

Edited by  
J. D. Williams and A. M. Geddes

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# CHEMOTHERAPY

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Volume 4

**Pharmacology of  
Antibiotics**

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## Volume 4 Pharmacology of Antibiotics

Edited by  
J.D. Williams  
*The London Hospital Medical College  
London, U.K.*

and  
A.M. Geddes  
*East Birmingham Hospital  
Birmingham, U.K.*

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Proceedings of the  
9th International Congress of Chemotherapy  
held in London, July, 1975

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## Preface

The International Society of Chemotherapy meets every two years to review progress in chemotherapy of infections and of malignant disease. Each meeting gets larger to encompass the extension of chemotherapy into new areas. In some instances, expansion has been rapid, for example in cephalosporins, penicillins and combination chemotherapy of cancer - in others slow, as in the field of parasitology. New problems of resistance and untoward effects arise; reduction of host toxicity without loss of antitumour activity by new substances occupies wide attention. The improved results with cancer chemotherapy, especially in leukaemias, are leading to a greater prevalence of severe infection in patients so treated, pharmacokinetics of drugs in normal and diseased subjects is receiving increasing attention along with related problems of bioavailability and interactions between drugs. Meanwhile the attack on some of the major bacterial infections, such as gonorrhoea and tuberculosis, which were among the first infections to feel the impact of chemotherapy, still continue to be major world problems and are now under attack with new agents and new methods.

From this wide field and the 1,000 papers read at the Congress we have produced Proceedings which reflect the variety and vigour of research in this important field of medicine. It was not possible to include all of the papers presented at the Congress but we have attempted to include most aspects of current progress in chemotherapy.

We thank the authors of these communications for their cooperation in enabling the Proceedings to be available at the earliest possible date. The method of preparation does not allow for uniformity of typefaces and presentation of the material and we hope that the blemishes of language and typographical errors do not detract from the understanding of the reader and the importance of the Proceedings.

K. HELLMANN, Imperial Cancer Research Fund  
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## TISSUE BINDING OF ANTIBIOTICS

Calvin M. Kunin

Department of Medicine, Veterans Administration Hospital  
and University of Wisconsin, School of Medicine  
Madison, Wisconsin, U.S.A.

### SUMMARY

Two groups of antibiotics, the polymyxins and the polyenes, owe their antimicrobial activity to their ability to bind to and disrupt microbial cell membranes. The polymyxins bind to acid phospholipids in gram-negative bacteria, whereas, the polyenes attach to sterols in membranes of fungi and mycoplasma. These drugs also bind to cell membranes of vertebrates and may not only owe their toxicity to this effect, but also may be largely inactivated at membrane-binding sites.

The aminoglycoside antibiotics, neomycin, streptomycin, kanamycin and gentamicin are inactivated when incubated with tissue homogenates particularly kidney and liver. They appear to be bound in relation to the number of free amino groups present in the molecule, and in relation to their inherent toxicity. Binding is most marked with the most highly toxic member - neomycin - and least with streptomycin, which is also least toxic. Kanamycin and gentamicin appear to be intermediate in both respects. All are highly basic drugs. Examination of their structures reveals neomycin to have 6, kanamycin 4 and gentamicin 3 free amino groups. The least toxic of the series, streptomycin, has 2 guanido groups. It is reasonable to expect that although these drugs penetrate cells poorly, breakdown products of cells would be liberated in pus and tend to bind and inactivate these drugs.

Binding to Cell Membrane. The polymyxin antibiotics (polymyxin B and colistin) exert their antibacterial effect by binding to acid phospholipids within the cell wall and membranes of gram-negative bacteria, (Newton, 1956). Similarly the polyene antibiotics such as

amphotericin B and nystatin bind to sterol containing membranes of fungi (Lampen et al., 1956). It is therefore, not surprising that these drugs have been found to bind to mammalian cell membranes and probably exert part of their toxic effect by this mechanism.

Polymyxin B and colistin were shown by Kunin (1970) to lose antibacterial activity when incubated with whole cells or homogenates of a wide variety of tissues. This was demonstrated to be due to binding to phospholipids in chloroform extracts of tissue (Kunin and Bugg, 1971). Further studies by Kunin and Bugg (1971) and Craig and Kunin (1973) demonstrated that these compounds when given intramuscularly to rabbits accumulate in high concentration in all tissues in two forms. One is a loosely associated tissue form which is extractable in aqueous solution and continues to exhibit antimicrobial activity; the other is a tightly bound form released only by mild acid hydrolysis of chloroform extracts of tissue.

Continuous administration of the drugs does not result in accumulation in serum, but is associated with very high and persistent concentrations in the tissues. Toxicity (renal failure and death) is observed once the tissues become saturated with drug. Release of tissue bound drug is very slow and not complete even at 5 days after the last dose is given. Polymyxin accumulates both as loose and tightly associated drug, but colistin accumulates mainly in the tightly bound form. The peculiar effect of colistin may be due to the fact that it is prepared as methane-sulfonate derivatives rather than as pure colistin. Methane sulfonation of colistin is used to reduce toxicity by covering several of the free amino groups of the drug. It also appears to decrease antibacterial activity and membrane binding as well. Once injected into the body the methane sulfonated compound is partly excreted unchanged (accounting for its greater renal clearance than polymyxin B) and hydrolyzed into more lightly substituted and free colistin. Colistin persists mainly in the tightly form in tissues, presumably because the methane-sulfonate derivative is excreted and does not remain behind.

Membrane binding of the polymyxin antibiotics appears to account for the cumulative toxicity of these drugs and also may explain why they are much less effective in vivo than in vitro. They appear to work well in the urine and on exposed surfaces, but have been disappointing in the treatment of systemic gram-negative infection. This may be due to inactivation in vivo by necrotic tissues and pus. Bryant and Hammond (1974) have recently shown that one milliliter of purulent sediment will bind and inactivate 1500 micrograms of polymyxin B or colistin sulfate.

Amphotericin B also binds to cell membranes. Butler and Cotlove (1971) demonstrated that binding of amphotericin B by human erythro-

cytes results in potassium leakage. This effect is abolished in the presence of serum. They postulate that sterols present in serum bind the drug and thus, exert a protective effect. Erythrocytes from patients treated intravenously with amphotericin B show no direct evidence of increased permeability to potassium during incubation in vitro and have normal fragility. It is well known however, that one of the major nephrotoxic effects of amphotericin B is renal potassium loss. It seems reasonable to suggest that the renal tubular cell exposed to amphotericin B in newly formed urine is not protected by serum and therefore, renal potassium loss occurs. Another explanation of specific nephrotoxicity of amphotericin B has been offered by Weissman et al., (1966). His work suggests that renal lysosomal membranes are relatively rich in cholesterol as compared to hepatic lysosomes and, therefore, more sensitive to the action of the drug.

Tetracyclines bind to areas of new bone formation are concentrated by some tumors, and accumulate in areas of inflammation such as in acute myocardial infarcts. They also have been shown, by fluorescence studies, to bind to mitochondrial membranes (Du Buy and Showacre, 1961). In recent studies conducted in our laboratory (Knornguth and Kunin, in press), both tetracycline and minocycline were shown to bind to membranes of human erythrocytes. The effect is diminished in the presence of serum. Minocycline, binds more extensively than tetracycline. The mechanism is unknown as yet, but tetracyclines have been reported to bind to a variety of metalloproteins, such as catalase, NADH-cytochrome oxidoreductase and pancreatic lipase. This may be due to their metal chelating properties.

Binding to Nonsoluble Intracellular Substances. Aminoglycoside antibiotics are inactivated when incubated with homogenates of normal tissues (Kunin, 1970). The effect appears to be best explained by nonspecific electrostatic binding to insoluble negatively charged intracellular substances. The effect is not temperature dependent and much of the drug can be released by high concentrations of protamine sulfate, heparin and electrolyte solutions. Acetone extracted tissue, free of lipids, binds the aminoglycosides indicating that the mechanism of their inactivation is quite distinct from that demonstrated with polymyxins. Binding to tissue homogenates is greatest with neomycin followed by kanamycin, gentamicin and streptomycin. This correlates well with the number of free amino groups and the relative toxicity of the drugs. For example, neomycin has 6, kanamycin has 4, and gentamicin has 3 free amino groups while streptomycin has only 2 guanido groups.

Binding of aminoglycoside antibiotics by tissues would ordinarily be of little interest since these drugs poorly enter cells and therefore would not be subject to much inactivation. Bryant and Hammond

(1974), however, have shown that 1 milliliter of pus will inactivate 700 micrograms of gentamicin. Presumably necrotic tissue will do the same and interfere with local activity of the drug. The effect is rather nonspecific since gentamicin and other basic antibiotics are absorbed and inactivated by feces (Wagman *et al.*, 1974) and even by the mycelium of fungi which produce these drugs or other antibiotics (Reiblein *et al.*, 1973). One wonders how, neomycin can be effective in reducing the bowel flora if it is inactivated by feces. Perhaps this is because relatively enormous quantities are given.

*Pseudomonas* is specifically protected from the action of gentamicin and other aminoglycoside antibiotics by  $\text{Ca}^{++}$  and  $\text{Mg}^{++}$  in the medium (Zimelis and Jackson, 1973). The drug is not bound or inactivated by these divalent cations, but the organism is protected. It is possible that  $\text{Ca}^{++}$  or  $\text{Mg}^{++}$  plays a permissive role in binding of these drugs to tissue sites.

Binding to Intracellular Parasites. Erythrocytes infected with malaria parasites exhibit a remarkable capacity for accumulating chloroquine and other structurally related drugs. These drugs rapidly enter uninfected erythrocytes, but the process is markedly increased in parasitized cells (Fitch *et al.*, 1974). There appears to be a specific receptor(s) on the parasite for the drug. In addition, accumulation is further enhanced in the presence of pyruvate, lactate, glucose or glycerol suggesting an active transport process.

#### REFERENCES

1. Bryant, R.E., and Hammond, D. Interaction of purulent material with antibiotics used to treat *Pseudomonas* infections. *Antimicrob. Agents Chemother.* 6:702-707, 1974.
2. Butler, W.T., and Cotlove, E. Increased permeability of human erythrocytes induced by amphotericin B. *J. Infect. Dis.* 123: No. 4, 341-350, 1971.
3. Craig, W.A., and Kunin, C.M. Dynamics of binding and release of the polymyxin antibiotics by tissues. *J. Pharm. Exp. Ther.* 184: 757-766, 1973.
4. DuBuy, H.G., and Showacre. Selective localization of tetracycline in mitochondria of living cells. *Science* 133:196-197, 1961.
5. Kornguth, M.L., and Kunin, C.M. Binding of antibiotics to human intracellular erythrocyte proteins: hemoglobin and carbonic anhydrase. In press.
6. Kunin, C.M. Binding of antibiotics to tissue homogenates. *J. Infect. Dis.* 121:55-64, 1970.