2. *No irritants.* Avoid such things as hot gravies, spices, vinegar, lemon juice, pepper, mustard, curry, pickles, chutney, and strong hot tea or coffee. Take salt in strict moderation. Take alcohol in strict moderation only. Avoid all drugs and patent medicine, especially aspirins and strong purgatives (see below). Smoking should be indulged in only after meals and in strict moderation (five cigarettes, or three small pipefuls daily).

3. *Overeating at one meal is as bad as going for long periods without food.* Both are harmful, and it is important to supplement the three principal meals by taking a milk drink with chocolate biscuits or bread in the middle of the morning and in the afternoon and last thing at night. All food must be carefully chewed before swallowing.

4. *It is a mistake to avoid certain foods* (with the exceptions mentioned above) on principle because they are supposed to be indigestible. Narrowing the diet down too much leads to a loss of weight and malnutrition, which will tend to cause a recurrence of the indigestion. Eat any food that is available, unless it is found that a certain food always disagrees, in which case it should be avoided.

5. *If constipated* take a teaspoonful of milk of magnesia at night or a dessertspoonful of liquid paraffin morning and evening.

6. *Try to avoid mental and physical overstrain.* Keep regular hours, regular habits, and, above all, regular mealtimes. During unavoidable periods of extra work, intensive activity, or excitement, or when worried or upset, take extra care with diet: avoid beef, pork, pastry, and greasy foods.

7. *If indigestion is felt* take a dose of alkaline powder (magnesium trisilicate if possible), but do not take powder as a routine. Otherwise avoid all medicines, unless ordered by your doctor. If the indigestion is severe and does not clear up in a few days go and see your doctor.

8. Do not spend all your time worrying about your stomach and about your diet and about your health generally. Stick to these instructions, but otherwise forget about your stomach and enjoy life.

The following is a copy of the questionnaire sent to each of the patients who failed to keep his final follow-up appointment:

"I am very interested to hear how your indigestion has been since I last saw you, as we are doing some investigations on the subject.

"I should be most grateful if you would write to me in confidence (envelope enclosed) telling me in detail about any symptoms you have noticed, and also whether you have had any further treatment or operations, the date and results of any further barium-meal x-ray films of your stomach, and any complications that have occurred.

"Are you keeping to a diet, are you working, and how much tobacco are you smoking?"

During the last quarter of 1953 the City Analyst of Birmingham carried out a survey of five popular brands of "pocket inhaler." These articles consist of a conical plastic outer case with a smaller inner chamber containing absorbent paper soaked in amphetamine, or a closely related compound, together with menthol and essential oils. Sixty-four inhalers were examined, an average of 13 of each of the five brands. The first of these brands to be put on the market showed a remarkably consistent amphetamine content. Three other brands were very similar, but their content of amphetamine was less constant, sometimes showing an excess of up to 30%, and sometimes a deficiency of as much as 22%. The last brand examined, however, presented a very different picture: of 13 samples examined every one was deficient in amphetamine by amounts varying from 31% to 90%, with an average shortage of nearly 60%. The City Analyst then wrote to the makers, who suggested that the loss was due to evaporation consequent on long storage. However, no particular relationship could be discovered between age and the strength of the samples. As a result of this investigation the firm in question agreed to recall all inhalers issued before last year. In Mr. Bagnall's view, this appears to be yet another case where certain pharmacists have retained stocks of a preparation long after the time when they should have been destroyed or returned to the suppliers.

A PLEA FOR THE LONGER TREATMENT OF CHRONIC PYELONEPHRITIS IN CHILDREN

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Acute pyelonephritis in children responds to sulphonamides so well that its treatment rarely presents a problem. Sixteen cases in infants and children were treated in the Radcliffe Infirmary during 1948 and 1949; all cleared up rapidly and only one relapsed. The latter responded to a second course of sulphonamide, and there was no recurrence.

In chronic pyelonephritis the results are very different. In the same two-year period there were 16 chronic cases at the Radcliffe. Symptoms had been present for at least two weeks, and in most cases for very much longer when treatment was started. They were all given a sulphonamide in full dosage for five to fourteen days. In every case the infection relapsed. In four of these cases further investigation showed lesions requiring surgery, but the other 12 remained essentially medical problems. Our experience since then suggests that these results are in no way exceptional, and it is with the treatment of chronic pyelonephritis without surgically treatable lesions that this paper is concerned. In most cases the infection is due to a coliform organism sensitive initially to all the readily available antibiotics except penicillin. The question to be decided is which antibiotic should be used, in what dose, and for how long.

General Considerations

In 1939 Weiss and Parker reviewed the post-mortem findings in 100 cases of chronic renal tract infection. In only one was inflammation confined to the renal pelvis and ureters; in 99 inflammation involved the renal parenchyma, and the disease was rightly called pyelonephritis. Birchall and Alexander (1950), in a review of the medical aspects of pyelonephritis, accepted this view of its pathology. They pointed out that in treatment it is the concentration of antibiotic in the plasma which is significant, and not the concentration in the urine. Therefore only full doses of a sulphonamide or antibiotic should be given in the initial treatment of pyelonephritis. Furthermore, there is no particular merit in a sulphonamide such as "urolucosil," which has been recommended because of the high concentration of the non-acetylated form obtained in the urine. Birchall and Alexander also draw attention to the fairly general experience that, with streptomycin, organisms become resistant very rapidly. They suggested, for this reason, that streptomycin should never be given for more than five to seven days. They also pointed out that as mandelic acid and related compounds are effective only in an acid medium, which cannot be attained in the interstitial tissues of the kidney, these drugs are unlikely to be of value in pyelonephritis, and should be reserved for infections of the lower renal tract. For the treatment of chronic pyelonephritis they recommended a 21-days course of a sulphonamide in

full dosage, together with intramuscular penicillin and streptomycin during the first week.

At the time their article was published we had no experience of this combined therapy, but we had already been using 14-days courses of a sulphonamide in full dosage, and had had four quite severe drug reactions. Two children on sulphadimidine developed rashes with generalized lymph-node enlargement on the seventh and eighth days of the course respectively. One child on "sulphatriad" developed fever and a rash on the eleventh day, and another on a rather large dose of sulphatriad—0.15 g. per lb. (0.33 g. per kg.) a day; body weight 20 lb. (9 kg.)—developed on the thirteenth day fever, generalized lymph-node enlargement with splenomegaly, and agranulocytosis with complete disappearance of polymorphs from the peripheral blood for nearly a week. This experience made us reluctant to give even longer courses of sulphonamides in full dosage. Furthermore, we already had, in one child, evidence of the value of a small dose of a sulphonamide continued over a very long period. We therefore decided to start treating all cases of chronic pyelonephritis with an initial 10-days course of sulphadimidine in full dosage, followed by a further variable period on a small dose.

It is clearly important to know whether this method of treatment gives better results than the orthodox short course. Only a planned investigation could give this information with certainty, and no such investigation has been made. However, during the last three and a half years we have treated over 40 infants and young children with chronic pyelonephritis in the Babies' Hospital, Newcastle-upon-Tyne, during the first half of this period with short courses of a sulphonamide or antibiotic, and during the second half with long courses. From among these infants it has been possible to form reasonably similar groups, and a comparison of the results of treatment in the two groups follows.

An Investigation

During this investigation the general management, nursing care, and follow-up of infants remained the same; only the length of treatment changed significantly.

Infants admitted before October, 1950, were treated with sulphadimidine, streptomycin, or chloramphenicol for five to fourteen days, seven days being the most usual. Dosage was standard—that is, sulphadimidine, 0.1 g. per lb. (0.22 g. per kg.) a day; streptomycin, 20 mg. per lb. (44 mg. per kg.) a day; and chloramphenicol, 50 mg. per lb. (110 mg. per kg.) a day. If the infection relapsed, a second similar course of appropriate antibiotic was given, and in some cases third and fourth courses. "Mandelix" was used in three cases after antibiotics had failed. If infection still persisted infants were kept on sodium citrate (average 90 gr. (6 g.) a day) for long periods.

After October, 1950, sulphadimidine was given in full dosage for an initial period, usually 10 days; the subsequent period on a reduced dose varied from only 10 days in two cases to over six months. If the infection did not respond to sulphadimidine or if the organism seemed unlikely to be sensitive—for example, *Staph. aureus*—chloramphenicol was used. Rather illogically, in the first case we treated with chloramphenicol (No. 17) this was given for only 16 days. The infection relapsed. Whenever we used chloramphenicol in subsequent cases we gave an initial course, usually of fourteen days, in full dosage and then a reduced dose for a period varying from six to sixteen weeks. Streptomycin was given in most cases during the first week of sulphadimidine. Alkalis were not used.

Only infants with a indisputable pyelonephritis who were under 1 year at the onset of symptoms, whose symptoms had been present for at least two weeks before the start of treatment, who had no evidence of renal acidosis or of hypercalcaemia, and who had no other illness which might have affected the course of the pyelonephritis have been included for analysis. Twelve infants in the early group and 11 in the later group satisfied these criteria.

The duration of symptoms before treatment is probably the most important single factor in determining prognosis. This was similar in the two groups. The results of treatment proved extremely difficult to assess. It was out of the question to use the urinary findings alone as an index of cure, and we therefore had to depend very much on the infant's general progress. Failure to thrive is so constantly present in infants with an active infection that a normal weight gain is a dependable sign of recovery. All weights were therefore graphed, and these, the mother's account of the infant, and the urinary findings were all taken into consideration. To express the results quantitatively, we tried to decide on a definite day, counting from the start of treatment, from which progress was uninterrupted and after which no significant pyuria was found. This was easy when there was a good immediate response to treatment with no relapse. Although there were minor variations in response, for the sake of clarity all such cases have been graded as 10—that is, progress uninterrupted from the tenth day of treatment. It was still fairly easy in the cases which relapsed but made a good recovery after further treatment, and all these have been given a definite grading. It was impossible in those cases in which, after months of ill-health with slow or fluctuating weight gains, gradual and possibly incomplete recovery occurred: in these no attempt has been made to be precise.

The results of this analysis are given in the Table. There is no doubt that the results of treatment are very much better in the later group. Six of the 11 made an uninter-

Results of Treatment

Early Group			Later Group		
Case No.	Duration of Symptoms in Days before Treatment	Days from Start of Treatment to Recovery	Case No.	Duration of Symptoms in Days before Treatment	Days from Start of Treatment to Recovery
1	210	90	13	? 184	> 120
2	182	> 150	14	182	10
3	119	10	15	154	10
4	119	10	16	119	51
5	98	10	17	91	90
6	98	60	18	70	10
7	84	200	19	70	10
8	70	10	20	56	* 78
9	56	> 90	21	49	10
10	35	300	22	42	10
11	35	> 60	23	28	110
12	17	60			
Average	93.6	$\frac{750}{9} = 83.3$ plus 3 indefinite	Average	95.0	$\frac{389}{10} = 38.9$ plus 1 indefinite

rupted recovery, against 4 out of 12. The average time from the start of treatment to recovery was less than half, and there was only one case with an indefinite end-point against three in the early group. However, in 5 of the 11 cases in the later group recovery was slow and interrupted. In two of these the reasons for this are obscure, but in three it is instructive to examine the treatment given in detail.

Case 17.—This child was in hospital at the same time as several infants with a gastro-enteritis due to *Bact. coli* D 433. He passed some loose stools shortly after admission, and it was because of the possible intercurrent gastro-enteritis that he was treated from the start with chloramphenicol rather than sulphadimidine. He responded well to a 16-days course, but the infection relapsed within a week. The infection then failed to respond to sulphadimidine given for 28 days when he was an out-patient, presumably because the organism was insensitive; so he was readmitted to hospital. A coliform organism sensitive to chloramphenicol was cultured from the urine, and he was given chloramphenicol, 250 mg. four-hourly for 14 days, 250 mg. twice-daily for 42 days, and 250 mg. once daily for 84 days. The infection responded promptly and has not relapsed in over a year's follow-up. He was given this very long course

because a persistently raised blood urea and no visible excretion of dye in an intravenous pyelogram suggested severe kidney damage.

Case 16.—This male child was treated initially with sulphadimidine, 0.25 g. four-hourly for ten days, with streptomycin during the first seven days. This was followed by sulphadimidine, 0.25 g. twice daily for seven days. The pyelonephritis had responded to this, but he then developed an abscess at the site of a streptomycin injection. Pus from this cultured *Staph. aureus* resistant to penicillin and streptomycin. Sulphadimidine was stopped and he was given chloramphenicol, 250 mg. eight-hourly for eight days. Total treatment was for only 25 days: the shortness of this course was due to a mistake, and was not in keeping with the general policy. The pyelonephritis relapsed after one week. His urine cultured coliform organisms still sensitive to chloramphenicol, and he was given chloramphenicol, 250 mg. eight-hourly for 21 days, and 125 mg. twice daily for 56 days. The infection responded promptly to this, and has not relapsed in nine months' follow-up.

Case 20.—A female child was treated initially with sulphadimidine, 0.5 g. six-hourly for 10 days followed by 0.5 g. twice daily for 21 days (total treatment 31 days). The infection responded promptly, but symptoms recurred a week after stopping treatment. They were at first attributed to a mild otitis media, for which penicillin was given for a week, but pyuria was found later. Urine culture revealed a chloramphenicol-sensitive coliform organism, and she was given chloramphenicol, 500 mg. eight-hourly for 14 days, and 250 mg. twice daily for 56 days. The infection responded, and there was no relapse in three months' follow-up.

In these three cases it seems probable that relapse could have been prevented by giving a longer course of treatment on the first occasion.

Conclusion and Discussion

From the evidence of this investigation it is clear that the plan of treatment followed in the later group offers a good chance of cure even in very long-standing infections. If the infection responds to the initial course of sulphadimidine or chloramphenicol in full dosage, relapse is most unlikely during the subsequent period on a reduced dose. We have in fact never seen this. The difficult question is how long the reduced dose should be continued. The results in Cases 16 and 20, which relapsed after 25 and 31 days of treatment respectively, suggest that the period must certainly be longer than a month, but we do not know how often we have used unnecessarily long courses.

It is perhaps worth considering at this point why the long period on a reduced dose prevents relapse. The following explanation seems reasonable. It is certain that in every case of long-standing pyelonephritis there is widespread disorganization of renal tissue. It is unlikely that this damaged tissue can be restored to normal in a period as short as two or three weeks, and while it remains incompletely healed it is presumably more liable to infection. The initial course of antibiotic in full dosage must kill most of the infecting organisms, but a few may survive in isolated foci. We imagine that the small dose of antibiotic is enough to protect the damaged tissue from infection spreading from the surviving foci. As the organism found in relapse is nearly always the same as in the original infection, relapse must usually occur by spread of infection from surviving foci rather than by reinfection with fresh organisms.

If this is the correct explanation the protective dose of antibiotic must be continued for as long as the damaged kidney will take to heal, and this will depend on the duration and severity of the infection before treatment was started. There can therefore be no final answer to this question of how long treatment should be continued. The length of history, the extent to which one or both kidneys have already been damaged, and the possible risk of toxic effects from the long course of antibiotic will all have to be taken into consideration.

Sulphadimidine is so cheap and safe that we are sure it should be used first whenever it is likely to be effective. For the same reasons, wherever the initial course in full dosage has proved effective it would seem wise to anticipate relapse and to give the reduced dose for a long period. As an approximate guide we would suggest eight weeks when infection has been present for less than two months, and up to six months or occasionally more in longer-standing infections.

When we have had to turn to another antibiotic we have used chloramphenicol, and our experience with this suggests that the same manner of dosage is needed as with sulphadimidine. We have used it in this way with good results and without any serious ill effects. However, reports (Hodgkinson, 1954) of aplastic anaemia following chloramphenicol suggest that it would be most unwise to make a practice of giving long courses. A final verdict on this question is not possible yet, but for the present it seems preferable to use aureomycin. It is most unlikely that aureomycin will prove effective in a significantly smaller dose or shorter time than chloramphenicol or sulphadimidine, and our very limited experience confirms this view. However, it is more expensive than sulphadimidine and its long-term toxic effects are less well explored. For both these reasons we are reluctant to advise giving really long courses unless they are absolutely essential. In the great majority of cases we believe they will be, but as a small proportion of cases clear up after a short course of treatment (see Cases 3, 4, 5, and 8) it may be wise to start with a 14-days course. If the infection relapses it is still likely to respond to a longer period of treatment as suggested for sulphadimidine.

Although most of those we have treated for pyelonephritis have been infants, limited experience with older children suggests that our conclusions are valid for them too. In older children, however, histories tend to be longer, and one occasionally meets with infections which are distressingly intractable. In such cases persistent treatment with frequent change of antibiotic as bacteriology indicates offers the only hope of cure.

Summary

All cases of pyelonephritis in infants and young children treated during 1948–9 at the Radcliffe Infirmary, Oxford, and in a 3½-year period (1949–52) at the Babies' Hospital, Newcastle-upon-Tyne, have been studied.

Attention is drawn to the possible chronicity of these infections and to the frequency of relapse after orthodox seven- to fourteen-days courses of a sulphonamide or antibiotic.

A new scheme of treatment has been described with an initial ten-days course of sulphadimidine or an antibiotic in full dosage, followed by a long period (two to six months) on a reduced dose.

Two similar groups of cases—one treated in the orthodox manner and the other according to the new scheme—are compared, and the superiority of the long course of treatment is shown.

The wisest plan of treatment to adopt in future is discussed.

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REFERENCES

- Birchall, R., and Alexander, J. E. (1950). *Medicine, Baltimore*, 29, 1.
- British Medical Journal*, 1952, 2, 136.
- Hodgkinson, R. (1954). *Lancet*, 1, 285.
- Weiss, S., and Parker, F. (1939). *Medicine, Baltimore*, 18, 221.