TREATMENT OF REITER'S SYNDROME BY GOLD SALTS

BY

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Arthritis and a non-specific urethritis, sometimes associated with conjunctivitis, have been described in relation to a number of different conditions. One of us (Findlay, 1946) has pointed out that in experimental animals—rats and mice—certain strains of pleuropneumonia-like organisms give rise to arthritis and conjunctivitis, while the same lesions have been noted in bovine pleuropneumonia and in contagious agalactia of sheep. In addition, pleuropneumonia-like organisms have been isolated from the urethras of normal persons and more frequently from those of patients with non-specific urethritis. In view of these findings it seemed to be worth while to attempt to isolate pleuropneumonia-like organisms from the conjunctiva and joint fluids of patients suffering from what has, perhaps prematurely, been called Reiter's disease.

Attempts to Isolate Pleuropneumonia-like Organisms

Two patients with arthritis and urethritis, one of them also having conjunctivitis, have been investigated for the presence of pleuropneumonia-like organisms by culture of the joint fluid and blood on suitable media rich in animal protein and by inoculation of blood and joint fluid into mice. The culture of pleuropneumonia-like organisms from the urethral tract is of questionable significance at this stage in view of reports by some workers of successful culture from the normal genital tract. In neither of these cases were positive cultures obtained from the blood or joint fluid. Blood and joint fluid, 0.2 ml., from both cases was injected into the dorsum of the hind feet of 12 mice. One of these mice developed arthritis of the joint after an incubation period of 15 days. We failed to transmit the condition to other mice.

No definite conclusions can be drawn from the production of arthritis in a single mouse: mice are naturally infected with a number of strains of pleuropneumonia-like organisms, some of which may cause arthritis; in addition, it must be remembered that certain rodent strains of pleuropneumonia-like organisms are species-specific. At present the majority of strains of pleuropneumonia-like organisms isolated from man have not been shown to be capable of producing arthritis in rodents; it is therefore merely an assumption that the hypothetical organisms from cases exhibiting Reiter's syndrome should be arthritis-producing in rats or mice.

One peculiarity shown by pleuropneumonia-like organisms is their sensitivity to gold salts. Thus it seemed worth while to study the reaction of patients with Reiter's syndrome to the injection of gold salts. Since these cases were treated Baxter (1946) has reported a case in which there was a slow response to "myocrisin." Details of the treatment of two cases are briefly as follows:

Case 1

A man aged 23 was admitted to hospital on July 17, 1946. In June he had been treated in Germany for non-specific urethritis with 30 g. of sulphathiazole given over five days. There was no further previous history of eye trouble,

gonorrhoea, or other venereal disease. The patient was admitted on account of a recurrence of the urethritis. He also had a dry balanitis of one week's duration, with numerous pin-point ulcers on the glans penis. A urethral smear showed many pus cells, but gonococci were not present; the urine was hazy. Three dark-ground tests were performed on exudate obtained from the balanitis with negative results for treponemata. The blood Wassermann and Kahn reactions were both negative. He was given 24 g. of sulphathiazole over four days, and on July 20 he complained of swelling of the terminal joint of the left ring-finger. Within two days the middle joint of the right middle finger and the right hallux were also red, swollen, and tender. A purulent urethral discharge was still present and the urine was slightly hazy. A gonococcal complement-fixation test on July 22 was negative; the blood sedimentation rate was 85 mm. in one hour.

On July 24 an intravenous T.A.B. vaccine, 50,000,000 organisms, was given with good response, the maximum temperature reaching 103° F. (39.4° C.). The following day there was improvement in the joints, but by the 29th they had relapsed somewhat. He was then given 2,400,000 units of penicillin (40,000 units three-hourly for seven and a half days), and by Aug. 5 the arthritis of the toe had improved, but improvement in the fingers was only slight. The urethral discharge was still detectable in the early morning, when many pus cells were present; the urine was clear. On Aug. 8 a blood count showed 10,600 white cells per c.mm. (66% polymorphs, 30% lymphocytes, 3.5% mononuclears, 0.5% eosinophils). On Aug. 10 an effusion appeared in both knees; this disappeared spontaneously from the right side within four days. On Aug. 18 the fingers were no longer red but still swollen, as was the right big toe. There was a marked effusion in the left knee and the balanitis had not cleared. The following investigations were done: blood sedimentation rate, 30 mm. in one hour; haemoglobin, 12.7 g. %; packed cell volume, 40%; white blood count, 12,000 (polymorphs, 84%; lymphocytes, 14%; mononuclears, 2%); blood uric acid, 3.3 mg. per 100 ml. Skiagrams of the affected joints showed no bony changes. Stool culture revealed no pathogens.

On Aug. 18 conjunctival and urethral smears were taken for special examination and the left knee was aspirated. It was then decided to employ gold therapy. Myocrisin was given intramuscularly. The dates of the various injections and the relevant sedimentation rates are as follows:

Date	B.S.R.	Myocrisin
Aug. 18	30 mm. in 1 hour	—
" 21	—	0.01 g.
" 26	—	0.02 g.
" 27	31 " "	—
Sept. 2	—	0.02 g.
" 7	18 " "	0.025 g.
" 13	11 " "	0.025 g.
" 19	12 " "	0.05 g.
" 25	—	0.05 g.
	Total in 5 weeks:	0.2 g.

The temperature was taken four-hourly, the urine was tested daily for albumin, the skin closely watched for dermatitis, and a blood count done twice weekly. No untoward reactions were noticed. The balanitis rapidly cleared, though the urethral discharge resolved but slowly. The joints showed slow but steady improvement.

On Sept. 18 there was a brief setback; fluid reappeared in the left knee and there was a slight swelling of the left ankle. This subsided within two days, and the patient was discharged to duty on Sept. 24. On Sept. 19 Flexner vaccine was instilled into the right eye (see below), with negative results.

Case 2

A man aged 23 was admitted to hospital on Aug. 20, 1946. In May, 1944, he had had acute gonorrhoea, which was treated with sulphathiazole, 5 g. daily for five days. In December, 1944, he developed pain and swelling in the right foot associated with balanitis, and gonococcal arthritis was diagnosed. He was treated with a penicillin drip (dosage unknown) without effect, and later received T.A.B. and physiotherapy; by April, 1945,

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he had fully recovered. Since that date he had been well except for occasional conjunctivitis and a very slight urethral discharge. There was no previous history of dysentery or venereal disease other than the above.

On Aug. 13 he sought advice on account of a slight urethral discharge of one week's duration. A smear showed pus cells but no gonococci; he was given sulphathiazole 5 g. daily for five days. On the following day he fell and injured his left knee. When he returned on Aug. 20 he showed an improvement in the urethral discharge, but a marked effusion was present in the left knee; moreover, there was a severe bilateral conjunctivitis of two days' and a balanitis of six weeks' duration.

He was admitted to hospital and given 200,000 units of penicillin in five three-hourly doses of 40,000 units. On the 21st his urethral smear continued to show many pus cells, while the urine was hazy in two glasses. The blood Wassermann and Kahn tests and the gonococcal complement-fixation test were negative; blood count: haemoglobin, 115%; red cells, 5,490,000; white cells, 10,600; polymorphs 61%, lymphocytes 35%, mononuclears 4%; urine: albumin, sugar, ketones, bile negative; stool: no pathogens found in culture; blood sedimentation rate, 6 mm. in 1 hour. A skiagram of the knee revealed no bone injury.

On the following day urethral and conjunctival smears were taken for special examination and the left knee was aspirated. Gold therapy with myocrisin was then begun. Temperature recordings, daily urine examination for albumin, and skin inspection and blood counts twice a week did not reveal any toxic reactions. The dates and amounts of the myocrisin, together with the relevant sedimentation rates, are as follows:

Date	B.S.R.	Myocrisin
Aug. 22	12 mm. in 1 hour	0.01 g.
" 28	" —	0.02 g.
Sept. 2	" —	0.02 g.
" 7	3 mm. in 1 hour	0.025 g.
" 13	4 " "	0.025 g.
" 19	5 " "	0.05 g.
" 25	" —	0.05 g.
	Total in 5 weeks:	0.2 g.

The eyes were treated locally with saline washes and resolution was rapid, both becoming normal within 72 hours. The balanitis showed steady improvement and had quite gone by Sept. 2. The urine cleared within three days, but a morning urethral discharge persisted for three and a half weeks. The knee filled up again after the initial tapping, but had begun to subside when a second aspiration was performed on Sept. 18, after which time it did not refill.

On the 19th Flexner vaccine was instilled into the right eye without result (see below). The patient was discharged to duty on Sept. 25. There was no improvement with penicillin, though with gold therapy it was steady and maintained.

The Eye Test

The possible dysenteric origin of some cases of Reiter's syndrome has recently received considerable attention. Wood (1946) states that he succeeded in reproducing the sterile conjunctivitis in three cases by instilling a drop of Flexner vaccine into the eye. It was decided to apply this test to these cases. Flexner bacteria (mixed I-VI) were killed by heat at 55° C., and a suspension of 3,000 million organisms per ml. was kindly prepared by Lieut.-Col. Archer, R.A.M.C., to whom due acknowledgment is given. It produced no reaction in three rabbits or in two human controls.

A drop of this material was placed in the right eye in the above two cases and in a third case which had previously shown polyarthritis, urethritis, and conjunctivitis and had apparently recovered. No reaction was noted in any of these cases. None of these patients' sera showed any agglutination with strains of dysentery bacilli of the Shiga type. It may be of interest to note that cases of non-specific urethritis, arthritis, and conjunctivitis are not

uncommon in West Africans among whom Shiga dysentery is exceptionally rare.

Discussion

Although the hyperthermia is probably the most satisfactory treatment for patients with Reiter's syndrome, gold salts appear capable of producing a satisfactory cure. It is, however, unwise to assume from the therapeutic action of a particular drug in different diseases that the causative organisms of these diseases are necessarily related. Antimony salts, for instance, have a curative action in schistosomiasis and in infections due to *Leishmania* and trypanosomes. Penicillin is known to be valueless in diseases due to pleuropneumonia-like organisms, but as streptomycin has been found to be curative in rodent arthritis due to similar organisms (Powell *et al.*, 1946) its action in patients with Reiter's syndrome would be of interest. Further investigation of patients with Reiter's syndrome for the presence of pleuropneumonia-like organisms is desirable.

Conclusions

Apart from the production of arthritis in a single mouse by the injection of joint fluid from one patient, an investigation of two patients with Reiter's syndrome was negative for the presence of pleuropneumonia-like organisms.

Gold salts were curative in two patients with Reiter's syndrome not associated with bacillary dysentery, while penicillin and sulphonamides were of little value.

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SCRUB TYPHUS VACCINE ITS EFFECT ON SIXTEEN CASES INCUBATING THE DISEASE

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On account of the high incidence of scrub typhus in Mandalay during the autumn of 1945 the D.M.S., Twelfth Army, decided that all troops in that area should receive scrub typhus prophylactic vaccine. Seven and a half litres of the special vaccine prepared in "Operation Tyburn" at the Wellcome Veterinary Research Station, Frant, Sussex (Buckland *et al.*, 1945), was employed in 1-ml. doses, on three occasions at weekly intervals. All the inoculations were given during November, 1945, and, since this was the month of peak incidence of scrub typhus, local commanding officers were glad to co-operate in arranging inoculation parades.

Initially the intention was to inoculate half of each company so that the remainder would serve as controls in the evaluation of the efficacy of the vaccine, but the increased incidence and the commanding officers' suspicion that it was something of an experiment resulted in a fresh instruction that all troops should be inoculated. Inoculation produced a slight local tingling lasting five minutes due to the formalin vehicle, but no immediate constitutional reaction resulted, though fever was reported in some cases, and these are included among the 16 cases which form the basis of this report. In all 2,500 troops were inoculated with prophylactic vaccine.