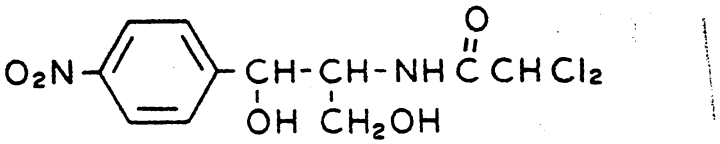
tion is extremely painful and is seldom tolerated by the patient for very long periods.[26, 27] Combining such preparations with a local anesthetic lessens the immediate pain, but persistent tenderness prevents prolonged administration by this route. If individual doses do not exceed 100 mg the drug is tolerated much better, but the levels achieved are lower than those that can be obtained when the drug is given orally or intravenously.

Preparations containing vitamins, acetylsalicylic acid (aspirin), acetophenetidin (phenacetin), caffeine, or antihistamines contain only 125 mg of tetracycline and have no advantage over the antibiotic alone.

Chloramphenicol

Chloramphenicol was isolated in 1947 from culture filtrates of *Streptomyces venezuelae.* The chemical formula was soon identified and the antibiotic was successfully synthesized. The formula is presented below:



The aromatic ring structure appears to be essential for biologic activity. The isomers of chloramphenicol are inactive. A wide variety of alterations in the molecule have been made, but most of these changes have resulted in loss of antibiotic potency, and none of the resulting formulations have been superior to the parent drug.

Chloramphenicol is generally considered to be a bacteriostatic agent, although, by varying the concentration, a bactericidal effect can be demonstrated against some strains of microorganisms. Chloramphenicol acts on sensitive bacteria by inhibiting protein synthesis. Considerable information is available as to the precise enzyme systems involved. These vary with different organisms.[28] In the light of the known toxicity of chloramphenicol, it is interesting that its effect on the host cells differs from its effect on bacterial cells.

Chloramphenicol has a broad antimicrobial spectrum and is active against many strains of gram-positive and gram-negative bacteria, the rickettsiae, and a few strains of viruses. There is, however, considerable variation in the sensitivity of different strains of organisms within the same species. Ths variability is most frequently encountered among the gram-negative bacilli. Although Fisher[29] and Hodgman[30] stated that staphylococci maintain their in vitro sensitivity to chloramphenicol despite its extensive use in hospitals, other investigators have noted chloramphenicol-resistant strains of staphylococci in increasing numbers.[31]

Antibiotic synergism and antagonism have been extensively studied in vitro and in experimental animals; however, these phenomena are difficult to assess clinically and there is little documentation of such a clinical phenomenon.

Pharmacology

Crystalline chloramphenicol is absorbed unchanged as the metabolically active form of the drug. It is almost completely absorbed from the gastrointestinal tract. Therapeutic levels appear in the blood within 30 min after ingestion, reach their peak in 2 hours, and disappear within 12 to 22 hours.[32,33] The height and duration of the blood levels are generally proportional to the dose. Circulating chloramphenicol is rapidly conjugated by the liver to a monoglucuronide which has no biological activity and is highly water soluble. A small amount of chloramphenicol is converted, probably also in the liver, to a biologically inactive aminodial hydrolysis product.[30, 32, 33]

Assays for chloramphenicol are carried out by two methods: (a) the microbial assay method, which uses a turbimetric procedure against *Shigella sonnei* and measures active chloramphenicol only and (b) the chemical assay method which determines total aromatic nitro compounds, including both active chloramphenicol and the inactive metabolites. Comparative determinations by the two methods indicate that most of the chloramphenicol in the blood is in the active form. Sixty per cent of the active chloramphenicol in the blood is reversibly bound to the plasma albumin.