrated in the groups treated by penicillin of 2,500 units per ml. The higher concentration of 10,000 units of pure penicillin and systemic injections considerably reduced the incidence of failures. As clinically there is nothing to distinguish one aetiological type of ophthalmia neonatorum from another, standard treatment must aim at overcoming

the most resistant organisms. For this reason penicillin drops in a concentration of 10,000 units per ml. are more desirable than lower concentrations, and it is possible that systemic injections are even preferable.

Choice of Method

For the present the choice of method in the treatment of ophthalmia neonatorum therefore lies between intensive local applications and massive systemic injections. So far as duration of treatment is concerned there is little to choose between the two methods. Intensive local treatment has the gratifying feature that pus is suppressed within 20 to 30 minutes; massive systemic therapy, though the suppression of pus is not so dramatically rapid, has the advantage of greater simplicity and perhaps greater efficacy.

Mode of Use

(*a*) *Intensive Local Therapy.*—(1) 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. Atropine sulphate 1% is instilled if the cornea is involved. (2) Any pus that may have accumulated is wiped away with moist pledgets of cotton-wool, and two drops of pure penicillin in a concentration of 10,000 units per ml. are instilled. (3) The baby is now placed on the nurse's lap, while another nurse sitting near by instils one drop of penicillin solution 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. (4) 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 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. (5) In some babies the lid margins still tend to be sticky. It is advisable in such cases to continue with penicillin at two-hourly intervals until the eye is dry, when treatment is continued for a further 12 hours.

(*b*) *Massive Systemic Injection.*—(1) Stage 1 is as with local therapy. (2) Any pus that may have accumulated during this preliminary procedure is wiped away with moist pledgets of cotton-wool. (3) An injection of 200,000 units of high-potency penicillin dissolved in 0.5 ml. of sterile water is made deep into the buttock, and the baby returned to its cot. (4) The injection is repeated after three, six, and nine hours. (5) At the end of this 12-hour treatment, during which time no local measures of any kind are carried out, most eyes are dry, though some babies still show sticky lid margins. Where there is any doubt as to a fully consolidated cure, pure penicillin 10,000 units per ml. in 1% methyl cellulose solution is instilled as drops into the eye at two-hourly intervals, and continued for 12 hours after clinical cure.

Comparison of Penicillin with "Marfanil" and "Gramicidin S"

Three cases were treated with marfanil locally and four cases with gramicidin S. Some improvement was obtained with both these agents but no cure, and treatment by a sulphonamide was necessary. The distribution of organisms and the mode of use in these seven cases are shown in Table XI.

TABLE XI.—*Distribution of Organisms in Cases Treated Unsuccessfully with Marfanil and Gramicidin S*

	Marfanil Drops at 1-minute Intervals for 10 Minutes		Gramicidin S., 4% Solution. Drops at 5-minute Intervals for 30 Minutes
	10%	25%	
	No. of Cases		
Staph. albus	—	2	—
Diphtheroids	1	—	—
Staph. aureus	—	—	3
Virus presumed from presence of inclusion bodies	—	—	1

Comparison with General Sulphonamide Therapy

As a standard method of treatment general sulphonamide therapy (Sorsby, 1945b) must now be regarded as obsolete, the results of penicillin therapy, whether by local or by systemic administration, being as strikingly superior to the sulphonamides as these in turn were to the classical methods. The sulphonamides are, however, invaluable as an alternative method of treatment when the response to penicillin is unsatisfactory. Moreover, for the present the sulphonamides still have the advantage of simplicity in administration over either of the two methods used with penicillin. Further simplifications of penicillin therapy and a reduction in the proportion of unsatisfactory responses do not, however, appear to be impossible.

Summary

1. In a series of 232 cases of ophthalmia neonatorum 224 were treated by penicillin in several different modes of applications. (*a*) Thirty cases were treated by instillation of watery drops of commercial penicillin in a concentration of 2,500 units per ml. at five-minute intervals initially. The good results recorded previously with a similar series of 25 cases were confirmed. (*b*) Seventy-one cases were treated with the same concentration of penicillin drops instilled at intervals of one minute for half an hour, and subsequently at less frequent intervals. In 19 cases the response to treatment was not good, or there was a relapse; the remaining 52 (73%) cleared rapidly, the total time of treatment needed being six to 96 hours, with an average of 33 hours. (*c*) Thirty-three cases were treated with more concentrated drops—10,000 units of pure penicillin per ml. Six cases gave an unsatisfactory response or relapsed, the remaining 27 (76%) cleared rapidly, requiring treatment for from 20 to 72 hours, with an average of 48 hours. (*d*) To obviate the need for frequent applications, oily or solid vehicles containing penicillin were tried out in 51 cases (lamellae in 14 cases, ointment in 12, oily suspensions in 13, and methyl cellulose in 12 cases). The results were unsatisfactory. (*e*) In a final series of 39 cases the initial local treatment was replaced by massive systemic injection (800,000 units in doses of 200,000 units at three-hourly intervals), followed on completion of the course by the instillation of pure penicillin 10,000 units per ml. in 1% methyl cellulose solution at two-hourly intervals. In 33 cases (84.6%) the response was good; in five of these the condition was cleared up by the systemic injections exclusively. The total duration of treatment in these 33 cases was from six to 120 hours, with an average of 46 hours.

2. Assessed against the causal organism the 30 cases treated by drops of commercial penicillin 2,500 units per ml. instilled initially at five-minute intervals gave four cases that required sulphonamide treatment. Of these four cases three showed inclusion bodies, of which there were a total of 11 cases. Both the cases in this series showing diphtheroids relapsed and required a further course of penicillin.

The 104 cases treated intensively at intervals of one minute showed a total of 25 cases that required sulphonamide treatment because of a poor response. Of these 25 cases 11 showed inclusion bodies and six showed diphtheroids; the remaining eight cases were distributed haphazardly among other organisms, though no failures were observed with *Staph. aureus*, streptococcus, and Koch-Weeks bacilli. There is nothing to suggest that the incidence of failures with diphtheroids could

be reduced by an increase in concentration of the drops, but a striking difference was noted in the case of inclusion bodies. Of the 16 cases of inclusion bodies treated by penicillin, 2,500 units per ml., nine gave an unsatisfactory response, while only four out of 15 failed to respond when the concentration was increased to 10,000 units per ml. Only one of the five cases with diphtheroids treated by systemic injection gave an unsatisfactory response; there were three cases with unsatisfactory response out of a total of 17 with inclusion bodies.

3. The poor responses and relapses recorded in this series are to be understood in a relative sense. A total failure to respond to penicillin treatment has not been observed, and in no case has penicillin treatment failed to influence the condition sufficiently to remove all anxiety within a matter of hours, or less. The optimum mode of use of penicillin is still to be determined, though even now the results obtainable are as great an advance on those of the sulphonamides as these in turn were over the classical methods of treatment.

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A FATAL CASE OF ACUTE PORPHYRIA WITH UNUSUAL FEATURES

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The following case is worthy of record because of the difficulty in diagnosis and the possible relationship to drug therapy. The type of porphyrin was also atypical, and there were signs suggestive of adrenal insufficiency.

Case Report

A woman teacher aged 34 was admitted to hospital on the 9th day of a febrile illness which began with hoarseness and intermittent severe pains and weakness in all limbs. Except for appendicectomy some years ago and sinusitis a month before, she had been active and well until the onset of the present illness. She was an only child of parents, now dead, of whom she knew little. The limb pains subsided in two days, but on the 6th day she had lower abdominal pain with slight tenderness in the right lumbar area. No relief was obtained from an enema. A second was given with some success, but soon the abdominal pain increased with vomiting. Morphine, 1/4 gr. (16 mg.), had been given a few hours before admission.

On admission she was drowsy. The temperature was 100.5° F. (38.05° C.), the pulse 120, and the respirations 28. Pallor was evident but her general nutrition was good. The tongue was furred and dry. Slight tenderness was elicited in the right iliac fossa and hypogastrium. Rectal examination was negative. The lungs and heart were normal except for an exocardiac murmur at the mitral area. The blood pressure was 120/80. The central nervous system was normal, though the tendon reflexes were sluggish. The urine—specific gravity 1020—was red, evidently from admixture with menstrual blood; albumin was present, sugar absent. Pus and *B. coli* were found in a catheter specimen. She had no frequency of micturition, but the urinary findings, coupled with abdominal tenderness, suggested pyelo-cystitis. On the 11th day sulphamezathine was given, 2 g. at once followed by 1 g. four-hourly, together with potassium citrate, 30 gr. (2 g.) four-hourly. The temperature fell to normal after 24 hours, she felt and looked better, and the dose of sulphamezathine was reduced to 1 g. thrice daily. She received "soneryl," 1½ gr. (0.1 g.), and tab. codein. co. on several occasions.

On the 12th day of the disease there was mental confusion, with marked nocturnal restlessness and recurrence of severe pain and tenderness in the hypogastrium. Similar symptoms were present during the following night, and on the 15th day she had a fit, during which she bit and chewed her tongue. Her temperature was 98° F. (36.7° C.), pulse 104, and blood pressure 130/80. She could with difficulty be roused. Sulphamezathine was suspended after a total of 20 g. had been given, and potassium citrate was also stopped, half-normal saline being administered by mouth on account of suspected salt deficiency. Improvement rapidly followed and she became coherent and co-operative. The tongue was much swollen; cervical adenitis was present, and for this penicillin, 30,000 units three-hourly, was given intramuscularly. The abdomen was distended but not tender. The knee-jerks were sluggish, but other tendon reflexes were normal and weakness or sensory loss was not apparent. A skiagram of the chest and abdomen was normal. The C.S.F. showed: a pressure of 114 mm. of fluid, with less than 1 cell per c.mm.; protein 25 mg. per 100 ml.; globulin nil; colloidal gold test, 000000. A blood count showed: white cells, 30,000 per c.mm. (polymorphs, 89%; lymphocytes, 10%; eosinophils, 1%); plasma chlorides, 416 mg. per 100 ml.; serum sodium, 253 mg. per 100 ml.; urea, 25 mg. per 100 ml.; alkali reserve, 64 vols. CO_2 %. On the 17th day the blood chemistry was: chlorides, 470 mg.; sodium, 272 mg.; potassium, 14.9 mg.; alkali reserve, 61 vols. CO_2 %. It is of interest to note that the urine contained chlorides in spite of the low plasma chloride level.

On the 18th day porphyrin was discovered in the urine. Some general clinical improvement was apparent: the blood pressure was 110/80. The knee-jerks were now absent, but the ankle-jerks remained brisk and there was no weakness of the legs. Complaint was made of numbness of the lower abdomen, buttocks, and thighs, and objectively there was some loss of sensation to cotton-wool over the abdomen, but pin-prick was felt normally here and elsewhere. No postural or vibratory loss was noted at any time during the illness. Blood culture was negative. The white cells numbered 11,550 per c.mm. (polymorphs 80%). The urine contained a few pus cells only, and culture was sterile.

20th Day.—There was sudden deterioration during the preceding night. Her temperature was 101.5° F. (38.6° C.), and pulse 130; there were abdominal and limb pains, and mental confusion with phobias and delusions; a toxic appearance; a false rigor; and loss of all limb reflexes. The right kidney was palpable and tender and the exocardiac murmur was more pronounced. Half-strength saline was administered by mouth. Blood chemistry: chlorides, 494 mg.; sodium, 298 mg.; potassium, 14.7 mg.; urea, 24 mg.; calcium, 9.1 mg.

21st Day.—The temperature was 101° F. (38.3° C.) and the pulse 110. She was cyanosed and drowsy but co-operative. Diminished movement and breath sounds at the right base were believed to be due to a high diaphragm, as shown by a skiagram. The right kidney was tender.

22nd Day.—She was less cyanosed and more rational and co-operative. Temperature had fallen to 99° F. (37.2° C.). Examination revealed the following: weak abduction of shoulders; weakness of extensors of wrist and fingers; tendon jerks absent but sensation normal; weakness of legs, especially quadriceps; ankle- and knee-jerks absent but no more pain; abdominal reflexes absent; plantar reflexes flexor; analgesia to pin-prick over lower limbs and lower trunk, and anaesthesia to cotton-wool over trunk.

23rd Day.—Kaolin, 1/2 oz. (14 g.) three-hourly, was administered in the hope of its adsorbing porphyrin. On sternal puncture no abnormal cells were seen, but the marrow was very active, with a high count of neutral polymorphs and large