

GONORRHEA AND THE BEGINNINGS OF CLINICAL RESEARCH ETHICS

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ABSTRACT Research on ocular inflammation associated with gonorrhea began in conjunction with the entry of trachoma into Europe during the Napoleonic wars. The initial questions involved the cause of the contagiousness of gonorrhea and how the contagion spreads from the genitalia to other sites. Because efforts to infect animals with gonorrheal matter were unsuccessful, all experiments were conducted on human subjects. Once these two causes of blindness were tentatively differentiated, attempts to restore vision in an eye that had been blinded by a trachomatous membrane over the cornea by instilling gonorrheal pus began to be practiced. In 1841, Joseph Píringier described his use of this method to determine infectiousness decades before the discovery of pathogenic bacteria, as well as ethical concerns about the associated endangerment of patients. Beginning in the 1880s, research focused on the identification of the gonococcus and assessment of its pathogenicity. The ethical dilemma of inducing a disease with an unpredictable outcome persisted until the 1940s, when gonorrhea could be reliably cured by penicillin.

RESEARCH INTO THE TRANSMISSION OF DISEASES, from person to person and to new sites within an individual, slowly began in the first quarter of the 19th century. The history of research on gonorrhea yields insights into some of the early considerations of the ethical ramifications of such research. Since this

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history begins before the recognition of bacteria, it falls into two parts: the first concerns the assessment of the role of “contagious matter,” while the second deals with the recognition and acceptance of a specific pathogenic bacterium. Because gonorrhea could not be transmitted to animals, all research on the disease was carried out in humans.

GONORRHEAL OPHTHALMIA IN THE PRE-BACTERIOLOGIC PERIOD

The Edinburgh surgeon Benjamin Bell (1749–1806) was the first to clearly differentiate gonorrhea and syphilis (Bell 1792). Bell was perplexed about the infectiousness of gonorrhea. He stated that “The period at which the discharge takes place, after exposure to [gonorrhoeal] infection, is always uncertain” (37). Moreover, “Why men should be more readily infected than women is difficult to explain, but that the disease should prove more violent in the former is evident” (91). The noted Paris venereologist, Philippe Ricord (1800–1889) wrote less prudently: “Women frequently give blennorrhagia without having it . . . it is as rare in woman as it is frequent in man” (Ricord 1850, 47). The lesser frequency of acute urogenital symptoms in women provides at least a partial explanation for the scarcity of inoculation experiments in female subjects.

Two French authors began the debate over whether urethral gonorrhea can “metastasis” from its primary urethral location to the eyes or can only be spread by direct contact. The pioneer ophthalmologist Charles de St. Yves (1667–1733) introduced the hypothesis that ocular inflammation may result from the “metastasis” of gonorrhoeal matter from its location in the genitalia (St. Yves 1741, 168). His contemporary, Jean Astruc (1684–1766), a physician to King Louis XV, in his book on venereal diseases, carefully described gonorrhoeal ophthalmia, and instead of metastasis advocated spread by direct contact, citing one peculiar case:

A young man had accustomed himself for a long time to wash his Eyes in his own Urine warm, every Morning, to strengthen his Sight. Unluckily he was infected with a violent Gonorrhoea, and, not expecting any Mischief, continued the former Practice. However, the Urine impregnated with the venereal Poison communicated the Contagion to the Conjunctiva and Eye-lids; whereby a violent venereal Ophthalmia was brought on, with a sharp Discharge of Tears and purulent Matter. (Astruc 1754, 306)

François Swediaur (1748–1824) introduced the terms *blennorrhagia* and *blennorrhoea* for acute and chronic gonorrhea, respectively (Swediaur 1815, 2). He adopted the idea of metastasis due to diminished urethral excretion of “seminal matter” to explain the occurrence of gonorrhoeal arthritis and by implication also of ophthalmia. The predominant hypothesis pertaining to gonorrhea, as proposed by St. Yves, was that when discharge of the pathogen through the urethra is blocked, either by treatment or other circumstances, it has to back up and then

inflames the tissues which in that individual are sensitive to it. The distinguished Scottish ophthalmologist William Mackenzie (1791–1868) conceded that some cases of ophthalmia are due to the inadvertent inoculation of the pathogenic secretion. However, he favored some sort of metastasis without stressing the concept of the pathogen backing up. The matter is transmitted either in the circulation or, “if we throw inoculation and metastasis aside, there appears to be no other means by which the diseases of remote organs can be connected, except by nervous communication” (called nervous sympathy; Mackenzie 1855, 472).

Gonorrheal ophthalmia was deemed a rare condition until the beginning of the 19th century, when, due to a diagnostic confusion, it assumed much greater prominence. Soon after Napoleon’s invasion of Egypt in 1798, many of the French soldiers developed severely inflamed eyes, often leading to blindness. In 1801 the same disaster befell British troops that had been sent to Egypt. When the soldiers returned home, physicians were confronted with a large number of cases of “Egyptian ophthalmia.” For some time this could not be differentiated from especially severe gonorrheal ophthalmia, thus resulting in greater interest in the investigation of the latter disease as well. The belief that gonorrheal ophthalmia occurs when the urethral symptoms diminish helped to discount the denial of urethral symptoms or recent sexual contact by many of the “Egyptian” patients (Collins 1904).

John Vetch (1783–1835), an ophthalmologist and former military surgeon, described a desperate therapeutic measure that was based on the idea of metastasis due to obstructed outflow of the pathogen:

In the case of a soldier, received in a very advanced state of the Egyptian Ophthalmia. . . . I took occasion to represent the possibility of diverting the disease from the eyes to the urethra, by applying the discharge to the latter surface, and he requested that this experiment, or any other, might be tried, which had the slightest chance of relieving the torture he endured, or of saving his sight; and accordingly some of the matter taken from the eyes was freely applied to the orifice of the urethra by one of my assistants. No effect following this trial, in order to establish many important facts, it was repeated in some others, all labouring under the most virulent state of the Egyptian disease; and in all, the application was perfectly innocuous. But, in another case, where the matter was taken from the eye of one man, labouring under purulent ophthalmia, and applied to the urethra of another, the purulent inflammation commenced in thirty-six hours afterwards and became . . . a very severe attack of that disease [i.e., gonorrhea]. (Vetch 1820, 242)

Vetch unfortunately concluded from these observations not that he was dealing with a different disease, but that gonorrheal inflammation could not be transmitted from one site to another in the same individual. Vetch’s experiments and conclusions were frequently quoted and became the stimulus for further human experimentation. The disease with which he was dealing was trachoma, of which he had already published a description in 1807 (Vetch 1807). As bacteriology

developed, trachoma was attributed to various bacteria, gonococci among them; its viral cause was identified in 1907 (Halberstaedter and von Prowazek 1907).

Sir William Lawrence (1783–1867), another influential ophthalmologist, made the most logical analysis of the available information without having dared experimental observations of his own. A part of his evidence was the above-cited experiments of Vetch. Because of the poor correlation between the stoppage of urethral discharge and the onset of ophthalmia, Lawrence discounted the metastasis hypothesis: “Gonorrhoeal ophthalmia cannot, according to my experience, be deemed metastatic in any cases. . . . I am inclined to refer its occurrence to the state of the constitution, without being able to point out in what that state consists; and to regard it as a pathological phenomenon analogous to those successive attacks of different parts which are observed in gout and rheumatism” (Lawrence 1854, 302).

This is the pathogenetic quandary that the Austrian ophthalmologist Joseph F. Piringer (1800–1879) sought to elucidate (Piringer 1841; Friedenwald 1897). Piringer’s second objective was to prove the therapeutic efficacy of infecting an eye blinded by pannus (a vascular membrane covering the cornea due to trachoma) with blennorrhoeal pus. Piringer’s book, with its numerous case reports and explanations of actions taken and avoided, provides an extraordinary glimpse at one man’s research methods and ethics in the mid-19th century. Piringer was unable to infect either the urethra or eye of dogs with blennorrhoeal pus (88), an observation that subsequently was confirmed by many investigators. Hence he conducted all of his investigations in the ophthalmologic hospital he had founded in Graz in 1829. Piringer was aware that it was important for the interpretation of his experiments on infectiousness to reliably differentiate gonorrhoeal blennorrhagia from Egyptian blennorrhagia (trachoma). To do so he created a list of differentiating characteristics (Table 1). This approach was essentially the same as the one devised to differentiate rheumatic fever from other rheumatic diseases by T. Duckett Jones (1944), to whom the invention of this technique is usually attributed. However, Piringer’s diagnostic approach was ignored. Thus, William Mackenzie wrote in 1855: “There are no marks which can be absolutely depended on, by which to distinguish gonorrhoeal ophthalmia, produced by inoculation, from the Egyptian or contagious ophthalmia. . . . The history of the two diseases will perhaps afford the best ground for diagnosis” (469).

The date of the first therapeutic application of blennorrhoea is uncertain, as is an observation on which it may have been based. Mackenzie attributed it to an Edinburgh physician in 1811 (Mackenzie 1855, 622). François Swediaur (1815) relates: “I have advised the inoculation of blennorrhagia, as the safest and most speedy way of curing the ophthalmia, and have had the satisfaction of seeing them generally cured without any external application” (108–9). He learned about the treatment from Joseph J. Plenck (1738–1807) of Vienna, who was best known as a dermatologist and therefore also specialized in venereal diseases. Piringer (1841) credited another ophthalmologist with this therapeutic innova-

TABLE 1 CHARACTERISTICS OF GONORRHEAL AND EGYPTIAN OPTHALMIA (TRACHOMA)

<i>Gonorrheal Ophthalmia</i>	<i>Egyptian Ophthalmia (Trachoma)</i>
Usually unilateral	Usually bilateral
Onset more rapid	Onset more gradual
Becomes severe more gradually	Becomes severe rapidly
Affects bulbar conjunctiva	Affects palpebral conjunctiva
Mucous is thicker, purulent	Secretion is pale, thinner
Keratitis occurs infrequently	Keratitis is usual
Cornea is destroyed from the surface	Cornea is destroyed from underside

Source: Piringer (1841, 147–50).

tion: “After so many highly successful experiments and unequivocal observations the inoculation of blennorhea for the healing of pannus no longer is a dubious risk that requires especial courage, but a marvelous technique that seems to have remained quite unused, ignored even though it has for many years been proposed and recommended by royal councilor, Professor Friedrich Jäger [1784–1871] of Vienna” (257).

The direct eye-to-eye transmissibility of blennorrhagia was proven in 1820. According to Mackenzie (1855), experiments conducted by Dr. Sébastien Guillié (1780–1865) “took the puriform [pus-like] mucous from the eyelids of some children with puro-mucous conjunctivitis, in the Hospital for Sick Children at Paris, and introduced it under the eyelids of four blind children belonging to the Institution for the Blind. These children were amaurotic [blind without apparent abnormalities of the eyes]. . . . In all four a regular puro-mucous conjunctivitis was produced” (441).

Piringer’s monograph was based on experience with 84 pannus-affected eyes of 59 patients and was important in publicizing the procedure. His favorable conclusions received a mixed reception. Friedrich Pauli (1804–1868), a German ophthalmologist, quoted Piringer almost verbatim: “This procedure no longer presents a questionable risk which requires particular courage, but a marvelous means which until now has remained unused” (Pauli 1847, 310). On the other hand, T. Wharton Jones (1808–1891), working in London, commented on “a peculiar plan of treating the pannus left by Egyptian ophthalmia: This, it is obvious, is a hit or miss proceeding, even if we could always calculate on the cornea becoming clear in the cases in which we might succeed in saving the eye from total destruction” (Jones 1847, 116). In 1855 Mackenzie opined: “Although the practice does by no means appear to be a very safe one, it is undeniable that cures have in this way been effected of the hypertrophied state of the conjunctiva, with the vasculo-nebulous condition of the cornea depending on it” (622). In a later British ophthalmologic text, this treatment is still described but with reserva-

tions: “[The infection] is sometimes followed by clearing up of the cornea. Not infrequently, however, the process is followed by complete destruction of the eye. The contagious and destructive nature of this remedy renders it very objectionable” (Juler 1884, 93). Ernst Fuchs (1851–1930), in Vienna, mentions it in the past tense: “[It has been] replaced by the treatment with jequirity [also known as Indian liquorice], which accomplishes the same thing without exposing the eye of the other side, or the eyes of other persons, to the danger of blennorrhoeal infection. . . . The action of jequirity depends upon . . . an unorganized ferment which is excessively poisonous” (Fuchs 1892, 80; Grieve 1931, 2:492).

Piringer (1841) clearly was aware of ethical problems in clinical research. Thus he wrote: “I have not seen an instance of the clinical development of gonorrhoea from an ocular secretion. I have not intentionally made an inoculation [of ocular secretion into the urethra] because I feared possible consequences and because human dignity seems to me to forbid such experiments” (88). Therein he was more concerned than Vetch had been. After blennorrhoeal mucous was kept for 24 hours in a closed vessel “in a warm time,” it had a terrible odor. “Because of fear that it could damage the eye,” Piringer reports, “I did not use it for any inoculation experiment” (92).

Since the bacterial cause of diseases had not yet been discovered, miasmatic infection by contact with a contaminant of the air remained a favored explanation. According to T. W. Jones (1847): “experience appears to show that infection *per distans* is the more common way [to contract gonorrhoeal ophthalmia], the air being the vehicle by which the infecting principle is conveyed.” Mackenzie (1855) wrote in regard to Egyptian ophthalmia (i.e., trachoma), but not gonorrhoeal ophthalmia: “Whether this disease be capable of propagating itself by infection—that is to say, whether the mere miasmata arising from the eyes of those affected with it, floating through the air, be capable of exciting the same disease in the eyes of others—is a point that is still in doubt” (452). Piringer doubted the miasmatic theory. In 1838 there were from eight to 11 bedfast patients with blennorrhoea in a crowded 17-bed ward in his hospital. Each patient had his own utensils, and the attendants had to wash and dry their hands before contact with the next patient. Despite the proximity of the beds, no non-blennorrhoeal patient became infected. To verify that miasmatic transmission played no role, four patients with severe blennorrhoea were crowded into a room that could barely accommodate them. The same precautions were taken, but the room was heated and its only window was kept closed. The question was whether in a situation that maximized the chance of miasmatic transmission would any attendants or visitors develop the disease? None did, thus supporting Piringer’s position.

In regard to the infectiousness of blennorrhoeal secretions, Piringer reached the following conclusions, based on numerous experiments: (1) a contaminated finger that had been washed and dried did not transmit the infection to an eye; (2) the appearance of the mucous did not indicate whether it was infectious; (3) blennorrhoeic mucous remained infectious after being diluted 50- to 100-fold

with water; (4) infectiousness of the secretion was unrelated to the severity of the inflammation, remaining infectious even when the inflammation had nearly resolved; (5) infectiousness of the secretion was unrelated to the season when it was obtained, or exposure to sunshine or cold; (6) a mucous-contaminated brush that had been left to dry for three to six hours did not transmit infection, but if the brush was left between the eyelids long enough for tears to dissolve the secretions, their infectiousness resumed; (7) a vaccination needle contaminated with mucous and kept enclosed was contagious for 48 hours, i.e., longer than a cloth left open to moving air.

Piringer appears to at least once have tricked a patient: "A linen cloth well impregnated with fresh blennorrhic mucous was immediately given to a pannus patient with the instruction that he was to carefully wipe and clean his eye with it." An infection was achieved. This never occurred when such a cloth had first been left to dry for several days. Nevertheless, if dried secretions were scraped from the cloth after no longer than 36 hours, they were infectious (91).

In the descriptions of his handling of two blind beggars, Piringer postulated a distinction between research from which a patient may obtain therapeutic benefit and research purely to gain information. The former case was a 67-year-old man who three years earlier had developed a small corneal opacity bilaterally: "Six months before he came to see me [in 1836] a dense vascular pannus developed on the left eye, resulting in blindness. I immediately decided to heal the pannus by inoculating blennorrhic matter. My newly employed assistant brought the inoculum from a newborn in the foundling home [across the street] and inoculated both eyes. After 16 hours blennorrhia developed in both eyes, more severe in the right eye without pannus, of which the conjunctiva had been entirely healthy" (43).

Piringer strongly believed that an eye could only be infected by direct contact with blennorrhic secretions. This hypothesis was derived from the sociologic observation that while gonorrhoea is about as prevalent in the educated and lower classes, blennorrhoea occurred much more frequently in the lower classes "whose cleanliness has not become habitual" (14). Mackenzie had expressed the same reasoning a decade earlier (Mackenzie 1830, 365). Thus it was important to determine the time after inadvertent contamination of an eye during which infection could be prevented by cleansing. So Piringer experimented with the blennorrhic treatment on the pannus-obscured right eye of patient number 34. Over a period of several days, he inserted blennorrhic mucous from a newborn into this eye and washed it out with a sponge soaked in cold water after one, two, and three minutes, followed by cold compresses for 10 hours. No inflammation occurred. In the fourth trial the mucous was washed out after five minutes and no compresses were applied. Increasingly severe inflammation began after several hours, and the pannus resolved. The left eye did not become inflamed.

But would the response time be the same in someone without pannus? Piringer states: "To test the validity of this observation I purchased permission to

repeat this experiment from a blind [cause unspecified] beggar. Again blennorrhagic pus was inserted into the right eye and washed out after one minute, into the left eye after two minutes, and into the right after three, each followed by hours of cold compresses." Finally mucous from a patient with Egyptian ophthalmia (trachoma) was instilled into the left eye, also without effect: "I did not dare to do more with this man, since these experiments had shown most clearly that no infection follows when the contaminated eye is carefully washed within three minutes and cold compresses are applied for several hours."

Further experiments, however, led to an unexpected conclusion. A woman had watery secretion from an adult case of blennorrhoea instilled and washed out after three minutes. On day four a severe blennorrhoea began. A different type of patient, a man whose pannus was 12 years old, had mucous from neonatal blennorrhoea instilled and cleansed after three minutes; on day five inflammation began. Piringer concluded that "These experiments showed that the application of cold compresses to the eye for several hours is essential and seems to achieve more than the cleansing of the mucous" (295–98).

A partially inadvertent sequential infection of four women was described with scrupulous honesty. In the first case, an 18-year-old girl with a three-year history of bilateral pannus was therapeutically infected with neonatal pus. In the second case, several unsuccessful attempts had been made to infect the pannus-bearing eye of a 49-year-old cretinoid woman, including pus from case number 1. Piringer notes that: "Therefore I dared to instill pus from this source into the normal eye with the expectation that it would be unsuccessful." The source was pus taken on day 12 of inflammation on vaccine needles that were then enclosed and kept in a warm room for 63 hours. However, on day eight blennorrhoea began. A week later this patient unexpectedly hugged her nurse, pressing her face against the nurse's. After two days the nurse's left eye was inflamed and remained so for six months. On day 11 of the nurse's disease, pus was taken from her eye on a brush and, after drying, the brush was put into an envelope and kept at about 20°C for two hours. Then it was inserted into the left eye of an amaurotic, otherwise healthy woman. Her tears softened the brush, but Piringer assumed "that a cold secretion would induce no harm in a healthy eye. However, on day three the eye became inflamed and five days later the right eye, that had not been protected, also" (124–31).

Julius Hirschberg (1843–1925) cited an instance from 1855 of serial infection analogous to the one initiated by Piringer's 49-year-old retarded patient (Hirschberg 1899–1918). A physician's eye inadvertently became infected while he was treating a case of neonatal ophthalmia. Pus from his eye was transferred to the atrophic but uninfected eye of another man, resulting in a purulent discharge. This discharge was inoculated into the urethra of a mentally retarded person, producing gonorrhoea. This gonorrhoeal pus was inoculated into two other urethras, again resulting within two days in gonorrhoea. Finally, the secretion from one of these urethras was placed on the conjunctiva of a traumatically destroyed eye, whereby a purulent discharge was reproduced. Hirschberg commented: "It

is important to collect such observations, because nowadays such experiments can, of course, not be performed anymore” (9:311).

In 1847, Friedrich Pauli sought by experiment to settle the debate whether the cause of gonorrhoea was a systemic poison that in some individuals, due to local susceptibility, happens to affect the genitalia, or whether it was a specific contagious matter associated with any affected organs. His principal argument for an organ-specific agent was that it was so rare for a disseminated disease to occur following acute gonorrhoea. Contrary to some later writers, Pauli assumed (correctly) that neonatal ophthalmia had the same cause as gonorrhoea, being transmitted during birth from the infected mother. Thus the experiment of trying to produce gonorrhoea from neonatal ophthalmia was not intended to prove the cause to be identical, but to prove that the cause was organ-specific. Had the experimentally induced disease shown systemic symptoms, this would have been interpreted as a toxemia. His report of the experiment follows:

[I saw] a child with ophthalmia neonatorum whom [a colleague] was treating at the time. There was thin, mucoid pus in one eye and a thick purulent discharge from the other eye, which had been affected first. The latter [type of pus] if taken from the urethra, as Ricord's experiments teach, is not as infectious as the former. I brought a vigorous, healthy 36 year old man to this experiment who was fully informed and paid. I inserted a bougie that had been moistened with the aforementioned thin ocular secretion into his normally sensitive urethra. In his early 20s this man had a gonorrhoea which however resolved without residual symptoms. Since then he had never had a genital illness and had no cause or concern in his eight years of marriage. . . . The experimental subject felt nothing for the first two days after the insertion of the bougie. On the morning of the third day the urethra was still dry, although he perceived a tickling in the glans; in the evening the first definite traces gonorrhoea appeared: sticking together of the urethral orifice, the sensation of pressure in the urethra, urinary frequency with mild dysuria. On the next, fourth, day no doubt remained regarding the presence of gonorrhoea: the discharge appeared pale yellow, the dysuria was more severe. The inflammation continued to increase on the fifth, sixth and seventh day: the entire penis was swollen, the urethral orifice was injected, the discharge was thick yellow, the pain not insignificant, the patient was tormented with painful nocturnal erections. From the tenth day on these symptoms diminished, so that it became possible on the twelfth day to make the first injections of very dilute silver nitrate. On the fourteenth, when the discharge had nearly disappeared, he had intercourse with his wife, but the discharge increased slightly on the next day. Two injections of somewhat more concentrated silver nitrate ended the discharge. Although the patient on the following day felt a mild tension and now and then a brief acute pain in the perineum, the urethra nevertheless remained dry. His wife, however, on the fourth day after intercourse developed a gonorrhoeal vaginitis, although with much milder inflammatory symptoms than the man had experienced, and could already be treated with silver nitrate injections on the eighth day. (Pauli 1847, 353–55)

Since the resulting inflammation was limited to the genitalia, Pauli could consider his hypothesis that only certain susceptible organs can be affected to have been proved.

RECOGNITION OF A MICROBE

In 1879 Albert Neisser (1855–1916), while a resident in the dermatology-venereology department at the University of Breslau, became engaged in a microscopic study of gonorrheal secretions. He detected a microbe in pus from 26 men and women with gonorrhea and in seven cases of neonatal and two of adult ophthalmia (Neisser 1879). At this time only anthrax, relapsing fever, and, equivocally, leprosy had been shown to have a bacterial etiology. Hence, reluctance to accept a specific bacterium as the cause of another disease was not surprising. Such doubt was quickly reinforced by failure to infect dogs and rabbits with cultures of this germ.

Ten months after Neisser's paper was published, Arpad Bokai (1856–1919), a resident at the University of Budapest, confirmed Neisser's microscopic findings and sought to determine whether these microbes actually were the pathogens of gonorrhea (Bokai 1880). Because cultures of this organism had no effect on animals, "we carried out six tests. The reason for this small number is that we found but a few individuals (mostly students) who offered themselves voluntarily and were known to us personally as reliable in every respect." Instilling two drops of fluid (seemingly from a culture) into the urethra of three healthy volunteers resulted in acute gonorrhea. Treatment of the discharge before culture with potassium hydroxide made no difference. Three other experiments gave negative results: placing urethral secretion beneath the prepuce, and in two cases using secretion from ophthalmia to insert in the urethra (the experiment which Vetch had performed and Piringer had refused to do for ethical reasons). Bokai's tentative conclusions were that he could not distinguish pathogenic from non-pathogenic micrococci, and that pathogenicity appeared to be influenced by both species and local tissue circumstances.

In 1882, Neisser introduced the term *gonococcus*. In this paper he conceded that "We still lack actual proof that these 'Gonococci' are the pathological principle of gonorrhea, that they are actually the contagion of gonorrheal affections." He made a more elaborate morphologic description of this bacterium, whereby he considered it to increase the probability that it must be the unique pathogen. Nevertheless, he erroneously believed that "The micrococci are found principally attached to the cells, both pus cells and epithelial cells. . . . I believe that they are simply located on the cells, that is, they certainly have nothing to do with the nuclei." He criticized Bokai's report and at least implied that more carefully designed human inoculation experiments were necessary to establish pathogenicity. In 1883, N. A. Keyser, a University of Maryland medical student, reviewed the conflict about the pathogenetic role of gonococci and described his

microscopic examinations of secretions from 67 cases of gonorrhoea. These led him to differ with Neisser about whether the bacteria lay upon the surface of the pus corpuscles. He concluded that he was “of the opinion that they are contained within the cells themselves.”

The course of acceptance of the pathogenicity of the gonococcus can be seen in the publications of one pioneer microbiologist, George M. Sternberg (1838–1915), from 1882 to 1887. Sternberg, who would become surgeon-general in 1893, was a major in the Army medical corps in California in 1883, when he published his first article about “The Micrococcus of Gonorrhoeal Pus” (Sternberg 1883a). He began: “Many physicians are inclined to make the generalization that all infectious diseases are parasitic, and it must be admitted that there is much to be said in favor of this hypothesis. A proper scientific conservatism, however, requires that the list shall be considerably extended before such a generalization can be considered safe.” Sternberg confirmed that with methyl violet staining, no microorganism other than a micrococcus could be detected in gonorrhoeal secretions. However, confirming Keyser and contrary to Neisser, some in each case were within pus cells. Sternberg (1883a) also concluded that he was examining “an accidental parasite which has nothing to do with the special virulence of this fluid.” Sternberg found that cultures made from gonorrhoeal pus injected subcutaneously into rabbits and into the eye or urogenital tract of dogs had no effect: “I accordingly determined to seek an opportunity to make it [inoculation] upon man. My first efforts, by the offer of a bribe, to find a willing subject, were unsuccessful.” However, a physician acquaintance provided him with three chronic patients at the San Francisco City and County Hospital. “These patients consented to the operation with a full knowledge of the possible results from a desire to please their doctor, and under the promise of speedy cure and a suitable recompense in case of successful inoculation.” None of the three developed inflammatory symptoms. A month later “several gentlemen connected with the City Dispensary had consented to furnish healthy urethras for the experiment.” When the time came, however, only one medical student agreed to undergo this: “Contrary to my expectation, Dr. Keirle himself had determined to test the ‘gonococcus’ in his own urethra, and with this example before me I could not do less than join in the experiment, although I confess that I did so with some hesitation.” All three inserted cotton that had been soaked in a presumed gonococcus culture into their urethras. Four days later none had experienced a reaction, and so Sternberg repeated the experiment on himself, again without an infection developing. He concluded that the gonococcus cannot be distinguished morphologically from micrococci from non-urethral sources, such as an oral species which he found to be infectious for rabbits (Sternberg 1883b).

Twenty-one months after his initial paper, Sternberg (1884) became ready “to confess that he claimed too much for his negative results in inoculations with pure cultures . . . that infective virulence is not due to the presence of this

microorganism.” His principal speculation was that the pathogenicity is altered by the circumstances of repeated subculturing. In his last article on the subject, in 1887, Sternberg again admitted his initial error, but now attributed it to confusion of the gonococcus with non-pathogenic cocci having an identical appearance. This probably was the correct interpretation and augured a decade of conflict about how to reliably detect and identify diplococci.

Conflicts About Identification

The impossibility of testing pathogenicity of the suspected pathogen of gonorrhea in animals necessitated testing in human subjects. Whether inoculations were to be made into animals or humans, however, two ascertainments had to be made: the inoculum had to be free of potentially pathogenic contaminants; and one had to be able to identify the organism that was being inoculated. The first criterion was dealt with by making the inoculum from late subcultures, the hypothesis being that contaminants would have been diluted out. No comparisons were made of the pathogenicity of different subcultures of the same organism, and so the possibility that repeated subculturing might alter the pathogenicity remained an unresolved concern.

Two methodologic problems were recognized: contrary to Neisser’s (1893) persistent opinion, the gonococcus could not reliably be differentiated from other cocci microscopically, and it was extremely difficult to obtain growth on culture media. In 1886, Gabriel Roux reported that a slightly modified version of the stain that Hans C. Gram (1853–1938) had devised would identify the gonococcus (Gram 1884). This finding rapidly initiated a study by two New York physicians, C. W. Allen (1887) and E. C. Wendt (1887), whose papers strongly endorsed the reliability of Roux’s procedure. Of importance for the ethical aspect of human inoculation experiments is Allen’s conclusion that “As regards treatment, the discovery of the gonococcus cannot as yet be said to have produced any decided advances” (Allen 1887). Thus the assurances of effective treatment if a gonococcal infection is experimentally induced was either based on misguided faith in a remedy or an outright falsehood.

The first medium that was specifically intended to facilitate the growth of gonococci was devised in 1885 (von Bumm 1885). In an experiment in 1890 by Steinschneider, working in Neisser’s laboratory, a tenth subculture of gonococci was inserted into the urethra of a man who had had gonorrhea more than 10 years before, from whom no gonococci could be detected. A transient urethritis with sparse gonococci developed, and symptoms disappeared after one week. There were two possible explanations. Virulence may have been lost, as indicated by their poor ability to enter cells, due to the medium on which they were grown. Alternatively, this may have been a heretofore-unknown, nearly non-virulent strain (Steinschneider 1890).

The Viennese gynecologist, Ernst Wertheim (1865–1920), believed that he had devised a better solid medium with the addition of human serum to a com-

mon bouillon-peptone-agar. However, even if gonococci would grow on this relatively rapidly, was their virulence affected? To test this he cultured pus both from acute urethritis and from fallopian tubes on this medium: "I undertook inoculations into the healthy urethra of five male paraplegics, and every time with a positive result" symptoms lasting four to five weeks (Wertheim 1891).

In 1893, Steinschneider performed two more inoculation experiments. His first volunteer was a young physician who was asymptomatic three months after having had acute gonorrhoea. A twelfth subculture of gonococci was introduced into his urethra resulting in only minimal symptoms. Therefore, "another colleague offered himself most obligingly." He had no history of gonorrhoea and received a fourth subculture of gonococci. This resulted in typical acute gonorrhoea. Steinschneider merely concluded that this proved that pure cultures could be obtained on Wertheim's medium, not commenting on the possible effect of the recent prior infection or the possible effect of the subculturing on pathogenicity. However, he also was curious whether the pathogenicity of gonococci was limited to the genitourinary tissues. Therefore one (unidentified) person was given a subcutaneous injection of a serum-enriched gonococcal culture. No reaction resulted, and this question seems not to have been pursued (Steinschneider 1893).

In 1893, Ernst A. Finger (1856–1939) and his colleagues in Vienna performed two series of experiments, the first of which sought to test whether a previous bout of gonorrhoea confers immunity against reinfection. The subjects were six men with a history of gonorrhoea, but considered healthy. The description of the first case includes the statement that the procedure was done "with the complete agreement of the intelligent patient." In four of the subjects no urethral gonococci were seen, and in two they were sparse, but seemingly no cultures were made. Three men had material from a third subculture of gonococci instilled in their urethra, and in the others later subcultures were used. Each subject, whether he had been asymptomatic or had chronic urethritis, developed an acute inflammation. Thus, "The gonorrhoeal process is capable of re-infection and superinfection" (Finger, Ghon, and Schlagenhauser 1894).

The second experiments concerned whether fever diminishes susceptibility to infection. The subjects were moribund febrile men: one from pneumonia, the others from tuberculosis. No information was provided whether there were histories of gonorrhoea or whether anyone had consented to these trials. Three died within 33 to 72 hours after gonococci were instilled in their urethras, and at autopsy these showed signs of urethritis. Four died three to seven days after inoculation, and one who survived for 18 days after the first inoculation was inoculated a second time. All were found to have normal urethras. It was concluded that "All patients with negative inoculation results . . . had elevated temperatures, most in the evenings exceeded 39°C. . . . We must arrive at the conclusion that febrile temperatures protect the individual against gonorrhoeal infection, or at least markedly impede it" (Finger, Ghon, and Schlagenhauser 1894).

Wertheim was stimulated by Finger's tests of immunity to perform the following experiments. First, he cultured urethral pus from the two-year-old gonorrhoea of a colleague and reintroduced this into the subject's urethra. No exacerbation occurred. In the second experiment, some of the same culture was introduced into the urethra of a man who had a remote history of gonorrhoea, but whose urethral cultures now were repeatedly negative. On day two symptoms of culture-positive gonorrhoea began and lasted seven weeks. In the third case, pus cultured from the inoculation-induced acute gonorrhoea of subject number 2 was inserted into the urethra of subject number 1, who now developed acute gonorrhoeal symptoms that lasted five to six weeks. Wertheim concluded that the two-year-old strain that was causing only mild symptoms had not lost its virulence. His preferred explanation was that the subject's failure to develop severe symptoms was probably determined by a local tissue factor. The gonorrhoeal [urethral] mucosa in case number 1 initially did not react to its own gonococci. However, once these had been detoured through another individual they again could induce acute inflammation (Wertheim 1894).

The instillation of 2% silver nitrate into the eyes of newborns, beginning in the mid-1880s, rapidly diminished the occurrence of gonococcal conjunctivitis, and consequently an indicator for less well-recognized manifestations of gonococcal disease also was lost (Credé 1881). Vulvo-vaginitis, inflammation of the external genitalia of female infants and young girls, was a common, etiologically confusing problem. Mothers in many cases lacked definite gonorrhoeal symptoms, and if cultures were taken, several bacterial species were usually obtained.

If bacteria that had the appearance of gonococci were found, were they also the pathogen of gonorrhoea? In 1892 Edward Martin, a Philadelphia urologist, sought to resolve this question. His source of pathogen was a five-month-old girl who had a severe purulent vulvo-vaginitis, on culture morphologically containing gonococci. The mother had a slight chronic leucorrhoea, microscopically negative for gonococci. Martin "found a man who had suffered from gonorrhoea some three years previously," who had neither symptoms nor signs of urethritis. At this time gonococci were microscopically absent from the infant's secretion, some of which was inserted into the man's urethra. On the fourth day symptoms of gonorrhoea began, and gonococci were detected on day 10. An orchitis developed, and inflammatory symptoms persisted after five months. Martin (1892) concluded: "Accepting this case, the proof is afforded that the micro-organisms of vulvo-vaginitis and gonorrhoea are alike both in physical and pathogenic attributes, that they are not merely similar but are the same" (417-18).

Investigators repeatedly justified their inoculation experiments by the inadequacy in number and methodology of prior research. For example, H. Heiman (1895) claimed that: "The crucial test for the establishment of the gonococcus on a true bacteriological basis is inoculation experiments in the human economy, since animals are to a certain extent refractory. And yet how seldom this method has been brought into play in connection with works of others becomes

apparent when we look up the literature of this special topic.” Yet Heiman essentially only duplicated the European experiments. He inserted a presumed gonococcal culture recovered from a male urethra into the urethra of “a boy aged four, suffering from idiocy.” Purulent urethritis developed after a longer than usual incubation period, and gonococci were recovered. The next subject was “an idiotic boy, aged sixteen,” into whose urethra a culture was inoculated that had originated from a child’s vulvo-vaginitis (a repeat of Martin’s experiment). This boy suffered a more acute gonococcal urethritis than the first subject. A third experiment was made to evaluate whether fever prevented gonococcal infection. An adult dying of tuberculosis with no history of gonorrhoea had a culture obtained from vulvo-vaginitis inserted into his urethra when his temperature was 40.2°C. A minimal urethritis with discharge containing a pure culture of gonococci resulted, replicating Finger’s observation. Heiman differed from most investigators in that he performed a few control experiments. He inoculated “a large diplococcus found in the normal urethra” and a similar microbe from a case of vaginitis each into the urethra of one healthy young man. No urethritis developed. His final conclusion was that “My inoculation experiments on the human urethra confirm the belief in the specific pathogenic power of the gonococcus (Neisser).”

In 1897, Swedish investigators modified Wertheim’s culture medium by substituting ascitic fluid for serum. Like other investigators, they then wanted to test whether gonococci grown on their medium were pathogenic. To do so they inoculated a third subculture of gonococci into the urethra of a patient with tertiary syphilis who was believed never to have had gonorrhoea. A typical gonorrhoea resulted, from which the patient was still symptomatic four months later (Jundell and Åhman 1897).

Neisser had commented in his 1882 paper that only in regard to conjunctivitis is the [extra-genital] role of gonococci “universally acknowledged.” He had made two unsuccessful attempts to demonstrate gonococci in synovial fluid in cases of presumed gonorrhoeal arthritis and cited the same experience of two other investigators. However, also in 1882, a Bolognese physician visualized bacteria he believed to be gonococci in fluid from an inflamed knee in each of two young men who had gonorrhoea (Petroni 1883). In 1884, this observation was confirmed in knee fluid from a man and a woman (Kammerer 1884). The first culture of gonococci from a case of arthritis was obtained by Neisser in 1894, using Wertheim’s medium for fluid from an ankle of a man who had no urethral symptoms. The critical proof of the pathogenetic relationship between gonorrhoea and arthritis was obtained by Guido Bordoni-Uffreduzzi (1894). During exploratory surgery on an ankle of a young woman who had gonorrhoea, he obtained pus that contained intracellular Gram-negative cocci, which he was able to culture. He found a healthy 23-year-old man who had no history of venereal disease or recent sexual intercourse who volunteered for the experiment. Some second subculture was inserted in his urethra, and two days later

typical gonorrhoea developed. Bordoni-Uffreduzzi concluded: "I believe that my examinations have provided incontrovertible proof that the gonococcus can also disseminate internally and there can elicit the signs of inflammation, as it does in the genitalia." Finger (1896) alluded to the same experiment having been carried out successfully in his department, also in 1894.

ETHICAL CONCERNS

Ethical concerns were occasionally expressed in the mid-19th-century about specific types of human infective experiments. Thus Homer Bostwick, a New York venereologist, writing in 1848 about the unpredictable effect of various allegedly anti-gonorrhoeal drugs, stated: "it is a matter which could only be tested by a series of difficult or nearly impossible experiments, for we are not to expect that men will voluntarily submit themselves to infection, merely to oblige a scientific experimentalist." William Lawrence (1854), directly counter to Piringer, stated: "Whether this dangerous ophthalmia can be produced by the application of gonorrhoeal matter to the organ, is a more doubtful point, which the nature of the subject prevents us from settling in the only satisfactory way, that is, by direct experiment" (300). The broadest statement of ethical concern was made by Philippe Ricord (1850): "The first method of experimenting, that is to say, the inoculation of a healthy individual . . . ought always to be rejected by the physician. I do not believe that we have the right to make such experiments. The physician not only ought not to use his natural authority to induce anyone to undergo experiments of this nature, but I farther think that he ought to resist the desires of individuals, who, seduced by a generous devotion, would voluntarily expose themselves to the chances of an inoculation" (38)

Human inoculation experiments with gonococci appear to have ceased by 1900. This probably is largely attributable to a conclusion that no more could be learned from such experiments, but perhaps also from greater attention to ethical considerations. The one piece of evidence in support of the latter is a regulation passed by the Prussian Ministry of Education in 1900 (Sass 1983). Prussia was the location of much of the early bacteriologic research, and this regulation, though technically not pertaining to all of Germany, was the first to address informed consent. It stated:

- I. The directors of clinics, outpatient departments and other medical facilities are advised that medical interventions for purposes other than diagnosis, treatment and immunization are prohibited even when other circumstances for legitimate and ethical permission are present when:
 1. It pertains to a person who is still a minor, or for other reasons is not competent;
 2. The person in question has not given her consent to the intervention unequivocally;

3. When the explanation does not provide adequate understanding of the possible injurious consequences of the intervention.
- II. 1. Interventions of this sort are to be undertaken only by the chief [of service] himself or by someone specifically designated by him.
2. In such an intervention the fulfillment of provisions I. 1–3, as well as all details of the case are to be entered into the medical record.

THE ADVENT OF CURATIVE THERAPY

In 1938, sulfanilamide became the first drug that could with fair reliability cure gonorrhea. Four grams per day by mouth for at least three weeks resulted in an overall cure rate of about 80%, although this achievement required a second course in about a quarter of the cases (Cokkinis 1938). The incidence of drug resistance increased rapidly, but the sequential introduction of sulfanilamide analogues maintained the cure rate.

The U.S. Public Health Service planned an investigation of possible anti-gonococcal prophylaxis undoubtedly before the anti-gonococcal effect of penicillin was recognized. The preliminary phase, which required the infection of men with the gonococcus, was conducted between October 1943 and January 1944. It is the largest study based on inducing a bacterial infection known to have been undertaken. A reliable method of experimental infection was deemed necessary, otherwise it could not be known whether lack of infection of an exposed individual was due to the prophylactic regimen or lack of exposure to the pathogen. The subjects were selected from among the prisoners in the federal penitentiary in Terre Haute, Indiana. Of 293 volunteers, 241 became participants. It was wartime, and it may be construed that some participants applied as their part of the war effort. To qualify they had to be between 21 and 45, and have no evidence of urinary tract infection based on cultures, anatomically normal genitalia, no other debility that might affect the course of the induced infection, an ability to cooperate, sufficiently long sentences that they could be observed for six months after being inoculated, and “assurance that the volunteer possessed a thorough understanding of the purpose underlying the study and the possible risks involved.” According to the study report: “Each volunteer received a financial reward and an official certificate of participation, and a suitable notation was incorporated into the records of the institution” (Mahoney et al. 1946).

Of the participants, 131 had no history suggestive of gonorrhea, and 43% of these became infected; of the 108 with a history of gonorrhea, infection occurred in only 24%. The most reliable method of infection was to inoculate gonorrheal secretions, rather than cultured bacteria, directly into the urethra. However, no technique produced infection with a consistency that was adequate for use in studying prophylaxis. Typical symptoms usually developed within six days of inoculation but were delayed for as long as 31 days. The majority of infections were

successfully treated with sulfanilamide or sulfathiazole. All cases that did not respond to the sulfa drugs were successfully treated with 150,000 units (a very small amount) of penicillin (Herrell, Cook, and Thompson 1943; Mahoney et al. 1946).

These attempts to induce a disease preceded both the 1946 publication of the AMA policy on experimentation and the 1947 Helsinki protocol on human experimentation that resulted from the Nuremberg war crimes trial (Judicial Council of the AMA 1946; Vollman and Winau 1996). Factors that affected these developments have been thoroughly reviewed by Weindling (2001). The first of the 10 paragraphs of the Nuremberg Code of 1947 states:

[The subject] should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision. The latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconvenience and hazards reasonably to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment.

Nevertheless, a paradox in the Nuremberg Code that was central to the ethical issues of human gonorrhoeal research was not resolved. According to paragraph three, "The experiment should be based on the results of animal experimentation." Numerous investigators, beginning with Piringer in the 1830s, sought unsuccessfully to use animals for their research before resorting to humans. The greatest ethical difference between the Public Health Service investigation from those done 50 or more years earlier was that it could now be guaranteed that no long-term harm would result from an induced infection.

The 19th-century history of research pertaining to gonorrhoea illustrates both the scientific problems that were addressed in the new science of bacteriology and the research ethics of the period. There were no acknowledged policies regarding the participation by or endangering of subjects, at least in regard to inducing or exacerbating morbidity. Any restrictions derived from the attitudes of individual investigators.

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