RECENT ADVANCES IN TREATMENT OF GONORRHOEA

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Before considering the effects of adjuvant sulphonamide therapy it is of advantage to recall the position before the introduction of these drugs. Since, also, the object of treatment is to attain cure as rapidly as possible, it is necessary to show to what extent the period of time taken has been shortened, first, with the introduction of uleron, and, later, of sulphapyridine (M & B 693).

Different Methods Compared

1. *Irrigation.*—A group of 3,454 men were treated in this clinic by irrigation with 1 in 8,000 potassium permanganate daily, but no sulphonamides. The average time taken to attain cure was 7.44 weeks. 5.83% developed right, left, or bilateral epididymo-orchitis, and 0.85% developed prostatitis without epididymo-orchitis—a total complication rate of 6.68%. None of this group, which was unselected and serial in time, “relapsed” after being discharged, following the usual provocative and other tests of cure.

2. *Uleron.*—On its introduction uleron was tried at first alone, without irrigation, but I abandoned this in a fortnight on account of obvious non-success. Combined with irrigation as in Treatment 1, however, it gave good results and shortened the time taken to attain cure to 5.28 weeks, compared with 7.44 weeks with irrigation alone. Two of the 50 men treated in this group developed right epididymo-orchitis. There were no other complications.

3. *Sulphapyridine with Irrigation.*—I have no direct personal experience of the use of sulphapyridine alone, since, having regard to our experience with uleron alone, it was considered inadvisable to adopt this method. Combined with irrigation, however, it still further reduced the time to attain cure to 3.71 weeks. Clinical appearances were found to be somewhat deceptive because if treatment was discontinued and tests of cure were started too soon a considerable proportion of “breakdowns” occurred. Experience showed that the minimal period of irrigation plus sulphapyridine likely to give 100% cure was approximately as follows: First week: irrigation with 1 in 8,000 potassium permanganate daily plus 0.5 gramme of sulphapyridine three times a day. Second week: irrigation plus 0.25 gramme of sulphapyridine three times a day. Third week: irrigation alone. Treatment was then discontinued, and provocative and other tests were carried out. Though epididymo-orchitis is rare (0.8%) in cases treated according to this scheme, it does occur, however.

Incidentally, two patients who had been treated in other clinics with sulphapyridine only, and who on reporting in this clinic with a purulent gonococcal urethritis were put on irrigation and sulphapyridine, “survived” all tests except the prostatic smear, which was positive. These cases took three months to clear up. We have also found, when epididymo-orchitis has arisen, that 20 c.cm. of 0.25% euflavine intravenously once a week is more effective than the sulphonamides. It is very useful, too, in simple cases of enlarged prostate and in severe urethral stricture when dilatation is difficult or only partly successful.

Limitations of Sulphonamides

The following case shows very clearly the limitations of the sulphonamides.

The patient, a boy aged 13, reported with gonorrhoea and meatal stenosis—the latter making efficient irrigation very difficult. He was put on irrigation with 1 in 8,000 potassium permanganate plus 0.5 gramme of uleron thrice daily for five weeks with little improvement. Treatment was then changed to irrigation plus 0.25 gramme of sulphapyridine three times daily for three weeks without any improvement. I then substituted instillations of argyrol 10% without change. We then reverted to uleron with the addition of vaccine plus irrigation without avail. The condition cleared up, however, with the intravenous injection of 15 c.cm. of 0.25% euflavine twice a week for two weeks. This gave an effect equivalent to a very weak euflavine irrigation—i.e., during micturition.

Despite this case, however, which is an exceptional though interesting one, it is obvious that, used in combination with irrigation, sulphapyridine has achieved a great improvement in the treatment of male gonorrhoea.

Results with Sulphapyridine plus Irrigation

The foregoing combined scheme of Treatment 3 was the one adopted on the introduction of sulphapyridine, and we still use it unchanged in the treatment of male gonorrhoea. It gives uniformly good results, no “relapses,” and very seldom indeed causes any toxic symptoms; the complication rate, too, is practically negligible.

The diagnosis in the cases described in this paper was established microscopically, and all were submitted to the same routine provocative and other tests before discharge. These were, in sequence: (1) Provocative vaccine. (2) Instillation of 25% argyrol into urethra: this was retained in the urethra for half an hour by means of a clamp. (3) Urethroscopy. (4) Prostatic “slide” and in some cases culture. All tests were done by me personally. Of these tests undoubtedly the most valuable is the provocative instillation. It restarts the discharge in about 5% of apparent cures. The prostatic smear was positive in about 0.5% of apparent cures. Tests 1 and 3 are of relatively much less value. These tests were naturally all carried out after cessation of treatment. Having “survived” these tests, patients were discharged cured, and none reported back as a “relapse” or “return” case.

When it is borne in mind that most general practitioners treat their gonorrhoea patients with sulphapyridine alone, and fail to apply any tests of cure, it is manifest that this abuse of a valuable agent will counterbalance its beneficial effects when scientifically used. This, I think, is at least partly the reason why there has been no marked reduction in the incidence of gonorrhoea. Furthermore, it was noticed that in smears taken in male gonorrhoea cases which had recently been treated in other clinics with sulphapyridine alone (and which incidentally had been reported as cures) the gonococci were practically exclusively intracellular. I could not find any extracellular ones. I think this fact is very significant, since in an untreated male gonorrhoea case the vast majority of the gonococci are extracellular and therefore easily accessible to the sulphonamides. A small minority, however, are intracellular, and protected against attack as it were. I think this explains the dramatic and immediate resolution of signs and symptoms followed later by “relapses” so frequently quoted by workers who employ sulphapyridine without irrigation. In other words, these apparent immediate cures are subsequently “reinfected” by their own intracellular gonococci lying in the urethral crypts. It is obvious that systematic aspiration of these by irrigation, combined with the powerful effect of sulphapyridine on the extracellular gonococci, will bring about a rapid cure. Where this aspirating effect is non-existent—as, for example, in cases of hypospadias with gonococcal infection of the exposed urethral glands—neither sulphapyridine nor uleron, etc., effects a cure even when combined with irrigation.

The condition clears up, however, when the tiny exposed infected ducts are directly instilled—gently—with 25% argyrol or protargol by means of a syringe and a fine blunt needle.

Adult Female Gonorrhoea

Taking adult female gonorrhoea as a whole, our experience is that while the introduction of uleron, sulphapyridine, etc., has considerably reduced the time required to attain cure, the reduction is not nearly so marked as in male gonorrhoea. This was not unexpected, and is probably due to: (1) the greater difficulty in penetrating or aspirating the cervical glands as compared with the relatively efficient aspiration of the urethral glands in the male by irrigation; and (2) the fact that gonococcal invasion of the female cervix is deeper—a considerable proportion of the gonococci being situated intra-epithelially. It is interesting that infected female urethrae clear up rapidly with sulphapyridine.

In the pre-sulphonamide days the average time we took to attain cure in women was 8.42 months; these were patients who had attended long enough for this desirable object to be achieved. Apart from these we had eight women with gonorrhoea in which 17.5 months' pre-sulphonamide therapy had failed but which was cured later with two "stosses" of uleron combined with "old" routine local therapy—that is, cervical wet swabbing with 3-volume hydrogen peroxide, followed by the insertion of spuman or euflavine styli, retained in the cervical canal by gauze packing. Eight other cases initially treated with uleron plus routine local therapy cleared up in 2.5 months.

On the introduction of sulphapyridine we found it more effective than uleron in recent acute infections. In female gonorrhoea our usual practice now is: (a) If acute (that is, of anything less than two months' duration) or if there is a flare-up of an old infection, routine local therapy plus sulphapyridine is given. (b) If the condition is of more than two months' duration we use routine local therapy plus vaccine plus uleron.

Our experience is that uleron is superior to sulphapyridine in chronic female gonorrhoea, but that the latter is superior in acute cases. Since, however, the great majority of female gonorrhoea cases are chronic—at least in this clinic—it is obvious that uleron has a wider scope of application in gonorrhoea in women. It must also be remembered that we have a considerable number of women still attending whom as yet we have failed to cure despite the use of sulphapyridine, uleron, albucid, plus local therapy, plus vaccines. It is obvious that so far as female chronic gonorrhoea is concerned new and more effective therapeutic agents are required.

Vulvovaginitis in Girls

The 20 patients treated were all infected by a bed-mate (18 by the mother, 1 by an aunt, and 1 by the father). The average time taken to attain cure was 8.3 weeks. The treatment used was superficial swabbing of the interlabial area and gentle irrigation of the vagina with 1-volume hydrogen peroxide, and dry swabbing and dusting of the vulva with calamine powder. We cannot compare these results with the effects of sulphapyridine, as we have not had enough cases since the introduction of the sulphonamides.

None of the above cases "relapsed," and we have not found it necessary to use any alternative methods of treatment. The peroxide was neutralized with sodium bicarbonate.

Conclusion

Our experience is that the sulphonamides are very successful when and where the gonococcus is accessible (that

is, extracellular), but they are not so successful when it is intracellular—as, for example, in chronic female gonorrhoea. As quite a proportion of gonococci are intracellular it is obvious that in men irrigation, with its aspirating effect on the infected urethral glands, cannot be discarded.

Clinical Memoranda

Osteomyelitis and Pericarditis treated with Sulphathiazole (M & B 760)

We consider the following case to be interesting enough to warrant publication.

CASE REPORT

A female infant aged 15 months, weighing 22 lb., was admitted to the Children's Department of Westminster Hospital with the following history. On May 13, 1940, she had a severe sty on the right eye, and on May 23 she became ill, with a temperature of 101° and higher. On May 26 she was seen by Dr. Coltart of Shortlands, who suspected a deep-seated pneumonia and gave the child 1.5 grammes of sulphapyridine daily for two and a half days, but with no improvement. She was then seen by one of us (D. H. P.), and pericarditis was diagnosed.

On admission she was extremely irritable and cyanosed; the pulse (170) and respirations (85) were rapid. The temperature varied between 101° and 103°. A harsh pericardial rub could be heard over the whole praecordium. The heart was much enlarged clinically, and this was confirmed by radiograph, but the picture did not suggest that a paracentesis was indicated. The child was put into an oxygen tent, in which she was nursed for the next ten days. Forty-eight hours after admission she was given 3 grammes of sulphathiazole (M & B 760) daily with marked improvement, so that in eight days her temperature had subsided, though her pulse rate was still raised. During these days it was noticed that she always lay on her right side with her hips flexed and that she resented extension of the right hip. In addition she developed a painful indurated swelling over the left ankle, which, however, subsided in the course of the next few days. As the pericarditis had improved, radiographs of the hip and ankle were taken; these showed an inflammatory lesion of the head of the right femur, but nothing in the ankle. Mr. Herbert Harding saw the child and made a diagnosis of osteomyelitis of the head of the femur, with an early pathological dislocation of the hip, and thought the swelling on the ankle was a metastatic abscess. A light extension was applied to the hip in order to correct the tendency to dislocation. Further progress was entirely satisfactory, and the patient was on her feet on August 22, twelve weeks from the date of diagnosis of the pericarditis.

Investigations revealed that the tuberculin patch test was negative. The urine showed a faint cloud of albumin, but no cellular deposits, and it was sterile. The white cell count on May 31 was 23,000—polymorphs 60%, lymphocytes 38%, monocytes 2%, no eosinophils; there was a marked shift to the left in the maturity of the polymorphs. Blood cultures on June 4 and 10 were sterile. On June 6 the concentration of sulphathiazole in the blood was 5.94 mg. per 100 c.cm. On June 15 (i.e., four days after the last dose of sulphathiazole) the white cell count was 11,800. The urine was repeatedly examined and was never found to contain any abnormality, except that on two occasions it showed a heavy white crystalline-like deposit, unlike a normal urinary deposit, which was probably an excretion product of sulphathiazole.

DISCUSSION

This case would seem to have been one of osteomyelitis of the head of the right femur complicated by a severe pericarditis. The clinical improvement coincided exactly with the introduction of sulphathiazole. A dramatic recovery occurred in what we assumed to be an otherwise hopeless