RELAPSES AFTER SULPHONAMIDE CURE OF GONORRHOEA

BY

A. J. COKKINIS, M.B., B.S., F.R.C.S.

*Surgeon, Emergency Medical Service; Surgeon, Wembley
Hospital; Assistant Director, Venereal Disease
Department, St. Mary's Hospital*

AND

G. L. M. McELLIGOTT, M.A., M.R.C.S., L.R.C.P.

*Director, Venereal Disease
Department, St. Mary's Hospital*

It is now established that three sulphonamide compounds—sulphanilamide, sulphapyridine (M & B 693), and uleron—can produce apparent cure of gonorrhoea in a few days. A year ago we showed that the first of these—sulphanilamide—needs the help of immunity to yield its optimum effects, having noted that better results are obtained when it is started on the eighth to the tenth day of symptoms instead of from the onset, and when it is combined with vaccine. The same policy of waiting has been found to increase the curative value of uleron, although this compound seems to be less effective than sulphanilamide.

After the introduction of sulphapyridine it became obvious that this is a more potent anti-gonococcal sulphonamide than the others, and articles have appeared which claim that it does not need the help of immunity but may be used from the onset of gonorrhoea with almost complete certainty of eliminating the infection. At St. Mary's Hospital we are not convinced that this optimistic claim will be confirmed by experience. While gladly recognizing the great potency of sulphapyridine, we have not yet abandoned its predecessors, and are still exploring ways of combining chemotherapy with immunotherapy in the hope of improving the chances of *permanent cure*. We had intended to publish the final results of our work with all three compounds in the near future, but owing to the present emergency this publication has had to be postponed.

In the present article, the preparatory material for which was collected before the onset of the war, we intend to give prominence to an aspect of chemotherapy which had for some time caused us considerable disquiet and which has an important bearing on the question of permanent cure (as distinct from elimination of symptoms). We refer to the occurrence of *late relapses*, weeks or months after apparently complete cure and after negative tests. The significance of such relapses, if they prove to be frequent, is obvious. Unfortunately they are becoming frequent enough, in our experience, to cause us real anxiety and to check the early enthusiasm with which we hailed the curative properties of these compounds in general and of sulphapyridine in particular.

It is easy to close one's eyes to unpleasant developments in what at first promised to be a perfect outlook, and to dismiss these cases as reinfections, however strenuous the denials of fresh exposure. But when these patients began to return to the clinic in large numbers it became obvious that some of them must be telling the truth and were, in fact, genuine relapses. With further experience we found that these latter cases present a clinical picture usually quite different from that of a reinfection, and we are now able to discriminate between them without having to rely solely on the patient's veracity. Quite

recently (July, 1939) we analysed our records of over 1,200 male and 200 female patients treated with sulphonamide compounds long enough ago to provide reliable information on remote results. This analysis reveals an incidence of late relapses sufficient to render unreliable any statistics of results based on a relatively short follow-up.

Significance of Late Post-chemotherapy Relapses

These late relapses have a significance quite distinct from that of the early relapses with which we have all been familiar since the early days of chemotherapy. The early relapse a few days after a sulphonamide course or after the first provocative tests is an immediate warning that infection is still present and that treatment must be continued. But a patient who has passed several tests and remains well for months, only to relapse ultimately, often believes himself cured and may indeed have been discharged. Such a case harbours the gonococcus, which can be transmitted during the quiescent stage, and especially during the early and often inconspicuous stage of the actual relapse. Indeed, the early signs may be so mild that the patient may not reappear until complications are present. Most significant of all is the influence these late relapses must exert on the reliability of tests of cure, on the length of the period of follow-up, and on the final discharge of the patient. Our own experience, as shown in this article, has made us reluctant to give any pronouncement of permanent cure at this stage of the new therapy. The most we feel justified in saying to a patient is that he is probably cured if he has passed exhaustive tests and at least a six-months uneventful follow-up. There are several reasons why this cautious attitude should be rigidly adopted in the conditions which prevail during war time.

LATE RELAPSES IN MALES

Recognition and Clinical Course

In males we employ the term "late relapse" when symptoms return three weeks or more after a successful sulphonamide course and after at least one negative series of tests. This critical period has been adopted because appreciable differences exist in the manifestations of relapses before and after it. The early relapse occurs usually within a week of the end of chemotherapy or of the first test, and resembles the original attack in its acute onset, profuse discharge, cloudy urine, and the rapidity with which pus cells and gonococci crowd the smears. The late relapse is usually quite different. Although it may be provoked by a late test or by alcohol, most of our cases passed several tests quite successfully and then relapsed for no obvious reason weeks or months afterwards. What usually happens is that the patient one morning discovers a slight urethral moisture which in a few days becomes a scanty mucoid discharge. The urine is clear or shows specks or a slight haze, while the smears contain scanty pus cells and either no gonococci or very few groups. The prostatic beads, after being quite negative, may now show pus. Sometimes pus cells and even gonococci appear in the prostatic secretion some days before the clinical relapse; but these "threats" do not always materialize, and the next prostatic test may be quite negative.

This mild urethritis may continue for a week or two and then subside. More often the discharge gradually becomes purulent, the urine more hazy, gonococci more

plentiful, and a definite relapse is established after a week or so. Some of our cases, however, developed no discharge, but showed a cloudy urine with prostatitis or basal cystitis; while a few came with other complications, such as periurethritis, epididymitis, or arthritis, but without a coexisting urethral relapse.

The outcome of these relapses has varied. Some cleared up with irrigations and vaccine, while most responded to sulphonamides as readily as the original attack. A number, however, resisted chemotherapy this time, or, after again responding, returned with another relapse. The treatment of these latter cases is a problem we have not as yet solved.

General Incidence of Late Post-chemotherapy Relapses

To discover this incidence an analysis has been made of 1,268 male cases of gonorrhoea the chemotherapy of which was completed more than six months previously. Of this total, 263 either failed to respond to the treatment or defaulted before tests, thus leaving a net total of 1,005 patients who remained well more than three weeks after their last sulphonamide course and who passed one or more series of tests. Of these cases, 118 (12 per cent.) have so far returned with late relapses (112 with one relapse, five with two, and one case with three relapses).

This figure of 12 per cent. cannot be an accurate estimate of the true relapse rate, since a large number of the 1,005 cases defaulted during the follow-up, and some of these must have relapsed subsequently. Another way of computing this incidence is to apportion the relapses into groups according to the time of their occurrence, and then to calculate the relapse rate for each period on the total cases whose follow-up extends into it (Table I).

TABLE I.—Incidence of Post-chemotherapy Relapses at Various Stages of Follow-up

Time Group (Period of Follow-up)	Followed-up Cases reaching Each Period	Late Relapses in Each Period	Late Relapse Rate for Each Period
4th week	1,005	20	2%
2nd-3rd month ..	948	48	5.1%
4th-6th „	652	41	6.3%
7th-9th „	173	11	6.4%
Over 9 months ..	68	5	7.3%

The full late relapse incidence, on this computation, is arrived at by adding together the relapse rate of all five groups, and works out at 27 per cent. It may be argued that this estimate is also inaccurate and that it exaggerates the chance of relapse, inasmuch as patients are more likely to return if they develop a relapse than if they remain well. This argument is incontrovertible. The true incidence, therefore, lies somewhere (perhaps half-way) between these two estimates—that is, between 12 and 27 per cent.

Incidence of Reinfections

The above 118 cases are in our opinion all genuine relapses. Another 100 of the 1,005 cases also returned with gonorrhoea in the same period: of these, eighty-seven were definite reinfections, while the other thirteen might have been relapses or reinfections, but for the purposes of this article are included with the latter. The time incidence (between end of chemotherapy and

return of symptoms) of both relapses and reinfections is compared in Table II, which reveals another noteworthy difference between them.

TABLE II.—Comparison of Time Incidence of Late Relapses and Reinfections

	Under 3 Months	4th-6th Month	7th-9th Month	Over 9 Months
Late relapses (125) ..	68 (54%)	41 (33%)	11 (9%)	5 (4%)
Reinfections (100) ..	23 (23%)	35 (35%)	26 (26%)	16 (16%)

Detailed Analysis of Relapses and Discussion

A special analysis of our material was made to provide answers to the following questions, which are of obvious importance: (1) Does the incidence of late relapses vary with individual sulphonamides? (2) Is this incidence diminished by delaying the chemotherapy? (3) What is the influence of dosage and period of administration? (4) Is the relapse rate diminished by adjuvant treatment—for example, vaccine? (5) Are cases which clear up rapidly less likely to relapse than those which do so slowly or only after multiple courses? (6) Are there periods when relapses are more likely to occur? (7) What proportion of late relapses show gonococci? (8) How do these relapses affect provocative and other tests?

Some of the above questions are answered in Table III, which gives our late relapse figures with sulphanilamide, sulphapyridine, and uleron, begun at various stages of gonorrhoea. For purposes of comparison the early relapse figures are also included. The late relapse figures (last column) are, as already stated, probably lower than the true incidence, and might be made more accurate by increasing each figure by half its total.

1. In answer to the first question it will be seen that *our male (uncorrected) late relapse rate with sulphapyridine (18.5 per cent.) is nearly two and a half times that with sulphanilamide (7.8 per cent.)*. On the other hand, the early relapse rate with sulphapyridine (8.6 per cent.) is less than half that with sulphanilamide (17.7 per cent.). This reversal of the ratio, together with the more rapid and certain immediate curative action of sulphapyridine, provides a negative answer to question No. 5. It may well be that the longer treatment and more frequent need for multiple courses with sulphanilamide explain the lower incidence of late relapses after this drug. Our late relapses with uleron show a rate very similar to that with sulphapyridine, but the uleron cases are too few for this resemblance to have any significance.

2. This table gives a positive answer to the second question, as it shows a fall in both early and late relapses (with all three drugs) when the chemotherapy was delayed until after the first week of symptoms. This fall is very pronounced in the sulphanilamide group, the figures of which provide justification for the policy of delay with this drug advocated by us a year ago. The increased relapse rate of very chronic cases is associated with chronic lesions—for example, urethral stricture and chronic prostatitis. With sulphapyridine the early relapse rate is again more than halved when chemotherapy is delayed to the second week, but the fall in the late relapse rate is relatively negligible. A very interesting difference is shown in the sulphapyridine cases treated after the second week, depending on whether or not the patient had had previous therapy with another sulphonamide. According to Table III previous (therefore unsuccessful) treatment with other compounds has raised the early relapse rate from 3 per cent. to 11.8 per cent. and the late relapse rate from 15.1 per cent. to 32.3 per cent. These figures suggest that a high proportion of such cases were infected either with a sulphonamide-resistant strain of gonococcus or with one which

TABLE III.—*Showing Early and Late Relapse Rate after Sulphonamide Therapy*

Compound	State of Gonorrhoea when Compound Begun	Gross Total of Cases*	Net Total†	Early Relapses‡	Early Relapse Rate	Late Relapses‡	Late Relapse Rate§
Sulphanilamide	1st week	216 (all Gc. +)	170	53 (all Gc. +)	31.2%	20 (16 Gc. +)	12%
	2nd week	230 (all Gc. +)	196	27 (23 Gc. +)	13.8%	12 (9 Gc. +)	6.1%
	3rd week to 12th month ..	248 (188 Gc. +)	227	26 (22 Gc. +)	11.5%	10 (5 Gc. +)	4.4%
	After 12th month	66 (25 Gc. +)	57	9 (3 Gc. +)	15.8%	9 (1 Gc. +)	15.8%
Total sulphanilamide cases		760 (659 Gc. +)	650	115 (101 Gc. +)	17.7%	51 (31 Gc. +)	7.8%
Sulphapyridine	1st week	168 (all Gc. +)	128	13 (all Gc. +)	10.2%	24 (17 Gc. +)	18.7%
	2nd week	142 (all Gc. +)	112	5 (all Gc. +)	4.5%	17 (14 Gc. +)	15%
	After 2nd week : Sulphapyridine only ..	47 (39 Gc. +)	33	1 (Gc. +)	3%	5 (3 Gc. +)	15.1%
	Sulphapyridine after other sulphonamides	51 (26 Gc. +)	31	6 (all Gc. +)	11.8%	10 (6 Gc. +)	32.3%
Total sulphapyridine cases		408 (375 Gc. +)	304	25 (all Gc. +)	8.6%	56 (40 Gc. +)	18.5%
Uleron	1st and 2nd weeks	46 (all Gc. +)	26	22 (all Gc. +)	84.6%	6 (all Gc. +)	23%
	After 2nd week	54 (34 Gc. +)	34	20 (16 Gc. +)	58.8%	5 (1 Gc. +)	15%
Total uleron cases		100 (80 Gc. +)	60	42 (37 Gc. +)	70%	11 (7 Gc. +)	18%

* All these are cases of proved gonococcal infection, but cases in which gonococci were seen at the start of chemotherapy are given in brackets.

† After deducting early defaulters and failures, and including only cases which passed at least one series of tests and a follow-up of at least three weeks.

‡ Cases which relapsed more than once are counted as only one relapse. Relapsed cases in which gonococci were actually seen are shown in brackets, but gonococcal infection was suspected and probably present in most of the others.

§ For reasons given in the text these figures are probably considerably below the true relapse rate.

had acquired sulphonamide-fastness through the previous chemotherapy. The high early relapse rate with uleron is a result of treatment with repeated short "stosses" necessitated by its tendency to cause peripheral neuritis if given in longer courses. Both the early and late relapse figures, however, are lower in cases treated after the second week of the disease.

3 and 4. These questions cannot be answered fully in this article. It may be pointed out, however, that only cases treated after the first week of gonorrhoea were given vaccine as a routine, and this may in part be responsible for the lower incidence of relapses in this group. On the other hand, it must be stated that most of the relapsed cases in this group had had some vaccine therapy. Thus far our vaccine dosage has been rather on the small side, and we are now experimenting with much larger doses in the hope of diminishing the relapse rate. With regard to dosage and period of administration of the drugs themselves, an analysis of the late relapses gives the following figures. Of the fifty-one late relapses after sulphanilamide only 18 per cent. had less than what we consider the minimal effective quantity of 56 grammes in fourteen days, while 61 per cent. had over 60 grammes and 18 per cent. over 80 grammes in one course of fourteen to twenty-one days. Of the fifty-six late relapses after sulphapyridine only 20 per cent. had less than a "minimal effective" course of 30 grammes in ten to twelve days; 36 per cent. had over 40 grammes and 9 per cent. over 60 grammes of this powerful sulphonamide in one course of fourteen to twenty-one days. These figures show that inadequate dosage does not account for more than a small proportion of late relapses, and that such relapses can occur after very full courses of both sulphanilamide and sulphapyridine. In other words, a quantity and a period which produce complete clinical cure may not suffice to eradicate the gonococcus, and if there is a quantity and a period which can be relied upon to do this they must be in excess of the very large dosage taken by some of our relapsed cases.

5. As far as can be done at present, the fifth question has been answered (with the first question).

6. Table I suggests that the chance of relapse remains fairly constant through the first year after chemotherapy. In view, however, of the probability that relapsed cases are more likely to return at a late stage of the follow-up than unrelapsed ones, it is likely that in actual fact there is a gradual fall in the chance of relapse with the passage of time.

7. The proportion of relapses in which gonococci were seen is given in Table III, and works out at 81 per cent. of late

relapses of cases treated in the first two weeks of gonorrhoea and 36 per cent. of cases treated at a more chronic stage. These figures are based mainly on the results of smear examinations, and it is likely that a greater use of cultures would have shown gonococci in many cases with negative urethral or prostatic smears.

8. The occurrence of so many late relapses throws considerable doubt on the reliability of provocative and other tests of cure in cases treated by chemotherapy. In the period when the cases under review were treated our usual practice was to start the first series of tests one to two weeks after the end of the chemotherapy. The series comprised (a) examination of prostatic beads, (b) complement-fixation test, (c) provocative gonococcal vaccine (400 to 500 millions), (d) urethroscopy, (e) massage of urethra on metal sound, (f) alcohol. Prostatic tests were repeated at intervals of two to four weeks, and larger injections of vaccine (500 to 1,000 millions) given at three-monthly intervals.

Whatever the value of these tests may have been in pre-sulphonamide days, the fact that 118 of our cases relapsed after successfully passing at least one series of tests (seventy-one of them passed two or more) shows that *negative tests are not proofs of cure in cases treated by chemotherapy*. And yet the fact that 20 per cent. of our late relapses were definitely provoked by vaccine, bougie, or alcohol as late as three to six months after apparently complete cure shows that these tests are still of value. In the present state of our knowledge they cannot be dispensed with, but we submit that great caution should be exercised in the interpretation of their results. Particularly we wish to stress the value of repeated examinations (including culture) of the prostatic secretion, as we have reason to believe that many post-sulphonamide relapses are started by gonococci in the prostate which were rendered only temporarily inactive.

A year ago we stated that a positive gonococcal complement fixation does not mean that a patient is uncured. Now we are in a position to add that negative G.C.F. tests do not indicate that a patient is cured. Of seventy-nine late relapses whose G.C.F. test was not vitiated by recent vaccine no fewer than thirty-four relapsed after a completely negative result. It may indeed be of some significance that most of these thirty-four cases never developed a positive fixation at all.

LATE RELAPSES IN FEMALES

In pre-sulphonamide days it was generally admitted that in most cases the female urethral infection was comparatively easy to eradicate, whereas the deep racemose glands of the cervix were apt to harbour gonococci over long periods. Bourne has recently challenged this hypothesis by histological examination of chronically infected cervixes, in most of which he found that the inflammatory reaction was superficial. In spite of these findings one cannot rule out the possibility of temporarily inactive gonococci being able to lurk in these glands without provoking an inflammatory reaction.

In most cases of proved female gonorrhoea gonococci are demonstrated only in the urethral discharge in spite of the fact that signs of cervicitis are usually present. When one considers that secondary infection from the vagina of an inflamed endocervix is inevitable, and that these vaginal organisms are able to outgrow the gonococcus, one can appreciate how a gonococcal cervicitis may in many cases be effectively masked. In view of the excellent blood supply of the cervix it is reasonable to suppose that cervical gonococci yield to sulphonamide therapy as readily as do those in the urethra, in spite of the fact that the secondary infection of the cervix with vaginal organisms, most of which are resistant to sulphonamides, appears to be unaffected. For this reason local treatment of the vagina, and in some cases the cervix itself, is nearly always necessary. That persistent cervicitis after chemotherapy is not due to the gonococcus is further suggested by the fact that in such cases no husband has so far been reinfected by his wife.

The difficulty of reliably ascertaining the relapse rate in women is fully appreciated, and the role of the laboratory animal must always be filled by the male. Janet's dictum that the best culture medium for the gonococcus is the uninfected male urethra is to-day as true as ever.

Though we have now treated many hundreds of cases of female gonorrhoea with sulphanilamide and sulphapyridine a large number have been excluded from this analysis on the ground that they did not show gonococci immediately before the beginning of chemotherapy or that they were early defaulters. The almost invariable secondary cervicitis has made it well-nigh impossible to distinguish between failures and early relapses, and we have classed as late relapses only those cases which showed at least two sets of gonococcus-negative smears and cultures and which have again shown gonococci more than one month after chemotherapy. A minimum follow-up of six months has been insisted on where possible, and in no case has provocation been carried out before the end of the third month. The results of an analysis of 210 female cases are given in Table IV; in spite of many obvious "snags," and possibly some concealed ones, the figures are not without interest.

TABLE IV.—Analysis of 210 Female Gc. + Cases treated with Sulphanilamide or Sulphapyridine

SULPHANILAMIDE	
Total Gc. + cases at start of chemotherapy	123 (26 defaulted before 3 months, leaving 97)
Failures and early relapses	18
Late relapses (Gc. +)	16 (11 relapsed after 3 months)
SULPHAPYRIDINE	
Total Gc. + cases at start	87 (5 defaulted before 3 months, leaving 82)
Failures and early relapses	5
Late relapses (Gc. +)	7 (4 relapsed after 3 months)

On the face of it the sulphapyridine figures are more encouraging than the sulphanilamide ones and do not appear to confirm the male findings, but against this it

must be remembered that the maximum follow-up period of the female sulphapyridine cases is so far only eight months as against two years in the sulphanilamide cases, so that it is reasonable to expect some further increase in the late relapse figures of the former. Furthermore, it will be appreciated that, as the smaller effective dose of sulphapyridine (2 grammes daily as against 3 grammes of sulphanilamide) was more easily tolerated by women patients, it is more likely that the doses prescribed were actually taken. Experience has taught us the paramount importance of avoiding toxic effects in the treatment of women out-patients.

Summary

This article deals with an important and hitherto neglected aspect of the new chemotherapy of gonorrhoea—namely, the occurrence of late relapses after apparently complete cure by sulphonamide compounds; it also gives the results of an investigation into the incidence, recognition, and causation of these relapses.

An analysis is given of 1,268 male and 210 female cases of gonorrhoea whose chemotherapy was completed from six months to two years previously. This analysis indicates that of cases which have been successfully treated with sulphonamide compounds and which have passed tests of cure about 20 per cent. relapse subsequently.

This figure of 20 per cent. is quite distinct from the incidence of chemotherapy failures and early relapses, and must therefore be added to the latter in any calculation which aims at showing the final results of sulphonamide treatment. In the present article no attempt is made to assess the full incidence of chemotherapy failures or the results obtained with individual compounds.

The analysis gives comparative figures of relapses after sulphanilamide, sulphapyridine, and uleron; it indicates also the effect on the relapse rate of delaying the chemotherapy and of combining it with adjuvant treatment, and provides answers to other pertinent questions.

Special attention is given to the clinical recognition of late post-chemotherapy relapses, and to their differentiation from reinfections and from early relapses. The course and treatment of late relapses are also indicated briefly.

Emphasis is laid on the influence this high relapse rate must exert on the reliability of tests of cure, on the length of a safe follow-up period, and on the responsibility inseparable from the final discharge of the patient.

The fact that half of these late relapses occurred more than three months after apparently complete cure throws doubt on the reliability of certain published statistics of results obtained with sulphapyridine and other sulphonamide compounds.

The first quarterly issue of the new series of reports by the British Association for the Advancement of Science has been received. It is dated October, 1939, and is obtainable at 5s. from the offices of the British Association at Burlington House, Piccadilly, W.1. It contains an introductory account of the history of the British Association, some of the proceedings of the meeting at Dundee, and abstracts of other communications. When that meeting was terminated by the outbreak of war after the first three days of scientific sessions, it was decided that all communications of which the delivery had thus been unavoidably cancelled should be taken as read, and be printed as such in the *Advancement of Science*, as this series of reports is termed. It is intended to supply an index to the four parts in each year, and to print it in the July issue. The papers appearing at length in the October, 1939, issue are the presidential address, "The Western Isles through the Mist of Ages"; the address by Professor W. E. Le Gros Clark, F.R.S., "The Scope and Limitations of Physical Anthropology"; as well as the first instalment of a scientific survey of Dundee and district, and the reports of the research committees of the British Association.