The Newer Antibiotics, with Special Reference to Chloromycetin

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Since the historical discovery of Penicillin by Fleming in 1929, about 150 substances have been isolated from moulds, fungi, bacteria and algae, which will antagonize or destroy micro-organisms. Unfortunately, the majority are too toxic for therapeutic use.

Penicillin was derived from a fungus, *Penicillium notatum,* and, so far, it is the only therapeutically significant antibiotic of fungal origin. Nearly all the newer antibiotics are produced by soil actinomycetes. The Streptomyces, which belong to this group, have yielded Streptomycin, Chloromycetin, Aureomycin, Terramycin, and the very recent Neomycin and Viomycin.

The newer antibiotics differ from Penicillin and Streptomycin in that they are effective when administered by mouth. They were all originally prepared by the deep fermentation process, as is still the case with Penicillin, Streptomycin, Aureomycin and Terramycin, but Chloromycetin is outstanding in that it has been synthesized. It is, in fact, the first and only antibiotic to be synthesized on a practical basis.

Penicillin, Streptomycin, Aureomycin and Terramycin have complex chemical structures, and while it is true that a gram or two of Penicillin has been synthesized at enormous cost it is extremely doubtful whether these antibiotics will ever be produced synthetically on a large scale.

Chloromycetin, or, to give it its generic name, Chloramphenicol, has a relatively simple structure. Chemically it is a substituted di-hydroxy-propane.

As far as we know this is the first time Nature has produced a compound containing the dichloracetamido and nitro groups.

Examination of the antibiotic spectrum shows that the range of Chloromycetin is much broader than that of Penicillin and Streptomycin. Not only is this new antibiotic strikingly effective against Gram-negative organisms, and, to a lesser extent, against Gram-positive organisms, but for the first time we have at our disposal an antibiotic which has a dramatic effect against Rickettsiae which range in size between the bacteria and the viruses. It is also effective against a number of the larger viruses. Aureomycin is probably rather more active against the staphylococcus than Chloromycetin. On the other hand, Chloromycetin is infinitely more effective against the Salmonella group than either Aureomycin or Terramycin.

It may be that we shall find micro-organisms becoming resistant to these newer antibiotics, although this has not to date been demonstrated to any marked extent *in vivo.* After all in the early days we heard very little of Penicillin-resistant strains. It is, of course, another example of Nature adapting herself to new conditions.

Blood Levels.

Chloromycetin is quickly absorbed and the onset of its action is rapid. Effective blood levels are attained in 30 minutes after oral administration. As a general rule the daily dose should be 50 mgm. per kgm. of body-weight, in divided amounts, doubling the dose for children. Experience has shown that the interval between the doses should never be longer than eight

hours in order to prevent the concentration of the drug falling below the minimum effective level, which is about 10 microgrammes per c.c. of serum.

Typhus.

Scrub typhus and typhoid fever were the two infectious diseases that responded so dramatically to Chloromycetin in the first trials carried out by Smadel and his colleagues in Malaya. Mention should also be made of the pioneer work by Payne on epidemic typhus in Bolivia. It is perhaps unnecessary to say much about the rickettsial group of infections except to emphasize that in cases of epidemic typhus, scrub typhus, tick typhus and Q. fever Chloromycetin is extraordinarily effective, in doses of 60 mgm. per kgm. of body-weight followed by doses of 0.25 gm. every three hours or 0.5 gm. every six hours until the patient becomes afebrile.

Typhoid.

At the outset I want to make it quite clear that it is no longer considered desirable or necessary to give a loading dose of Chloromycetin in typhoid fever. I am satisfied that when we hear of vasomotor collapse following the administration of Chloromycetin in typhoid fever it is associated with the loading dose originally suggested by Woodward and his colleagues in Malaya, and may conceivably be due to the liberation of endotoxins, or perhaps more correctly stated, lysis of the organisms.

We now think in terms of 60 mgm. of Chloromycetin per kgm. of body-weight as a daily dose in typhoid fever. In a man weighing 65 kilos this would mean 4 gms. in the 24 hours, reducing the dose by half when the patient becomes afebrile, which is usually between the third and fourth day, after which it is important that treatment should be continued for a further ten to fourteen days. Even with this scheme of dosage there has been an appreciable number of relapses. Fortunately, the patient invariably responds to a further course of treatment. In fact, it is rather striking that the response is even more dramatic than when Chloromycetin is given in the first instance, presumably because the patient's defensive mechanism has already got to work.

In January of this year Smadel and his colleagues reported that they had treated eight cases of typhoid fever with a combination of Chloromycetin and Cortisone. With fairly large doses of Cortisone along with Chloromycetin the patients became afebrile on an average in 15.5 hours, whereas with Chloromycetin alone the temperature usually falls between the third and fourth day.

These workers prefer to consider the beneficial effect of Cortisone in the typhoid patient resulting from the action on the human host rather than directly on the typhoid organism or its products. Nevertheless, the combined therapy appears to be of sufficient theoretical and practical interest to warrant further studies.

The use of Anti-Typhoid-Paratyphoid Vaccine in conjunction with Chloromycetin has resulted in a drop in the relapse rate from 20 to 25 per cent to 4 to 5 per cent. These striking results have been obtained amongst the British troops stationed in the Canal Zone in Egypt. The dose of T.A.B. Vaccine should be small, 0.02 c.c. — in other words, 60 million organisms daily — for ten days after the patient has become afebrile.

Unfortunately, Chloromycetin is ineffective in eradicating the chronic typhoid "carrier" state. According to Smadel the balance between the host, the parasite and immune mechanism is already established, and the added factor of a transient suppressant, such as Chloromycetin, is unlikely to produce much in the way of a permanent effect on the bacterium.

In this connection it is interesting to note that a paper in the Lancet a few weeks ago described the successful eradicatioin of Salmonella paratyphi B from the urine of a boy aged 8, who had been a "carrier" for three years. One gramme

of Chloromycetin was administered daily for ten days.

Infantile Gastro-Enteritis.

Infantile gastro-enterits is another condition which responds in almost dramatic fashion to Chloromycetin. Professor Smellie is satisfied that in adequate dosage —he uses 165 mgm. per kgm. of body-weight daily in divided doses — the average case will respond to treatment in from ten to twelve days. The cases that I am referring to come within the group usually designated non-specific gastro-enteritis. Some authorities take the view that the infection is due to a specific type of B. coli named B.G.T.

Enteritis.

Chloromycetin is also very effective in other forms of enterites, such as bacillary dysentery and food poisoning. The latter has taken a new form in England. In the past the symptoms were believed to be produced by toxins traceable to foods which had either been directly infected—duck eggs were an excellent example — or contaminated by animal excretions. According to Grant, about three years ago a change occurred in the Salmonellae enabling them to live in the human intestine and pass from man to man. He attributes the change to the repeated consumption of living Salmonella in imported egg powder, which unfortunately we had to use in large quantities during the war owing to difficulties in the food supply.

A recent paper in the British Medical Journal referred to the successful treatment of a dysentery "carrier" with Chloromycetin after repeated attempts with various sulphonamides had been ineffective. 29 consecutive stool cultures in the 50 days following the completion of the treatment failed to grow the causative organism and they were still negative four months later.

Urinary Infections.

Amongst the microbial diseases which respond to Chloromycetin and the other newer antibiotics, I would mention particularly bacillary and coccal urinary infections.

Apart from the fact that Chloromycetin has a marked antibiotic action on micro-organisms invading the urinary tract the success which has followed its use is due to its high concentration in the urine following moderate dosage. Here again a suitable dose is 3 gms. daily, in divided doses, continuing the treatment for five to seven days after the urine has been cleared of the principal invader, or until operative measures have ensured eradication of the focus.

Chloromycetin appears to be the most effective of all the antibiotics in the treatment of infections due to Bacillus proteus. In the case of such a resistant organism as Ps. pyocyanea it is not claimed that Chloromycetin will be effective in more than 40 per cent. of cases.

In a recent issue of the American Journal of Obstetrics and Gynaecology there was a report to the effect that the Aerobacter aerogenes appears to be occurring with increasing frequency in urinary tract infections and can generally be cultured in at least 50 per cent of cases of sub-acute pelvic inflammatory diseases with pelvic abscess. The organism is particularly susceptible to Chloromycetin.

May I remind you that if necessary Penicillin, Streptomycin and the Sulpha drugs may be used concurrently with Chloromycetin.

Antagonism has been reported when Chloromycetin is given prior to or simultaneously with Penicillin, but not if Penicillin is administered first.

Antibiotics synergistic with Penicillin, e.g. Streptomycin or Bacitracin can overcome the antagonism between Chloromycetin and Penicillin. A suggested explanation is that Chloromycetin can modify the characteristics of the bacterial population, so as to make it less susceptible to Penicillin action.

I would point out that the report from

which quote refers to laboratory experiments. To the best of my knowledge there is no evidence that antagonism has been reported in vivo.

Pertussis.

In England pertussis is responsible for a mortality rate of 1,000 per annum. The *Haemophilus pertussis* is extremely sensitive to Chloromycetin, and provided the dosage is adequate — according to one authority it should be at least 100 mgm. per kgm. each night for five nights — the results have been most encouraging. My own experience has been that when Chloromycetin fails in whooping cough it is entirely a question of inadequate dosage.

In order to enable the patient to develop some immunity against whooping cough a prominent paediatrician in London prefers to wait for seven days before commencing treatment with Chloromycetin.

The most recent study from the United States contrasts the use of Penicillin, Aureomycin, Chloromycetin and Terramycin in 150 children with pertussis. Children who received Penicillin appeared to have obtained some slight benefit which developed slowly, but in those receiving one of the other three antibiotics there was a more rapid decrease in the frequency and severity of the paroxysmal action. In children under one year Aureomycin gave better results, but in children over one year Chloromycetin appeared to be the product of choice. The dosage in each case was 60 mgm. per kgm. of body-weight for ten days, a dose which our experience in England would suggest was on the small side.

Chloromycetin is intensely bitter, and it has been extremely difficult to administer this antibiotic to children between the ages of 1 and 3 years. It has been administered in suppository form with some measure of success, but it has not yet been possible to obtain any consistent blood levels by this method. This difficulty has now been overcome, using Chloromycetin Palmitate in a pleasantly-flavoured emulsion, 8 c.c. of which represent approximately 250 mgm. of Chloromycetin. Perhaps I ought to add that Chloromycetin Palmitate is made by a process of esterification.

Pneumonias.

Bacterial pneumonia, whatever the causative organism, as well as atypical or virus pneumonia, respond to Chloromycetin and Aureomycin. It appears to be an advantage to give a loading dose of Chloromycetin when the infection is above the diaphragm, and it is suggested that this loading dose should be 80 to 100 mgm. per kgm. of body-weight.

Last year Cray made the remarkable observation that Chloromycetin is capable of completely sterilizing the upper respiratory tract, and expressed the opinion that the future use of Chloromycetin in respiratory infections seemed almost limitless if observations made on the upper respiratory tract can be extended to include the whole tract.

Both Chloromycetin and Aureomycin received much attention in England during the last influenza epidemic. Unfortunately, I cannot subscribe to the observation that has been made from time to time that these newer antibiotics seem to have a direct effect on the virus of influenza. I take the view that the excellent results that have followed Chloromycetin and Aureomycin in epidemic influenza have been due to the fact that they satisfactorily deal with the secondary infection, notably the Haemophilus influenzae.

In this connection Smadel has stated that those influenzal patients who develop pulmonary consolidation usually warrant treatment with one or other of the newer antibiotics.

Surgical Infections.

To date Chloromycetin, and presumably the same applies to the other newer antibiotics, does not appear to have been widely investigated as a prophylactic and

therapeutic agent in surgical infections, but it should have considerable possibities in this direction. Cellulitis, lymphangitis, lymphadenitis and abscess caused by pyogenic cocci respond rapidly to Chloromycetin, the afebrile stage terminating in the majority of cases within 72 hours.

Chronic wound infections of mixed bacterial aetiology show less response to Chloromycetin, and in some instances concurrent use of Penicillin would seem to be indicated.

It is not difficult to prophesy that Chloromycetin will be shown to be a valuable agent not only in surgical prophylaxis but in post-operative surgical infections, and post-partum sepsis following complicated obstetrical deliveries, to cite only two examples.

I would also include peritonitis following perforated appendix with, of course, appropriate surgical procedures. Again it may be necessary to use Chloromycetin concurrently with Penicillin.

Venereal Diseases.

Other microbial infections which respond to Chloromycetin include undulant fever, Haemophilus influenzae infections, subacute bacterial endocarditis, and the venereal diseases.

In acute gonorrhoea in males an effective dose is 3 gms. initially, followed by 1 gm. every eight hours for two or three days to prevent relapse.

Despite the fact that Chloromycetin exhibits a low antitreponemal action in vitro, Romansky and his colleagues have reported good results with Chloromycetin clinically. These investigators noted that the mechanism of action of Chloromycetin differed from that of Penicillin in that healing of the lesions appeared to originate at its base instead of its periphery.

Non-specific urethritis and Reiter's disease also respond to Chloromycetin.

Virus Diseases.

Chloromycetin is not effective against the smaller viruses, poliomyelitis, epidemic influenza and yellow fever. It appears to have no effect on the viraemia in smallpox, although it is useful in dealing with the septic condition.

Mumps, chicken-pox, herpes zoster, infectious mononucleosis and trachoma all seem to be favourably influenced by this new synthetic antibiotic. In mumps the condition responds in 24 to 48 hours to the average dose for the various age groups. In no instance has orchitis developed in a patient after initiation of treatment with this drug.

Clinical evidence indicates a high order of specificity for Chloromycetin in the treatment of herpes zoster, notably in herpes zoster ophthalmicus. In 24 hours a definite improvement has been noted, and complete recovery has followed with no relapse or residual pain. It is not effective in the post-herpetic stage.

The results in infectious mononucleosis are very striking. One may expect the patient to become afebrile within 24 hours after the commencement of treatment.

Smadel has reported that viruses of the psittacosis-lymphogranuloma venereum group are rather closely related to the rickettsiae, and are highly susceptible to the new rickettsiostatic agents.

Eye Infections.

Recent work by Leopold and his colleagues in Philadelphia has shown that Chloromycetin penetrates the cornea following the local instillation of drops or the application of ointment. The rate and amount of penetration are greater in the presence of an abraded cornea. There are no serious irritating effects following the topical administration of Chloromycetin in aqueous solution into the eye, and the antibiotic does not interfere with the regeneration of corneal epithelium. Chloromycetin penetrates all the ocular tissues and humours with the exception of the lens. There is suggestive evidence that higher concentrations will be found where there is inflammation of the eyes. All the available evidence indicates that intra-

ocular concentrations, sufficient to control most infections due to susceptible organisms, can be obtained either by oral administration or by the instillation of drops.

Chloromycetin appears to be definitely more effective than Aureomycin and Terramycin, which, according to Leopold and his co-workers, penetrate poorly, if at all, into the fluids and tissues of the normal eye. Furthermore, solutions of Chloromycetin are relatively stable.

On the basis of penetrating studies and accumulating clinical evidence, Chloromycetin can be administered orally in doses of 3 to 6 grammes daily in eye infections, and locally in solutions, containing 5 mgm. per millilitre. An ointment containing 1 per cent of Chloromycetin has also been shown to be effective in a variety of ocular conditions, such as keratitis, uveitis, iritis, dacryocystitis and herpes zoster ophthalmicus. The results of the solution in keratoconjunctivitis, which is believed to be a virus infection, to quote from a distinguished English ophthalmologist, have been "extremely gratifying".

Topical Application.

Chloromycetin would appear to have considerable possibilities when applied topically. It has been used in a solution in propylene glycol in chronic otorrhoea, and such a solution is suggested in chronic osteomyelitis, varicose ulcer, as a dressing in burns and in plastic repairs. In a clinical note in the Lancet a few weeks ago an Australian surgeon recorded his experiences with powdered Chloromycetin in the treatment of infected wounds, ulcers, burns and wounds infected by gas-forming organisms. In fact, he went so far as to state that in some cases the results were superior to administration by mouth.

Chloromycetin in powder form has also been reported to have given excellent results in external otitis, chronic suppurative otitis media, infection of fenestration and mastoid cavities, and sinusitis.

I have already referred to the topical application of Chloromycetin Ointment in ophthalmology, but it has also been used as a cream in impetigo, acute folliculitis, and infectious eczematoid dermatitis, and is indicated generally in superficial infections and dermatological conditions complicated by organisms which fall within the spectrum of Chloromycetin antibacterial activity.

Chloromycetin has also been used topically with excellent results in dentistry. In a recent paper in the American Journal of Dental Research Chloromycetin is described as almost the ideal antibiotic, and extremely well suited for use in root canal therapy. Dissolved in propylene glycol it is stable for an indefinite period at room temperatures.

The authors of the paper state that such a solution is effective against certain micro-organisms which are resistant to Penicillin and Aureomycin, and has specific therapeutic action against a wide range of pathogenic organisms.

Administration of Chloromycetin.

It may be necessary, particularly if the patient is in extremis, to administer Chloromycetin parenterally. A solution in propylene glycol has been administered intravenously, but there is reason to believe that dimethyl acetamide will prove to be a more suitable solvent. Suitably diluted such solutions can be given intravenously, or, undiluted, intramuscularly. The doses suggested are ½ to 1 gm. of Chloromycetin, followed by doses of ¼ to ½ gm. every six hours.

Pharmacology.

I have left myself very little time to say anything about the pharmacological and biological studies of Chloromycetin. It passes the placental barrier, and in contrast to some of the other newer antibiotics has also been shown to be present in the spinal fluid in concentrations of 30 to 50 per cent of that in the blood stream, following oral dosage. A practical application of this is seen in the remarkable

results that have followed its administration in Haemophilus influenzae meningitis.

The fate of Chloromycetin in the body has been extensively investigated. Chemical analysis of the urine collected over a 24-hour period disclosed the presence of nitro compounds — accounting for approximately 90 per cent. of a given daily dose — of Chloromycetin. The bile, on the other hand, contains only small amounts.

Mode of Action of Chloromycetin.

It is interesting to speculate how Chloromycetin acts in the body. Smadel considers that Chloromycetin is essentially bacteriostatic. Gray, on the other hand, is of the opinion that Chloromycetin is bactericidal, but that in concentrations below a critical level there is a zone of bacteriostasis which in turn gives way to ineffectual concentrations.

Evidence seems to suggest that Chloromycetin may interfere with carbohydrate metabolism, more exactly with the normal functions of vitamins B^1, B^2, and nicotinic acid, all of which act in dehydrogenase systems. In other words, it inhibits the co-enzyme essential to carbohydrate metabolism.

Another theory that has been put forward is the possibility of Chloromycetin interfering with fat rather than carbohydrate metabolism. In other words, it may relate to its inhibitory action on esterase.

Whether Chloromycetin is bacteriostatic, or, as we are beginning to believe, bactericidal, there is one aspect of antibiotic therapy we must not forget, and that is that Nature still has her part to play in developing antibodies.

Fortunately, any side-reactions that may occur with Chloromycetin — they include slight nausea, muscle fatigue, temporary ophthalmoplegia, dry mouth, diarrhoea, and possibly moniliasis (for the inhibition of which normal bacterial flora appears to be essential) — all disappear quickly with the cessation of treatment. In the great majority of cases Chloromycetin is extremely well tolerated.

Chloromycetin has made history by being the first antibiotic to be prepared in the chemical laboratory. It offers great promise as a useful therapeutic agent in the treatment of some entities in which laboratory results did not suggest clinical effectiveness, such as mumps and syphilis, and perhaps other conditions will present themselves.

In view of the potentialities thus far demonstrated by Chloromycetin in the clinic and with its extention over promising segments of the antibiotic spectrum, Chloromycetin and the other new antibiotics represent outstanding contributions to modern therapy.

"Where a problem excites strong protagonists and equally strong opposition its solution often lies between the extremes containing the reliable elements of each."

KEITH SIMPSON.

"Patients are connoisseurs in sincerity and he deceives him self who imagines that they are easily hoodwinked by an impressive manner alone."

W. M. MILLAR.