History of the Medical Treatment of Gonorrhea

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In his textbook "A Complete Practical Work on the Nature and Treatment of Venereal Diseases", Homer Bostwick stated that "We do not know of any substance, which, taken into the system, is an antidote to the infection of gonorrheal matter. Such an antidote has been long sought for, and its pretended discovery has been often announced, but we have no good reason to believe that any of these pretended prophylactics are infallible. It is natural to suppose that a small dose of the essence or extract of cubebs, or of turpentine, might have such an effect, but 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."(1)

At that time, the two most consistently used medications for both acute and chronic gonorrhea were cubebs, an Indonesian variety of pepper of which the dried powdered unripe fruit was used, and balsam of copaiba (or copaiva), which was extracted from a South American tree. In 1859, 151,000 pounds of copaiba balsam were imported into Great Britain, largely for the treatment of gonorrhea! (2) The indication of their effectiveness was cessation of the discharge. The main difficulty with both agents was their irritating gastrointestinal effect, cubebs being only tolerated a little better of the two. Therefore many prescriptions were tried to mask the taste and toxicity, such as mixing copaiba with liquorice or either with magnesium hydroxide or ammonium carbonate, or using gelatin capsules.3 According to Bumstead (1864) these drugs "…are of undoubted efficacy in the treatment of many cases of gonorrhea, but in others they utterly fail; nor have we any means of distinguishing these two classes of cases beforehand…. They are by no means indispensable in the treatment of every case of gonorrhea."(3)

However, most publications into the '90s were more enthusiastic about these two botanicals. According to the 1874 edition of Dunglison's Dictionary of Medical Science: "Gonorrhea of every kind, attended with any inflammatory symptoms, is best treated by the antiphlogistic regimen, avoiding every kind of irritation, and keeping the body cool by small doses of salts, and the urine diluted by the mildest fluids. After the inflammatory symptoms have subsided, cubebs, or the balsam of copaiba exhibited in the doses of 1 ½ to 2 drams (2.7-3.6 gm) three times a day, will be found effectual; indeed, during the existence of the inflammatory symptoms it often affords decided relief (4).

In 1879 Neisser discovered the gonococcus and it was soon proven to be the etiologic agent of gonorrhea. He demonstrated its presence consistently in patients with characteristic symptoms (5). Cultures of gonococci when introduced into the urethra of healthy men, caused the disease.6 Although the possibility of etiologically focused therapy was now raised, no rapid therapeutic advances resulted.

Encouraged by the success of diphtheria and tetanus antitoxins in the 1890s the first vaccine prepared from killed gonococci taken from Neisser's laboratory was introduced in 19097. The investigators' impression was that this treatment benefited arthritis, but was less reliable against urethritis. Nevertheless, variously prepared anti-gonococcal vaccines gained considerable use with, at best, equivocal results. The first American vaccine was produced by the New York City Health Department in 1910. An injection about every third day for two months was recommended (8). In 1916 the effect of vaccines of killed gonococci, meningococci and colon bacilli administered intravenously in cases of gonorrhea, some with epididymitis or arthritis, was

compared. The effects were most consistently beneficial in regard to arthritis. However, the responses were not specific to the gonococcus vaccine. The author speculated that the effects resulted from the fever that the vaccines elicited (9). According to the 1920 edition of Osler's "Principles and Practice of Medicine" "…the use of antigonococcus serum and vaccine treatment are worthy of a trial; either will help in some cases, both fail in many." Osler still favored the ancient approach: "good food, fresh air, and open bowels… Drugs are of little value, especially sodium salicylate and potassium iodide."(10) In 1932 "The general condition of the patient must be treated with a view to raising the resistance to the (gonococcal) infection" still was an authoritative statement (11).

The search for specific anti-bacterial drugs began in the 1890s. Most of those that preceded sulfanilamide were metallic: compounds of arsenic, antimony, bismuth, gold, and mercury. Hugh H. Young (1870-1945), the professor of urology at the Johns Hopkins Hospital, focused on mercury compounds in seeking to develop a urinary tract antiseptic. From among "more than 260 compounds that have been prepared" merbromin (Mercurochrome-220), first tried in 1919, achieved considerable use. It is a derivative of fluorescein, complexed with bromine and mercury. In vitro studies in 1921 showed Mercurochrome to be effective against N. gonorrhoe in a 40-fold higher dilution than against E. coli. Young's usual treatment consisted of a one per cent Mercurochrome solution injected intravenously, with the volume adjusted to the patient's weight. Three to six infusions with increasing dosage, typically from 12 to 21 ml., were administered a few days apart (12). Redewill et al. concluded from experiments that the safety and efficacy of this treatment was improved by injecting the one per cent Mercurochrome in a 50% glucose solution. They advocated more doses of a smaller volume than previously advocated (up to 20 doses in seven weeks). In keeping with the theories of Ehrlich, they presumed that in practical dosage the main action of Mercurochrome is in that it "directly stimulates the outpouring of anti-bacterial substances" and only secondarily is bactericidal (13). Young still wondered in 1932: "It seems remarkable after Ehrlich's great work with arsphenamine…. and his prediction that in a few years many infectious diseases would be treated by chemotherapy, that so many of the medical profession should still remain hostile to chemotherapy."(11) The clinical data of Redewill et al. indicate that the Mercurochrome therapy was added to unspecified "routine treatment" and reduced the time to effect a "cure" by one half: acute gonorrhea from about 45 days to 21 days and chronic gonorrhea from 95 days to 46. Eventually Young et al. found that this treatment did not sterilize the urethra. In 1932 he was instilling a silver protein complex or Mercurochrome into the urethra or irrigations of potassium permanganate into the seminal vesicles in addition to the intravenous Mercurochrome, and "The splendid results obtained speak for themselves."(11)

Exposure to heat has been used to treat various diseases since ancient times. According to a report from the "electrical departments" of two London hospitals in 1923 "the clinical investigation of the treatment of gonococcal infection by diathermy" had been initiated in 1913. At first heating was limited to affected joints in cases of gonococcal arthritis. Genitalia began to be treated when some cases of arthritis only began to respond with the addition of genital heat treatments. The optimistic report was based on experience with 25 cases of arthritis, 26 men and 16 women with gonorrhea, but reports of additional cases did not follow (14).

Heat therapy of gonococcal infection achieved scientific justification in 1932 when investigators at the University of Rochester, NY discovered that, in vitro, 99% of a gonococcus culture is killed by two hours of exposure to 41.5°-42.0° C., although heat resistance varied among strains (15). These investigators administered this level of hyperthermia in five hour treatments to 20 women with gonorrhea, two of whom also had arthritis. The arthritis responded particularly rapidly (16). Of the several modalities that were used to heat the body, the Mayo Clinic approach was favored. A fever cabinet was used in which all but the head was enclosed. It took at least an

hour to raise the temperature above 41°C. which was then maintained for 4-6 hours. Treatments were given every third day and 5-6 treatments were usually required to effect a cure (17). This protocol became the standard technic, but a history of cardiovascular disease excluded patients. The effect of hyperthermia for gonococcal and rheumatoid arthritis was compared and found it to be curative in 80-90% of the former, but not particularly useful in the latter (18). A decade after the use of intravenous treatment with mercurochrome in hypertonic glucose, it was soon accepted that pre-treatment with such infusions facilitated the efficacy of hyperthermia (19).

Since the focus of gonococcal infection usually is in the pelvis or external genitalia some investigators concluded that a curative effect might be facilitated by greater heating of the pelvis than the entire body might tolerate (20). Thus heating elements were inserted for about two hours in the vagina and sometimes also in the rectum in women, as well as in the rectum in men, achieving local temperatures approaching 44° C (111° F) for up to two hours. With the addition of pelvic heating, fewer treatments were usually required. Consensus developed that hyperthermia is the most reliable treatment for gonococcal arthritis, with genital symptoms most often also disappearing (21). Nevertheless, heat therapy gradually became obsolete after the introduction of sulfonamides.

The advent of antibiotics "1937 might well be tagged sufanilamide year….Seldom has any new drug aroused so much enthusiasm or so rapidly gained attention….The advent of sulfanilamide has established beyond all doubt that effective chemotherapy of microbial diseases is attainable."(22) However, by 1941 disappointment had set in: "The chemotherapeutic treatment of gonorrhea, when first inaugurated, promised Utopia to the physician in the ease of management and to the patient in the rapidity of cure. Sufficient evidence has accumulated and adequate time has now elapsed to point out the fallacy of first impressions…"(23) What happened?

The first reports of the effect of sulfanilamide on gonorrhea appeared in 1937. Treatment at the Johns Hopkins University Clinic lasted four weeks with the divided daily dosage decreasing from 4.8 gm to 1.2 gm per day (total 65.6 gm). Fifty-eight patients became asymptomatic in about four days, but six initial responders relapsed (24). A much larger investigation was carried out in London in which the effect of sulfanilamide was compared to the results of standard therapy in 1936. Indeed the sulfanilamide cases responded much faster and exhibited fewer relapses. Lengthier treatment was considered optimal, 70-80 gm. total at four gm./day. Best results were obtained in patients whose treatment began during the second rather than the first week of gonorrheal symptoms. This was explained by conclusions that sulfanilamide is only bacteriostatic and buys time for immune mechanisms to effect the cure – the Ehrlich hypothesis. While symptoms cleared in one week three weeks of treatment obtained cures in 80% of cases. Re-treatment could raise cures to 90% (25).

Sulfapyridine, soon followed by sulfathiazol, analogues of sulfanilamide, became available in 1940-41. A one week course of sulfapyridine cured three fourths of cases for whom sulfanilamide had failed, as well as 87% of previously untreated patients (26). The efficacy of sulfathiazol was equal to that of sulfapyridine, but sulfathiazol was tolerated better and so it became preferred. The cure rate of about 80% with sulfathiazol 2 gm per day for 6-10 days not improved by larger doses (27,28).

Data from the U.S. Army demonstrate the profound effect the sulfonamide drugs had on disability related to gonorrhea. During 1934-1937 gonorrhea resulted on average in a hospitalization of more than 50 days with 28% of the patients having complications. By 1941 hospitalization had diminished to 22 days and complications to six per cent. Half the days of incapacity were attributed to the 10 to 20 per cent of patients who failed to respond to two courses

of sulfonamide (29). Uhle et al. pointed out the danger that the asymptomatic but still infectious phase not only facilitated spreading of the infection to sexual contacts, but because of exposure of the strain to the drug for it to become drug resistant (26).

In a survey conducted from 1936 to 1947, increasing amounts of a sulfonamide were required to be curative year-by-year. Heat treatment using the Mayo Clinic approach was curative in 63% of cases, but combined sulfonamide and heat treatment was consistently curative. Nevertheless, they recommended that hyperthermia be withheld until drug therapy had proven ineffective, because of its potential cardiovascular hazards (30).

In 1943 U.S. military hospitals began to evaluate penicillin for treatment of gonorrhea in patients whose sulfonamide treatment had been unsuccessful. Because of impurity of the available penicillin and lack of a reliable means to quantitate the actual dosages, the dosages were certainly small. 80,000 to 160,000 units given in divided doses in 12 hours effected a cure in 96% of cases; a second course cured the remainder (31).

In 1946 four cases of gonorrhea were reported in whom the infection was resistant to "large" amounts of penicillin (0.6 to 1.6 million units). Resistance was confirmed by in vitro testing. A gradual increase in the number of strains of gonococci with increasing resistance to penicillin occurred a decade later (32). In a Toronto study between 1959 and 1966, the number of strains sensitive to 0.01 units/ml decreased from 63% to 13% and strains that required at least 1.0 units/ml for eradication increased from none to 27% (33).

Two mechanisms for resistance to penicillin were eventually discovered. In 1976 resistant strains were found in California and London that produced beta-lactamase (penicillinase) – an enzyme that inactivates penicillin (34,35). Epidemiologic surveys showed the prevalence of such strains to be increasing rapidly, so that the identification of such strains at the CDC increased from 328 in 197936 to 3717 in 1983 (37). They appeared initially to be imported by military personnel returning from East Asia. While about 0.1 per cent of isolates in the U.S. were resistant in 1980, predominantly in California, 30-40% of isolates obtained in Philippine clinics were resistant (36).

In 1980 the first gonococcus isolates were identified that were resistant to penicillin without producing penicillinase (38). This was found due to a chromosomal mutation. In 1983 a local epidemic caused by such a strain occurred in North Carolina. Patients were successfully treated with spectinomycin (39).

Attempts to find an antibiotic alternative to penicillin for the treatment of gonococcal infections were begun. This was mostly due to a concern for patients with a penicillin allergy rather than infection with a resistant strain. In 1949 chlortetracycline (Aureomycin) was found to be effective, with the additional advantage of oral administration.(40) In 1966 94% of gonococcal strains were found to be highly sensitive to tetracycline while 22% of these showed some increased resistance to penicillin (33). Unfortunately resistance has begun to develop after a few years against each new, initially effective antibiotic. Spectinomycin, introduced in 1967, replaced tetracycline as the alternative to penicillin in the 1970s (42), and ceftriaxone was recommended for primary anti-gonococcal therapy in 1989 (43).

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