LATE RELAPSE FOLLOWING TREATMENT OF GONORRHOEA WITH SULPHAPYRIDINE

BY

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The consensus of opinion, among British venereologists at least, is that sulphapyridine is the most potent drug at present available for the treatment of gonococcal infections. Certain problems connected with this chemotherapy, however, still await solution, and one of the most important concerns the assessment of permanent cure by appropriate tests and a period of clinical observation. The need for thoroughness and completeness in such tests and for an adequate period of clinical observation in cases treated in general as well as in clinic practice is conceded by all venereologists, and has been emphasized in particular by Forgan (1939) and myself (Laird, 1939). Always important, these precautions have become more than ever necessary following the use of the sulphanilamide drugs in cases of gonorrhoea, as the rapid abatement of symptoms might otherwise favour the dissemination of the disease by symptomless carriers of the gonococcus. This danger was recognized soon after the introduction of chemotherapy, and further experience of the sulphanilamide drugs confirmed the early suspicion that relapse may occur as in pre-chemotherapy days.

The difficulty in determining whether the recurrence of symptoms or signs is due to reinfection or to true relapse has always been considerable, but chemotherapy has now been in use long enough for a study of the position with regard to relapse. Relapse may be early or late, and from the epidemiological standpoint the latter is of greater significance. Early relapse occurs soon after the completion of a course of sulphonamide, and indicates that a further course should be prescribed. Late relapse takes place after treatment and the initial tests of cure, and may occur from several weeks to several months after chemotherapy has been completed.

Present Investigation

The material used in this study comprises 162 cases of urethritis in the male treated with sulphapyridine between September, 1938, and June, 1939. Complete continuity of observation and consistency in case-recording may be claimed for this series as all the patients were under my sole care. Gonococci were demonstrated in the majority of these cases and in all patients in whom relapse occurred, but, unfortunately, facilities for cultural studies were not available. The follow-up in this series was as long as possible, but twenty-five patients attended for less than twenty-eight days, with a mean of 18.5 days from the start of chemotherapy. The period of observation of the remaining 137 cases averaged 135 days, giving a mean of 118 days for the whole series. The maximum period in any case was 318 days, and it is reasonable to assume that during the observation period maintained in this series a large proportion of late relapses would be detected. Furthermore, any case of relapse reporting at the only other clinic in the neighbourhood would be referred back to me.

Twenty-five cases of this series reported with a recurrence of symptoms or signs after clinical cure had been achieved. The criteria of clinical cure were absence of urethral discharge when examined at least two hours after

the last urination, urine clear in both first and second glasses and free from shreds and debris, and the absence of symptoms. The evidence in thirteen of these cases indicated that reinfection had occurred, and thus the incidence of relapse was twelve out of 162 cases, a rate of 7.4 per cent. Six cases of late relapse were noted, giving a late relapse rate of 3.7 per cent. Table I presents

TABLE I.—Showing the Clinical Classification of Cases at the Outset and Type of Case in which Relapse Occurred

Clinical Classification	Total Cases	Early Relapse	Late Relapse	All Relapses
Acute anterior urethritis of less than one month	126 (100%)	5 (4%)	3 (2.4%)	8 (6.4%)
Acute posterior urethritis of less than one month	12 (100%)	1 (8.3%)	0	1 (8.3%)
Urethritis for more than one month	24 (100%)	0	3 (12.5%)	3 (12.5%)
All cases	162 (100%)	6 (3.7%)	6 (3.7%)	12 (7.4%)

the material classified according to the clinical condition at the outset of sulphapyridine treatment and indicates the type of case in which late relapse occurred. Table II

TABLE II.—Showing Date at which Early and Late Relapse and Reinfection Occurred

Time in Days	Early Relapse	Late Relapse	Reinfection
1 to 30	6	0	2
31 to 60	0	5	0
61 to 90	0	1	2
91 to 120	0	0	2
121 to 150	0	0	3
151 to 180	0	0	1
181 to 210	0	0	2
211 to 240	0	0	1
Totals	6	6	13

shows the time at which early relapses, late relapses, and reinfections occurred during the follow-up, all figures being calculated from the start of chemotherapy. The salient features of each of the six cases of late relapse are summarized in Table III, to which explanatory notes are appended.

Discussion

The recurrence of signs or symptoms during the follow-up of a case of gonorrhoea in which apparent cure has been achieved signifies either relapse or reinfection. The differentiation between these two entities defies dogmatism, but a sound opinion can often be advanced after an assessment of the history and clinical and laboratory findings. The venereologist in close touch with his patient may often be in a position to weigh up the latter's statements and distinguish between fact and fiction, while the clinical findings, although sometimes difficult to interpret correctly, are easily determined. In some cases of early relapse in which gonococci have been demonstrated in the urethral smear it has been found that these organisms differ in their grouping and degree of staining from the gonococci in a fresh infection, the appearances being suggestive of impaired vitality or effete-ness. This impression has not been obtained in cases considered to be suffering from late relapse. Pelouze (1939) and Jones (1938) have also described these morphological and tinctorial changes in gonococci following inadequate chemotherapy. The natural history of late relapse as described by Cokkinis and McElligott (1939) bears some resemblance to the findings I have obtained in cases of early relapse attending the clinic after tentative attempts at chemotherapy with inadequate dosage, and definite instances of self-treatment with sulphapyridine have been

TABLE III.—Showing the Salient Features of Six Cases of Late Relapse

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Previous Gc. infection ..	3	Nil	Nil	Nil	Nil	Nil
Previous treatment ..	Nil	Sulphonamide	Irrig. (a) and sulphon.	Irrig. (a) and sulphon.	Nil	Nil
Duration of symptoms ..	3 days	124 days	98 days	62 days	3 days	2 days
Clinical diagnosis ..	A.A.U.	Acute tysonitis	S.P.U.	C.U.	A.A.U.	V.A.A.U.
Gonococci ..	Present	Present	Present	Present	Present	Present
Dosage of sulphapyridine (b) ..	18 gm.	18 and 18 gm.	12 gm.	9 gm.	9 gm.	30 gm.
Local treatment ..	Nil	Nil	Irrig. (a)	Irrig. (a)	Nil	Irrig. from 2nd day
Time of clinical cure (c) ..	11 days	6 days	Not known	2 days	Not known	4 days
Time of relapse (d) in days ..	85	49	85	41	49	36
Extent of relapse ..	(e)	(f)	(g)	A.A.U. Gc. +	A.A.U. Gc. +	(e)
Complications found ..	Chr. pro. and ves.	Nil	Chr. pro.	Nil	Nil	Chr. pro. and littritis
Ultimate result ..	Defaulted	Cured by local treatment	Defaulted	Cured by more sulphapyr.	Cured by more sulphapyr.	Cured by local treatment

(a)—Posterior irrigation with 1 : 8,000 mercury oxycyanide at 105° F.

(b)—The sulphapyridine dosage consisted of 3 grammes daily, given in divided dosage (2, 1, 1, 2 tablets). In the earlier stage of this investigation the course lasted six days, while at a later stage the standard course adopted was of ten days' duration, the total dosage per course being 18 grammes and 30 grammes respectively. Cases in which the total dosage was less than 18 grammes defaulted before receiving the full standard course.

(c)—The time required for clinical cure represents the time in days which elapsed between beginning sulphapyridine and the establishment of clinical cure as defined in the text.

(d)—Time of relapse is calculated from start of sulphapyridine treatment.

(e)—Scanty mucoid urethral discharge; pus cells only.

(f)—Acute tysonitis, gonococci present. No urethritis.

(g)—Acute epididymitis; no Gc. found.

A.A.U.—Acute anterior urethritis for less than one month.

V.A.A.U.—Very acute anterior urethritis for less than one month.

S.P.U.—Subacute posterior urethritis for less than one month.

C.U.—Urethritis for more than one month.

Chr. pro. and ves.—Chronic prostatitis and vesiculitis.

Sulphon.—Sulphonamide preparation other than sulphapyridine.

Sulphapyr.—Sulphapyridine.

met with among such cases. The latter type of patient frequently fails to respond to further chemotherapy, and it may be significant that Cokkinis and McElligott found certain of their cases of late relapse similarly unresponsive. In the light of present knowledge, therefore, the differentiation between relapse and reinfection must often remain a difficult diagnostic problem, demanding the careful consideration of all the available evidence. A study of probabilities, however, suggests the general principle that the longer recurrence of symptoms is delayed the greater is the likelihood that reinfection, rather than relapse, is responsible. This, as indicated in Table II, has been my own experience in the present series of cases treated with sulphapyridine.

The incidence of relapse in this series of 162 cases of male urethritis treated with sulphapyridine is 7.4 per cent., the late relapse rate being 3.7 per cent. (Table I). Belcher (1939), in a series of 150 cases of gonorrhoea treated with sulphapyridine, reports a relapse rate of approximately 6 per cent. Although he does not distinguish between early and late relapse, it is stated that all recurrences developed four to six weeks after return to duty, and in 74 per cent. of the series this took place within twenty-eight days of the beginning of treatment. It appears, therefore, that the 6 per cent. represent late relapses. It is interesting to note that as this series of cases was treated under Service conditions there were no defaulters, and measures were adopted to ensure that any case which appeared elsewhere with a recurrence of symptoms within a period of six months was reported to him. Cokkinis and McElligott, in their series of cases treated with sulphapyridine, have recorded a late relapse rate of 18.5 per cent., with a total relapse rate of 27.1 per cent. That these latter figures do not reflect the experience of other clinics has been indicated by Assinder and Knight (1939), Erskine (1940), Stuart (1939), and Purcell (1940). In an analysis of 205 male cases of gonorrhoea treated with sulphapyridine Prebble (1940) reports that failure or relapse occurred in only 9.7 per cent., while Lick and Rowntree (1939) had 11 per cent. of recurrences in a series of 175 cases of acute gonococcal urethritis treated with sulphapyridine. Wilkie (1939) found 9 per cent. relapses in 100 cases of acute gonococcal urethritis in which treatment with uleron was begun, on an average, 17.9 days after the appearance of urethral discharge. The corresponding figure reported by Cokkinis and McElligott for their series of 100 cases treated with uleron is 18 per cent., and it would appear, therefore, that the incidence of late relapse which they

have experienced in using both uleron and sulphapyridine is in excess of that met with by other venereologists.

The clinical findings in late relapse are variable. Acute urethritis with gonococci demonstrable in the urethral pus may occur in these cases, while in others only a scanty discharge containing pus and epithelial cells, accompanied by a clear urine, is found. In some cases relapse may take the form of some well-recognized acute complication of urethritis. In the cases reported herewith late relapse was heralded by acute urethritis in two cases (Nos. 4 and 5), and by an acute complication in two cases (Nos. 2 and 3); while the remaining two patients (Nos. 1 and 6) had only a scanty urethral discharge (Table III).

It is important to discover the factors which contribute to late relapse, and in this connexion a study of the findings presented in Table III may be of interest. It will be noted that in Cases 1, 2, 3, and 6 the presence of a closed focus of infection was discovered previous or subsequent to the occurrence of relapse, and ultimate cure was achieved only after this closed focus had been successfully eradicated by local measures. In Cases 4 and 5 clinical cure followed the administration of only 9 grammes of sulphapyridine; the subsequent relapse, which took the form of acute urethritis, was successfully cured by further chemotherapy with an adequate dosage of sulphapyridine. These latter two cases might well be included in the category of early relapse, but in view of the date at which clinical manifestations reappeared they have actually been classed as examples of late relapse. In my experience late relapse in cases adequately treated with sulphapyridine should always arouse the suspicion that a closed focus of infection is present, and the search for such a focus is always urgently necessary in these cases. These pockets of infection may occur in the glands of Tyson, Littre, and Cowper, and in the posterior urethra, prostate, and seminal vesicles, and may have arisen as a result of the late institution of chemotherapy, the extreme virulence of the infection, the indiscretion of the patient during treatment, or the incomplete cure of a previous urethritis. Furthermore, I believe that further chemotherapy is of little value without the concomitant treatment of the closed focus by such local measures as massage, dilatation of the urethra, and diathermy, which are designed to promote drainage and increase the local blood supply.

The prophylaxis of late relapse includes adequate early sulphapyridine therapy combined with urethral irrigation. The importance of proper lavage in the prevention of chronic littritis has been emphasized elsewhere (Laird,

1938), and the early chemotherapy with sulphapyridine reduces the possibility of involvement of the posterior urethra and its related structures. In addition, it is still important to enlist the co-operation of the patient in avoiding any form of sexual excitement and in carrying out the detailed instructions with regard to the taking of the tablets. These measures, combined with thorough tests of cure and a detailed clinical and bacteriological examination of the urethra and the associated structures following upon clinical cure, can do much to reduce the incidence of late relapse.

Conclusions and Summary

The differentiation between late relapse and reinfection may on occasion present real difficulty. It is evident, however, from a careful analysis of a personal series of cases of urethritis treated with sulphapyridine, that late relapse may occur in a proportion of such cases. The incidence found in the present series was 3.7 per cent., and it seems that the unusually high rate of late relapse reported by Cokkinis and McElligott has not been the experience of other venereologists.

While the clinical picture may vary widely in this condition the cause of the recurrence of signs and symptoms is often to be found in a closed focus of infection situated in the various glandular structures which normally communicate with the urethra.

The prophylaxis of late relapse is described: the successful treatment of the condition is usually dependent on the discovery and eradication of such closed foci by local measures.

The wider appreciation of these conclusions is required for a deeper understanding of the epidemiological problem presented by late relapse in gonorrhoea.

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The annual medical report of the King Edward VII Sanatorium, Midhurst, now in its thirty-third year, is full as usual of statistical tables. The number of patients discharged during the year, leaving out readmissions and a certain number who were in the sanatorium for less than nine weeks, was 174, and of these 55 per cent. were discharged with the disease arrested and just below 25 per cent. were discharged much improved. In the course of the last fourteen years artificial pneumothorax has been attempted in 280 cases, of which 220 were successful. Attention is drawn to the apparently small number of pneumothoraces induced in the sanatorium (only nineteen during the year under review); the reason is that owing to the long waiting list many cases have their treatment started before admission. The after-history of 327 patients who had had gold treatment in previous years shows that 229 are known to be alive. Only twenty-nine were treated with sanocrysin during the year under review, and of these fourteen ceased the treatment owing to various complications. The drug is considered dangerous enough to be stopped at the first appearance of complications, and if stopped for any reason it is never again administered to the same patient. In the surgical department 120 major operations were carried out, principally thoracoplasty and thoracoscopy and division of adhesions.

TREATMENT OF SPASMODIC TORTICOLLIS BY PSYCHOTHERAPY

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The following series of cases seems to be worthy of record because the recent literature contains few instances of treatment of spasmodic torticollis by psychotherapy.

Since Brissaud first urged the importance of mental infantilism in the *ticeur* most authorities have considered that some cases of spasmodic torticollis have a neurotic or psychopathic factor. This is particularly stressed by Finney and Hughson (1925), Brain (1928), and Frazier (1930). Yaskin (1935) after an extensive survey of the literature concludes: "There are but few cases in which an organic brain lesion is proven. These were associated principally with encephalitis or torsion spasm, and the torticollis merely formed part of the clinical picture. In some of these surgery is reported to have been of benefit. For the majority the organic origin of spasmodic torticollis is unproven. Nevertheless a number benefited by removal of septic foci and surgical interference. The rest probably have a psychogenic origin, and so every case should receive the benefit of modern psychotherapy before surgery is attempted." Turning to the application of psychotherapy, Meige and Feindel (1907) refer to cases treated by re-education, gymnastics, and persuasion. The relative failure of such methods is understandable, as they do not reach the fundamental causes. In fact, physical exercises often seem to become bound up with the patient's symptom, and to fix attention upon it still further. Schaller (1913) records two cases treated by psychotherapy with benefit. Clark (1912, 1914, 1917) describes five cases, four of which recovered; the fifth had had spastic ataxia since childhood, but the torticollis developed later as the result of psychological strain. Clark draws the conclusion that in spasmodic torticollis there is a mental infantilism, with persistence of a childish pattern of reaction, emotional instability, and frequently obsessive thinking. The underlying factor is held to be an abnormal infantile sexual attachment resulting in unconscious conflict, which may express itself in motor or psychic restlessness, or both. Three of Clark's cases had had various forms of treatment without benefit before psychotherapy was begun; in one instance surgical division of the spinal accessory nerve had also been performed without benefit. Yaskin (1935) gives a detailed account of a case which showed faulty psychosexual development, with varying anxiety as the fundamental cause. Partial resolution of the underlying conflict brought recovery.

The cases here presented are confined to those in which muscular spasm was of the spinal accessory distribution and in which there were no other neurological signs and no history of rheumatism. The spasm had assumed a compulsive character and had been of long duration. The case histories are much abbreviated.

Case I

A single woman aged 37 first attended the clinic on November 11, 1937, complaining of twitching and turning of her head to the right.

Clinical Examination.—The patient's face was turned to the right with her chin upwards. There was spasm of the left sterno-mastoid muscle, but no pain or spasm of other muscles.