this technique may help us to obtain pure water from sea water and if this can be achieved, it will be of the greatest consequence for the welfare of humanity in general.

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Some Aspects of Drug Resistance

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THE exact mechanism of drug action is, as yet only imperfectly understood. The majority of drugs used in the treatment of infections exert their effect primarily by inhibiting the formation or utilisation of certain metabolites essential for the multiplication of the parasite. With such cases, it frequently happens that on repeated exposure to a drug, especially at sublethal concentrations, micro-organisms become resistant to it. In recent years considerable work has been done to elucidate the mechanism by which micro-organism may become drug resistant. Knowledge gained on the mode of acquirement of drug resistance has to some extent enabled the adoption of methods to deal with drug-resistant microbes.

Postulated mechanisms by which drug resistance has been explained are outlined below :

Prevention of drug from reacting site of action :—

A number of organisms develop resistance to toxic agents by becoming impermeable to them. Trypanosomes become resistant to the inhibitory action of basic dyes presumably by modification in cell-membrane ; resistant trypanosomes are no longer stained by basic dyes. Quite often micro-organisms are known to develop capsules which protect them from lethal agents.

Inactivation of drug :—

Certain organisms acquire resistance to drugs by developing a capacity to destroy or detoxicate them. A few penicillin-resistant organisms are so by virtue of the fact that they elaborate an enzyme penicillinase which destroys it. The tubercle bacillus is resistant to crystal violet because it possesses a mechanism to inactivate it. Pyrithiamine is a powerful analogue antagonist of thiamine. Instances are known where a microbial strain could become resistant to pyrithiamine by developing a capacity to split pyrithiamine into two non-toxic parts. One of the postulated mechanisms by which micro-organisms become resistant to sulpha drugs is by acetylating them ;

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the acetyl derivatives of these drugs are comparatively less active.

Production of large amounts of competing metabolite or drug antagonist :

The theory of metabolite—analogue antagonism is well-known. Several toxic agents and drugs could be related structurally to certain essential metabolites. Sulpha drugs exert their bacteriostatic effect by competing with *p*-aminobenzoic acid which either acts as a substrate for the formation of an essential nutrient or mediates in the biosynthesis or other nutritites. Some, but not all, micro-organisms acquire resistance to sulphonamides by synthesising large amounts of *p*-aminobenzoic acid. An interesting instance is that of a *Neurospora* strain which on acclimatization to sulphonamides actually requires this drug for growth and is inhibited by *p*-aminobenzoic acid. In a similar manner, acclimatization to streptomycin or aminopterin has produced strains requiring these for growth.

Development of non-sensitive alternate pathway(s) :

Penicillin is known to inhibit the transfer from the growth media of certain amino acids through the cell membrane. Some organisms acquire resistance by developing the capacity to synthesise these amino acids within the cell. A strain of *Staphylococcus aureus* made resistant to sulphonamides in presence of glucose is no longer resistant to these drugs if glucose is replaced by pyruvate, suggesting that sulpha drugs block some step in the normal metabolism of glucose through pyruvate and that the resistant organism develops an alternate metabolic process which by-passes pyruvate. In the streptomycin-resistant strain of *Escherichia coli* the oxidation processes apparently do not involve the Krebs' cycle. Having dispensed with this pathway it is presumed that they have developed some alternative, but just what this may consist of is at present obscure.

Increased production of an inhibited enzyme :

A possible means by which some micro-organisms may require drug resistance is by increased synthesis of the inhibited enzyme so that there is enough enzyme to unite with the inhibitor and for action with the appropriate metabolite. Bacteria growth at pH too acid for optimum activity of urease and catalase produce more of these enzymes and thus compensate for lessened activity.

Cross-resistance :

Sometimes when micro-organisms are acclimatized to one drug they become resistant to other drugs as well. This phenomenon is known as cross-resistance. Cross-resistance is commonly encountered with drugs belonging to the same group, like the sulpha drugs, as their point of action is the same and the resistant organism has developed a mechanism to overcome this impediment. Cross-resistance to aureomycin is observed with bacteria made resistant to terramycin undoubtedly because these antibiotics have a similar structure and hence mode of action. However the mechanism or mechanisms developed in acquiring resistance may so alter the metabolic processes of the micro-organism that it may show cross-resistance with drugs differing considerably in their point of action.

Slow-absorbing drugs :

Drug resistance presents a serious challenge to chemotherapy. Indiscriminate use of antibiotics could render them ineffective in major infections which are otherwise known to respond to them. This has been evident, particularly with penicillin. To prevent or ganisms becoming drug-resistant it is essential that high concentrations of the

drug be used and it be present at the site of action over a long period of time. It is with this latter consideration in mind that the procaine salt of penicillin and penicillin oil emulsion have been developed; these are absorbed slowly into the system thus enabling the maintenance of a high concentration in the body over prolonged periods. Treatment of intestinal infections is best achieved with certain slow absorbing sulpha drugs such as sulphaguanidine.

Combination therapy:

Adequate therapy becomes important especially in infections comparatively refractory such as tuberculosis, which require a long continued course of treatment.

The rare acquirement of resistance by an organism to two or more structurally unrelated drugs when used simultaneously has made possible the application of combination therapy. In the treatment of tuberculosis use of streptomycin along with *p*-aminosalicyic acid and more recently isonicotinic acid hydrazide is advocated. It has been found in our laboratory that certain anionic surface active compounds potentiate the bacteriostatic properties of sulpha drugs and are besides effective against the acquirement of drug resistance. Use of a combination of sulpha drugs is now an established practice (*e.g.* sulphatrial, tricombisul, etc.). Together these drugs are more effective than either of them alone. Quite often, though not always, a combination of antibiotics such as penicillin and bacitracin not only result in enhanced activity; but also greatly minimises chances of drug resistance.

Treatment of resistant infections presents a poser to the clinician and pharmaceutical chemist. Once resistance to an antimicrobial agent is established it is logical to use a different type of agent for which no cross-resistance exists. A limited success has been attained in resensitising resistant organisms. For instance, penicillin-resistant staphylococcus have been made susceptible to the drug by growing in association with a sensitive streptococcus or addition of cell extracts to the growth medium. One could thus hope to succeed in altering organisms to suit drugs to which they are resistant.