Cerebrospinal Fluid from Cisternal Puncture.—White cells, 23 per c.mm.; red cells, *nil*. Differential count: small mononuclears, 20 per cent.; large mononuclears, 80 per cent.; polymorphs, *nil*. *B. tuberculosis* was not detected, and no growth was obtained after aerobic cultivation at 37° C.

The Wassermann reaction was negative, and the blood sedimentation rate 22 mm. per hour on October 26, 1937, and 11 mm. per hour on January 1, 1938.

Summary

1. A short review of the literature and an account of the condition are given.
2. A case is described in which early operation was followed by complete recovery.
3. The importance of full investigation in cases presenting severe and persistent pain in the back with motor symptoms in the lower extremities is stressed, in order to eliminate a diagnosis of myelitis or poliomyelitis, which would prevent an operation that might be the means of saving the patient's life.

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SULPHONAMIDE CHEMOTHERAPY IN GENITO-URINARY (NON-GONOCOCCAL) INFECTIONS

BY

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During the past year I have treated with the recently introduced compounds containing the sulphonamide (NH_2SO_2) and aniline ($\text{C}_6\text{H}_5\text{NH}_2$) chemical chains upwards of 900 cases infected by various organisms. A preliminary report (Cokkinis, 1937) described my experiences in the treatment of gonorrhoea; below are recorded the results obtained with these preparations in non-gonococcal genito-urinary conditions. Experiences in their use for acute abdominal lesions and other surgical infections have also been extensive, but are not reported in this paper. They have, however, been of considerable interest, and although there have been enough failures and disappointments to show the limitations and difficulties of this form of treatment, the successes have been sufficiently numerous and striking to convince me that the new chemotherapy has very definite surgical possibilities which are worthy of further exploration.

The Drugs Employed

Sulphanilamide (syn., prontosil album, streptocide, sulphonamide, etc.).—In my hands this appears to have the widest range of use and to offer the greatest bacteriostatic activity. Unfortunately it is much the most toxic of all these compounds, and although haemolytic anaemia and agranulocytosis have not been my experience, the less serious toxic manifestations have proved extremely common, often troublesome, and occasionally alarming.

In surgical cases and after major operations (particularly abdominal and genito-urinary) the most troublesome toxic effects have been prostration (sometimes severe), gastric irritation, and cyanosis. I am now developing the conviction that sulphanilamide should not be given to debilitated patients or to major operation cases if a less toxic chemotherapeutic substance can be used, even though this may be of slightly lower bacteriostatic potency.

Prontosil Soluble.—This azo dye compound, which I have given by deep subcutaneous injection, has shown itself especially useful in operation cases, for it causes neither gastric irritation nor prostration. The only toxic effect I have seen with it is a slight cyanosis, and this in a very small proportion of cases. To obtain bacteriostatic action comparable to that of sulphanilamide it has to be given in rather large doses—for example, 30 to 50 c.cm. of the 5 per cent. solution daily.

Prontosil Rubrum.—Of this I have as yet had little experience.

Proseptasine and Soluseptasine.—These are remarkably free from toxic effects, but in my experience their bacteriostatic action has proved somewhat disappointing, and I have used them in only a few of my surgical cases.

Uleron.—This new disulphonamide product, which I am now trying extensively, has shown a bacteriostatic potency in infections by several bacteria, which include gonococci, streptococci, and coliform bacilli. In 100 cases of gonorrhoea (not reported here) and in a smaller number of surgical cases it has been extremely well tolerated and has shown no immediate toxic effects. The absence, following its use, of such symptoms as prostration, cyanosis, gastro-intestinal irritation, and cardiovascular effects makes it particularly suitable for debilitated and seriously ill patients—for example, after major operations. One disadvantage, however, should be mentioned. This is the possibility of the appearance of toxic peripheral neuritis of a curiously constant and symmetrical motor distribution (adductors and opponens pollicis, interosseous muscles of the hand, and flexors and extensors of the foot and toes). This has occurred in less than 4 per cent. of my cases, and only when the drug was continued over a period of weeks. There is good reason for supposing that if administration is limited to a few days this toxic effect will not make its appearance even when large enough doses are used to obtain a rapid bacteriostatic action. Though uleron, for the reason given above, should not be used for long periods, I believe that, employed judiciously, it may prove to be the non-toxic substitute for sulphanilamide which I have been looking for, although on the whole it appears to be less potent.

In debilitated cases, and those suffering from a severe surgical illness or recovering from a major operation, when rapid bacteriostatic effect is required over a short period, the drug used should not add in the way of toxic manifestations to the strain already imposed on the patient. For this purpose I have employed prontosil soluble in the past, but I am now combining it with uleron, with promising results. When, however, a bacteriostatic action is required for longer periods—that is, more than a week or ten days—I still believe that sulphanilamide, however toxic it may be, is the best and safest substance to employ in most infections by sulphonamide-susceptible organisms.

A total of fifty-seven genito-urinary cases have been treated. These can be divided into three main groups: (a) non-gonococcal genital infections (thirty cases); (b) "primary" urinary infections (twelve cases); and (c) "secondary" urinary infections (fifteen cases).

(a) Non-gonococcal Genital Infections

In this group are twenty-six cases of urethritis (males) and four of acute epididymitis. All gave negative tests for gonococci and complement fixation. One was an unmixed infection of *Strep. viridans*, while ten were proved cases of mixed infection with various bacteria. Organisms were found in the other cases, but their exact nature was not proved by culture.

The following five cases were treated with uleron:

Case	Condition	Duration Before Uleron	Organisms Found	Total Uleron	Period of Uleron	Result	Follow-up
1	Left epididymitis. Anterior and posterior urethritis	Seven days. No previous treatment	Coliforms on culture	16 grammes	Four days	Discharge ceased in two days. Testis normal in nine days	Still well three weeks later
2	Anterior and posterior urethritis	Nine days. Resisted previous treatment	Various organisms in smear. No culture	36 grammes	Six days	Discharge ceased in four days. Urine clear in seven days	Still well five weeks later
3	Anterior urethritis	Fifteen days. Resisted previous treatment	Strepts. and diphtheroids in smears. No culture	18 grammes	Six days	Discharge ceased in five days. Urine clear in five days	Still well two months later
4	Anterior urethritis	Twelve days. Resisted previous treatment	Strepts., coliforms, and diphtheroids in smears. No culture	18 grammes	Six days	Discharge ceased in four days. Urine clear in three days	Still well three weeks later
5	Anterior urethritis	Twenty-three days. Resisted previous treatment	Coliforms and <i>Strep. faecalis</i> on culture	28 grammes	Seven days	Discharge ceased in one day. Urine clear in five days	Still well six weeks later

The other twenty-five cases were treated with sulphanilamide, and can be divided into two subgroups.

SUBGROUP I

This subgroup comprises three cases of acute epididymitis.

Case 1.—Right epididymitis, with anterior and posterior urethritis of five days' duration. Streptococci and diphtheroids in smears. Thirty-three grammes sulphanilamide were given in fifteen days. Discharge ceased in one day, urine was clear in three days, and the testis normal in nine days. Patient still well two months later.

Case 2.—Left epididymitis, with anterior and posterior urethritis of eighteen days' duration. Resisted ordinary treatment. Coliforms and *Strep. faecalis* on culture. Forty grammes of sulphanilamide were given in ten days. Discharge ceased and the urine was clear in two days and the testis normal in ten days (apart from small residual hydrocele). Still well two weeks later.

Case 3.—Left epididymitis of twelve days' duration, with no signs of urethritis. Coliforms, streptococci, and staphylococci in prostatic bead. Twenty-six grammes of sulphanilamide were given in seven days. No appreciable improvement.

SUBGROUP II

This comprises twenty-two cases of urethritis, fourteen anterior and eight anterior and posterior, which are summarized as follows:

The duration of symptoms (mostly intermittent) varied from three days to four years (average eight and a half months), and nearly all had resisted ordinary treatment. One case was a pure *Strep. viridans* infection; five were proved mixed infections with two or more of the following organisms: streptococci, staphylococci, coliforms, and diphtheroids; in the remainder some of these organisms were seen in smears, but no cultures were made. The patients were given an average total quantity of 37 grammes of sulphanilamide over an average period of thirteen days.

Nineteen of the twenty-two cases were quite clear in one to seven days from the beginning of chemotherapy (average of just under three days), and were still well at an average period of nine weeks later.

Three cases failed to clear up. Two of them showed temporary improvement but relapsed later; one showed no

improvement at all. One of the relapsed cases gave on culture a growth of *Strep. faecalis*, *Staph. albus*, and diphtheroids one week after 40 grammes of sulphanilamide in sixteen days; the other two failures had no cultures taken.

DISCUSSION

This group thus shows four cases of epididymitis with one failure and twenty-six cases of urethritis with three failures. It is interesting to observe that all five cases treated with uleron were successes, although the average

period before clinical cure was slightly longer than with sulphanilamide (approximately five days instead of approximately three days). It is also of interest to note that in two of the sulphanilamide failures staphylococci were found with other organisms.

The following case is worthy of special mention in view of the infecting organism:

A man aged 24 had an intermittent urethral discharge and pyuria for four years, following repeated instrumentation for a congenital defect of the urethra. Examination revealed a purulent anterior urethritis, and two separate cultures gave an abundant growth of *Strep. viridans*. Thirty-five grammes of sulphanilamide were given in ten days with complete success; the discharge ceased after one day, the urine was clear in two days, while cultures taken on the fourth and seventh days showed no growth of *Strep. viridans*.

(b) "Primary" Urinary Infections

This group comprises nine cases of acute or subacute pyelitis and three of acute cystitis in which no other lesion was found in the urogenital tract.

SUBGROUP I

All the pyelitis cases had an acid urine at the start of treatment. Two were reported as *B. coli* infections, four as coliform infections, and one as a mixed infection of "coliform and other organisms"; the remaining two cases had no bacteriological examination.

One case (subacute pyelitis) was treated with uleron (16 grammes in four days). She was symptom-free, with clear urine, after two days, and was still clear ten days later.

The other eight cases were treated with sulphanilamide, receiving an average quantity of 32 grammes over an average period of nearly eleven days, combined with large doses of alkalis. Five of them cleared up completely in from two to six days (two having previously resisted mandelic acid therapy) without subsequent relapse. The sixth case relapsed four days after 15 grammes (given in five days). In the seventh case the sulphanilamide was stopped after two doses, owing to severe vomiting, without improvement of the pyelitis.

The eighth case is of considerable interest and merits a detailed description:

Mrs. K. was admitted to hospital on January 25, 1938, with acute pyelitis in the sixth month of pregnancy. Next day she was very ill, with rigors, pain, and tenderness in the right loin, a temperature of 102°, a pulse of 128, and heavy acid pyuria. Films of the urinary deposit showed very numerous pus cells and bacilli, while cultures produced a heavy growth of coliform bacilli. On January 28 the temperature rose to 103°, and sulphanilamide therapy was instituted. Three grammes daily were given for a period of thirteen days, combined with alkalis. Within twenty-four hours all symptoms and signs of the pyelitis had subsided and the temperature came down to subnormal and stayed down. The urine cleared rapidly and became alkaline. On January 31 cultures showed but a moderate growth of coliform bacilli, while on February 2 only a very scanty growth was obtained. Chemotherapy was discontinued on February 9 and she remained quite well until February 15, when a sudden relapse occurred. On the 16th she had rigors, a temperature of 104°, and pyuria, with a heavy growth of coliform bacilli on culture. Three grammes of sulphanilamide daily were now given for a period of eleven days. The subsidence of symptoms this time was less dramatic, and the temperature did not reach the normal till the fourth day. The urine, however, became quite clear again, and cultures taken on February 25 proved sterile. Once again she remained quite well for one week after the end of the sulphanilamide course, and then on March 6 relapsed as suddenly as before, with rigors, a temperature of 103°, and heavy pyuria. Cultures taken on March 7 once more showed a heavy growth of coliform bacilli. A third course of sulphanilamide was now commenced and is still in progress. For the third time the infection has yielded completely to the chemotherapy, but the patient is now beginning to reveal toxic effects and is showing signs of secondary anaemia. A blood count on March 10 gave 70 per cent. of haemoglobin, 3,200,000 red cells, and 7,800 leucocytes. A serial temperature chart is appended.

Temperature chart of Mrs. K. (pyelitis of pregnancy).
Sulphanilamide treatment; two relapses.

SUBGROUP II

The three cases of "primary" cystitis had an acid pyuria. They all presented well-marked basal symptoms (trigonitis), and two of them gave a culture of coliform bacilli. They received an average quantity of 22 grammes of sulphanilamide over an average period of approximately ten days. Two were quite clear after two days and did not relapse while under observation. The third was very intolerant to the drug and developed a relapse after clinical cure on a four-day course of 3 grammes daily; this cleared up with a second course of 7 grammes in three days.

DISCUSSION

There was thus only one complete failure in this group of twelve cases, the chemotherapy being abandoned on account of toxic effects. The rapidity with which the others cleared up was most striking, but relapse occurred in more than a quarter of them. It may be of interest to observe that the average concentration of detectable sulphanilamide in the urine of these patients (on 2 to 3 grammes daily) was about 1 in 3,500 (employing the

sodium-nitrite-beta-naphthol colour test, against a standard solution of 1 in 5,000).

(c) "Secondary" Urinary Infections

I now come to a group of fifteen cases of great surgical interest. They are examples of the "secondary" cystitis which complicates such lesions as senile enlargement of the prostate and stricture of the urethra. It is obvious that a rapid clearing up of urinary infection in such patients would prove of real value in the surgical treatment of the primary lesion, and would also benefit cases which for various reasons are not suitable for radical operation. For the sake of uniformity cases of gonococcal cystitis are not included in this series.

SUBGROUP I

This comprises nine cases of senile enlargement of the prostate with urinary infection. In four of them the chemotherapy was given before and after suprapubic prostatectomy; in two before or after preliminary cystotomy; in the other three no operation was performed. Brief details of the cases follow.

Cases 1, 2, and 3.—These had a moderate pyuria, with less than 3 ounces of residual urine. One was a *B. coli* infection, the others did not have the urine cultured. They received an average quantity of 10 grammes of sulphanilamide over an average period of five days, within which the pyuria cleared up completely. All three had good renal function, and a one-stage suprapubic prostatectomy was done at an average period of seven days after starting the chemotherapy. Only minor toxic effects were produced by the drug, but in two of the patients they were rather troublesome.

After operation all three patients had prontosisol soluble (10 c.cm. of 5 per cent.) injected twice daily for the first three days. All the cases healed rapidly without demonstrable post-operative sepsis, but it must be stated that they were also given saline irrigation for the first eight to ten days.

Case 4.—Moderate pyuria and renal insufficiency (blood urea of 110 mg.). Catheter drainage was established, and 2 grammes of sulphanilamide were given daily for three days. After this the urine was quite clear, but the drug was discontinued owing to severe intolerance. At the end of one week suprapubic cystotomy was performed and suprapubic drainage established. A few days later the pyuria recurred, and a culture of the urine showed coliforms, *B. proteus*, and streptococci. This again cleared up with 2 grammes of sulphanilamide daily for three days, the drug being better tolerated this time. Two weeks after the cystotomy the blood urea dropped to 54 mg., and prostatectomy was performed. The after-treatment and result were the same as in the above three cases.

Case 5.—A man of 69 with heavy pyuria and marked renal insufficiency. Two grammes of sulphanilamide daily for four days were well tolerated, and produced an almost clear urine. Suprapubic drainage was established three days later, but no further chemotherapy was given. Following the operation progressive renal failure developed, and he died eight days afterwards.

Case 6.—A man of 74 with heavy pyuria and residual urine of 10 ounces. Suprapubic drainage (under local anaesthesia) was established at once with small self-retaining catheter, after which 2 grammes of sulphanilamide were given daily.

He developed cyanosis and severe prostration after two days, and the sulphanilamide was discontinued. By this time the urine was quite clear and remained clear for seven days, at the end of which time the blood urea had dropped from over 100 to 46 mg. The pyuria then recurred and increased; one culture gave coliforms only, but a second three days later showed coliforms and *Strep. faecalis*. The infection became worse, and the blood urea rose once more to over 100 mg. He was now given 3 grammes of uleron daily for four days, without toxic effects, and the urine became clear again, although a growth of coliform bacilli was still obtained on culture. The blood urea dropped once more to 52 mg., and the prostate was successfully enucleated a few days later.

Case 7.—Good renal function and moderate pyuria, which cleared completely with 9 grammes of sulphanilamide in four days, but the patient refused operation. The urine was still clear two weeks later, but further infection is likely.

Cases 8 and 9.—These proved complete failures. Both are elderly hospital out-patients, with chronic retention of urine and a thick alkaline pyuria, showing very heavy mixed infection. One completely resisted a two-weeks course of 30 grammes of sulphanilamide, which was well tolerated; the other has been on 2 grammes of sulphanilamide daily for six days without improvement.

It will have been noticed that (with one exception) these cases were given very small quantities of sulphanilamide. The drug was on the whole badly tolerated by these elderly patients, and I was afraid of doing additional injury to kidneys already damaged by obstruction. Actually, in no case was there the least evidence of toxic action on the kidneys, and in the one fatal case the renal failure could not in fairness be attributed to the sulphanilamide. Two-thirds of the patients were definitely benefited by the chemotherapy, which proved of real service in combating both pre-operative and post-operative urinary sepsis, although it is of interest to note that the incidence of relapse (over 25 per cent.) is the same as in the cases of "primary" urinary infection already submitted. On account of the marked intolerance to sulphanilamide shown by most of these elderly and debilitated patients I intend in future to make further trial of the less toxic uleron in its stead.

SUBGROUP II

This consists of four cases of urethral stricture with secondary cystitis, and one case of epididymitis with pyelocystitis.

Case 1.—This patient was admitted as a case of acute epididymitis and (non-gonococcal) urethritis. After admission he developed symptoms of acute pyelocystitis, with marked pyuria, a temperature of 103°, and pain and tenderness over the left kidney. Cultures of the urine showed a heavy *B. coli* infection. He was given 9 grammes of sulphanilamide in three days, and responded in a few hours. On the third day he was symptom-free, with clear urine, which on culture showed a very scanty growth of *B. coli*.

Case 2.—Moderate bulbar stricture, with heavy (mixed) urinary infection. Forty-two grammes of sulphanilamide were given in two weeks. The urine was clear in four days, and remained clear. Afterwards the stricture was treated by intermittent dilatation, without recurrence of the infection.

Case 3.—Moderately severe stricture, with heavy pyuria. Forty-two grammes of sulphanilamide were given in two weeks. There was partial improvement after one week, but still slight pyuria at the end of the second week.

Cases 4 and 5.—Severe strictures, with severe cystitis and heavy alkaline pyuria and repeated attacks of retention. Three grammes of sulphanilamide were given daily for twelve and fourteen days. Case 5 was also given 4 grammes of uleron daily for four days. Symptoms of cystitis improved, but pyuria slightly diminished only during chemotherapy, and relapsed afterwards.

DISCUSSION

The four complete failures thus far described in this group of cases of "secondary" urinary infection show a strange similarity. Two are cases of senile prostate and two are severe stricture, but they all had chronic retention of urine and an alkaline cystitis with heavy mixed infection. Whether their non-response to chemotherapy is due to the presence of sulphonamide-resistant organisms in the alkaline urine—for example, staphylococci or *B. proteus*—or to a submucous fibrosis of the chronically inflamed and thickened bladder can only be a matter for speculation. The fifteenth and last case in this group is also a chemotherapy failure, but for a very different reason:

Mrs. R., aged 55, was first seen with a short history of intermittent cystitis and heavy pyuria. *B. coli*, *Strep. faecalis*, and other organisms were isolated from the urine, and she was given 3 grammes of sulphanilamide daily for one week. The urine cleared rapidly, but while still under treatment the pyuria recurred more heavily than before. Further investigation, which included cystoscopy and laparotomy, revealed a carcinoma of the pelvic colon, with a very small vesico-colic fistula.

Conclusions

It seems both justifiable and opportune, on the basis of the experience reported here (which represents incidentally a small fraction of the total experience), to make a few comments on the mode of action and cause of failure of chemotherapy applied to these and other cases. It is obvious that bacterial sensitivity to these substances is highly selective. Indeed, it appears to vary not only with each group of organisms but also with individual strains of the same organism. No organism is 100 per cent. susceptible, and it may be that few are 100 per cent. resistant. Other things being equal, the highest incidence of success is likely to be obtained in infections by organisms which are highly susceptible as a group and which have the lowest proportion of resistant strains. A less obvious fact which experience suggests is that the susceptibility of a given strain may vary in the same patient from time to time, a highly susceptible strain becoming resistant after a while, or vice versa. This difference in degree of sensitiveness to sulphonamide compounds on the part of individual bacteria is well shown by the variation in what one might call the "effective" dosage. Thus where Méave Kenny (1937) found 1.5 grammes of sulphanilamide given daily sufficient to overcome coliform infection of the urine, Colebrook and Purdie (1937) have used from four to ten times as much as this for streptococcal infections of the puerperium.

The bacteriostatic action of the various sulphonamide compounds used in practice is also relative. In addition to differences in their general potency against the whole group of susceptible organisms, each may show some variation in its action against individual bacteria and even individual strains. Thus although sulphanilamide seems to inhibit a somewhat larger proportion of gonococcal strains than does uleron, the latter may succeed against an individual strain which has repeatedly proved resistant to the former. Furthermore, a strain of susceptible organisms may become "fast" to one compound and yet capitulate to another.

In my experience the coliform group possesses the lowest proportion of sulphonamide-resistant strains and the highest degree of sensitivity to these compounds. This is particularly the case in infections of the urinary and genital tracts, where the growth of coliform bacilli can be rapidly arrested with quite small doses and where there is only a low proportion of failures. Gonococci are less

susceptible as a group, requiring fairly intensive and prolonged treatment before they are completely and permanently eradicated, and there is a higher proportion of resistant cases. The high susceptibility of the haemolytic streptococcus (especially the A group) to sulphonamide compounds is well known, but I have convincing evidence that certain non-haemolytic streptococci—for example, *Strep. viridans* and *Strep. faecalis*—can also be partly or completely inhibited by both sulphanilamide and uleron. I have also seen cases of mixed genito-urinary infections in which such organisms as *B. proteus*, *B. aerogenes*, and diphtheroid bacilli are concerned completely clear up with both those substances. The staphylococcus and the pneumococcus, on the other hand, have proved almost entirely resistant in my experience.

It is now generally realized that whatever the exact mode of action of sulphonamide compounds may be they act only as blood-borne antiseptics, and their direct application to an infected focus is of comparatively little value. Reaching the blood and tissues quickly, they are also rapidly excreted, and in practice unless they are correctly administered their concentration will soon be found to fall to a subefficient level. An adequate blood supply to a focus of infection is, of course, an essential condition for success; avascular foci, such as blood clots, cardiac vegetations, necrotic areas, and chronic foci embedded in scar tissue or sclerosed bone, will resist chemotherapeutic attack no matter how susceptible the enclosed organisms may be.

One cannot help feeling that all these substances exert a purely bacteriostatic action, and that they do nothing to stimulate the defence mechanisms of the host. The final result of any infection must largely depend on this defence mechanism, and many failures with chemotherapy are probably to be attributed to its faulty operation. Again, chemotherapy does not appear to have any action in neutralizing existing toxins or those liberated by the bacteria which these drugs destroy. Above all, it in no way protects the patient against relapse or recurrence, as is shown by the high relapse rate in the present series and in my other groups of cases. Indeed, I have reason to believe that the opposite effect is sometimes produced, and that chemotherapy at the very onset of an infection may actually inhibit those anti-bacterial processes which confer immunity against recurrence or relapse of an infection. This would explain the fact observed in practice that a higher incidence of ultimate success is obtained when infections are treated some time after rather than at their onset.

Reflection on these and many other problems connected with the great therapeutic possibilities which have been opened by the discovery of sulphonamide compounds shows that a great deal of bacteriological and immunological work will have to be done before the new chemotherapy finds its proper level in the treatment of disease.

Summary

1. Clinical experiences are reported with several sulphonamide-containing chemotherapeutic substances (one of which, recently introduced under the trade name of uleron, is a di-sulphonamide).

2. Fifty-seven cases, with illustrative records, of genito-urinary infection are reviewed.

3. In a group including four cases of epididymitis and twenty-six of urethritis chemotherapeutically treated (in both instances non-gonococcal) there were respectively one and three failures.

4. Twelve cases, similarly treated and constituting a mixture of acute and subacute pyelitis and cystitis, showed one failure and three relapses.

5. Fifteen cases of "secondary" urinary infection, nine of them with senile prostatic enlargement, four with urethral stricture, one with epididymitis, and one with vesico-colic fistula, were treated with these drugs. In the prostatic cases two-thirds of the patients were benefited by chemotherapy, which proved of value in combating pre-operative and post-operative urinary sepsis, although the relapse rate was again high. Two prostatic and two stricture cases—all with chronic retention and heavy alkaline mixed infection—completely failed to respond.

6. The selective action of these drugs on various organisms and strains and their mode of action *in vivo* are discussed.

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A NEW CONTRAST STAIN FOR GONOCOCCI AND MENINGOCOCCI IN SMEARS

BY

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The examination of smears for gonococci, particularly from women, is facilitated by a method of staining described elsewhere (Sandiford, 1937). It consists of Gram's method with Pappenheim's stain in place of a simple red counterstain. The organisms stain as in the usual Gram stain; while the polymorph cells show blue-violet nuclei and rose-violet cytoplasm, the red gonococci standing out much more clearly against the blue-violet background of cells than against the red background afforded by the ordinary counterstain. While the method was independently evolved, an acknowledgment was given in the paper to Fauth (1918), who, it was found, had previously described a similar method of staining. Recently I have received reprints of papers by Scudder and Lisa (1931) and Scudder (1931), who, apparently unaware of Fauth's paper, described such a stain and recommended it for *Neisseriae* in sections and smears.

The present paper is the outcome of an attempt to devise a method of staining which would not diminish the contrast between cells and Gram-positive organisms as does the Gram-Pappenheim combination, yet which would retain and, if possible, still further improve the contrast between Gram-negative organisms and cells. To this end attention was directed to the staining of the Gram-positive organisms and to the staining of the cells.

The Gram-positive Organisms

Effect of Acid.—It was found that when, as sometimes happened in dealing with large batches of routine specimens, the counterstain was left on rather too long, the Gram-positive organisms tended to decolorize. In view of the reported effect of acid vaginal secretion on the Gram-staining of organisms (see below), it seemed probable that the 2 per cent. carbolic acid which forms the bulk of Pappenheim's stain was responsible for this decolorization. Experiments on stained films with 2 per cent. carbolic acid alone showed this supposition to be correct.

The Violet Stain.—Improvement was effected by the use of crystal violet with ammonium oxalate as the initial stain and acetone as the decolorizer. (I am indebted to Major Beamish, R.A.M.C., for drawing my attention to the method, which seems to be the same as that described