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THE SULPHONAMIDE TREATMENT OF GONORRHOEA RESULTS OF TREATMENT

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The advent of the sulphonamides marked an important point in the history of the treatment of gonorrhoea, probably as important as the introduction of salvarsan for the treatment of syphilis. For the first time a drug with a specific attack on the gonococcus was available. The first wave of therapeutic enthusiasm led to widespread experimentation and to extravagant claims for the method, and then to a period of apprehension regarding its toxic effects. There was a repetition of these phenomena with each member of the series—prontosil, sulphanilamide, uleron, albucid, and sulphapyridine (M & B 693). The greater potency and relatively low toxicity of sulphapyridine renewed the optimism of the therapeutic enthusiasts and led to frequent use of the drugs in a manner unlikely to produce the best results.

The stage is now reached in which critical observers realize that sulphapyridine is not an easy panacea in the problems of gonorrhoea. The results of a large series of gonorrhoea cases adequately observed for a long period should aid in assessing the value of the drug in producing cure and in the indication of essential precautions in this new therapy.

Recently it has been suggested that many patients were not cured by this treatment, but that they were suffering from latent gonorrhoea, almost certain to recur, probably contagious, and possibly liable to cause late metastatic lesions. If this assertion were proven such a grave charge would throw suspicion on the present methods of using the sulphonamides, and we would anticipate in the near future a great epidemic of gonorrhoea, probably in a modified form. This would be a serious danger to the public health. To secure data on this question we have reviewed the results of 810 male cases and 129 female cases of gonorrhoea treated in the Edinburgh area from January 1, 1939, to June 30, 1939. Our records, however, have been scrutinized up to date to ensure that cases treated in this period have not returned to our care subsequent to July 1, 1939. The cases are unselected, they are all hospital cases, and the entire venereal disease service of the Edinburgh area is included. The outbreak of war and the removal of the younger men from the

population may have slightly affected our estimates of "return cases" and "relapses"; but this will produce only a small reduction in the figures, and this factor operates in other areas to a similar extent.

The study refers to patients treated by sulphanilamide, uleron, albucid, "M 541," and sulphapyridine. All cases were diagnosed and controlled bacteriologically—principally by examination of smears, but by culture also in case of doubt.

Definition of Terms employed in this Study

It is necessary at this stage to define some terms used in the following descriptions and discussions, and to outline briefly the lines on which the therapeutic experiments have been conducted.

"Drug Resistance."—By this term we designate the phenomenon in which the disease appears partially or completely unaffected by the drug administered. For example, in a case of anterior urethritis the discharge continues, and films from the urethra contain numerous gonococci after treatment by our usual dosage over the usual period of time. Drug resistance may be "primary" or "acquired"—the latter referring to the phenomenon, commonly observed, that inadequate doses failed to bring about cure and adequate or intensive doses later proved ineffective.

"Relapse" is used to designate the return of symptoms and signs, with return of positive bacteriological tests which had previously been rendered negative by treatment. Relapse is classified arbitrarily as "early" (within four weeks of cessation of drug administration) and "late" (over four weeks from cessation). Relapse is quite distinct in our series from the next group, which we call "return cases."

A "return case" is a patient who has been discharged as cured or defaulted and who has subsequently returned to the clinic. A very careful search has been made for such cases, and in this respect it is worthy of notice that one authority controls all the venereal diseases in the Edinburgh area, and the medical officers and orderlies readily recognize men previously treated, even though false names and addresses may be used. The principal interest of this study may well lie in the analysis of the "return cases," as there is only one instance in which a man previously treated for gonorrhoea has returned with gonorrhoea without having been exposed to reinfection.

"Defaulter."—Any patient who ceases to attend the clinic before all tests of cure are satisfied is classed as a defaulter. These cases are studied in detail later in an attempt to guess their probable fate and the individual and public importance of their condition. The tests of cure employed in our routine management are described below. Many of our "return cases" had previously defaulted.

ROUTINE MANAGEMENT OF GONORRHOEA (MALE)

Before treatment a full clinical examination is carried out and smears are made from the urethral discharge. These are stained by Gram's method, and are examined immediately. If doubt exists regarding the diagnosis further tests are done, including cultures of the secretions. Administration of the drug is started as soon as the diagnosis has been established: we have not practised "delayed chemotherapy." No irrigation or antiseptic treatment has been used as a rule in these cases: certainly during the first week irrigation has been avoided. In this way the value of the drug alone can be assessed more accurately than in many other reported series of cases. The dosage employed is readily seen in Table I.

TABLE I.—Dosage in Grammes

Days	Sulphanilamide		Sulphapyridine	
	M.	F.	M.	F.
1	8	6	3	3
2	8	6	3	3
3	6	4	3	1.5
4	6	4	3	1.5
5	4	3	3	1.5
6	4	3	—	1.5
7	4	3	—	1.5
8	4	3	—	—
9	3	2	—	—
10	3	2	—	—
11	3	2	—	—
12	3	2	—	—
13	3	2	3	—
14	3	2	3	—
15	—	—	3	3
16	—	—	3	1.5
17	—	—	3	1.5
18	—	—	—	1.5
19	—	—	—	1.5
20	—	—	—	1.5

Observations.—Repeat course in few cases after interval of 7 days. Second course given only in exceptional cases.

During chemotherapy with sulphanilamide the patients were forbidden to take foods or drugs rich in sulphur or sulphates. Toxic effects were frequent, and often severe but not dangerous. This prohibition was found unnecessary in using sulphapyridine.

The points emphasized in the management of chemotherapy are:

1. The exact dose prescribed must be taken.
2. The drug must be taken regularly at the prescribed intervals—for example, a man on day work has a dose at 8 a.m., lunch-, tea-, and bed-time. Night-shift workers often take five doses—a larger one always being taken before the patient goes to bed.
3. The tablets must not be given to another person. Some men treat their consorts or friends who have a similar disease, or keep a few tablets for a future occasion—for example, should they be reinfected.
4. Enough of the drug to last until his next visit is supplied. A few extra tablets may be given in case he cannot attend at the precise time advised: this tends to prevent gaps in the administration of the drug. Prescriptions should limit the amount of the drug to be supplied and should be marked "Not to be repeated." In hospital practice we avoid giving prescriptions for sulphonamides.
5. Observation must be regular and at frequent intervals—as a rule every two days during chemotherapy and twice a week during the first month, then once a week until cure is established.

6. Tests of cure are carried out during the latter part of the observation period. The period of observation after negative bacteriological tests and cessation of clinical signs of the disease should not be less than three months. The tests of cure consist of repeated urethral and prostatic smears, passage of large bougies, urethroscopic examinations, "provocative" injections of gonococcal vaccine with examinations of urethral and prostatic and vesicular secretion twenty-four and forty-eight hours subsequently, and repeated tests of the blood serum by gonococcus complement-fixation and Wassermann tests. We have not advised the consumption of alcohol as a test, though patients often test themselves in this way. Instillation of silver nitrate, glycerine, etc., is not used as a routine. Principal reliance is placed on repeated examinations of smears, urethroscopic examinations, and the gonococcus complement-fixation test.

TABLE II.—Results of Treatment

	Males			Females		
	No.	Cures	Defaulters	No.	Cures	Defaulters
Sulphanilamide	365	197 (54%)	168 (46%)	54	41 (76%)	13 (24%)
Sulphapyridine	445	209 (47%)	236 (53%)	75	52 (69.9%)	23 (39.1%)

From Table II it will be noted that there is a lower percentage of cure with sulphapyridine (47) than with sulphanilamide (54), but this is largely explained by the higher percentage of defaulters (sulphapyridine, 53; sulphanilamide, 46). There is no doubt in our minds that sulphapyridine is greatly superior to the other drugs of the series; it produces a more rapid curative effect, toxic effects are less severe, drug resistance is much less common (5.7 per cent.), and the complications of gonorrhoea are similarly low (4 per cent.) (Table III).

TABLE III.—Males

	No. of Cases	Defaulters	Drug Resistance	Complications	Relapse
Sulphanilamide ..	365	46%	32.1%	13.7%	1.9%
Sulphapyridine ..	445	53%	5.7%	4%	2.9%

Default

The question of default is a major issue in the management of all venereal diseases; the large percentage who do not have any tests of cure has become even larger since the sulphonamides were introduced. We have therefore devoted some space to the study of this group (404). The time at which male patients default is shown graphically in the figure reproduced below.

Fortnightly estimate of sulphonamide defaulters: males.

The number of defaulters is estimated at fortnightly intervals. The large numbers who cease attendance during the first two weeks present a menace to the success of this therapy.

(a) Contagious Defaulters.—Fifty-four cases showed a positive urethral smear immediately before defaulting (seventeen

(4.6 per cent.) on sulphanilamide and thirty-seven (8.3 per cent.) on sulphapyridine. The marital state of these infectious defaulters was: married, twenty-one; single, thirty-three. From the public health point of view cases in this group are the most serious danger.

(b) *Potentially Infectious Defaulters* (defaulters who have not had a period of observation or any test of cure).—These number 158 (19.5 per cent. of 810 cases). A comparable analysis for twenty-one months in 1935–6 gave the figures of 12.6 per cent. The conclusion is that this defaulter rate has risen by over 50 per cent.

(c) *Defaulters Presumably Cured*.—Total 246. These are patients who cease attendance after completing a period of observation and who have then satisfied one or more tests of cure. An empirical clinical classification emphasizes the same points of importance regarding default, especially the high incidence of early default in the sulphapyridine series.

TABLE IV

Stage of Default	Sulphanilamide	Sulphapyridine
Early	39 (23.2%)	106 (44.8%)
On observation	48 (28.6%)	36 (15.2%)
During tests of cure	81 (48.2%)	94 (40%)

It is interesting to speculate on the probable fate of many of these defaulters. The fifty-four cases who were certainly contagious have probably spread the disease in the population. They may have sought treatment elsewhere or attempted self-treatment. On reviewing our "return cases" we find that of thirteen defaulters who later returned to the clinic eleven had been re-exposed to infection, and nine of these defaulted during treatment for their second infection. Their condition on return to the clinic was: gonorrhoea, eight; non-gonococcal urethritis, two; syphilis, one; no evidence of V.D., two.

It is recognized in every large V.D. clinic that a small proportion of men are habitually promiscuous. They are quite careless regarding their own health and indifferent to the transmission of infection to others. They must be responsible for a considerable spread of venereal disease, but it is extremely difficult to secure control of such disease carriers by legislative or other means. They represent a public danger as great as the prostitute or habitually promiscuous woman.

Complications of Gonorrhoea

The reduction in the incidence of major complications of gonorrhoea occurring *during* sulphonamide treatment is one of the principal merits of this therapy. Our observations are presented in Table V.

TABLE V.—Complications during Treatment

	No. with Complications	Folliculitis	Periurethral Abscess	Prostatovesiculitis	Epididymitis	Arthritis	Typhoid
Sulphanilamide (365 cases) ..	50 (13.7%)	4	4	17	20	4	1
Sulphapyridine (445 cases) ..	18 (4%)	1	1	9	6	1	—

The much lower proportion of complications in the sulphapyridine series (4 per cent.) than in the sulphanilamide series (13.7 per cent.) is striking. Such complications respond almost invariably and with rapidity to further sulphanilamide administration, supplemented by measures to ensure drainage and sterilization of the focus of infection, and the patients eventually show as high a percentage of cures as the uncomplicated cases. The only "return case" who had gonorrhoea without re-exposure

to infection had suffered from epididymitis. This emphasizes that the utmost care in testing for cure is essential in every patient who has suffered from infection of the prostate or seminal vesicles.

Drug Resistance

A failure to respond to adequate doses of the drug may occur primarily. Drug resistance was observed in 116 (32.4 per cent.) of 358 cases treated with sulphanilamide, and in 24 (5.7 per cent.) of 417 cases treated with sulphapyridine. Defaulters who did not complete one course of the drug are excluded from this survey. The much lower percentage of sulphapyridine-resistant cases is a point much in favour of this remedy. We are unable at present to furnish conclusive observations on the cause of primary drug resistance.

Acquired Drug Resistance is a most important phenomenon. We have very frequently observed that if insufficient dosage of a sulphonamide is employed, even for a short time, the gonococcus quickly becomes resistant to all sulphonamides. This acquired drug resistance is retained for several weeks or even months, but does not appear to be permanent. We have found no evidence in our survey to suggest the existence of a "sulphonamide-resistant" strain of gonococci. The causal factor appears to be an idiosyncrasy shown by the patient. For example, we have several times observed that a husband and wife were presumably infected with the same strain of gonococci, or two men were infected by the same woman, and yet only one of each couple was "drug-resistant." Sulphapyridine may produce rapid cure in patients who have resisted adequate doses of sulphanilamide, but a number resist repeated courses or intensive doses of sulphapyridine.

It appears to be essential to give a high dosage of sulphonamides at the outset, and after a high blood concentration has been secured the dose may be reduced. Regular intervals not exceeding four hours between doses appear desirable, otherwise the drug is rapidly excreted and the blood concentration falls below the effective level. Intervals in treatment are also undesirable. Our standard course in the present series was five days' treatment with sulphapyridine, but this probably represents a minimum rather than an optimum.

The ultimate fate of cases presenting drug resistance has been studied and is set out in Tables VI and VII.

TABLE VI.—Sulphanilamide-resistant—116 (32.4 per cent. of 358 cases)

Result	Irrigation	Repeat Course of Sulphanilamide with Irrigation	Sulphapyridine	Totals
Discharged cured ..	27 (45%)	5	21 (45%)	53
Defaulted ..	29	6	22	57
Transferred ..	3	0	3	6
Totals ..	59	11	46	116

TABLE VII.—Sulphapyridine-resistant

Result	Irrigations	Albucid + Irrigations	Repeat Course of Sulphapyridine + Irrigation	Totals
Discharged cured ..	5	4	4	13
Defaulted ..	0	5	6	11
Totals ..	5	9	10	24

It is observed that these sulphanilamide-resistant and sulphapyridine-resistant cases ultimately reach as high a percentage of cure as the more fortunate cases, though a much longer time, as a rule, is required to obtain a cure.

Relapses

Relapse has been classified clinically as: (a) early (occurring during the first four weeks after cessation of sulphonamide treatment), and (b) late (occurring later than four weeks). From the outset of sulphonamide usage it was recognized that the results observed in some cases were not permanent. After an initial favourable response there was a latent interval in which few or no clinical signs of disease were seen and the bacteriological tests were negative; then signs of disease and positive tests recurred. (The latent interval of apparent cure varied in our series from two to twenty-four weeks.) In several cases of relapse the symptoms and signs were slight, and the recurrence of the infection might have been overlooked readily if regular observation and tests had not been conducted as a routine. In the great majority of our "relapse" cases, however, there had been some evidence indicating the existence of a deep-seated or resistant focus of infection. For example, an abnormal prostatic fluid often foretold prostatitis and epididymitis, or urethoscopic examination revealed a submucous infiltration and infected follicles.

There were twenty cases of relapse during treatment and observation—twelve early and eight late—the shortest interval being two weeks and the longest twenty-four weeks. Sixteen cases of anterior urethritis and four cases of posterior urethritis relapsed—seven had been treated by sulphanilamide and thirteen by sulphapyridine. All of the twenty cases were positive to bacteriological tests, one showing gonococci in the prostatic fluid alone. Five patients showed enlargement of the prostate—usually slight—and one of these developed epididymitis. One patient had an intrameatal wart.

While this number of twenty relapses out of a series of 810 cases is not large enough to justify very dogmatic conclusions some factors are worthy of note:

1. The great majority of these patients had shown evidence to suggest incomplete healing or a latent focus of disease.
2. Alcohol was stated to be the cause of relapse in six cases—all of which had previously been treated with sulphapyridine and all of which relapsed early.
3. Relapse associated with prostatitis tends to occur later, and often without symptoms.
4. The "infectious defaulter" rate is high—six cases out of twenty (30 per cent.) in this series of relapses.
5. One patient relapsed twice—first five weeks after sulphanilamide, and then six weeks after apparent recovery with sulphapyridine. On each occasion alcohol was the provocative agent.

Return Cases

It is essential to differentiate clearly between relapse (that is, recurrence during treatment or observation) and a "return case" who has been discharged as cured or who has defaulted and then subsequently returns to the clinic for any reason. A man is not classified as a defaulter unless he has been absent from the clinic for three months or longer. Great care has been taken to detect patients who have previously been treated for gonorrhoea by sulphonamide drugs and have later returned to the Edinburgh clinics. There were forty-four

such cases—thirty were single and fourteen married—giving the following particulars:

Re-exposure :

A history of one re-exposure (in four cases with their wives)	38
A history of repeated re-exposures	1
No coitus since their previous attendance at the clinic	5

Condition on Return to the Clinic :

Gonorrhoea	22	Non-gonococcal urethritis	8
Primary syphilis	1	No V.D.	12

On their first spell of attendance at the clinic thirty had been discharged cured, thirteen defaulted, and one had been transferred.

The principal interest lies in the five "return cases" which had not been re-exposed to infection, as they might at first indicate that we had failed to detect a latent infection and that they had later suffered a reactivation of the disease; they were therefore subjected to most careful inquiry and full investigation. The result was that three of these patients were found to be free from venereal disease and symptoms, but had returned to the clinic to reassure themselves—for example, before marriage. One had a non-gonococcal urethritis due to *B. coli* urinary infection. This patient recovered rapidly: there was never any evidence suggestive of latent gonorrhoea, and he defaulted while undergoing final tests of cure of this urethritis.

One patient (Ref. No. D 216) had been treated for acute gonorrhoea by sulphanilamide, and responded favourably; but there was an early relapse, after which he developed epididymitis, which was treated in the usual way. He was eventually observed for several months and after satisfying our routine test of cure was discharged. He returned to the clinic forty-eight weeks later (Ref. D 2217) on account of a reappearance of the urethral discharge. Smears of the urethral pus contained gonococci. He was treated with sulphapyridine, responded favourably, and eventually was discharged again as cured. He has not since returned to the clinic. This man did not volunteer any reason for recurrence of his symptoms: he denied re-exposure, but was not subjected to cross-examination. On the data available we must admit that this patient had suffered from latent gonorrhoea which our routine tests of cure failed to detect and that his disease became active forty-eight weeks later. However, this is the only instance in the series of 810 cases in which our tests of cure have failed. This is in striking contrast with the results reported by Cockkinis and McElligott (*British Medical Journal*, 1939, **2**, 1081): "The true incidence [of relapse] lies somewhere (perhaps halfway) between 12 and 27 per cent."

Notes on Other Sulphonamides

Certain other members of the sulphonamide group have been subjected to clinical trial. They are not included in the previous review or in Table II as the method of dosage was different; several of the patients are still under observation, and the drugs were not tested in routine out-patient practice.

Uleron (Bayer).—This drug is claimed to be a very potent sulphonamide, but it is affirmed that the best results are obtained in delayed chemotherapy only—that is, by withholding uleron until after the third week of the infection. Uleron has a tendency to damage peripheral nerves, and has to be given in short courses of four days, with an interval of four days between courses, to permit excretion. If this precaution is neglected the patient may readily develop peripheral neuritis. One of us (R. L.) has observed a very severe case of peripheral neuritis affecting both legs and arms in a German sailor who consumed 90 tablets (45 grammes) of uleron without an interval. The dosage employed in our series was 4 grammes a day for four days; there was then an interval of four days,

and the course was repeated in this way three or four times, according to the clinical and bacteriological response. The results are summarized below, but it is fair to point out that the majority were complicated cases.

Immediate Treatment:

- 11 cases (2 uncomplicated urethritis and 9 prostatitis and/or epididymitis).
- 3 cases became gonococcus-negative in urethral smears after two courses.
- 2 cases became gonococcus-negative in urethral smears after three courses.

Delayed Treatment:

- 11 cases (1 urethritis and 10 prostatitis and/or epididymitis).
- 6 cases became gonococcus-negative in urethral smears after two courses.
- 3 cases remained gonococcus-positive in urethral smears after two courses.
- 2 cases still positive after one course were treated by irrigation, etc.

Result:

- 22 cases (discharged cured, 9; defaulted, 13).

Our conclusion on the result of our observations on these twenty-two cases is: (1) uleron is more dangerous than sulphanilamide and sulphapyridine; (2) it is less potent than sulphapyridine, but about equal to sulphanilamide; (3) delayed chemotherapy with uleron does not give results as good as those of immediate treatment with sulphapyridine.

Albucid (Schering).—Albucid is a modification of the sulphanilamide formula with a view to reducing toxicity. This drug gives practically no toxic effects, even in high dosage, but its curative action on the gonococcus is much weaker than that of sulphanilamide and very much weaker than that of sulphapyridine. The system of dosage suggested by the makers was followed: first day, 15 tablets; second day, 12 tablets; third day, 9 tablets; fourth day, 6 tablets—a total of 21 grammes. Several courses were given, and as delayed chemotherapy was advocated it was practised. Only thirteen cases were treated; of these, four became gonococcus-negative and nine remained gonococcus-positive, and were not improved clinically. Albucid is a very feeble curative agent in gonorrhoea. The claims made for low toxicity were substantiated, but this drug seems to have no place in the treatment of gonorrhoea except in a very few individuals who prove highly intolerant of sulphapyridine.

"M 541" (I.C.I.).—This is sulphanilamide-ethyl-sulphonate, and is a compound of low toxicity but very feeble curative power; patients treated by it subsequently proved resistant to sulphapyridine. A very poor response, clinical and bacteriological, was obtained from the experimental product "M 541," and subsequent administration of sulphapyridine in the usual dosage completely failed to produce any improvement. Nine cases were treated. One showed an initial response, and gonococci disappeared. The remaining eight were positive after "M 541" and after one or more courses of sulphapyridine. Its use has been discontinued, as it is not suitable for the treatment of gonorrhoea.

GONORRHOEA OF WOMEN

Sulphonamide treatment of gonorrhoea of women is discussed separately because, although the chemotherapeutic principles are the same, the details of management of the patient and estimation of cure are necessarily different.

Diagnosis.—In all cases smears are taken from the urethra, cervix uteri, Bartholin glands, and vagina. The vaginal secretion is examined by appropriate methods for *Trichomonas vaginalis*, as we have found that infestation with this parasite keeps up the symptoms and signs and may retard the cure of gonorrhoea. In case of doubt the secretions are cultured for gonococci. Progress is

assessed by re-examination at intervals of two days in the acute stage and seven days in the subacute or observation period. Tests of cure are conducted over a minimum period of three months; where possible the patient is examined after three successive menstrual periods.

Treatment.—Sulphonamide has been given immediately the diagnosis has been established. The dosage tolerated is lower than in the male cases: the average doses are shown in Table I. The results are presented in Table II, part of which is for convenience set out in detail in Table VIII.

TABLE VIII

	Sulphanilamide (54 cases)	Sulphapyridine (75 cases)
Cure	41 (76%)	52 (60.9%)
Default	13 (24%)	23 (39.1%)
Complications	2 (3.7%)	5 (6.6%)
Relapse	1 (1.85%)	1 (1.3%)
Drug resistance	10 (18.5%)	4 (5.3%)

Cure.—The percentage cured is higher with sulphanilamide than with sulphapyridine, and the default rate is lower; but sulphapyridine shows a lower incidence of complications and drug resistance. In this small series there is on the whole little to choose between the drugs in the final analysis of results. In the management of cases in the clinic, however, sulphapyridine gives more rapid control of contagion and relief of acute symptoms, and a lower incidence of toxic symptoms and signs from the drug.

Default is again a serious problem, and female defaulters have been classified in Table IX.

TABLE IX

	Sulphanilamide (54 cases)	Sulphapyridine (75 cases)
Contagious	4 (7.4%)	9 (12%)
Potentially cured	2 (3.7%)	1 (1.3%)
Presumed cured	7 (13%)	13 (17.3%)
Totals	13 (24%)	23 (30.6%)

As in the case of male defaulters, some of these patients returned to the clinic later, giving a history of recent coitus, often with a superadded infection such as syphilis, and they must be regarded as serious enemies of the public.

It is admittedly difficult to ascertain when a woman is cured of gonorrhoea, and there have been many difficulties in solving such problems in this series, particularly when a husband and wife attend the clinic simultaneously, or when they are habitually drunk or sexually promiscuous, or when marital relations continue during the period of observation and tests of cure. We had one such couple, and it is quite impossible to assess whether the frequent return of gonococci in one or both parties was due to failure of treatment, unreliability of tests of cure, or just a fresh reinfection. The possibility of the latter was readily admitted by both parties.

Complications of gonorrhoea arising during treatment in women were few, and are shown in Table X.

TABLE X

	No. of Cases	Bartholin Abscess	Salpingitis	Totals
Sulphanilamide	54	0	2	2 (3.7%)
Sulphapyridine	75	2	3	5 (6.6%)

As with the male patients, we have not included in Table X any complications present at the first examination of the patient before sulphonamide treatment was given. In every case the complications developed after administration of the drug had ceased. The majority of the complicated cases responded rapidly to treatment: in some the final verdict cannot yet be pronounced, but none of them required major operative treatment. The series is too small to allow of definite conclusions, except that the total incidence of complications is not high.

Relapse occurred in one patient treated by sulphanilamide and one treated by sulphapyridine. In the former it was difficult to exclude reinfection. Both responded favourably to additional treatment, and appear to have remained well.

Drug resistance occurred in ten cases treated with sulphanilamide (18.5 per cent.) and in four cases treated with sulphapyridine (5.3 per cent.). No reason for such drug resistance was found. Some patients were given several courses of the drug with no benefit, but they all responded slowly to local antiseptic treatment. Here again default becomes a serious matter, as the patient may readily be discouraged and content herself with douches, etc., at home.

Return Cases.—There were seven patients who had been discharged or had defaulted after sulphonamide treatment and later came back to the clinic.

Of these seven cases six gave a history of coitus since leaving the clinic: two suffered from gonorrhoea, one from syphilis, one from gonorrhoea and syphilis, and three from trichomonas vaginitis. One of the above patients has been referred to previously, and it is difficult to assess whether her case represents a genuine failure of our tests to detect latent infection or whether there was a reinfection from her husband or some other source. The one patient who had not had coitus suffered from a recurrence of vaginitis due to *Trichomonas vaginalis* infestation; she did not suffer from a recurrence of gonococcal infection, and numerous tests proved negative.

We accordingly find in this series no reason to believe that tests of cure efficiently conducted during an adequate period of observation (not less than three months) are likely to fail. We do not find that many cases previously regarded as cured by the aid of sulphonamides are merely latent and subsequently relapse. We maintain that those which have been "cured" are permanently cured. If any substantial proportion were latent gonococcus carriers the fact would have become obvious long ago in our venereal diseases organization, where the male and female clinics work side by side, under the same control, and are closely co-ordinated.

General Notes

The preceding pages record some observations on a large clinical experiment. So far as was expedient we tried to observe and test the effects of sulphonamides alone, unaided by antiseptic treatment, irrigations, etc. We do not advocate the treatment described as the best—indeed, by observation of this series we have learned the limitations of sulphonamide therapy. The problem of default is the major one, and improvement in this respect may be achieved by securing more lasting co-operation of the patient through explanation of the difference between apparent and proved cure. An additional period of active treatment by irrigations, etc., may secure longer observation and more tests of cure, and so reduce the number of "contagious defaulters." We now consider that treat-

ment with sulphapyridine should follow the lines indicated below:

1st-4th day	..	4 gm. daily	..	..	..	16 gm.
5th-8th day	..	3 gm. "	..	..	..	12 gm.
9th-14th day	..	2 gm. "	..	..	..	12 gm.
Total						40 gm.

Irrigation and local antiseptic treatment should not be employed during the first week, but may profitably be used thereafter if clinical signs of incomplete healing are present. Tests of cure must be more stringent in sulphonamide-treated cases. A minimum period of observation is three months after the last positive bacteriological test or clinical sign of disease.

Conclusions

Sulphanilamide and sulphapyridine are both potent drugs in assisting or securing cure of gonorrhoea, and give approximately the same percentage cured.

Sulphapyridine is much easier to use, with a lower incidence of drug resistance and complications of gonorrhoea.

Toxic effects were almost invariable and often severe when sulphanilamide is used, but less severe in the sulphapyridine series, and not dangerous with either drug.

There is a high rate of defaulters with both drugs. Every effort should be made to minimize this tendency.

The tests of cure employed appear to be very reliable, and cases returning to the clinic after default or cure are almost all cases of re-exposure (? reinfection) or do not suffer from venereal disease. The late recurrence of gonorrhoea after satisfying tests of cure was noted definitely in only one male patient of this series.

Drug resistance appears to be a personal idiosyncrasy, the nature of which has not been studied in this paper. Drug resistance is readily acquired if subcurative doses of any sulphonamide are given. Such acquired drug resistance is not permanent.

The treatment described has been conducted as a large-scale clinical investigation on the value of the sulphonamides in gonorrhoea. Experience and the results presented have suggested some modifications of the scheme originally used.

Sulphonamides are powerful anti-gonorrhoeal agents, though not an easy panacea. They must be skilfully used and accurately controlled, and should only be employed where the results of treatment can be accurately ascertained.

Summary

810 male cases and 129 female cases of gonorrhoea have been studied.

The results have been assessed six months or longer after completion of treatment.

Strict tests of cure have been employed. All patients who have not completed all the tests of cure are "defaulters."

Search for "return cases" has been conducted up to date.

The incidence of complications of gonorrhoea arising during treatment is noted.

Drug resistance—its incidence, and its relation to cure—is discussed.

Cases of small-pox reported in 1939 in the United States numbered 14,939, or about twice the median for 1933-7. There has been a steady increase of the disease since 1910, when about 5,000 cases were reported.