TREATMENT-RESISTANT SYPHILIS SHORT REVIEW AND REPORT OF A CASE*

BY

R. V. RAJAM AND P. N. RANGIAH

From the Venereal Diseases Department, Government General Hospital, Madras, India

During four centuries of mercurial treatment of syphilis there has been little documentary evidence of the concept of treatment-resistance in syphilis. Mercury, on account of its feeble treponemicidal action, did not interfere to any significant extent with the natural course of infection, and the question of resistance to treatment did not arise. In the decade following the introduction of the organic arsenical compounds, Ehrlich's concept of "therapia sterilisans magna" dominated the field, but Ehrlich himself foresaw the problem of drug-fastness in chemotherapy and, recognizing inadequate dosage as its most frequent cause, emphasized the dangers of under-treatment at several international conferences. From 1920 to 1940 many reports on treatment-resistant syphilis were published by German and French workers. Beerman (1936) lists 430 references. Most of these reports discuss resistance to arsenical therapy and some to bismuth.

Silberstein (1924) classified treatment-resistance in primary and secondary syphilis as follows :

- (1) Primary Resistance—resistant from the start.
- (2) Primary-Secondary Resistance—after initial involution a resistant recurrence develops.
- (3) Secondary Resistance—arsenical treatment heals the lesions, but after a latent period a resistant recurrence appears.

Gougerot (1923, 1931) and Nicolas, Lacassagne, and Froment (1930), cited by Beerman (1936), give a more elaborate classification based on the degree of resistance.

- (1) Attenuated resistance.
- (2) Treatment recurrence.
- (3) True treatment-resistance :
 - (a) primary,
 - (b) secondary.
- (4) Treatment activation or stimulation.

The increase of treatment-resistant syphilis in the pre-penicillin era was reported almost exclusively from France and Germany, the criteria of resistance being :

- (a) persistence of lesions,

- (b) persistently positive blood serology tests,

- (c) persistence of *Treponema pallidum* in spite of adequate treatment, the last being the most reliable.

The most common clinical types of treatment-resistant syphilis occur in early infections and are usually cutaneous. The lesions may be typical or atypical. They are stated to have a predilection for the face, nose, neck, penis, and upper extremities, and are usually atypical at the time of their appearance. Precocious tertiarism is present in many of these cases and chancroidal recurrences are frequently reported. The blood serological reaction tends to be negative more frequently in treatment-resistant early syphilis. The host seems to play the key role in treatment-resistance through inability to metabolize the drugs used, failure of defensive powers, endocrine dysfunction, hepatic insufficiency, and so on. Clinical evidence supported by *in vitro* laboratory studies suggests that small subcurative doses of a treponemicidal drug and inadequate treatment are more likely to cause treatment-resistance than the quality or brand of the drug used. Sometimes resistance may be overcome by changing to another drug.

The concept of drug-fast strains of *Treponema pallidum* is discounted by failure to transfer chemoresistance from a case of treatment-resistant syphilis to rabbits.

Before the discovery of penicillin numerous methods of circumventing treatment-resistance were advocated : raising the arseno-bismuth dosage, changing the drug, and non-specific measures such as injections of liver extract and malarial therapy. Only fever therapy gave satisfactory results. With the advent of penicillin, however, a safe and effective treatment for early syphilis resistant to arsenobismuth became available (Nelson and Duncan, 1945 ; Noojin and others, 1945 ; cited by Moore, 1947). Although thousands of cases of syphilis have been treated with penicillin during the past decade, only one patient with dark-field positive primary syphilis, reported by Tyson (1945), cited by Moore (1947), failed to improve with 2.4 mega units penicillin

* Received for publication August, 10 1954.

for a period of 4 months and subsequently responded to penicillin and fever therapy.

Hahn (1947) reported a case of late gummatous syphilis of the penis which failed to heal after 4.8 mega units penicillin but which responded promptly to therapy with mapharsen and bismuth. Reynolds (1948), reporting treatment failures with penicillin in late syphilis, cautioned against the *a priori* supposition that penicillin alone would be as efficacious in late as in early syphilis. He classified penicillin failure in late syphilis as follows :

- (1) drug resistance with failure of overt manifestations to heal,
- (2) clinical progression despite therapy,
- (3) recurrence of lesions after an initially favourable response,
- (4) subsequent development of new lesions elsewhere in the body.

In laboratory studies of susceptible bacteria it has been demonstrated that penicillin has been found to be active *in vitro* against rapidly multiplying organisms in the phase of active growth, but inactive against the same organism in the resting phase. Reynolds (1948) postulates a comparable activity *in vivo* of penicillin against *Treponema pallidum* and tries to explain the failure of penicillin in late syphilis when the organisms are supposed to be few in number and not rapidly multiplying as in acute early syphilis.

Most of the reported failures belong to the first two or three years of penicillin therapy, when the antibiotic was impure and dosage schedules were still in the trial stage. Since the isolation of pure crystalline penicillin G and the introduction of repository penicillin, we find fewer reports of failure or of resistance to penicillin therapy in late syphilis. Furthermore, in late syphilis resulting in destruction or degeneration of tissues, penicillin cannot be expected to achieve a miracle of quick healing or to repair the damage. While penicillin destroys the treponemata, the reparative powers of the body must produce healing. Again, the pathology of late syphilis, with its vascular occlusion and fibrosis, prevents the circulating penicillin from gaining access to the active foci of infection ; hence its

action is delayed, and a larger total dosage over a longer period of time may be necessary to cure or arrest the disease process. The concept of true resistance, either primary or secondary, cannot be strictly applied to the lesions of late syphilis, on account of its inherent pathology and immunology. Reynolds was right in suggesting that adjuvant measures, such as the concurrent use of fever therapy, may be necessary to achieve rapid healing and avoid relapse. The iodides, which promote the absorption of granulomatous and fibrous tissues, have recently gone out of use, but they may still have some value in late syphilis.

Case Report

The authors are not aware of a case similar to the following having been described in the literature. This patient has been under observation for 11 years, from August, 1943, to May, 1954, and has been given various courses of treatment with every available form of therapy punctuated by periods of default. In April, 1949, he appeared to be clinically cured, but as he was still strongly sero-positive further malarial therapy was suggested ; however, he could not be persuaded to undergo the ordeal of fever, which he had already tried in 1946, and was discharged.

After 5 years of well-being with no clinical recurrence, he again presented himself on May 15, 1954, with a fresh ulceration of the orbit of one month's duration. At the time of writing he is still under treatment with PAM and bismuth and the ulceration is healing.

The progress of this patient for over 10 years is set out in the Table. This prolonged resistance to treatment of syphilitic infection is unique in that it cannot be classified by any of the criteria outlined by various European investigators. The initial inadequate therapy of early syphilis is the basis of the subsequent evolution of the disease. After mapharsen, bismuth, and fever had failed, the resistance to therapy was broken in 1947 by the introduction of penicillin, but two fresh successive penile gummata appeared in 1948, the first of which responded promptly to mapharsen and bismuth and the second to penicillin. Then, after 5 years' freedom from symptoms, the disease broke out again. When he was examined on February 14, 1955, the ulceration at the orbital margin had healed and there was no evidence of fresh lesions. He was still VDRL positive but showed decline from 128 to 32.

TABLE
PROGRESS OF TREATMENT-RESISTANT SYPHILIS

Epi- sode	Period of Observation		Clinical Findings	Laboratory Findings	No. of Injec- tions	Treatment	Remarks
	Year	Date				Drug	
I	1943	Aug. 19-30	Florid secondary syphilis with indurated penile lesions	Dark-field positive for <i>T. pallidum</i> Kahn and W.R. strong positive	3	0.04 g. mapharsen	Lesions healing
					3	0.2 g. bismuth	

continued

TABLE—continued

Epi- sode	Period of Observation		Clinical Findings	Laboratory Findings	Treatment		Remarks
	Year	Date			No. of Injec- tions	Drug	
FIRST DEFAULT							
II	1943 1944	Dec. 23 to Feb. 14	Penile lesions healed Cutaneous papular eruptions com- pletely disappeared Multiple discrete destructive crusted ulcers on face, trunk, and limbs. Loss of weight	Dark-field positive Kahn and W.R. strong positive	6 6	mapharsen bismuth	Malignant precocious ter- tiarism
SECOND DEFAULT							
III	1944	Mar. 3 to Aug. 30	Ulcers not healed. Lesions on left knee showing evidence of exten- sion	—	18 18	mapharsen bismuth	Lesions on trunk and face slowly healing, but on left knee refractory and spreading
THIRD DEFAULT							
IV	1944 1945	Dec. 4 to Mar. 28	Nodulo-cutaneous ulcerations on left knee and leg unhealed (Fig. 1)	Kahn and W.R. strong positive	13 13	mapharsen bismuth	No evidence of healing
FOURTH DEFAULT							
V	1945	April 28 to July 23	Lesions on left knee and leg unhealed and slowly spreading Ulcers on trunk and face completely healed	—	10 10	mapharsen bismuth	No evidence of healing
	1945	Aug. 4 to	Lesions on left knee and leg showed a little healing but were spreading peripherally. Painful, tender swelling on dorsum of right hand Commencing gummatous osteo- myelitis of metacarpal bone of middle finger (Fig. 2)	—	13	mapharsen	Cerebrospinal fluid no abnormality
	1946	Feb. 6			11	bismuth	
	1946	Feb. 22 to Mar. 5	—	—	Six sessions of fever with T.A.B. vaccine		—
	1946	Mar. 16 to Aug. 24	—	—	25 14	mapharsen bismuth	On August 24, 1946, lesions on left knee and leg completely healed. Swelling of dorsum of right hand persisting
FIFTH DEFAULT							
VI	1947	Nov. 7 to 28	Multiple crusted sinus ulcers on dorsum of right hand (Fig. 3). Extensive necrotic ulceration with polycyclic border on lateral aspect of right upper arm (Fig. 3). Nodulo-cutaneous ulceration on left side of nape of neck. Ulcera- tion of right nostril	Kahn and W.R. strong positive	3.8 mega units aqueous penicillin. Pot. iodide by mouth. Course of liver extract injections		All lesions dramatically healed by Nov. 28, 1947. Shortening of middle finger of right hand with complete destruc- tion and disappearance of distal half of meta- carpal bone (Fig. 4)
DISCHARGED							
VII	1948	Feb. 27 to July 17	Gummatous ulcer on dorsal aspect of prepuce	Dark-field negative Kahn and W.R. strong positive	10 10	mapharsen bismuth	Ulcer healed
DISCHARGED							
VIII	1948	Dec. 22	Gummatous destructive ulceration on penoscrotal junction extending to under surface of penis (Fig. 5)	Dark-field negative Kahn and W.R. strong positive	6 mega units aqueous penicillin		—
	1948 1949	Dec. 26 to Jan. 11	—	—	—		Ulceration rapidly healed
	1949	April 27	No fresh recurrence and clinically free	Kahn and W.R. strong positive	Further fever therapy refused		Cerebrospinal fluid nega- tive. Cardiovascular system normal
FIVE YEARS SYMPTOM-FREE							
IX	1954	May 15	Nodulo-cutaneous crusted ulceration on lateral aspects of left orbital margin (Fig. 6). Scars of past ulceration	VDRL positive Titre 128 dilu- tions	PAM 2 ml. daily for 25 days. Bismuth 1 ml. weekly		Ulcer healing. Patient still under observation
X	1955	Feb. 14	No ulceration or fresh lesions	VDRL positive Titre 32 dilu- tions.	—		Cerebrospinal fluid no abnormality

FIG. 1.—Scar of resistant nodulo-cutaneous ulceration on left knee and leg (1944-46). See Table, part IV.

FIG. 2.—Scar of healed gummatous ulceration of dorsum of hand and right upper arm (1945-47). Note shortening of middle finger. See Table, part V.

FIG. 3.—Gummatous ulcerations of dorsum of right hand and upper arm (1947). See Table, part VI.

FIG. 4.—Radiograph showing destruction and shortening of metacarpal bone of right middle finger (1947). See Table, part VI.

FIG. 5.—Hypopigmented scar of gummatous ulceration on under surface of penis (1948). See Table, part VIII.

FIG. 6.—Nodulo-cutaneous ulceration of left orbital margin (1954). See Table, part IX.

Comment

The prolonged resistance of the infection to mapharsen, bismuth, and fever over a period of 3 years, after penicillin therapy, the subsequent response to penicillin, the three further recurrences, and the satisfactory healing of these later lesions with mapharsen, bismuth, and penicillin seem to suggest that not the drugs but the tissues of the host are responsible for treatment-resistance and recurrence. The role of the parasite in treatment-resistance is difficult to evaluate unless the chemo-resistance can be transferred to experimental animals.

Summary

A case of unusually prolonged, treatment-resistant syphilis with recurrences is reported. Inadequate treatment of the original infection seems to have induced an inveterate allergic sensitivity in the tissues of the host. After 3 years of resistance to prolonged concurrent therapy with mapharsen and bismuth, the lesions responded dramatically to the first course of penicillin, but new manifestations appeared at varying intervals from 4 months to 5

years after the first course of penicillin. These new lesions have healed both with the arseno-bismuth combination and with penicillin. It is not possible to foresee whether the patient will be free from further trouble. The treatment-resistant lesions were cutaneous and skeletal.

The authors wish to express their thanks to the staff of the Barnard Institute of Radiology for the clinical photographs and radiograph and to Sri. K. Parthasarathy of the Venereal Diseases Department, Government General Hospital, Madras, for his help rendered in bringing in the patient periodically for examination.

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