Histological Study Of The Effects Of Aminoglycoside , Cephalosporin And The Combination Of Both On The Kidneys Of Albino Rat

THESIS
SUBMITTED FOR PARTIAL FULFILMENT OF THE M.D. DEGREE IN "HISTOLOGY"

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TO.....

MY MOTHER

AND THE SOLE OF MY FATHER

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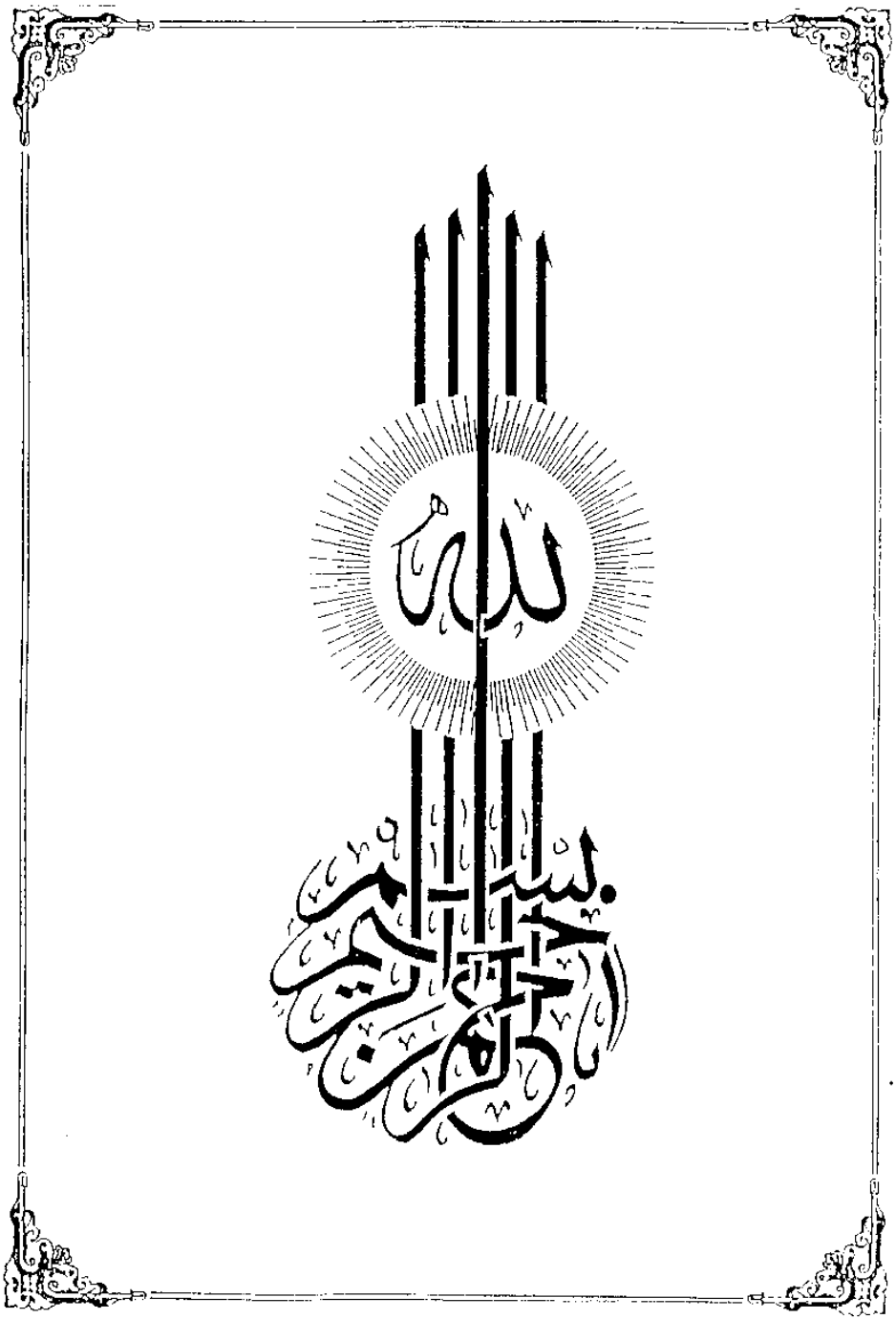

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Abbreviations And Glossary

Gent 5 days ttt gr.	Gentamicin 5 days treated group.
Gent 10 days ttt gr.	Gentamicin 10 days treated group.
Gent 15 days ttt gr.	Gentamicin 15 days treated group.
Ceph ttt gr.	cephradine treated group.
Combined ttt gr.	Gentamicin- Cephradine combined treated group.
B.M.	basement membrane.
P.C.Ts.	proximal convoluted tubules.
D.C.Ts.	distal convoluted tubules.
GBM	glomerular basement membrane.
L/M	light microscopy
E/M	electron microscopy.
+ve	positive.
-ve	negative.
P	probability.
BUN	blood urea nitrogen.

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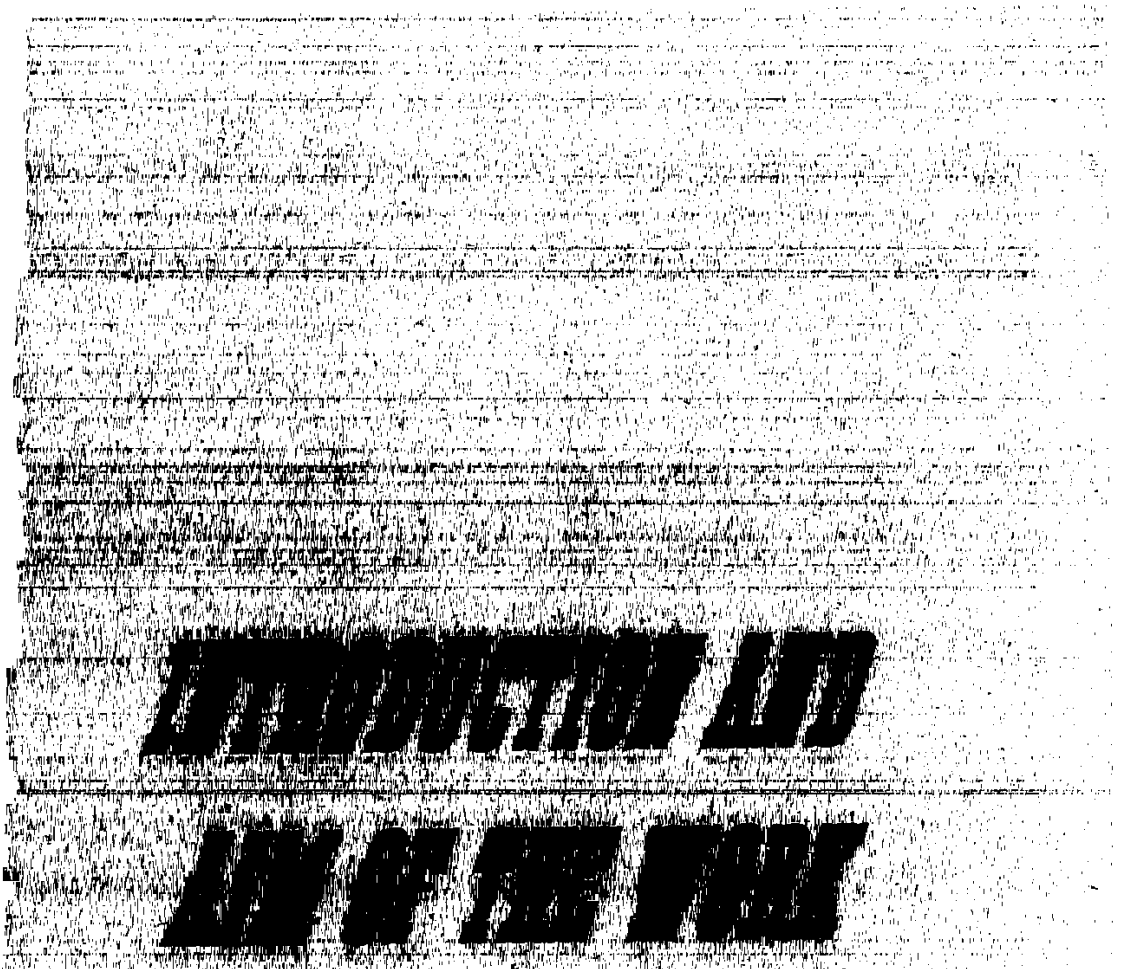

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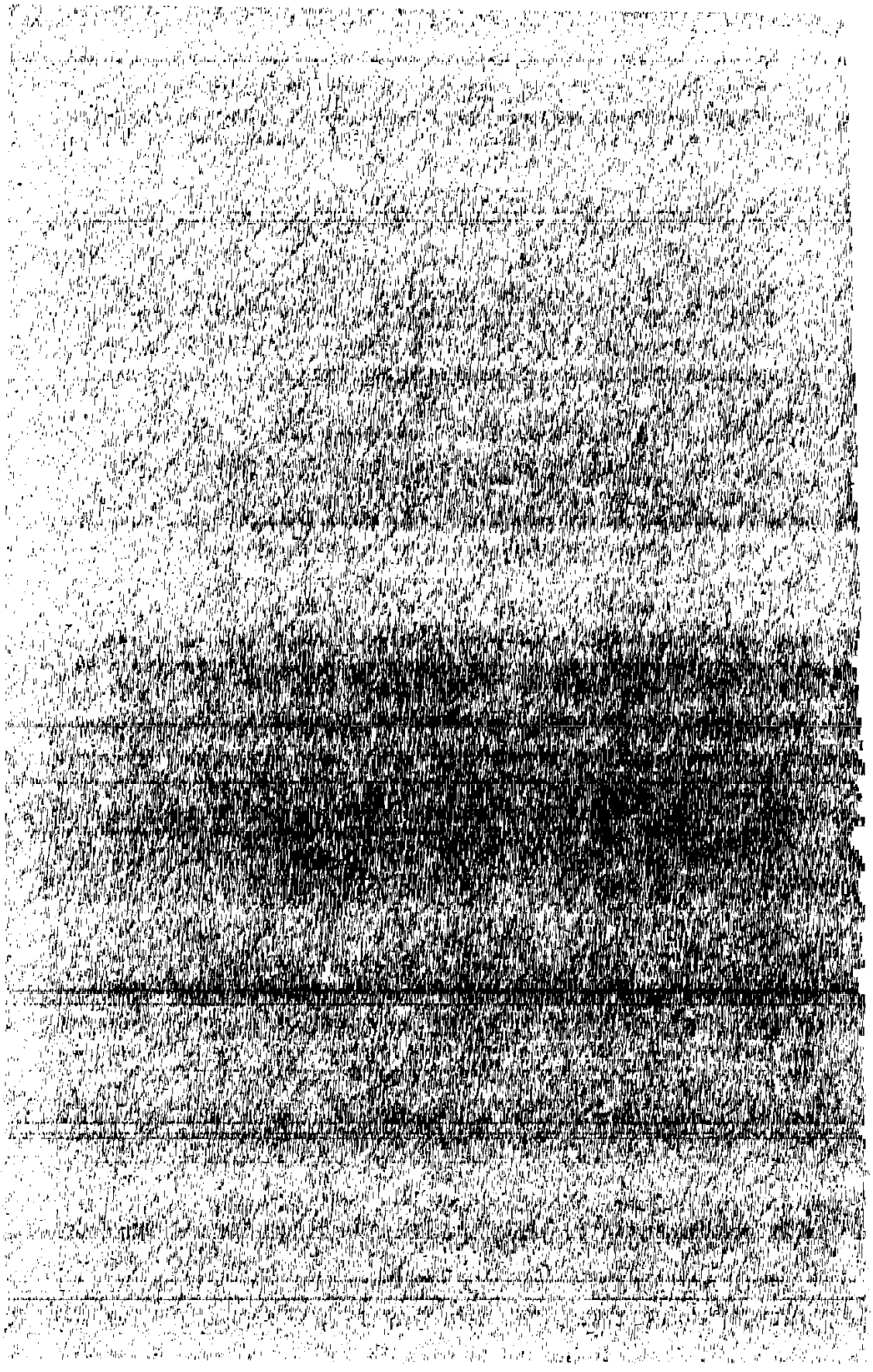

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Introduction & Aim Of The Work

Nowadays, the incidence of renal troubles is greatly increased due to the physician abuse of antibiotics. Based on the fact that the kidneys are the major route of drug excretion, it is not surprising that nephrotoxicity is relatively frequent. The most important group of drugs producing tubular damage, are the antibacterials. (Davis, 1986)

These accused antibiotics like the aminoglycosides, are widely used in the clinical field . It is used primarily by hospitalized patients in the treatment of sepsis of unknown origin and serious gram-negative infections. However its clinical use is limited by its potential nephrotoxicity. As approximately 8 to 26% of patients who receive an aminoglycoside for more than several days will develop mild renal impairment that is almost always reversible (Gilman, Rall, Nies and Taylor 1991).

Cephalosporins have been implicated as potentially nephrotoxic agents, although they are not nearly as toxic to the kidney as are the aminoglycosides. (Barza, 1978)

cephalosporins are bactericidal and they act by inhibiting synthesis of the bacterial cell wall. They are active against a wide range of gram-positive and gram-negative bacteria, including pencillinase-producing staphylococci, but not against enterococci (Gilman, et al. 1991).

There is a good evidence that the concurrent administration of cephalosporin and aminoglycoside causes nephrtoxicity synergistically. (Wade, Petty, Conard, Smith, Lipsky, Ellner and Lietman, 1978)

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Aim of work :-

The present investigation is aiming to study the non warranted effects of aminoglycoside, cephalosporin and to reevaluate the effect of the combination of both drugs on the structure of the kidney of albino rats which is still a matter of controversy.

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REVIEW OF LITERATURE

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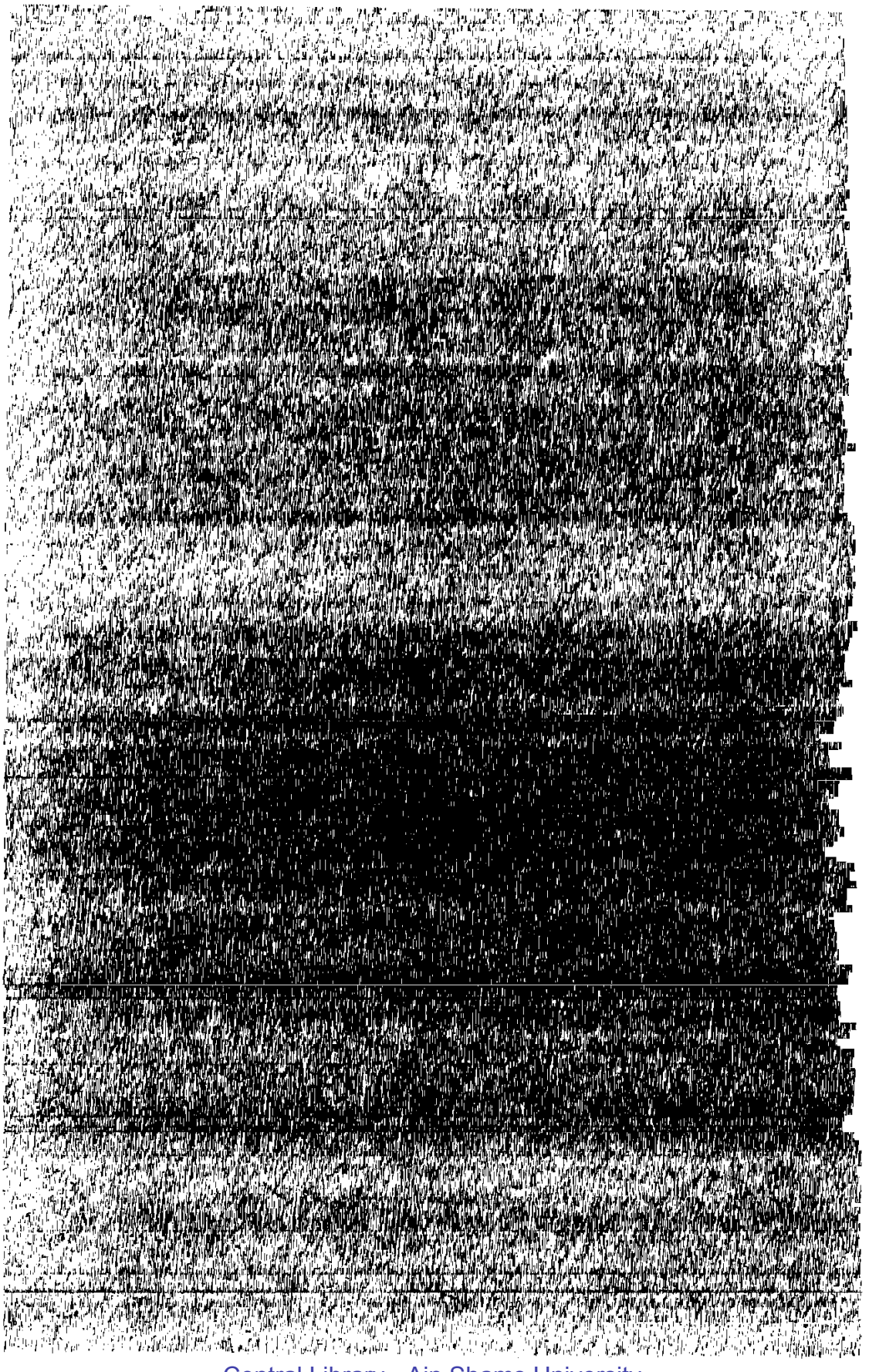

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Review of literature

Pharmacological basis of antibiotics:

I. Aminoglycosides:

The aminoglycoside antibiotics– gentamicin, tobramycin, amikacin, netilmicin, kanamicin, streptomycin and neomycin– contain aminosugars linked to an aminocyclitol ring by glycosidic bonds. They are polycations, and their polarity is in part responsible for pharmacokinetic properties shared by all members of this group. For example, non is adequately absorbed after oral administration, inadequate concentrations are found in cerebrospinal fluid, and all are excreted relatively rapidly by the normal kidney.

The aminoglycosides are used primarily to treat infections caused by aerobic gram-negative bacteria; they act to interfere with protein synthesis in susceptible microorganisms. Although most inhibitors of microbial protein synthesis are bacteriostatic, the aminoglycosides are bactericidal. Mutations affecting proteins in the bacterial ribosome, the target for these drugs, can confer marked resistance to their action. Resistance can also result from the acquisition of plasmids that contain genes that incode aminoglycoside-metabolizing enzymes. Bacteria that acquire resistance to one aminoglycoside may exhibit resistance to others.

Serious toxicity is a major limitation to the usefulness of the aminoglycosides, and the same spectrum of toxicity is shared by all members of the group. Most notable are ototoxicity, which can involve both the auditory and vestibular functions of the eighth cranial nerve, and nephrotoxicity.

Gentamicin is a broad-spectrum antibiotic derived from

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species of the actinomycete Micromonospora. Gentamicin has a broader spectrum of activity than kanamycin and is currently widely used. In contrast to the other aminoglycosides, amikacin and netilmicin are semisynthetic products.

The aminoglycosides are highly polar cations; they are thus poorly absorbed from the gastrointestinal tract. The drugs are eliminated quantitatively in the faeces. They are absorbed rapidly from intramuscular sites of injection. Peak concentrations in plasma occur after 30-90 minutes . Because of their polar nature, the aminoglycosides are largely excluded from most cells. High concentrations are found in the renal cortex and in the endolymph and perilymph of inner ear; this may contribute to the nephrotoxicity and ototoxicity caused by these drugs. Concentrations in bile approach 30% of those found in plasma as a result of active hepatic secretion, but this represents a very minor excretory route for the aminoglycosides. Penetration into respiratory secretions is poor, diffusion into pleural and synovial fluid is relatively slow , but concentrations that approximate those in the plasma may be achieved after repeated administration.

The concentration of aminoglycoside in plasma produced by the initial or loading dose is dependent only on the volume of distribution of the drug. Since the elimination of aminoglycosides is almost entirely dependent on the kidney, a linear relationship exists between the concentration of creatinine in plasma and the half-life of all aminoglycosides in patients with moderately compromised renal function. In anephric patients, the half-life varies from 20 to 40 times that determined in normal individuals. Since the incidence of nephrotoxicity and ototoxicity is related to the concentration to which an aminoglycoside accumulates, it is critical to reduce the maintenance dosage of these drugs in patients with impaired renal function. This must be done with precision, since the concentration in plasma that is associated with toxicity is not much greater than that required for treatment of many bacterial infections.

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II. Cephalosporins:

cephalosporins are semisynthetic antibiotics driven from cephalosporin C, a natural antibiotic produced by mold cephalosporin acremorium.

Cephalosporin C contains a side chain at position 7, derived from D aminoadipic acid which is not condensed with a dihydrothiazine beta lactam ring at position 3. Chemical modification at position 3 and 7 has resulted in a series of antibiotics with different characteristics. They are very active against gram positive and gram negative bacteria.

Classification of cephalosporins, by generations is based on general features of antimicrobial activity. The first generation cephalosporins have good activity against gram-positive bacteria and relatively modest activity against gram-negative microorganism. The second generation cephalosporins have some what increased activity against gram-negative microorganism but are much less active than the third- generation agents. Third generation cephalosporins are generally less active than first generation agents against gram-positive cocci, but they are much more active against Enterobacteriaceae, including beta-lactamase-producing strains.

Cephalosporins are primarily excreted by the kidney. Several cephalosporins penetrate into C.S.F. in sufficient concentration to be useful for the treatment of meningitis. Also they cross the placenta and they are present in high concentration in synovial fluid and pericardial fluid. Concentrations in bile are usually high. Cephalosporins, either with or without aminoglycosides, have been considered to be the drug of choice for serious infections caused by

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