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daughter.' In this connexion reference may be made to McLaurin's suggestion that Nell Gwyn's sterility was due to salpingitis which was probably of a syphilitic nature in view of the fact that she developed hemiplegia at the comparatively early age of thirty-seven.

Other notorious prostitutes mentioned by Pepys are Lady Bennett (I, 228, VII, 32) and Damaris Page, "the greatest bawd of the Seamen" (VII, 351).

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OPHTHALMIA NEONATORUM

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Ophthalmia neonatorum is a serious disease and in view of the rather vague ideas which some people have, it would seem necessary to state what the condition really is. The Ministry of Health *Statutory Rules and Orders* (1926) have defined it clearly so that there should be no doubt on the matter. The definition given is "Ophthalmia neonatorum means a purulent discharge from the eyes of an infant, commencing within twenty-one days from the date of its birth." It will be seen that no mention is made of the gonococcus or of any other infecting organism; neither is the degree of the purulent discharge a matter for differentiation. A purulent discharge, however slight, occurring in a baby up to three weeks of age should be notified as ophthalmia neonatorum. I venture to state that this is not being done in many places.

Notification fallacies

From time to time I look at the returns given in the medical press under the heading of Notifiable Diseases. For England and Wales the average number of cases of ophthalmia neonatorum each week seems to be well under 100, and yet the average weekly number from Birmingham alone in 1942 was about twenty-three cases. In fact, the cases notified from Birmingham, a city of a million inhabitants, accounted for nearly one-quarter of the total cases from the whole country. In my view it is idle to suggest that the condition is more prevalent in this city than it is elsewhere. In Birmingham the doctors and midwives are encouraged to notify these cases and to send them for diagnosis and treatment to a central depot. I contend that for this reason the number of cases notified is far greater than that from any other town in the country. Although I do not believe that the cases are more numerous now than they were fifteen years ago, it is interesting to note the rise in the number of notifications.

Results of notification and visiting

In view of the large number of notifications one naturally asks whether all notifications are of value and whether they are justifiable. The answer to such a question can be given by an investigation of the results obtained as seen in the number of eyes which have been permanently damaged as a result of this disease. In 1930 the Birmingham Eye Hospital accepted a joint scheme with the Birmingham

Note.—In 1932-3 a Resident House Surgeon at the Eye Hospital considered general notification unjustifiable. This probably accounts for the marked decrease in the number of cases notified at this time. The grounds on which he did notify the disease are not known.

Public Health Committee for home visitation and observation of patients who had suffered from ophthalmia neonatorum. Notification, treatment and visiting must be regarded as complementary and visiting obviously could not be done without notification. A comparison of the results obtained for the city of Birmingham during the ten year period before the inauguration of the Joint Hospital and Public Health Scheme with those of the ten year period after it became operative appears to me to be very striking. For such a scheme to get into working order takes time and I have taken the year 1932 as the dividing line. This shows that from 1923 to 1932 the total number of babies blind in one or both eyes or with impaired vision was sixty, whereas from 1933 to 1942 the total number of these babies was only six. (These figures were kindly supplied by Dr. H. P. Newsholme, Medical Officer of Health, Birmingham.) Such results speak for themselves and further comment is unnecessary, although it might be added that the improvement is certainly not due to the advent of the sulphonamide compounds since these did not come into use at the Birmingham Eye Hospital until 1938.

Diagnosis and nature of the infection in ophthalmia neonatorum

An accurate diagnosis depends entirely upon the result of bacteriological

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examinations. Nearly every case of gonococcal infection showed a purulent discharge within three days of birth but every case of severe purulent discharge occurring within this period was certainly not gonococcal in origin. On the other hand if a case of ophthalmia neonatorum occurs after the fifth or sixth day of infant life it is fairly certain that the condition is not due to a gonococcal infection, unless the latter has occurred subsequent to delivery from the use of infected towels to wipe the baby's eyes or by some similar means of inoculation. Very rarely infection may take place in utero. Parischeff reported such a case as long ago as 1892 in which the membranes had ruptured three days before birth. It is not difficult to understand the route of infection from the cervix under these conditions but it is very difficult to credit reports which have been made of cases occurring at birth with intact membranes.

There seems to be a prevalent idea that the gonococcus is a common cause of ophthalmia neonatorum. Harrison (1921) describing the condition states, "ophthalmia may be rarely due to other infections." Wolff (1934) estimated that 60 per cent of all cases were due to the gonococcus. On the other hand Browning (1936) in an analysis somewhat similar to that given below, found 15 per cent positive for gonococci. I suggest that a high percentage of gonococcal infections is found only when an inadequate number of cases have been reported and examined, whereas had the Act been observed properly, ophthalmia neonatorum would have been proved to be rarely caused by the gonococcus and very commonly by other organisms.

The procedure adopted at the Birmingham Eye Hospital is a simple one. In every baby whose eye shows a discharge of an apparently purulent nature a film and a culture are taken from the discharge at once. The film is stained by Gram's method. The discharge is also inoculated on trypsinized heart-broth-blood-agar (pH 7.5) and incubated for a minimum period of forty-eight hours. It should be emphasized that Gram negative intracellular diplococci found in the film from a case of ophthalmia neonatorum are not necessarily gonococci. In every case an attempt at culture should be made and the organism should be identified when possible. I know identification is not always an easy matter and for some unexplained reason it has been found more difficult to grow the gonococcus since the present war started although apparently the medium used has been the same.

Results of bacteriological examinations

The tables shown on the next page give the results of films and cultures examined as a routine at the Birmingham Eye Hospital. The items given are under the two headings as described.

The years 1934 and 1941 may perhaps be taken as typical. Notified cases do not quite correspond with cases examined at hospital, as some of the latter may not have been notified when perhaps xerosis bacilli only or no organisms were found. In 1934 the number of cases notified as ophthalmia neonatorum was 554; in 1934 the cases examined were 585; in 1941 the cases notified as ophthalmia neonatorum 928; and in 1941 cases examined 944.

Gonococci were responsible for ophthalmia neonatorum in approximately 1.8 per cent of the notified cases in 1934, and 0.86 per cent in 1941. Up to September, 1943, there has been no increase in the number of cases of gonococcal ophthalmia neonatorum. It would seem likely that such an increase due to the war would have arisen but for the general use of sulphonamides in pregnant women suffering from gonorrhoea.

Some explanatory observations are necessary upon these tables.

(1) It will be noted that in a large number of cases the *Staphylococcus albus* was present. I am convinced that the *S. albus* may be pathogenic in some individuals and cause a purulent discharge with severe inflammation.

(2) Xerosis bacilli appear very frequently in cultures from the conjunctiva. These have not been included excepting when they were the only organisms

present on culture, and it is not suggested that they were the cause of the purulent discharge.

(3) In a number of cases no growth has occurred on culture and pus cells only have been found in a stained film of the discharge. In my opinion a chemical conjunctivitis is frequently produced by the use of silver nitrate drops in a baby's eye.

TABLE 1
CASES SHOWING A SINGLE INFECTION (EXCEPT FOR XEROSIS BACILLI)
(Single infections—1934, 457 cases ; 1941, 838 cases)

ORGANISMS FOUND IN FILM AND/OR CULTURE	1934	1941
Staphylococcus aureus	133	285
Staphylococcus albus	113	263
Streptococci (including pneumococci)	83	86
Small Gram negative bacilli (Koch-Weeks or influenza type)	25	32
Coliform bacilli	9	19
Xerosis bacilli only	49	76
No growth	29	63
Gram negative diplococci (not gonococci)	8	11
Gonococci	8	3
Totals	457	838

(4) In general, gonococci have been diagnosed after culture and identification on sugar medium. If culture fails other considerations have been taken into account. In addition, the mother should be examined whenever gonococcal ophthalmia neonatorum is suspected in her child.

(5) Gram negative diplococci, which are not gonococci, occur in conjunctivitis and are indistinguishable from the gonococcus in stained films as suggested above. Some of these are of the flavus group ; others are *Micrococcus catarrhalis* : a few in my experience are very difficult to distinguish from the gonococcus, even on culture, until fermentation tests have been made.

(6) No attempt has been made to state the degree of inflammation caused by the different organisms but it may be taken as quite certain that, although the gonococcus has caused a severe ophthalmia in practically every case, other organisms, particularly *Staphylococcus aureus* and streptococci often cause an equally severe reaction. I estimate that of those cases which resulted in blindness or corneal nebulae one-third were due to the gonococcus.

TABLE 2
CASES SHOWING TWO OR MORE ORGANISMS
(Mixed infections—1934, 128 cases ; 1941, 106 cases)

ORGANISMS FOUND IN FILM AND/OR CULTURE	1934	1941
Staphylococcus aureus	45	49
Staphylococcus albus	51	63
Streptococci (including pneumococci)	98	56
Small Gram negative bacilli (Koch-Weeks influenza type)	66	29
Coliform bacilli	8	6
Xerosis bacilli only	—	—
No growth	—	—
Gram negative diplococci (not gonococci)	5	9
Gonococci	2	5
Totals	275	217

Treatment

The first essential in the treatment of a child with ophthalmia neonatorum is to ensure that the treatment is given by an expert. The expert nurse is just as important as the expert doctor. The reason why the decrease in the number of

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blind children, as a result of ophthalmia neonatorum, as stated above, has been so marked in the past ten years is that nearly every baby with severe conjunctivitis has been under the supervision of doctors and nurses who are experienced in this work. The nursing staff is highly skilled in dealing with a baby's eyes and can do their work without causing injury—only a slight abrasion of the cornea is needed during manipulative treatment to ensure a subsequent opacity. Treatment by anyone who is not doing such work regularly, however skilled he or she may be in other matters, is dangerous to the child with conjunctivitis. I contend, therefore, that the first essential in treatment is a central depot in every large town to which, at least, the severe cases of ophthalmia neonatorum can be admitted. The second point I would make is that we should know what the cause of the condition is, so that if possible, specific treatment may be given. The third important factor is the immediate application of appropriate treatment.

I have seen many infants sent to the Eye Hospital who have had active (perhaps too active) local treatment elsewhere with strong antiseptic solutions, particularly silver nitrate. Such treatment has often been prolonged for weeks by the amateur and the result has been a perforated or damaged cornea with blindness or permanent injury.

Non-specific treatment.—As indicated above, the majority of cases of ophthalmia neonatorum are due to staphylococci. For pure *S. aureus* or *S. albus* infections sulphonamide drugs seem to me to be quite useless. Irrigation of the conjunctival sac with normal saline (some prefer 3 per cent sodium bicarbonate) followed by instillation of acriflavine drops in castor oil (1 in 1,000 or 2,000) every four hours, is generally sufficient and effective. I would here sound a warning about acriflavine-in-oil drops which are now also commonly used as a prophylactic measure immediately after birth. These are difficult to prepare; the best suspension is made by the use of rivanol, a Dutch preparation not at the moment obtainable. It will often be seen that after preparation the acriflavine tends to become deposited and, unless care is taken, the concentrated deposit of acriflavine from the bottom of the drop bottle may be applied to the conjunctiva. Acriflavine, 1 in 1,000, is not in any way irritating, but the effect of acriflavine 1 in 10 is a very different matter. Various other antiseptics, such as 5 per cent protargol are in common use. Silver nitrate, 1 or 2 per cent, is also commonly used. If the response to treatment is slow, silver nitrate, preferably in the weaker solution, will often stimulate reaction but for general or prolonged use it is not to be recommended. I doubt whether the particular antiseptic used is of great importance so long as irritants are avoided. The main objective is to cleanse the infected surface and promote free drainage; in most cases the natural reaction of the tissues will promote recovery.

Specific treatment.—Sulphonamides have been used as routine since August, 1938, for cases in which the infection of the conjunctiva has been diagnosed as gonococcal. In my opinion every case of gonococcal ophthalmia ought to be admitted to hospital, otherwise dangerous complications may ensue and the infection is also a menace to others. The results, which in general have been highly satisfactory, can perhaps be seen best by a comparison of the length of stay in hospital which was deemed necessary by the surgeon in charge, of those children who were treated with a sulphonamide compound (1938-42) and those who were not (pre-1938).

Average length of stay in hospital for gonococcal ophthalmia, pre-1938, 41 days.

Average length of stay in hospital of 39 cases of gonococcal ophthalmia treated with a sulphonamide, 1938-42, 10.5 days.

Dosage.—The drugs used as routine have been sulphapyridine and sulphathiazole. The general oral dosage has been one-eighth of a gramme given in the milk four times daily or one-sixth of a gramme given three times daily. As a rule such treatment given for a period of from three to five days has been sufficient to cure the conjunctivitis, clinically and bacteriologically. The amount of the drug given will depend in some measure upon the weight and condition of the baby. Some babies have shown intolerance to sulphapyridine in the form of

vomiting or slight cyanosis, and I have found from cases which I have been asked to see that sulphathiazole has been much better tolerated and quite as effective. Supplementary treatment as for non-gonococcal cases has been given as a routine.

Unsatisfactory cases

The results of treatment of thirty-nine cases have been on the whole highly satisfactory ; comment is however necessary in four of them.

Case 1.—Baby P.A., aged six weeks, had received routine local treatment with anti-septic solutions for nearly six weeks before admission to the Eye Hospital, but oral sulphonamides had not been given. At this stage gonococci were still present in the conjunctival discharge and in addition the eye showed a perforated corneal ulcer. Sulphapyridine tablets, one-sixth gramme t.d.s., were given for three days. The discharge cleared up rapidly and the child was sent home in nine days but, as might be expected, a corneal nebula remained.

Case 2.—Baby R., aged one day. There was a purulent discharge containing gonococci from both conjunctival sacs ; the corneae were clear. Hospital treatment with protargol and boric acid lotion was continued for three days, when keratitis developed in the left cornea. Sulphapyridine tablets were then given. In the notes on this case no reason is given for the delay in starting sulphapyridine treatment, but it would seem likely that this delay in treatment was responsible for the corneal nebula which followed the keratitis.

Case 3.—Baby P., aged four days. Severe conjunctivitis ; gonococci were present. This baby was given sulphapyridine, one-eighth gramme, for three days. The conjunctival inflammation cleared up rapidly and the patient was discharged at the end of five days. One day later she was readmitted with a purulent discharge containing gonococci. The discharge again cleared up with sulphathiazole, one-eighth of a gramme, t.d.s.

In my view, it is inadvisable to discharge cases of this kind from hospital so quickly, although one is bound to admit that relapses have been very rare.

Case 4.—Baby B., aged 28 days. Gonococci were present in films and cultures from the conjunctival discharge. In this case sulphapyridine, one-eighth of a gramme, was given t.d.s. Vomiting and slight cyanosis were evident on the second day of treatment. During the third day the total amount was only one-eighth of a gramme and on resumption of the original daily dose on the fourth day vomiting started again. The amount was again reduced but the tablets were discontinued on the sixth day on account of cyanosis. The discharge from the conjunctiva was still present. On the eighth day sulphathiazole, one-eighth of a gramme, was given four times daily, and continued for a further six days without incident. The conjunctival inflammation cleared rapidly and the baby left hospital a week later.

In view of the vomiting, it would seem probable that little of the sulphonamide ever went beyond the child's stomach. In my experience toxic symptoms are much less common with sulphathiazole than with sulphapyridine.

Cases of resistance to sulphonamide compounds.—It is common knowledge that, in adults suffering from gonorrhoea, cases of resistance and failure in sulphonamide treatment occur occasionally, and it is generally considered that this is due to a resistant strain of the gonococcus. In the above cases, treated at the Birmingham Eye Hospital from 1938 to 1942, no such cases occurred. However, in August, 1943, the following case occurred.

Case 5.—Baby H., aged three days, was admitted with a profuse purulent discharge from both conjunctivae ; gonococci were present. Treatment with sulphapyridine, one-eighth of a gramme, four times daily and local irrigation treatment four-hourly were given for a week. The drugs were tolerated well but the eyes continued to discharge and at the end of a week the pus still contained gonococci. Sulphathiazole, one-eighth of a gramme, q.i.d., was then substituted and continued for a fortnight. At the end of that period a purulent discharge containing gonococci was still present.

I have no doubt that the above is an example of the effects of a sulphonamide-resistant strain of gonococci.

Conclusions

- (1) The notification of ophthalmia neonatorum should be observed more generally.
- (2) A central clinic with a visiting staff should be set up in all large towns and should be available to patients from the surrounding districts.
- (3) A bacteriological investigation should be made in every case.
- (4) Treatment should be commenced early and if possible should be specific ; it should be given by experts.

RECENT PROGRESS IN ARSENICAL COMPOUNDS

I wish to express my thanks to the Honorary Surgeons at the Birmingham and Midland Eye Hospital for their kindness in giving me permission to use the various notes and case sheets on the above cases, and also to Miss Marshall, Assistant Pathologist, who has done so much of the bacteriological investigation.

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ANNOTATIONS

RECENT PROGRESS IN ARSENICAL COMPOUNDS

The present day galaxy of drugs of the sulphonamide and allied groups, of which a new member appears on the therapeutic horizon every few months, appears to reflect a comparative lack of progress in the development of new organic arsenical compounds. We are apt to forget that in the decade following the introduction of the original salvarsan (606) and neo-salvarsan (914) many other organic arsenical preparations were launched for experimental and clinical work in syphilis. Many of their names are now scarcely known to the younger generation of workers in this therapeutic field. They represented the outcome of intense activity on the part of research chemists and manufacturers as well as steady patient trials on the part of the clinicians. Some of these compounds were used extensively in this country. Silver-salvarsan and neo-silver-salvarsan, with their additional component of silver, were used for many years with good results. Galyl, tetraoxy diphosphotetra-amino-diarsenobenzene, which was unique in including phosphorus in its structure was in use from 1913 until the early 1920's. Sulphoxyl-salvarsan, although apparently not a true salvarsan derivative, achieved a modest popularity particularly for resistant syphilis also in the 1920's.

Many other arsenical compounds appeared in these active years which saw the birth of sulpharsphenamine, stabilarsan, tryparsamide, stovarsol and acetylarsan, all of which have stayed in use until today. Others such as luargol, an antimony arsenobenzol preparation, ludyl, Albert 202, hectine, arsenomyl and arsaminol have fallen out of use long ago. Their names are now but a dim memory.

Little further progress was made until a re-investigation of the properties of *m*-amino-*p*. hydroxyphenylarsine oxide by Tatum and Cooper. This substance frequently termed "arsenoxide" had been suggested by Ehrlich as the active principle emanating from the breakdown of salvarsan but its toxicity for the lower animals appeared then too great to consider its use in human therapeutics. Tatum and Cooper in 1934 considered that "arsenoxide" possessed a therapeutic index in syphilis equal to or greater than most other effective agents, also that in rabbit syphilis this index was higher than for any other single antisiphilitic agent known to them. This compound now in use under the name of "Mapharsen," has made great headway in therapeutics since 1935 particularly in the United States of America where it has been used extensively for the treatment of syphilis along customary lines as well as for intensive arsenotherapy. In this country, where it is known as Mapharside, its employment is on a smaller scale. A recent report by Ross (1943) in 150 cases indicates satisfactory results.

Trisodarsen

Progress along these lines has continued. Stokes and Beerman in 1937 gave an account of a five year period study of the value in syphilis of a new member of the sulpharsphenamine series, tri-sodium-sulpharsphenamine, known as