

This section looks back to some ground-breaking contributions to public health, reproducing them in their original form and adding a commentary on their significance from a modern-day perspective. To complement the theme of this month's *Bulletin*, Ulrich C. Schaller and Volker Krauss review the 1881 paper by Carl S.F. Credé on the use of silver nitrate for the treatment of neonatal inflammatory eye disease. A translation follows of the original paper from *Archiv für Gynaekologie*.

Is Credé's prophylaxis for ophthalmia neonatorum still valid?

Ulrich C. Schaller¹ & Volker Krauss²

Ophthalmia neonatorum (ON), or neonatal conjunctivitis, has been a major health problem in many parts of the world for centuries. At the end of the 19th century in Europe, for example, the prevalence of ON among live births in maternity hospitals exceeded 10%, producing corneal damage in 20% and blindness in approximately 3% of affected infants (1–3). Up to 50% of children in blind schools were there because of ON (1, 2). Credé noticed that ON was transmitted from mother to infant by contagion during delivery, mostly caused by *Neisseria gonorrhoeae*, and introduced the simple technique of cleaning the eyes of newborn infants with a 2% aqueous solution of silver nitrate. This intervention alone reduced the number of cases of ON in Credé's maternity hospital in Leipzig from 30–35 per year to only one in the second half of 1880 (4), and led ultimately to a dramatic reduction in the prevalence of ON in Europe and around the world.

Today, blindness from ON is rare. In industrialized countries this is because of a lower prevalence of sexually transmitted disease (STD) in pregnant women and prophylaxis at birth (1, 2). The prevalence of ophthalmia due to gonococcal infection is reported as 0.04 per 1000 live births in Belgium and the Netherlands and 0.3 per 1000 live births in the USA (1). However, the spectrum of infectious agents has changed since Credé's time. Nowadays *Chlamydia trachomatis* is the most frequent sexually transmitted pathogen in industrialized countries (1, 2, 5, 7): prevalence ranges from 5 to 60 per 1000 live births in the USA, 4 per 1000 in the United Kingdom, and 40 per 1000 in Belgium (1). Our own data have shown a

chlamydial infection in 34.4% of 15 neonates with ON: *N. gonorrhoeae* could not be isolated, and other pathogens found were *Staphylococcus* spp., *Streptococcus* sp., *Haemophilus influenzae* and Enterobacteriaceae (7).

The prevalence of ON varies considerably around the world. In a study from Kenya in which 1000 mothers and children were examined, 28.5% of mothers were infected with *C. trachomatis* and 9.5% with *N. gonorrhoeae*. Neonates with clinical signs of conjunctivitis had chlamydia in 28.7% of cases and gonorrhoea in 20.2%. This was in contrast to infants seen at an STD clinic, where *N. gonorrhoeae* was the predominant cause of conjunctivitis (1, 2). Worldwide, 1000–4000 newborn babies become blind every year because of ON. In the United Arab Emirates, 81.5% of children with ON showed bacterial or fungal infection, but only 5% of all cases were caused by *C. trachomatis* or *N. gonorrhoeae* (6).

ON can be infectious or chemical in origin. The two agents of major health importance are *N. gonorrhoeae* and *C. trachomatis* (1, 2, 5–8). Other causes of ON include *Escherichia coli* and *Haemophilus* and *Enterococcus* spp. Herpes simplex virus may cause neonatal keratoconjunctivitis but this is rare, and usually occurs in the setting of a more generalized herpes simplex virus infection. In some patients the cause of ON remains unknown.

The risk of blindness due to ON depends on the availability of medical care, which is still a problem in rural areas of developing countries and in urban slums. As a public health measure it is important to prevent STDs and their consequences in pregnant women and the neonates. The choice of different intervention strategies will depend on the prevalence of the causative STD agents in the population and on financial, laboratory and diagnostic resources. Therefore the "gold standard" in most parts of the world is still the method that was introduced by Credé, though the recommended concentration was later reduced to 1% silver nitrate solution to lessen irritation (1, 2). The

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preventive measure was very effective, and within a few years the prevalence of gonococcal ophthalmia declined from 10% to 0.3% of births.

However, *C. trachomatis* has become more frequent than *N. gonorrhoeae* in many parts of the world, and Credé's prophylaxis has therefore become a controversial issue because of its ineffectiveness against the former pathogen. In addition, silver nitrate was criticized as being a cause of chemical conjunctivitis (1, 2, 5, 8). For these reasons, prophylaxis with silver nitrate has been abandoned in several countries (e.g. USA) and replaced by prophylaxis with 0.5% erythromycin or 1% tetracycline ointment, which is presumed to be more effective in preventing chlamydial ophthalmia. A problem with antibiotics is the high incidence of multidrug-resistant gonococcal strains, including penicillinase strains and strains with relatively high minimum inhibitory concentrations for tetracycline (1, 5).

Some countries (e.g. Denmark, Sweden, and the United Kingdom) discontinued general prophylaxis for ON altogether, arguing that no substance is 100% safe for the purpose. In these countries the risk of contracting a sight-threatening infection with *N. gonorrhoeae* is extremely low (5). However, in Denmark there were 8 cases of ON caused by *N. gonorrhoeae* within 3 years of discontinuing a general use of Credé's prophylaxis in 1985. Also, in Florida, there was an increase of incidence of gonococcal ophthalmia within 5 years of discontinuing Credé's prophylaxis (55 cases in 1984–89). In Sweden, an increase of the prevalence of infections with *N. gonorrhoeae* was noticed (5). In many industrialized countries only vague data on the incidence of ON are available, and the condition still represents a serious health problem worldwide, mainly in Africa, with a risk of blindness. The prevalence of *N. gonorrhoeae* among antenatal outpatients in Africa ranges from 4% to 15%. Data from developing and industrialized countries alike would argue for a general enforcement of prophylaxis for ON (1, 2).

Preventing infection of the neonate by treating infection in pregnant women (1, 5) can only be carried out in places where medical care is well organized, so that pregnant women at risk can easily be screened for STDs and treated accordingly. However, screening for chlamydial infection in

pregnant women is not easily implemented, and re-infection often occurs. In developing countries a general screening would be too costly.

Recently, povidone-iodine has been shown to be effective in preventing ON (5, 8). Treatment results were comparable with those obtained with silver nitrate and erythromycin for gonococcal ON and superior in the prophylaxis of chlamydial ON. In addition, povidone-iodine offers added antiviral activity against both human immunodeficiency virus and herpes simplex virus, produces no chemical conjunctivitis or antibiotic resistance, and is cheap. In the developing world a 5-ml container of povidone-iodine costs US\$ 0.10, whereas tetracycline ointment costs US\$ 0.31, erythromycin ointment US\$ 0.74 and one dose of silver nitrate US\$ 7.30. Clearly, povidone-iodine may be an ideal antiseptic for widespread prevention of ON, especially in developing countries. At a recent meeting of the Ophthalmic Society of Austria, povidone-iodine was considered to be the substance of choice for the prophylaxis of newborns against ON (5).

Credé's prophylaxis represented a tremendous step forward in the prevention of inflammatory eye disease in newborns in the late 19th century. But his original prophylaxis is mainly effective against gonococcal ophthalmia whereas chlamydial ON is now more widespread, and silver nitrate may cause chemical conjunctivitis. In industrialized countries ON is no longer a public health problem and different strategies for prevention are available, so some countries have chosen to stop prophylaxis at birth and to opt instead for early treatment. But growing populations, urbanization and increasing promiscuity cause a rising incidence of ON in developing countries.

Routine prophylaxis with topical antibiotics carries the risk of resistance, especially in patients with ON due to gonococcal infection. Povidone-iodine as a topical anti-infective appears to be an effective and cheap alternative. Further epidemiological research and monitoring on the incidence of ON and the prevalence of the various agents in different parts of the world are needed, so that prevention and treatment can be adjusted accordingly and experience with new options can be analysed for wide use. ■

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REDIGIRT VON

CRÉDÉ UND SPIEGELBERG.

SIEBZEHNTER BAND.

BERLIN, 1881

VERLAG VON AUGUST HIRSCHWALD.

Mittheilungen aus der geburtshülflichen Klinik in Leipzig.

Die Verhütung der Augentzündung der Neugeborenen.

Von
Crédé.

Die folgenden Mittheilungen über die Verhütung der Augentzündung der Neugeborenen veröffentliche ich deshalb nicht in einem Fachjournale der Ophthalmologie, sondern in diesem Archiv, weil die Krankheit fast ausschliesslich durch eine Infection während des Geburtsactes entsteht, also mit einer Erkrankung der weiblichen Genitalien unmittelbar zusammenhängt. Auch muss die Verhütung der Krankheit allein in die Hände der Geburtshelfer und Hebammen gelegt werden. Ich beschränke mich ausschliesslich auf die praktische Frage der Prophylaxis.

Im Allgemeinen kommen die Augentzündungen der Neugeborenen zeltener in den höheren Ständen vor, häufig schon im Proletariate, aber in den Entbindungsanstalten gehören sie zu einer fortlaufenden, höchst lästigen Plage und Sorge. Deshalb wende ich auch zunächst meine Aufforderung, die von mir zu empfehlende Prophylaxis weiter zu erproben, an diejenigen Herren Collegen, welche in Entbindungsanstalten oder in geburtshülflichen Polikliniken thätig sind und, gleich mir, häufige Erkrankungen zu beobachten haben.

Wohl von den meisten Geburtshelfern wird meine Ansicht getheilt werden, dass die so überaus häufig vorkommenden Katarrhe und Entzündungen der Vagina auf gonorrhöischer Infection beruhen und dass die Ansteckungsfähigkeit des Secretes noch fortbesteht, nachdem lange die specifisch gonorrhöischen Erscheinungen verschwunden sind, ja dass in Fällen, wo fast kein Secret mehr gefunden wird, doch noch die erfolgte Ansteckung in der Mutterscheide stattgefunden hat, wenn in den ersten Tagen nach der Geburt eine Augentzündung sich entwickelt.

Eine Uebertragung des Infectionsstoffes von einem anderen augenkranken Kinde ist für die Leipziger Entbindungsanstalte völlig auszuschliessen, da jenes inficirte augenkranke Kind mit seiner Mutter auf die Krankenstation verlegt wird, welche von der Station der Wöchnerinnen nach allen Richtungen hin vollständig getrennt ist. Auch können die Wöchnerinnen die Kinder mittels ihrer Finger, welche etwa durch Lochialsecret verunreinigt wären, kaum inficiren, weil die Kinder stets von den Müttern so weit entfernt in ihren Bettchen liegen, dass die Mütter sie nicht erreichen können und nur dann mit den Kindern in Berührung kommen, wenn diese ihnen von den Wärterinnen an die Brust gelegt werden.

Somit bin ich nach meinen Beobachtungen und Einrichtungen der Ueberzeugung,

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AUGUST HIRSCHWALD PUBLISHING HOUSE

Information from the Maternity Clinic in Leipzig

Prevention of Inflammatory Eye Disease in the Newborn

by
Crédé

I am not publishing the following information concerning the prevention of inflammatory eye disease in the newborn in a specialist journal on ophthalmology but in this Archive because the disease is almost invariably caused by infection during delivery and is therefore directly related to a diseased condition of the female genitals. Responsibility for prevention of the disease must also lie solely with obstetricians and midwives. I shall confine my remarks exclusively to the practical question of prophylaxis.

In general, inflammatory eye disease in the newborn occurs relatively seldom in the upper classes and quite frequently in the working class, but it constitutes an ongoing and highly troublesome complication and concern in maternity hospitals. My request for further testing of the prophylaxis I am recommending is therefore addressed to those of my colleagues who work in maternity hospitals or obstetric clinics and who, like me, are frequently confronted with this condition.

Most obstetricians would probably share my view that the cases of vaginal catarrh and infections that are so frequently encountered are attributable to gonorrhoeal infection and that the discharge remain infectious long after the specific symptoms of gonorrhoea have disappeared; moreover, in some cases where there is virtually no further trace of discharge, the infection may still be considered to have occurred in the mother's vagina when an inflammatory eye condition develops in the first few days after birth.

Transmission of the infectious substance from another child with eye disease is inconceivable in the Leipzig Maternity Hospital inasmuch as every child who is suffering from inflammatory eye disease is moved with its mother to a ward that is entirely separate in all respects from the maternity ward. The possibility of mothers infecting their children, for example through fingers soiled by lochial discharge, is also remote because the child's cot is always placed beyond reach of the mother, who only comes into contact with the child when the nurse places it on her breast.

I am therefore convinced, in the light of my observations and arrangements, that all affected children in this hospital virtually without exception were infected solely by direct transmission of vaginal discharge to the eye during delivery. The infected eye usually begins to show symptoms of disease two or three days after birth, but also sooner or later – the sooner, the more serious the condition.

For some time now, I have set myself the doubtless worthwhile task of finding effective ways and

means of preventing this disease with its pernicious consequences for so many eyes and of detecting the infectious discharge.

I initially focused on ensuring extensive and effective treatment and cleansing of the diseased vaginas of pregnant and delivering women. But the results were poor and unsatisfactory; although there were fewer cases of eye disease, they were not eradicated. I then began to disinfect the children's eyes themselves and from then on the success recorded was surprisingly encouraging.

My experiments proceeded as follows: first, the vaginas of all pregnant and delivering women admitted to the hospital with gonorrhoea or chronic vaginal catarrh were cleaned out with lukewarm water or a light solution (2 : 100) of carbolic or salicylic acid as frequently as possible – every half hour in the case of delivering women. The incidence of eye disease declined but the problem persisted; indeed there continued to be a number of tenacious and virulent cases.

In October 1879, I carried out my first test involving the introduction of prophylactic eyedrops into the eyes of newborn babies immediately after birth, using a borax solution (1 : 60) because it seemed to be the mildest and least caustic substance. This was only done, however, in the case of children whose mothers were ill and whose vaginas had been cleansed during the whole delivery process in the manner described above. From December 1879, I replaced the borax by solutions of *Argentum nitricum* (1 : 40), which were injected into the eyes shortly after birth. The eyes were carefully washed beforehand with a solution of salicylic acid (2 : 100). The children of sick mothers who were treated in this way remained healthy, while other children who had not been given preventive treatment (nor their mothers either because we thought they were not infected) still fell ill, in two cases quite seriously.

From 1 June 1880, all eyes without exception were disinfected immediately after birth by means of a weaker solution of *Argentum nitricum* (1 : 50). Moreover, the liquid was no longer injected into the eyes but a glass stick was used to introduce a single drop of liquid into each eye, which was gently opened by an assistant and which had been cleaned beforehand with ordinary water. Then the eyes were cooled for 24 hours with a canvas cloth soaked in salicylic water (2 : 100). The numerous vaginal douches, on the other hand, were abandoned and used only for other reasons entirely unrelated to the cases of vaginal catarrh. All children treated in this way remained free from even mild attacks of inflammatory eye disease, although many mothers showed advanced symptoms of vaginal blenorhoea and trachomatous growths. Only one child (annual number 339) fell ill on the sixth day with a moderate inflammation of the conjunctiva of the left eye, without swelling of the eyelid, which healed within three days. It emerged that, quite by chance, owing to pressure of work, the prophylactic eyedrops had not been administered to this child.

To date, no adverse effect on the treated eyes has been observed. Not infrequently the administration of the eyedrops is followed by a slight hyperaemia and in some cases by slightly increased secretion from the conjunctiva in the first 24 hours. Then these symptoms also disappear. They could perhaps be avoided if further tests indicate that a weaker solution of *Argentum nitricum* is sufficient.

As has been shown, the procedure is simple, easy to follow under all circumstances by anybody with fairly skilful hands, completely without risk and seemingly reliable in terms of its effect.

Although my set of observations is still too limited to draw firm conclusions, it is still sufficiently extensive and striking to warrant further urgent application of the procedure. I wish to lay special emphasis on the finding that the desired effects are achieved through disinfection of the eyes themselves rather than the vagina. It is to be hoped that the future will tell whether the eye procedure that I have been using is the best and most reliable one, or whether an even more effective procedure can be found. For the time being, I have no reason to deviate from my own method.

Needless to say, the successful banishment of inflammatory eye diseases at least from maternity hospitals and clinics would constitute a major achievement in many respects.

Lastly, I wish to present some figures for cases of inflammatory eye disease observed in this maternity hospital in recent years. Perhaps vaginal disease and hence also eye disease in the newborn occur less frequently elsewhere than in Leipzig. The distinctive conditions here, which differ from those prevailing in many other towns and even cities, must be taken into account in this connection.

Year	Number of births	Number of cases of inflammatory eye disease	Percentage
1874	323	45	13.6
1875	287	37	12.9
1876	367	29	9.1
1877	360	30	8.3
1878	353	35	9.8
1879	389	36	8.2
1880 (until 31 May)	187	14	7.6
1880 (from 1 June to 8 December)	200	1*	0.6

* This is the case in which the eyes were not disinfected; the figure should therefore read 0.0%.