Susceptibility of N. Gonorrhoeae to Antibiotics: A Study of 200 Consecutive Strains Isolated in Winnipeg in 1962

E. SNELL, L.R.C.P.(Ed.), D.P.H.,* D. A. NORRIS, M.Sc.,† and JUNE STRONG, R.T.,‡ *Winnipeg, Man.*

ABSTRACT

Gonorrhea has increased in incidence over the past five years in Manitoba as elsewhere. Cases which did not respond to routine penicillin treatment were noted to be occurring more often. In 1948, strains of *N. gonorrhoeae* isolated in Canada were all sensitive to 0.06 unit of penicillin per c.c. *in vitro*. Commencing in May 1962, strains of *N. gonorrhoeae* were isolated from 100 patients of each sex attending the clinic at the St. Boniface General Hospital. Eighteen per cent required concentrations of more than 0.05 unit of penicillin per ml. to inhibit growth; 31% were not inhibited by the 2 μg. disc of dihydrostreptomycin; but only one strain was found resistant to sulfisoxazole and none to oxytetracycline. Results of penicillin treatment were markedly less successful in the patients with strains that demonstrated reduced penicillin sensitivity. Use of streptomycin and a sulfonamide proved to be a satisfactory substitute. Intramuscular oxytetracycline was less successful despite the laboratory findings.

AT the European Symposium on Gonorrhea and Non-gonococcal Genitourinary Infections held in 1960,[1] the following remarks formed part of the report which was unanimously approved by the delegates:

"The overall incidence of gonorrhea has increased in many countries in recent years. . . . The increased incidence is particularly marked in the younger age groups. . . . Increasingly, clinical resistance is now being observed to penicillin treatment in many countries and to streptomycin in some countries. This development may continue. Microbiological evidence suggests a gradual development in the laboratory of penicillin resistance of *N. gonorrhoeae* and in some instances of a more abrupt development of resistance to streptomycin. It will be extremely important to the medical profession and health departments in all countries to follow this problem closely in the future. However, laboratory methods for the determination of susceptibility of *N. gonorrhoeae* to antibiotics—particularly penicillin—do not permit meaningful comparisons within or between countries at the present time. The establishment of international standard methods in this respect is, therefore, urgent."

A recent editorial in this journal also drew attention to the increasing failure rates in the treatment of gonorrhea with penicillin and streptomycin and remarked that this may make a significant contribution to the rising incidence of this disease, especially where post-treatment defaulter rates are high.[2]

Willcox[3] has collected information regarding the reported incidence of gonorrhea in 22 countries, in a survey carried out for the World Health Organization. Between 1950 and 1958 he noted that there had been an increase in incidence in 15 of these countries, including Canada. The incidence of gonorrhea in Canada has continued to increase and the number of reported cases for the last five years is recorded in Table I.

Our records in Manitoba show the same trend and can be illustrated (Table II) by the reported cases of gonorrhea in Manitoba and in the city of Winnipeg as well as by the numbers of new cases attending the government clinic at the St. Boniface General Hospital each year. A very marked increase in the number of isolations of *N. gonorrhoeae* has also been noticed recently at the Winnipeg General Hospital. Warner and Chorney[5] reported a 30-fold increase in 1961 as compared with 1958. This was attributed mainly to the introduction in 1960 of the use of Stuart's transport medium, but it is conceded that an increased incidence of gonorrhea may have contributed to their findings.

The sulfonamides were the first chemotherapeutic agents to be used successfully in the treatment of gonorrhea, and in the early 1940's[6] more than 80% of the isolated strains of *N. gonorrhoeae*

TABLE I.—REPORTED CASES OF GONORRHEA IN CANADA (1957-61)[4]

Year	*1957*	*1958*	*1959*	*1960*	*1961*
Cases reported	14,313	14,836	14,826	15,661	16,463

TABLE II.—REPORTED CASES OF GONORRHEA IN MANITOBA AND IN THE CITY OF WINNIPEG; NEW CASES OF GONORRHEA ATTENDING THE GOVERNMENT CLINIC (1957-61)

Year	*1957*	*1958*	*1959*	*1960*	*1961*
Cases reported (Manitoba)	1226	1362	1636	1892	2178
Cases reported (Winnipeg)	601	630	841	980	1038
New cases seen at the clinic	513	548	775	920	943

*Director, Venereal Disease Control, Manitoba; Consultant Venereologist, St. Boniface General Hospital.
†Bacteriologist, St. Boniface General Hospital.
‡Laboratory Technician, St. Boniface General Hospital.

were sensitive to these drugs. However, after 1945 the situation was reversed and between 76% and 84% of isolated strains were resistant to the sulfonamides. By 1949 Dunlop[7] was able to report failure of sulfathiazole in 85.8% of the patients treated.

The development of strains relatively insensitive to penicillin has been very ably demonstrated by the work of the Statens Seruminstitut in Copenhagen.[6] Strains of *N. gonorrhoeae* isolated in 1944 and freeze-dried were compared with strains isolated in 1957. The 1944 strains showed a peak sensitivity level at 0.01 μg./ml., with a range of 0.004 to 0.024 μg./ml. The 1957 strains obtained for diagnostic purposes showed two sensitivity peaks, one at 0.01 μg. and the other at 0.2 μg./ml. (range 0.006-0.4 μg./ml.). The 1957 strains obtained from patients classed as treatment failures also showed two peaks, but the one at 0.2 μg. was even more pronounced (range 0.003-0.5 μg./ml.). In 1960 a further increase in relatively insensitive strains was noted.

A Medical Research Council[8] working party, investigating the problem, examined 1984 strains of *N. gonorrhoeae* isolated at nine clinics in the United Kingdom before treatment, between April 1959 and March 1960. The majority were highly sensitive to penicillin, but 262 (13.2%) were inhibited only by a concentration of 0.125-1.0 units. Thirty-two of the 38 treatment failures yielded strains which were relatively insensitive *in vitro*.

The same trend has also been noted in the United States. Thayer and his co-workers[9] have reported the increased number of less sensitive strains found in 1959 compared with 1955, with an even higher proportion of these from treatment failure cases. Epstein[10] failed to cure 20% of 146 military personnel in Korea treated for gonorrhea by a course of five daily injections of 600,000 units of aqueous crystalline procaine penicillin G. He felt that increased penicillin resistance on the part of *N. gonorrhoeae* was the probable cause.

There may, however, be other causes for apparent treatment failure. Organisms of the Mimeae family may cause an infection with the clinical picture of gonorrhea and show a very poor response to penicillin. Svihus[11] described 37 such patients, of whom only 12 were actually infected with Neisseria. Of the 22 infected with organisms of the family Mimeae, 18 did not respond to penicillin treatment. In the investigation we have carried out in Manitoba we have, therefore, taken particular care to identify the causative organisms as true *N. gonorrhoeae*.

Resistance to streptomycin was noted as early as 1952 by Ryan,[12] whose patient, infected in Hong Kong, failed to respond to two separate injections of 1 g. of streptomycin. He was able to isolate a strain of *N. gonorrhoeae* resistant to at least 1000 μg. streptomycin per ml., compared with a sensitive strain which was inhibited by 1 μg. In France,[13] where streptomycin has been extensively used to treat gonorrhea, 22.9% of strains are resistant to 1000 μg./ml. In Denmark[6] in 1960, 10% of the diagnostic strains were resistant to more than 2000 μg., and 26% of the strains sent in with a request for sensitivity determination showed resistance of a similar degree, whereas in 1944 all the strains isolated were sensitive to streptomycin with a range of 3-11 μg./ml. *N. gonorrhoeae* is apparently very sensitive to streptomycin or develops almost complete resistance in a one-step mutation.

No resistance has been shown so far[14] by gonococci to the tetracycline group of drugs. A single injection of 500 mg. intramuscular oxytetracycline (Terramycin), used by Van der Stoep, Montgomery and Knox,[15] cured gonorrhea in 92% of the 197 patients treated by this method.

It is of some interest that the wild strains of *N. gonorrhoeae* may show increased susceptibility to a type of treatment which has not been used for a number of years. Craddock-Watson, Shooter and Nicol[16] tested 200 strains of gonococci for sensitivity to sulfathiazole in 1958 and found, to his surprise, that 199 of them were inhibited by 8 mg. or less per 100 ml. This was confirmed by Reyn,[6] who found that in 1960 only 3% of her strains of *N. gonorrhoeae* were resistant to sulfathiazole.

In Canada in 1948 the position with regard to penicillin was apparently much the same as throughout the rest of the world. At that time, Hawks and Greey[17] carried out sensitivity tests on 64 strains of gonococci isolated before general distribution of penicillin to the medical profession, and 266 strains isolated subsequently, when penicillin was used extensively in the treatment of gonorrhea. The largest amount of penicillin to inhibit growth completely was found to be 0.06 unit per c.c. No resistant strains were found.

At our clinic in Winnipeg, during 1961, we were struck by the apparent increase in the number of patients suffering from gonorrhea who failed to respond to routine treatment with penicillin. Laboratory tests of *in vitro* sensitivity, using discs impregnated with 8, 4 and 2 units of penicillin, did not disclose any resistant organisms. It became apparent that we would have to change our technique to enable us to detect strains of *N. gonorrhoeae* which were only relatively insensitive to penicillin. At the same time we decided to test sensitivity to dihydrostreptomycin, oxytetracycline and a sulfonamide. Commencing in May 1962, 100 strains were obtained from consecutive male patients and 100 from consecutive females. The series was completed by September 1962.

MATERIALS AND METHOD

A. 1. *Media.*—Stuart's transport medium; 0.4 ml. trypticase soy broth in screw cap tubes; chocolate agar in petri dishes—standard round and in slants; chocolate agar in quad-complate dishes (Fisher); penicillin chocolate agar in quad-complate dishes; trypticase soy

agar slants; cystine trypticase glucose agar deeps with 20% ascitic fluid; and cystine trypticase maltose agar deeps with 20% ascitic fluid.

2. Other materials included standard penicillin G sodium (assay grade); gonococcus of low susceptibility to penicillin (P-1 strain with MIC* of 0.132 μ/ml.);† *Sarcina lutea* (A.T.C.C. No. 9341)—strain of high susceptibility to penicillin (MIC of 0.006 μ/ml.);† cotton swabs soaked in 1% activated charcoal before sterilization; and the following sensitivity discs: oxytetracycline 5 μg. and 30 μg., dihydrostreptomycin 2 μg. and 10 μg., and sulfisoxizole 2 mg.

B. *Method.*—Gram-stained smears were prepared and read. In addition, cervical and urethral secretions were collected on charcoal swabs which were placed in Stuart's medium until they were ready for plating on to chocolate agar plates. The inoculated plates were incubated in a carbon dioxide candle jar for 48 hours at 36° C. At the completion of the incubation period, colonies suggestive of a gonococcus were selected and tested by the oxidase reaction. If the colony was oxidase-positive, a Gram smear was prepared to check if they were Gram-negative diplococci. Those which were had an identical appearing colony selected and inoculated into 0.4 ml. of soy broth, then a drop of the oxidase reagent was applied to the remaining portion of the colony on the agar plate. If this portion was oxidase positive, a Gram-smear was prepared of the soy broth and, if morphologically characteristic, it was held for further study. A cystine trypticase glucose and maltose deep, plus a chocolate and soy agar slant, were inoculated from the soy broth culture. The chocolate agar slant was incubated in a carbon dioxide candle jar at 36° C. and the glucose and maltose deeps as well as the soy agar slant were incubated aerobically at 36° C. Those colonies which fermented only glucose and not maltose, and which revealed no growth on the soy agar slant after 48 hours, were then selected for sensitivity testing. The soy agar slant was used to distinguish the Mima-Herella group from *N. gonorrhoeae* as recorded by Gangarosa and Cary's[18] study of penicillin-resistant gonococci.

Sensitivity to penicillin was determined by incorporating the antibiotic into chocolate agar in final concentrations of 0.4, 0.2, 0.1 and 0.05 unit/ml. and poured into quad-complate dishes so that each concentration was in one separate quadrant of the plate. The sensitivity agar plates were checked for accuracy as to their penicillin concentration by the use of low-susceptible and high-susceptible bacterial strains (P-1 gonococcus for the low and *S. lutea* for the high) at the time of each test series. The minimal inhibitory concentration (MIC) was determined by inoculating one loopful of an emulsified growth of the chocolate agar slant on to each quadrant of the quad-complate and one quadrant of a high chocolate agar quad-complate with no penicillin added. That concentration of penicillin which inhibited 50% of the growth as compared to the control, plain chocolate agar, was considered the MIC for the strain tested. Sensitivity to oxytetracycline, dihydrostreptomycin and sulfisoxazole was determined by the dry disc method. A loopful of the stock chocolate slant culture was streaked over a plain chocolate agar plate and the following concentration discs were used: oxytetracycline, 5 μg. and 30 μg.; dihydrostreptomycin, 2 μg. and 10 μg.; and sulfisoxazole, 2 mg. Variation in the sensitivity testing methods was found to be a necessity from previous trials in our laboratory. Correlation of the information supplied by the disc method with the *in vivo* effectiveness of that agent revealed that there was a reasonable degree of accuracy with those results of the disc method using oxytetracycline, dihydrostreptomycin and sulfisoxazole, but not so with penicillin discs of a low level of concentration as required for our tests. We would surmise that the low concentration required, plus the instability of penicillin discs, was responsible for the erratic results which we obtained. When penicillin was incorporated into the agar, the information supplied by this method gave a greater degree of correlation with the *in vivo* effectiveness.

*Minimal Inhibitory Concentration.
†P-1 strain of gonococcus and *S. lutea* cultures were kindly supplied by Dr. J. D. Thayer of the Venereal Disease Research Laboratory, Atlanta, Georgia, U.S.A.

RESULTS

Table III indicates the results obtained in the sensitivity tests. It can be seen that the strains of *N. gonorrhoeae* at present causing infection in Canada are showing lessened sensitivity to penicillin. Seventeen per cent of strains isolated from female patients and 19% from males required more than 0.05 unit of penicillin per ml. to inhibit growth.

TABLE III.—MINIMAL INHIBITORY CONCENTRATION OF *N. gonorrhoeae* STRAINS ISOLATED

		100 female-originating strains	*100 male-originating strains*
Penicillin	0.05 unit	83	81
	0.1 unit	17	16
	0.2 unit	0	3
	0.4 unit	0	0
Oxytetracycline	5 μg.	100	100
	30 μg.	0	0
Dihydrostreptomycin	2 μg.	70	67
	10 μg.	29	32
	Greater than 10 μg.	1	1
Sulfisoxazole	2 mg.	100	99
	Greater than 2 mg.	0	1

Of cases resistant to 0.1 unit penicillin—
60% females } sensitive to 2 μg. of
40% males } dihydrostreptomycin or less.
Of cases resistant to 2 μg. of dihydrostreptomycin—
81% females } sensitive to less than
64% males } 0.1 unit of penicillin.

Resistance to streptomycin does not appear to have developed to the same extent as elsewhere, and this probably is a reflection of the fact that this antibiotic has not to our knowledge been used very extensively in the treatment of gonorrhea in this part of the world.

Resistance to sulfisoxazole *in vitro* was encountered only once in our 200 cases. No strains resistant to oxytetracycline *in vitro* were discovered. We consider organisms requiring 0.1 ml. of penicillin per ml. or the 10 μg. disc of dihydrostreptomycin to inhibit growth as being partially resistant to the respective antibiotics.

TREATMENT

Treatment was tailored to meet individual requirements. For clinic patients we prefer parenteral therapy to oral medication because of the greater certainty that the treatment prescribed is actually carried out. Schedules of treatment have to be adapted to the fact that regular clinics are held only on certain specified days of the week and treatment at other times is less convenient. Our treatment of choice consists essentially of two injections of PAM (procaine penicillin G in oil with 2% aluminum monostearate), each containing 600,000 units of penicillin, at an interval of three to four days. Where the response to the first injection is not dramatic, the second dose is increased to 1,200,000 units of PAM. Patients unlikely or unable to attend for their second injection at the appropriate time are given one injection of 1,250,000 units of a mixture of short-acting and medium-acting penicillins (Plucillin-Glaxo). Where there is a history of allergy to penicillin, an alternative method of treatment has to be used. This consists of administering either two doses of intramuscular oxytetracycline, each containing 250 mg., injected at three- to four-day intervals, or one injection of a stabilized solution containing 1 g. of streptomycin sulfate (Strepolin) with the concurrent administration of triple sulfonamide tablets, 0.5 g., two tablets every six hours for five days. Such preparations as oral penicillin, oral tetracycline or erythromycin, etc., are used when there are special indications.

FOLLOW-UP

Male patients are normally followed up for two months. At the end of this period they have a serological test for syphilis. Cure is denoted by the absence of symptoms and signs and a clear urine. Female patients have three consecutive smears and cultures from the cervix and urethra at weekly intervals after completion of treatment, and this is followed by a serological test for syphilis before they are discharged as cured. Many of the patients in the present series did not complete this follow-up schedule. However, if the man was free of symptoms and had a clear urine when last seen, and if the woman had at least one negative smear and culture and symptoms were absent, they were considered cured. Otherwise the follow-up was considered inadequate.

Treatment failures consisted of men whose symptoms persisted after treatment or women who still yielded a positive culture, or, in both sexes, those cases in which symptoms or a positive culture recurred within four weeks after treatment without a history of contact with an infected person in the meantime.

Reinfections include those cases with a definite admission of further exposure, where, in males, symptoms developed within two to 10 days thereafter, or, in females with at least one negative smear and culture, who subsequently developed a positive culture after an appropriate incubation period.

TABLE IV.—100 MALE CASES OF GONORRHEA: RELATIONSHIP BETWEEN *in vitro* SENSITIVITY AND RESULTS OF TREATMENT

	Sensitivity in vitro	*Sensitive*		*Resistant to 2 μg. dihydrostreptomycin*		*Resistant to 0.05 unit of penicillin*		*Resistant to 2 μg. dihydrostreptomycin and 0.05 unit penicillin*		*Total*	
		No.	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
Treated with penicillin and followed up	Cured	33	72	13	81	3	60	4	50	53	71
	Cured but reinfected	9	20	2	13	0	0	2	25	13	17
	Treatment failures	4	8	1	6	2	40	2	25	9	12
	Total	46	100	16	100	5	100	8	100	75	100
Allergic to penicillin		4		2		1		0		7	
Inadequate follow-up		10		3		1		4		18	
Total patients		60		21		7		12		100	

The relation between the sensitivity of the organism *in vitro* and the results of treatment in 100 male patients is recorded in Table IV. As far as penicillin treatment is concerned, definitely better results were obtained where the laboratory grew a sensitive strain, compared with those cases in which the strain was less sensitive *in vitro*.

Of the nine male patients with sensitive strains who were reinfected during the follow-up period, six were cured by a second course of penicillin and the remaining three were not adequately followed up.

Two patients whose organisms were resistant to 2 μg. streptomycin and who were reinfected following penicillin treatment responded to a second course of the same antibiotic.

Of two patients with strains less sensitive to both penicillin and streptomycin, one was cured by a second course of penicillin and the other was lost to follow-up after reinfection.

Of 60 patients with sensitive organisms, four failed to respond to an initial course of penicillin.

Two of these responded to a second course of penicillin; one responded to streptomycin and sulfonamide; and one was inadequately followed up after further treatment. Four patients gave a history of allergy to penicillin. Two of these were treated with intramuscular oxytetracycline but did not respond satisfactorily. All four cleared up on treatment with streptomycin and triple sulfonamides.

Of 21 patients with organisms resistant to 2 μg. of streptomycin, one failed to respond to an initial course of penicillin but cure followed a second course. Two who were allergic to penicillin were cured by administration of streptomycin and sulfonamide.

Seven patients were resistant to a level of 0.05 unit of penicillin. Two of these failed to respond to their initial penicillin course, and one was subsequently treated by intramuscular oxytetracycline without success. Cure was achieved by treatment with streptomycin and sulfonamide. The other was treated again with penicillin but did not return for adequate follow-up. A third patient in this group was allergic to penicillin and was cured by a course of streptomycin and sulfonamide.

There were 12 male patients whose organisms showed diminished sensitivity to both penicillin and streptomycin. One of these, with an organism resistant to 0.1 unit of penicillin, 2 μg. of streptomycin and 2 mg. of sulfisoxazole, nevertheless responded to the initial course of two injections of PAM. He was subsequently reinfected with a sensitive organism. Two of this group failed to respond to initial PAM treatment and one of these responded to intramuscular oxytetracycline. The other harboured organisms resistant to 0.1 unit of penicillin and 10 μg. of streptomycin. He was treated serially with PAM 1,800,000 units, intramuscular oxytetracycline 500 mg., streptomycin 1 g. and sulfonamide 20 g., and erythromycin 5 g., with no response. Eventually he had to be admitted to hospital where six daily doses of 1,000,000 units of aqueous procaine penicillin G eventually cured him of his infection.

The relation between the *in vitro* sensitivity of the organism and the results of treatment in the 100 female patients (Table V) shows a very similar pattern, and once again the response to penicillin was much better in those whose organisms were most sensitive.

Out of a total of 59 patients with sensitive organisms two were reinfected after successful initial treatment with PAM. Both responded to a second course of treatment with the same antibiotic. Two patients failed to respond to their initial penicillin course; one of these later responded to streptomycin and sulfonamide therapy whilst the other could not be adequately followed up. Eight patients in this group were allergic to penicillin. Four of these were treated with intramuscular oxytetracycline, with two successes and two failures. Three were given streptomycin and sulfonamide with one successful result, and two were inadequately followed up. The final patient in this group was cured by one dose of PAM (given before signs of allergy developed) and subsequently one dose of streptomycin.

There were 24 female patients with organisms showing resistance to streptomycin. After successful initial treatment with PAM three were reinfected. A second course of PAM cured two of these and the third could not be followed up. Two of this group were allergic to penicillin and both were treated successfully by intramusclar oxytetracycline.

Of the 11 patients with organisms resistant to 0.05 unit of penicillin, the initial PAM course failed in four instances. One of these was cured by a second course of PAM, one was cured with streptomycin in a daily dose of 1 g. for five days, and the other two responded to oral tetracycline to a total dose of 4 g.

Six female patients had organisms partially resistant to both penicillin and streptomycin. Of those treated with PAM (three patients) there was one failure which responded to intramuscular oxytetracycline. One of this group was allergic to

TABLE V.—100 FEMALE CASES OF GONORRHEA: RELATIONSHIP BETWEEN *in vitro* SENSITIVITY AND RESULTS OF TREATMENT

	Sensitivity in vitro	*Sensitive*		*Resistant to 2 μg. dihydrostreptomycin*		*Resistant to 0.05 unit of penicillin*		*Resistant to 2 μg. dihydrostreptomycin and 0.05 unit penicillin*		*Total*	
		No.	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
Treated with penicillin and followed up	Cured	32	88	16	84	5	56	2	67	55	82
	Cured but reinfected	2	6	3	16	0	0	0	0	5	7
	Treatment failures	2	6	0	0	4	44	1	33	7	10
	Total	36	100	19	100	9	100	3	100	67	100
Allergic to penicillin		8		2		0		1		11	
Inadequate follow-up		15		3		2		2		22	
Total patients		59		24		11		6		100	

penicillin, and in her case treatment with intramuscular oxytetracycline was unsuccessful and subsequently streptomycin and sulfonamide were administered with uncertain results.

CONCLUSIONS

Consideration of these results in patients of both sexes would seem to indicate that penicillin in adequate dosage remains the treatment of choice in gonorrhea because of its effectiveness, relative lack of toxicity, ease of administration and low cost. An increasing number of treatment failures are being encountered, however, and these correlate with the reports from the laboratory of the isolation of strains which are less sensitive to penicillin. If this trend continues, alternative methods of treatment may become necessary. There is much to be said for doing routine sensitivity studies on strains of organisms obtained from cases which do not respond rapidly to penicillin treatment. *N. gonorrhoeae* is fortunately susceptible to a wide range of antibiotics.

Our results with intramuscular oxytetracycline have been disappointing despite the fact that *in vitro* studies have shown all the strains to be sensitive to this antibiotic. Probably increasing the dose to 500 mg.[15] or giving daily doses for two or three days would have produced a more satisfactory result.

The administration of streptomycin and a sulfonamide simultaneously has proved to be a reasonably satisfactory alternative to penicillin at the present time, and this conforms to the results obtained by testing the *in vitro* sensitivity of the isolated strains. Where the patient can be relied upon to take oral medication, there may be a place for the tetracycline group of drugs given by mouth. It seems obvious that the changing sensitivity pattern of *N. gonorrhoeae* will have to be watched carefully and methods of treatment altered to conform to the existing pattern in any given locality.

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PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

TREATMENT OF UTERINE FIBROIDS BY X-RAYS

Bloodless ovariotomy is the aim of x-rays in the treatment of uterine fibroma. The experimental stage is past, and definite results can now be promised in the treatment of uterine fibroma by x-rays. The introduction of the treatment came from theoretical reasoning. In 1903, it was shown that the spermatogenic cells of the testicles could be killed, or stunned by x-rays in suitable doses. Soon after this was discovered, Haberstaedter showed that the ovaries of rabbits atrophied under x-ray applications. In 1904, cases of fibroma uteri were treated with x-rays and good results were reported. In 1909, the treatment began to be used more extensively. Before that year it had remained in the hands of a few experimenters, of whom Foveau de Courmelles was the most energetic, and he was able to report success in fifty-three cases. In successful cases the haemorrhage is arrested, the menstrual period is suppressed, and the fibroid cannot be felt, or is considerably reduced in volume. The x-ray treatment is in fact a bloodless ovariotomy which brings on an artificial menopause. It is probable that the internal secretion of the ovary is not destroyed. The method as now employed is the same wherever the treatment is in use, but techniques differ. Every operator endeavours to get a large dose of x-rays to reach the ovaries without causing injury to the skin. This is most successfully accomplished by the method used in the Frauenklinik at Freiburg in Germany.

The treatment has proved successful in myoma uteri and in climacteric flooding. The dose of x-rays required to produce an artificial menopause varies with the patient's age. The nearer she is to the climacteric period the smaller is the dose required.

Bordier gives the following indications and contra-indications for treatment by x-rays: (1) patients under thirty-nine years of age should not be treated by x-rays, (Gaus states that amenorrhoea can be produced at any age); (2) interstitial fibroma is the most suited for x-rays; pedunculated fibroma should be treated surgically; (3) radiotherapy acts like a charm in cases with profuse menstrual haemorrhage; (4) moderate sized tumours are most suitable; (5) haemorrhages of the menopause are successfully terminated by x-ray treatment. One or two treatments are sufficient for the purpose. Though this method will never surpass the surgical removal of a fibroid, yet there are cases in which the x-ray method has proved a great boon to patients suffering from fibroma uteri.

Such treatment with massive doses should only be carried out by those who are expert at measuring large filtered doses of x-rays.—A. Howard Pirie: *Canad. Med. Ass. J.*, 3: 710, 1913.