THE TREATMENT OF GONORRHOEA WITH SULPHANILAMIDE.

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In August, 1937, a trial of sulphonamide P (Burroughs Wellcome and Co.) as a treatment for gonorrhoea was commenced at the Connaught Hospital, Aldershot. It was very soon apparent that this drug had a lethal action on the gonococcus, and it remained to be ascertained if the minimum amount which would effect a cure could be safely given as a routine treatment. A total of one hundred and one fresh and relapse cases of gonorrhoea and sixteen non-specific cases of urethral infection which have been treated with sulphanilamide and discharged from hospital as cured are considered in this article.

Forty-five grains daily for about seven days was tried at first on fresh and old infections, normal treatment being uninterrupted. This dosage did not effect a cure in any early case, and though all were very definitely improved while taking sulphanilamide, improvement was not maintained after the termination of the course. On the other hand, old-standing cases became rapidly dry and cleared up completely.

There were twenty-six old infections in hospital to whom sulphanilamide in approximately the above doses was given, and whose periods in hospital at the time this treatment was commenced ranged from one to five months. A rapid cure was effected in each case, all being discharged from hospital in an average of seventeen days from the commencement of treatment. Three of these cases required a second seven-day course to effect a cure and two were admitted to another hospital about two months later as relapses; the possibility of reinfection could not however be excluded.

The results thus obtained in old-standing infections were remarkably good and with a dosage smaller than that which is now employed even the most intractable cases, of whose recovery one had almost despaired, became free from all signs and symptoms of gonorrhoea within two or three days.

Forty-five grains daily having been found insufficient for early cases the dose was gradually increased up to the following, which has so far given satisfactory results and has not produced any serious toxic reactions, i.e. twelve 7½ grain tablets daily for four days followed by nine daily for three days, and six daily for a further two to four days, the course thus lasting nine to eleven days. In order to maintain a constant concentration in the body the drug is given four times daily, at 6 a.m., noon, 6 p.m., and midnight, ninety grains daily being given for the first four days in an endeavour to overcome the infection as rapidly as possible from the commencement of treatment.
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With the above amount I have obtained my best results and it is the maximum which I have given, though provided no serious toxic symptoms occur it is very possible that a bigger percentage of successful cases could be obtained by larger doses. Patients vary greatly in their reaction to sulphanilamide, and one can only hope to arrive at a dosage which, while producing no severe ill-effect on the majority will yet be sufficient to effect a large percentage of cures. As all the toxic effects in my cases commenced about the fourth day of treatment, before any large amount of the drug had been taken, it may be that a susceptible subject may be rendered equally ill by a large or small quantity. I do not consider that a course of treatment exceeding twelve to fourteen days is advisable, as provided a sufficiency of sulphanilamide has been given at the commencement, the patient will have been already cured by at least the twelfth day, if not resistant to the drug.

All cases, i.e. gonorrhoea, fresh and relapse, and non-specific urethritis, are treated as follows, in addition to sulphanilamide given as above. Treatment is commenced from admission. Patients are confined to bed on an alkaline mixture and an egg-free "milk" diet, liquids being freely given. A daily evacuation is ensured by paraffin liq. or enema and the temperature is recorded twice daily.

No irrigations are now given to patients while taking sulphonilamide, it having been found that the number of cases relapsing in hospital, after apparent cure, was very much greater if lavage, especially with potassium permanganate, was employed.

Each morning at 6 a.m. patients are taken to the laboratory where, before passing urine, they are examined for urethral discharge and slides prepared. All are seen later by the medical officer, who records the condition of the first urine passed that day and examines the patient for any evidence of toxic effects.

Some twenty of the first early fresh infections were put through a test for cure lasting over ten to fourteen days, and only discharged hospital if all findings had been negative over the test period and for some days prior to it. As it was found that only those who had been irrigated broke down under test, this procedure was cut out and it was thus possible to reduce each patient's stay in hospital by about seven days. When all signs and symptoms of the disease are absent for about a week one can generally consider the patient as cured. His urethra and prostate are then examined and if the findings are negative he can be discharged from hospital. As no relapses have occurred amongst the thirty-eight cases thus dealt with it is considered that this procedure is so far justified. Weekly inspections and examinations are, however, subsequently carried out for two months.

The course of 80.5 per cent of cases was practically uniform and was as follows: By the third day of treatment gonococci had permanently disappeared from the urethral discharge, which sometimes persisted for
two or three more days. It was, however, only a "pinhead" obtained by "milking" the urethra, and contained a few pus and epithelial cells but no organisms, being the result of the urethral inflammation which had not yet completely subsided. In many cases, however, the patient was dry in thirty-six hours, and the urine was clear in all by the third day. All these cases remained dry and made uninterrupted recoveries without complications. None had any signs of gonorrhea after the first three days in hospital.

The remaining 19.5 per cent of cases were not cured by sulphanilamide; in a few the disease appeared entirely unaffected. Most of these patients, however, progressed in a very satisfactory manner for a few days, becoming dry, etc., but after about a week of treatment a discharge containing gonococci reappeared. Further sulphanilamide had then little influence on the subsequent course of the disease, which assumed chronic characteristics.

An explanation for these failures has not as yet been arrived at. A study of the urine for pH values and their comparison with those of successful cases did not reveal any difference. In view of the possibility that these cases were not absorbing the drug from the alimentary canal, soluseptasine was given intramuscularly but without any beneficial effect. The blood-count of these failures did not show any variation from that of the successes. Though there is a possibility that a strain of the gonococcus exists which is wholly or partially resistant to sulphanilamide, a lack of resistance on the part of the patient is a more likely cause of failure. Efforts were made to stimulate the resistance of these cases by mild pyrotherapy, shock treatment, vaccines, etc., but no definitely successful results were obtained. Some were cured by a second or third course of sulphanilamide given after intervals of fifteen to twenty days. Many were, however, entirely unaffected by these subsequent courses. It has been suggested by some writers on this subject that no further sulphanilamide treatment should be given if the first course fails, and that these patients be then treated on accepted lines. In dealing with out-patients this is probably the better procedure; as however one is considering the treatment of patients kept strictly in hospital throughout the course of their illness under control and observation, I consider that further sulphanilamide treatment should be given after an interval of three to four weeks, as many of those who failed to respond to the first course were cured by a second or third. In the interval between courses the patient is treated on routine lines with irrigation and local treatment as indicated, and efforts are made to stimulate his resistance by vaccines, etc. Recently "Uleron" (Bayer) has been used in a few resistant cases. The results were most promising, and I consider that this preparation should be tried out in all cases not cured by sulphanilamide. Uleron is not on the market at the time of writing.
GONORRHOEA RELAPSE.

These cases ran a very favourable course under sulphanilamide treatment. The period spent in hospital was markedly reduced. No unfavourable cases were encountered.

URETHRITIS NON-SPECIFIC.

As might be expected, the dramatic cures experienced in the sulphanilamide treatment of gonorrhoea were not seen when dealing with non-specific urethritis. Though some cases appeared only slightly influenced, the results of the drug treatment in this disease were far superior to those of cases treated on accepted lines.

RESULTS.

GONORRHOEA, FRESH CASES.

| Cases treated in accordance with the latest plan of treatment as outlined above | Number | Average number days in hospital | Complications — arthritis, epididymitis | Known relapses to date |
|———|———|———|———|———|
| Cases treated with sulphanilamide from admission. | 38 | 14.5 | Nil | Nil |
| All cases treated with sulphanilamide from admission. | 71 | 21 | Nil | Nil |
| All cases treated with sulphanilamide from admission: | | | | |
| (a) Favourable cases | 61 | 16 | Nil | Nil |
| (b) Unfavourable cases | 12* | 53+ | Nil | Nil |
| All cases treated during 1937 with polyvalent vaccine (many were finally cleared up with sulphanilamide on reaching the chronic stage). | 82 | 62 | Urethritis 10 | Epididymitis 9 |

* Includes two cases remaining in hospital.
† Does not include two cases remaining in hospital.

GONORRHOEA, RELAPSE.

| Cases treated with sulphanilamide from admission. | 7 | 20 | Nil | Nil |
| Cases treated on routine lines from admission. (Some were finally cleared up with sulphanilamide.) | 31 | 43 | Nil | 1 |

URETHRITIS.

| Cases treated with sulphanilamide from admission. | 12 | 13 | Nil | Nil |
| Cases treated on routine lines from admission. (Some were finally cleared up with sulphanilamide.) | 55 | 27 | Nil | Nil |

TOXIC EFFECTS.

Cases under sulphanilamide treatment must be carefully observed from the beginning, but provided the drug is stopped on the first appearance of a serious toxic effect it seems probable that no danger need be anticipated. Any intolerance amongst my cases appeared about the third day of treatment, and the first toxic signs may be easily missed unless carefully looked
for. Hæmoglobin estimations and differential white blood-counts were
carried out before and after treatment in forty-one cases, and though they
all received approximately forty grammes within ten days no evidence of
agranulocytosis or other morbid condition of the blood was noted. Patients
confined to bed apparently do not suffer from many of the minor ill-effects
common in those who have had to be up and about while taking the drug.

Most of my patients seemed to cerebrate slowly for the first few days,
and a few complained of giddiness. Two cases of severe headache occurred,
Pallor was fairly common. Pyrexia is a sign of intolerance to be always
watched for. It is liable to commence at any time during treatment. It
is at first unaccompanied by any symptoms and so is liable to pass
unnoticed for two or three days. At first the temperature does not exceed
100°F. and disappears in twenty-four hours after the cessation of sulphanilamide. If, however, this pyrexia is overlooked and the drug continued it
increases rapidly so that by the third day it may reach 105°F. and the
patient appears very seriously ill. This severe condition takes about three
or four days to subside provided the administration of the drug is at once
stopped. Temperatures of all cases are taken twice daily and treatment
discontinued for a time if pyrexia supervenes. It would appear desirable
that all cases treated with large doses of sulphanilamide should be kept in
hospital and under strict observation, as otherwise unfortunate results
might occur which would bring this drug into discredit.

EFFECT ON COMPLICATIONS.

There was no means of ascertaining the effect of sulphanilamide on
epididymitis, as no case was admitted with this complication and none
arose during treatment.

Arthritis and Synovitis.—One case of gonorrhoea of a month’s standing
was admitted with pyrexia, and synovial effusion into both knee-joints. He
was unable to stand and was in considerable pain, but there was no
involvement of the articular surfaces. Under sulphanilamide treatment
the pain, swelling and temperature subsided in a few days, and he was
clear of active gonorrhoea in ten days from the date of commencement
of treatment. The knee-joints are recovering rapidly. One case had severe
arthritis of the knee of one month’s standing; the bone ends were involved
and the patient was suffering considerable pain. The infection at once
cleared up, and though prolonged surgical treatment was necessary before
his joint became serviceable he ultimately recovered and was sent home
on leave.

Posterior Urethritis.—Two cases were admitted with blood in the urine.
This condition cleared up completely in a few days and the patients
recovered rapidly.

To conclude I wish to stress the following points in connexion with the
series of cases treated by sulphanilamide:
The Treatment of Gonorrhoea with Sulphanilamide

(1) The average period spent in hospital by fresh gonorrhoeas has been reduced from sixty-two days to twenty-one days.

(2) No complications have occurred in any case. Even those resistant to the drug have run an uncomplicated course.

(3) There has been a complete absence of relapses in cases treated with adequate doses from the commencement of their illness.

(4) Toxic effects can be controlled by careful observation and appropriate treatment.

(5) The graph shows the marked reduction of venereal patients in the Connaught Hospital as a result of sulphanilamide treatment.

(6) The results obtained with large doses of sulphanilamide are far better than those obtained with smaller doses, cases are cured more rapidly, and the percentage of unsuccessful cases is lower.

(7) The results in my series have been very constant, and provided treatment is fully and carefully carried out, it should be possible to repeat these results indefinitely. It is hoped that in the future means will be found to diminish the percentage of resistant cases.

(8) It has been suggested that sulphanilamide treatment should not be commenced till the disease has been in existence for from ten days to a fortnight in order to enable the patient to develop his natural resistance and thus cut down the number of unfavourable cases. This procedure entails the following drawbacks: (i) Average stay in hospital of all cases is prolonged. (ii) Complications in a considerable percentage of cases would occur before sulphanilamide was given.

In my opinion the above procedure would be desirable did not the disadvantages outweigh the advantages.
(9) Below is a list of all cases of gonorrhoea remaining in this hospital on January 15, 1938, the date on which this article was completed.

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Date of admission</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>22.10.37</td>
<td>Unaffected by sulphanilamide—continues to show gonococci in urethral discharge. No complications.</td>
</tr>
<tr>
<td>3</td>
<td>30.12.37</td>
<td>ditto. ditto.</td>
</tr>
<tr>
<td>4</td>
<td>3.1.38</td>
<td>ditto. ditto.</td>
</tr>
<tr>
<td>5</td>
<td>13.12.37</td>
<td>Unaffected by a first course of sulphanilamide. A second course after an interval of fourteen days, during which protein shock therapy was given, has apparently cured the disease.</td>
</tr>
<tr>
<td>6</td>
<td>29.12.37</td>
<td>Sulphanilamide was stopped on the second day on account of toxic reaction—pyrexia. Three days later developed epididymitis with much albumin and blood in urine. This condition rapidly subsided. Patient is now dry and progressing favourably on a course of sulphanilamide commenced on 10.1.38.</td>
</tr>
<tr>
<td>7</td>
<td>5.1.38</td>
<td>All progressing favourably to date.</td>
</tr>
<tr>
<td>8</td>
<td>8.1.38</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>10.1.38</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>11.1.38</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>11.1.38</td>
<td></td>
</tr>
</tbody>
</table>

Admissions subsequent to 11.1.38, are not considered, as no opinion can yet be formed as to their progress.

The unfavourable cases amongst them have been taken into account in assessing the percentage of those failing to respond to treatment. Cases 6 to 11 have not been considered in my figures as the success or otherwise of their treatment is still undecided.

My thanks are due to Major-General F. D. G. Howell, D.S.O., M.C., K.H.S., D.D.M.S., Aldershot Command, and to Lieutenant-Colonel J. R. Hill, R.A.M.C., Officer Commanding the Connaught Hospital, Aldershot, for permission to forward these notes for publication. I am indebted to Lieutenant-Colonel L. Dunbar, O.B.E., R.A.M.C., A.D.P., Aldershot Command, for undertaking the blood examinations of these cases, and to Cpl. F. J. Hopewell and Pte. E. T. R. Whittle, R.A.M.C., for their invaluable assistance.

NOTE.

ON TREATMENT OF CASES RESISTANT TO SULPHANILAMIDE.

It has been observed, very recently, that resistant cases, showing gonococci in their urethral smear on and after the third day of sulphanilamide treatment without lavage, can be rendered dry in a few days by potassium permanganate irrigations. In such cases the course of the drug is extended to a fortnight while lavage is carried out concurrently twice daily. The ultimate results of this procedure are not yet known; there are indications, however, that they may prove satisfactory.