PAEDIATRICS

SUPPLEMENT

1958

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FOR THE PRACTITIONER

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Under the General Editorship of

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PUBLISHERS' ANNOUNCEMENT

This is the third Supplement to Paediatrics for the Practitioner. New thoughts and work are introduced in original articles and, in the future, paediatric practice will be surveyed from time to time by means of critical papers. Subjects in the main volumes will also be revised when extensive changes in practice have occurred. Subjects in the original articles are fully indexed independently of the Noter-up.

The Noter-up section keeps readers up to date with advances made in paediatrics and will also show where, as a result of more recently acquired knowledge, the practice to be recommended now differs from that in the main volumes. Each year's Noter-up section replaces completely the previous edition.

To make full use of the main work and Noter-up, readers should first refer to the main volume in which the particular subject appears. To ascertain whether changes have occurred they should then refer to the Supplement, turning first to the specific volume number shown at the top of the left-hand margin of each page of the Noter-up. By reference to the details ranged beneath this, readers can then easily find the Part, page and sub-title referring to the original article in the main volume. In each case, where alteration has occurred or new material has been inserted, the text is placed under the same heading as that which appears in the main work.

October, 1958 *THE PUBLISHERS*

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CHEMOTHERAPY

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INTRODUCTION

Historical

Chemotherapy for infective conditions is not a recent development, for in 1891 Ehrlich treated malarial patients with methylene blue and in 1911 Morgenroth and Levy introduced optochin, a quinine derivative, for the treatment of pneumonia. Antibiotics also have a longer history than is generally recognized; in 1899 Emmerich and Low prepared pyocyanase and found it active against *Eberthella typhosa* and *Corynebacterium diphtheriae*. However, there was a long interval before further progress was made and it was not until 1935 that the modern era really started, with Domagk's discovery of the value of Prontosil in the treatment of streptococcal infections. Interestingly, again there was a parallel development in antibiotics, for in 1929 Fleming isolated penicillin and recognized its potential value which was confirmed by Chain and Florey in 1940. Since then there has been a steady flow of new compounds, both chemotherapeutic and antibiotic.

Today the practitioner is faced with a bewildering choice of agents and some of the newer preparations he is offered may have had inadequate clinical trials or soon become ineffective on account of the emergence of new resistant strains of organisms. The recognition of the viruses as aetiological factors in many infections, possibly brought about in part by the subjugation of the commoner bacterial pathogens by the earlier sulphonamides and penicillin, has added to the practitioner's diagnostic and therapeutic problems.

Mode of action

The sulphonamides and the antibiotics both exert their action by interference with the organisms' nutrition, though they act through different enzyme systems. With their nutrition impaired, the organisms can no longer multiply and they rapidly succumb to the host's normal defence mechanisms. As Ehrlich observed, the maximal response is obtained when the organisms are in their most active stage of multiplication, and at this time a single dose of appropriate sulphonamide or antibiotic, if sufficiently large, can annihilate the infecting organism. This should be the basic principle of chemotherapy in acute infections. For example, lobar pneumonia caused by pneumococci, and meningitis caused by meningococci, can, if treated early in the course of the infection, be cured by a single massive dose. Unfortunately this does not hold true for the majority of infections, but many can certainly be treated without a *course* of chemotherapy. The dose should be as large as possible and repeated as dictated by the clinical response, not by any set regime. When the maximal dose is given for the minimal time complications are fewest and the results most satisfactory.

Combinations of sulphonamides or of antibiotics, or both, may prove of value

but, although synergism has been claimed in certain cases, the effect is usually merely additive. Occasionally it may be antagonistic (*see* page 12).

Most of the available substances are more truly bacteriostatic than bactericidal, though some of them become bactericidal when large doses are used.

Although most organisms can be attacked by one or more chemotherapeutic agents, there are still some which are recalcitrant in certain cases—for example, some staphylococci, *Proteus vulgaris* and *Pseudomonas aeruginosa*. The fact that comparatively few pathogenic viruses are susceptible to antibiotics presents a challenge to virologists, chemists and clinicians.

The need for new compounds therefore exists and there is a continuing search for methods of improving the present ones and for producing new ones. Antibiotics and sulphonamides alike are subject to this research and the latest developments are in the direction of long-acting sulphonamides and antibiotics with a wider spectrum of activity, and also in the combination of antibiotics with adjuvants or buffering agents such as sodium metaphosphate or glucosamine which have been found to yield higher blood levels and to be less prone to give rise to unpleasant side-effects.

When used in combination with cortisone, antibiotics have considerably improved the prognosis in acute and previously often overwhelming infections. Care should be exercised in the choice of antibiotic, however, for although they are similar they act differently. Tetracycline is closely allied structurally to oxytetracycline and chlortetracycline yet they have different spectra of activity. Further, it has been shown experimentally that chlortetracycline and oxytetracycline were not effective against streptococcal infections in mice given large doses of cortisone, whereas penicillin was. Clearly chlortetracycline and oxytetracycline are dependent on host defence mechanism to complete their chemotherapeutic effect (Foley, 1955).

Complications

It is inevitable that the really potent agents should engender certain risks to the host. The chief drawback to the development of new compounds is their toxicity, and many that have proved experimentally of outstanding value have been found unsuitable for clinical use on these grounds. This fate befell the first compounds introduced; optochin was successful in curing patients with pneumonia but it caused blindness, and pyocyanase also proved too toxic to justify its further use.

With regard to the antibiotics the chief problem is the development of bacterial resistance. This severely curtails the efficacy of many antibiotics and there is a tendency for cross-resistance to occur—that is, an organism which has become resistant to one antibiotic may become resistant to similar antibiotics and, once developed, this phenomenon persists more or less indefinitely.

Certain strains of staphylococci have proved difficult in this respect, particularly those occurring in hospitals. They first became resistant to increasingly large doses of penicillin and later developed resistance to other antibiotics; the situation now is that unless some new agent is discovered soon there is a real danger that a universally resistant staphylococcus will be prevalent and there will be no specific therapy available to combat it.

Almost all the other common infecting organisms have also, on occasion, developed resistance to one or more drugs—though not as yet to the extent that staphylococci have. For example, *Mycobacterium tuberculosis*, in adults, readily becomes resistant to streptomycin, particularly in chronic cases. The prevention

of the emergence of resistant strains is best achieved by using the correct antibiotic initially, giving it in large dosage, and for a short time. Courses of chemotherapy should be avoided whenever possible, and it *is* possible in many acute infections, although for chronic infections, for example, tuberculosis, prolonged treatment is essential. It is also necessary in the prophylactic regimes which have proved of the greatest value in the prevention of recurrences of rheumatic infection and of pulmonary infections in children with fibrocystic disease of the pancreas. In some cases the hazard of the development of a resistant organism must be accepted, constant watch being kept on the flora concerned and appropriate alteration in therapy undertaken when necessary. This involves repeated bacteriological control.

There may be difficulty in obtaining suitable specimens (for example, blood culture, sputum, pus or urine) for culturing the infecting organism and for testing its sensitivity to a variety of antibiotics and sulphonamides, and it may not always be reasonable to wait until the bacteriologist's report is received. Furthermore, satisfactory clinical improvement may be achieved with the first antibiotic or sulphonamide chosen, although the bacteriologist may have found that the organism is, *in vitro*, insensitive to that drug. In these circumstances what should the doctor do? Should he continue with the drug he has chosen and which is working well, or change to one which shows *in vitro* sensitivity? Clinical judgment should surely take precedence over laboratory findings. The bacteriologist's findings are only relative and, with the increased therapeutic doses being prescribed today, do not necessarily reflect the outcome of therapy.

It is inevitable that occasions will arise when the practitioner is unable to obtain a bacteriological diagnosis and he must then be guided by his experience. If there is an epidemic and he has been fortunate enough to find out early that a certain sulphonamide or antibiotic is proving effective, that drug will be his natural first choice for all children in whom he diagnoses the epidemic infection. When the diagnosis is not clear he has the choice of sulphonamide or penicillin (or both together) or of starting treatment with one of the newer antibiotics. Undoubtedly the best procedure, from the long-term point of view, would be to use sulphonamides and penicillin and to keep the broad-spectrum antibiotics in reserve. Many childhood infections and epidemics are of viral origin and unlikely to be affected by sulphonamides or penicillin, which can, at best, only prevent the secondary infections which so often accompany viral diseases; therefore the temptation to start with a broad-spectrum antibiotic is hard to resist. Whether or not antibiotics should be given routinely is a matter about which opinion is divided. In the dangerous bronchopneumonias encountered in infants and children suffering from influenza or occurring after upper respiratory tract infections the secondary organism may be *Haemophilus influenzae*, against which sulphonamides and penicillin are both inactive; this fact is a sound reason for exhibiting chloramphenicol or erythromycin. In older children most influenzal and upper respiratory infections are successfully overcome without recourse to chemotherapy.

Infants and children suffering from fibrocystic disease of the pancreas, when receiving chemoprophylaxis, may develop antibiotic-resistant organisms, but often their life depends on the control of the recurring attacks of pneumonitis to which they are liable. Prolonged prophylaxis, interspersed with periods of intensive therapy, is usually necessary and, as the infecting organism is most often a staphylococcus, delaying the development of resistance is, though difficult, a vital part of the management. Repeated bacteriological examinations of the

sputum with sensitivity tests are essential and the antibiotic should be changed appropriately as soon as evidence of resistance appears or the flora change to an insensitive type.

In addition to the difficulties arising from the development of resistant strains of organisms there is another complication which antibiotics specifically may produce and that is the invasion of the body by thrush fungus of enhanced virulence. In normal infants thrush infection is merely a disagreeable and undesirable acquisition, usually limited to the mouth; it responds promptly to treatment with gentian violet and is a cause of minor morbidity rather than mortality. When antibiotics are being, or have recently been, administered for any length of time a superimposed infection with monilia may produce a different picture. The infant is more ill and toxic, and the patches of thrush do not disappear after application of gentian violet. On the contrary, there is a great tendency for them to spread down the oesophagus and into the gut and, in the severest cases, the fungus may penetrate into the bloodstream and become widely disseminated, causing death from generalized moniliasis, with particular involvement of the lungs.

Although a number of fungicidal antibiotics have been tried, systemic moniliasis remains a most serious condition and every care must be taken to prevent oral contamination; for example, there must be scrupulous cleanliness in the preparation and administration of infants' feeds, an extra supply of vitamins B and C must be given, and careful inspections must be carried out for the earliest signs of thrush in the mouth.

Vitamin B complex should be prescribed for all children receiving antibiotic treatment for any length of time. Not only is the intake of vitamins likely to be lessened as a result of the infection which is being treated, because of either anorexia or vomiting or diarrhoea, but the normal intestinal synthesis of certain fractions of the B complex is inhibited by the antibiotic.

Additional vitamin K is also advisable when chloramphenicol, chlortetracycline or streptomycin is being administered for a long period.

SULPHONAMIDES

Although there is a tendency to consider sulphonamides as old-fashioned they are still useful, and may be the sole or chief drugs used in the treatment of meningococcal meningitis and pneumococcal lobar pneumonia. They are also valuable in some forms of dysentery and in gonococcal infections in children who are allergic to penicillin. In those children with infections shown bacteriologically to be due to organisms sensitive to sulphonamide their use may spare the antibiotics—to which resistance, when it develops, is usually more rapid and more common than to sulphonamide. A combination, as for example, of sulphadiazine, sulphadimidine and sulphathiazole in equal parts, is probably preferable to any single sulphonamide.

Sulphonamides combine well with penicillin, and a single dose of a mixture of sulphadiazine, sulphadimidine and sulphathiazole—for example, 2 grammes at 5 years and 3 grammes at 8 years given by mouth—together with an intramuscular injection of 1 or 2 million units of penicillin may be all that is necessary to effect a cure in a child with lobar pneumonia or meningococcal meningitis. Infants respond equally well with appropriately reduced doses; for example, 1 gramme of the sulphonamide mixture and $\frac{1}{2}$ million units of penicillin at 1 year, or even at 6 months, in a severely ill infant. The pneumococcus appears to retain its

sensitivity both to sulphonamide and penicillin, but recent experience in parts of England has shown that the meningococcus—which used to be the most sensitive—is now developing a degree of resistance; and if, in an infant with cerebrospinal meningitis, clinical improvement is not prompt after such a "stosstherapy", further treatment should be prescribed forthwith, according to the sensitivities of the organism. Nevertheless, sulphonamide and penicillin should be the first drugs used in these infections, and other antibiotics held in reserve. It must be stressed that the clinical response to treatment is much the most important factor in determining the need for further or altered therapy. There is no need to repeat lumbar punctures in infants suffering from meningitis: an initial puncture, for bacteriological purposes, is essential in every case of meningitis. Thereafter, if the patient is improving clinically, lumbar puncture need not be repeated—and, as quiet and freedom from disturbance are integral parts of the treatment of any child suffering from meningitis, this is not unimportant. If the child is not improving, or there are signs of the development of a block in the circulation of the cerebrospinal fluid, further examination of the fluid and of its pressure must be undertaken. Intrathecal therapy is no longer advised, except in unusual circumstances, as, for example, when an intracisternal injection of hydrocortisone hemisuccinate is given to an infant with tuberculous or influenzal meningitis who is developing a block. The appropriate antibiotic should then always be instilled together with the hydrocortisone.

Sulphonamides have been used extensively in the long-term prophylaxis of streptococcal infection of the throat in children who have had rheumatism, but more recently penicillin has been preferred and is to be recommended. There are a number of long-acting sulphonamide derivatives available now, some of them being composed of more than one compound, but consisting chiefly of sulphamethoxypyridazine which is rapidly absorbed and slowly excreted. They are particularly valuable in the treatment of urinary infections which demand continued treatment for several weeks and are also helpful in the prophylactic treatment of rheumatism in those few children who show allergic reactions after penicillin.

It is possible that, with the extension of antibiotic-resistant organisms, particularly staphylococci, there may be a return to the sulphonamides. Sulphathiazole, for example, when first introduced in 1940 proved of some value in the treatment of staphylococcal infections, and some modified compound may be found which will be more potent in this respect.

Another recent development is the introduction of sulphanilyl-n-butyl urea which has a marked hypoglycaemic action. It is not, however, advised for the treatment of diabetes in childhood.

The recommended sulphonamides are sulphadiazine, sulphadimidine and sulphathiazole, either separately or in combination. Sulphafurazole (Gantrisin) is also of value but should not be used in premature infants in the first 2 weeks of life (*see* page 6). Sulphaguanidine and succinylsulphathiazole may be used in the treatment of dysentery but are probably less valuable than sulphadiazine.

Dosage

This will vary according to the condition being treated, the length of treatment proposed and the age of the child. For single-dose therapy of acute infections 75 milligrams per pound is usually adequate (the dose may be repeated twice or thrice if necessary at intervals of 8, 12 or 24 hours as the clinical response

demands). When treatment is being continued over a period of days, 50 milligrams per pound per day should be sufficient. For dysentery, sulphadiazine (75 milligrams per pound per day) should be administered until diarrhoea ceases and the stools no longer contain the pathogenic organism. In the treatment of urinary infections, which demand more prolonged chemotherapy, doses of the order of 25 milligrams per pound per day need not be exceeded. For prolonged prophylactic therapy (in children who are allergic to penicillin) 0·5–1 gramme daily of a triple mixture or 0·5 gramme of long-acting sulphonamide once daily may be used.

Complications

On the whole, sulphonamides are freer from complications than many other chemotherapeutic agents, particularly when used in intensive dosage and for very short periods, but care must be exercised to avoid the occurrence of crystalluria, which has been particularly evident after sulphamerazine. The use of a triple sulphonamide mixture minimizes this risk. In premature infants sulphafurazole (Gantrisin) is not advised during the first two weeks of life as a prophylactic against infection because of its tendency to increase haemolysis to the extent of causing hyperbilirubinaemia of such a degree as to engender the risk of kernicterus.

Rarely, skin rashes, urticarial or morbilliform, may occur. More serious is leucopenia—this is rare but if not recognized it may progress to a fatal agranulocytosis.

To avoid these complications it is important to make sure that children, and particularly infants, who are being treated with sulphonamides are also given plenty of fluid as shown by output of urine. Treatment should be stopped at once if a rash appears. If the drug is being given over a period of days, the leucocyte count should be recorded and treatment stopped if the polymorphonuclear cells drop excessively.

PENICILLIN

Penicillin, like the sulphonamides, is sometimes wrongly regarded as being outmoded. It retains its value in the treatment of a wide variety of bacterial and coccal infections and should probably be the antibiotic of first choice except in urinary infections due to *Escherichia coli* or *Proteus vulgaris*. Despite the many reports of the development of resistance by staphylococci the fact remains that most staphylococci, except some of those encountered in hospitals, retain their sensitivity. Partial resistance, as determined *in vitro*, can be overcome clinically by increasing the dose and, as the doses currently prescribed enormously exceed those recommended even 5 years ago, failure to produce a satisfactory clinical response is the main indication for changing the antibiotic.

The absorption, excretion and action of penicillin have been intensively studied. Methods of delaying its excretion by the use of Caronamide and other substances, formation of depots by addition of aluminium stearate, and combination with procaine giving a slower absorption rate, were followed by the production of benzylpenicillin, and this has been succeeded by the phenoxymethyl derivative. Now attention has been turned to the development of an oral preparation which will resist inactivation by the gastric juices and can be given effectively by mouth. This is a great advantage in paediatrics and would clearly be the method of choice if vomiting does not prevent absorption of an adequate amount and if blood levels as high as those obtained by the parenteral route can be secured.

Potassium phenoxymethyl penicillin promises to fulfil these requirements. Nevertheless, in severe infections it is probably wise always to give an initial intramuscular injection of penicillin and not to rely on oral treatment if there is any likelihood of even part of the dose being vomited. It is unlikely that any form of oral therapy will completely replace parenteral treatment in severely ill patients but it may well materially reduce the number of injections. In such conditions as subacute bacterial endocarditis, mastoiditis and osteomyelitis, when treatment has to be continued for some weeks, and in the prolonged prophylactic therapy of rheumatic children and in patients undergoing cortisone treatment, the substitution of oral penicillin is indeed a great advance. Penicillin may be combined with sulphonamides or with streptomycin—possibly synergistically—and additively with the tetracyclines (*see* page 12).

Dosage

Because of its very low toxicity and rapid excretion by the kidneys penicillin is remarkably safe, and may be given in very high dosage when necessary. The dose will vary more with the nature and severity of the infection than with the age of the child. It is no longer possible, or even advisable, to recommend dosage in terms of units or milligrams per pound per day. For example, a newborn infant with osteomyelitis caused by a penicillin-sensitive staphylococcus may be given 500,000 units initially, followed by 250,000 twice daily. In older children with a similar infection as many as 2 million units may be given daily, or even twice daily, until the severe initial toxaemia has been overcome, and then further treatment may be ordered by mouth. The highest blood levels are obtained by parenteral injections of crystalline penicillin. Whether repeated peaks are preferable to continued high blood levels, such as may be obtained with mixtures of crystalline penicillin and procaine penicillin, is still undecided. Both give good results. In intramuscular treatment in children the volume injected is of considerable importance; whenever possible no single injection should exceed 1 millilitre, and preferably 0·5 millilitre, especially when the treatment is to be repeated frequently. Any volume in excess of 2 millilitres is likely to cause great pain.

Potassium phenoxymethyl penicillin contains the equivalent of 200,000 units per tablet of 125 milligrams and the dose may vary from half a tablet once or twice daily (prophylactically) to 1 tablet 6-hourly (therapeutically).

Complications

Penicillin is remarkably free from toxic effects; a few children become sensitized and react with skin rashes sufficiently severe to necessitate stopping treatment; occasionally a more unpleasant and severe anaphylaxis may follow, particularly if the compound in use contains procain. Any child who has reacted in any way adversely to penicillin should not be given this antibiotic on future occasions. The parents should be warned that their child is sensitive and should, if they change their doctor, or the child is taken to hospital, be told to request that penicillin be *not* given.

STREPTOMYCIN

Streptomycin remains a most active drug against *Mycobacterium tuberculosis* but suffers from certain disadvantages.

First, the organism may become resistant (though this is less common in children than in adults). Secondly, the drug, although well absorbed after intramuscular

injection, does not act intracellularly (as isoniazid does) and thirdly, it is extremely toxic when given in large doses for long periods, particularly in its effect on the vestibular and cochlear systems. With regard to this last action the dihydro-derivative is much more likely than the simple streptomycin salt to cause deafness. As the effect of the two salts is similar, and the degree of resistance achieved by the organism is equal and one which becomes resistant to streptomycin will also resist dihydrostreptomycin, there seems no good reason for prescribing this latter preparation, either alone or combined with streptomycin. In the treatment of tuberculosis it is customary (and considered mandatory in adults) to combine two or more chemotherapeutic agents in order to prevent the emergence of resistant strains. The three drugs used chiefly are isoniazid, streptomycin and para-aminosalicylic acid (PAS). They may be given in any combination or all three may be used at the same time. It is now generally recognized that streptomycin need not be given so frequently—once daily or on alternate days being adequate. In infants and children the development of resistant strains of *Myco. tuberculosis* has been recorded only on very rare occasions and therefore there is less need for streptomycin in uncomplicated cases. In the author's experience isoniazid alone is highly effective but most authorities still recommend the use of two drugs concurrently, usually isoniazid and PAS.

Streptomycin is of particular value in the prevention and treatment of infections in the newborn, when *Esch. coli* is very likely to be the causative organism. It is also active against *Pr. vulgaris* infections and is therefore useful in the treatment of infections of the urinary tract. It has some action on *H. influenzae*. Although it acts as potently as penicillin on all the organisms against which penicillin is bacteriocidal or bacteriostatic, it is not to be recommended in preference, because of its toxic effects.

Dosage

In the treatment of tuberculosis the recommended dose is 20 milligrams per pound per day and it is administered intramuscularly daily, on alternate days, or twice a week, according to the severity of the infection.

As a prophylactic measure in the newborn it may be given in doses of 62·5 –125 milligrams according to the weight of the infant and repeated at 12-hour intervals for from 2 to 6 doses. In infants whose birth has been delayed for more than 24 hours after the membranes have been ruptured it is customary to give one such injection immediately after birth, although if the mother has been treated with streptomycin during this time there may be a good placental transfer to the foetus. After any such procedure as catheterization of the umbilical vein for exchange transfusion in haemolytic disease of the newborn it is wise to give a prophylactic injection immediately. Purulent conjunctivitis and skin infections in the newborn respond well to 1 or 2 injections. For infants weighing less than 5 pounds, 62·5 milligrams is usually an adequate dose and for those weighing more than this, 125 milligrams.

For the treatment of other infections by sensitive organisms the dose is usually 20 milligrams per pound per day, the injections being given once or twice daily.

PARA-AMINOSALICYLIC ACID

In comparison with streptomycin and isoniazid, PAS may be considered more as an ancillary than a curative drug for it is much less active and is bacteriostatic rather than bactericidal. It does, however, delay the emergence of resistant strains of organisms when prescribed in conjunction with streptomycin or isoniazid.

The effective dose is large (from 10 to 15 grammes daily) and is not always well tolerated. As well as nausea and vomiting, diarrhoea may occur. When PAS and isoniazid are prescribed together they should be given in those forms, rather than as the PAS salt of isoniazid which contains insufficient PAS to act effectively as a deterrent to the development of resistance. As, however, children respond so well to isoniazid alone and the chances of resistance developing are small, PAS may well be omitted from the treatment.

ISONIAZID

Since isoniazid was introduced in 1951 tuberculosis has become an eminently curable infection, particularly in children. Isoniazid has many advantages over streptomycin. It is much less toxic; it is better absorbed; it can penetrate into the cells and destroy the organisms there—where streptomycin cannot; it is administered by mouth; it is tolerated in large doses and, in children, has shown little tendency to cause the evolution of resistant strains of the *Myco. tuberculosis.*

It has replaced streptomycin as the drug of first choice in the treatment of tuberculosis and may, in simple primary infections, obviate the need for streptomycin. However, in serious and progressive infections a combination of the two is still advised. PAS may also be added but this is rarely necessary.

Dosage

The dose is from 5 to 10 milligrams per pound per day orally. Treatment must be continued for long periods: how long is not yet known. It is wiser to err on the side of too prolonged administration than too short. Six months is probably the minimal period for any child with primary tuberculosis and associated radiological evidence of hilar gland or parenchymal involvement, and twelve months for infants and children suffering from tuberculous meningitis.

The possibility that isoniazid may prove a valuable prophylactic in the prevention of post-primary lesions is being investigated in a large-scale controlled trial in the United States of America and the preliminary reports (Lincoln, 1957) suggest that it is in fact immensely helpful.

It is also the treatment to be recommended for complications arising after B.C.G. vaccination, chiefly adenitis, although these complications are becoming much less common since the introduction of freeze-dried vaccines with standardized antigenicity and content of viable organisms.

A number of isoniazid compounds and derivatives have been investigated, but so far none has been produced which—in children—surpasses the value of isoniazid.

Isoniazid may be given intramuscularly, in the same dose as that used orally, and is of use in the case of unconscious or vomiting patients. Intrathecal administration is not recommended.

Complications

There are virtually no complications. The pyridoxin deficiency which arises after prolonged high dosage treatment in adults has not been seen in children.

CHLORAMPHENICOL

Chloramphenicol retains its position among the antibiotics of everyday value, despite the fact that it was the first to be synthesized.

It is of particular value in the treatment of children suffering from typhoid fever and typhus and from infections by the dysentery group of organisms. It is also valuable in the treatment of pertussis and acute laryngo-tracheo-bronchitis and may well be considered as the first choice in infants with undiagnosed sudden and severe respiratory infection, particularly as *H. influenzae* may be associated in such cases. It is not to be preferred to penicillin in the treatment of streptococcal, staphylococcal and pneumococcal infections. Recent work from America (Mudd, 1958) suggests that it may, however, be more useful than the tetracyclines in the control of resistant staphylococci.

Dosage

It may be given in doses of 125 milligrams 3-hourly or 4-hourly to infants in the acute stages of a severe respiratory infection, the dose being diminished —or the interval between doses being increased—as the condition improves. For older children 250 milligrams may be prescribed 3 or 4 times daily.

In emergency it may be given intramuscularly, the dose for an infant being 125–250 milligrams. A soluble preparation is available, containing 1 gramme in 5 millilitres of solution.

Complications

Although the occurrence of a number of cases of aplastic anaemia and agranulocytosis rightly gave rise to considerable anxiety, these complications are singularly rare and must not be allowed to detract from the value of chloramphenicol. They are unlikely in the treatment of acute infections, in which it remains of the greatest use.

THE TETRACYCLINES

Under this heading are included tetracycline, oxytetracycline and chlortetracycline. These are all useful antibiotics with a wide range of activity.

Tetracycline, the parent substance, was the last of the three to be introduced. It is well tolerated by most children and produces few unpleasant side-effects. The most recent modification has been the combination with sodium metaphosphate, which is said to produce higher blood levels more quickly and to maintain bacteriostatic activity longer. This complex is more readily absorbed than the ordinary hydrochloride. Tetracycline is available in 250-milligram capsules for older children or as a suspension containing 50 milligrams per millilitre and may be prescribed in doses of 10–15 milligrams per pound per day. It may also be given intramuscularly in a solution containing 50 milligrams per millilitre, 0·5 millilitre twice daily for infants and 1 millilitre twice daily for older children. In emergency it may be given by drip intravenously in 1 per cent solution in normal saline or 5 per cent dextrose solution.

Oxytetracycline (Terramycin) is particularly valuable in enteral infections and has also been shown to have a certain tuberculostatic activity in large doses. Its use in tuberculosis, however, will probably be limited to that of an adjuvant in the treatment of patients with streptomycin-resistant or isoniazid-resistant organisms and it is unlikely to find a place in the treatment of tuberculous infections of childhood.

The dose is 20–25 milligrams per pound per day by mouth. A suspension containing 125 milligrams in 5 millilitres is available for infants and younger children. There is also an intramuscular preparation, combined with procaine

hydrochloride, which may be given in doses of 2–3 milligrams per pound per day in children with severe infections or who, because of persistent vomiting, are unable to retain the oral preparation.

In emergency it may be given as the hydrochloride intravenously as an infusion in normal saline, using 5–10 milligrams per pound.

Chlortetracycline (Aureomycin) has a similar field of usefulness to chloramphenicol—that is, it is particularly valuable in the acute respiratory infections of infancy, in primary atypical pneumonia, pertussis, and in the subjugation of the staphylococci so frequently found in the episodes of recurring pneumonitis in infants and children suffering from fibrocystic disease of the pancreas.

The dose is similar to that of oxytetracycline and it is available as capsules and granules; in emergency it may be given intravenously, well diluted, or intramuscularly, 50–100 milligrams daily or twice daily as necessary.

Complications

Nausea, vomiting and diarrhoea, soreness of the mouth, with or without visible ulceration, and napkin rash in infants, have all been recorded after treatment with the tetracyclines. Any of these side-effects may be sufficiently severe to necessitate stopping treatment. In infants particularly, the oral condition may make them refuse their feeds and so lead to dehydration. Infection by monilia must be guarded against, especially in infants (*see* page 4).

ERYTHROMYCIN

Erythromycin was heralded as the antibiotic with the greatest resistance to the production of resistant organisms and this reputation has largely been upheld. It is now appreciated that resistance may occur and that staphylococci which have become resistant to penicillin, streptomycin and the tetracyclines may likewise prove unresponsive to erythromycin.

It should not be the antibiotic of first choice in the treatment of children with acute infections, nor should it be used prophylactically. If it is kept in reserve and exhibited in those infections not responding to penicillin, streptomycin or the tetracyclines, it is likely to have a much longer therapeutic existence than if it is prescribed indiscriminately. It is undoubtedly an active and powerful drug of the greatest value. Its field of activity is as wide as that of the tetracyclines and its dosage is similar.

There have been a few reported cases of toxic effects, usually involving the kidney.

An oral preparation (Ilotycin) is available which contains 100 milligrams in 5 millilitres and a compound for intramuscular or intravenous injection, erythromycin lactobionate, may be given in 5 per cent solution, that is, 50 milligrams per millilitre.

NOVOBIOCIN

This recent addition, developed from two different *streptomyces—niveus* and *spheroides*—is likely to be of value in the treatment of staphylococcal infections with resistant organisms, for it has shown no cross-resistance with penicillin, streptomycin, the tetracyclines or erythromycin. It gives high blood levels quickly and needs to be given no more often than twice daily. The dose may vary from 62·5 to 125 milligrams twice daily according to age. It may also be given intramuscularly or intravenously.