MEDICAL PRACTICE

Occasional Survey

Perspectives in Chemotherapy*

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Sir Thomas Linacre intended that the person appointed to his lectureship should devote his time to an exposition of the works of Galen. As a young man Galen was responsible for seeing that the gladiators in his native Pergamum were suitably fit for battle and death in the arena. Consequently he was deeply concerned with the maintenance of health and fitness. He wrote a treatise on hygiene and laid down what can still be taken as acceptable rules "in order that one may be tried as little as possible by disease and grow old agreeably," but he would lose the sympathy of a modern class of students by adding that these rules were not applicable to the poor, "who cannot change their condition." Some of the reasons given for his rules also sound somewhat odd today, thus "to give a boy wine can do him no good—as the humoral type of children is humid and this deviation is exacerbated by alcohol." Galen was thus concerned with the avoidance of disease and we can regard him as one of the first epidemiologists, and this in turn provides us with an excuse to discuss chemotherapy without going too far outside our terms of reference. In fact, three previous Linacre lecturers have discussed the progress of chemotherapy—Sir Walter Langdon-Brown in 1941, Sir Alexander Fleming in 1946, and Sir Howard Florey in 1954.

I, my colleagues, and our research students have over the past 25 to 30 years investigated the mode of action of antibiotics and antibacterial drugs. After such a period it seems fitting that we should look back on what we have tried to do, to see to what extent we have succeeded and to ask what is nowadays the all important question What use has it all been? We began these investigations in the middle of the second world war when penicillin first became available for laboratory study. The first preparation that we had to investigate was an orange amorphous powder of potency 60 units per mg compared with 1,900 units per mg for today's colourless crystalline material, and our first studies were prompted mainly by curiosity. Here we had a substance which was intensely toxic to certain bacteria but was without obvious effect on man. What was the basis of this selective toxicity? The material became available at a time when Sir Frederick Gowland Hopkins in Cambridge, Professor Kluyver in Holland, and biochemists and microbiologists all over the world were discovering that the fundamental metabolic and biosynthetic systems were essentially the same for all cells and were developing the idea of the uniformity of the biochemistry of life. Yet in penicillin we had a substance that indicated not only must there be essential differences between microbe and man but that Ehrlich was right when he postulated that it should be possible to find targets in parasitic protoplasm that could be attacked differentially by chemical means.

After the war, when the American pharmaceutical firms began their great screening programmes, other antibiotics were discovered and it became clear that different antibiotics worked in different ways and that we had a whole range of new selective inhibitors arrayed before us. These drugs were available for use long before we knew how they worked; biochemistry and cell biology had not then developed sufficiently for the underlying mechanisms to be understood. In fact, the antibiotics have contributed substantially to the development of this understanding. As time went by many other laboratories and many other workers became interested in the mode of action of these selective antibiotics and today a vast literature has grown up around the subject.

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Mode of Action of Antibiotics

We can set out the objectives of work in this field over the past 20 years as follows.

(1) To define the component or reaction attacked by the drug in the sensitive cell.
(2) To explain the selective nature of this action of the drug.
(3) To define the molecular basis of the reaction between the drug and its receptor in the cell.
(4) To improve the selective efficiency of the drug by suitable chemical modification.
(5) To develop new drugs on a rational basis as the result of information obtained in the investigation of the above objectives.

The first three objectives give us an understanding of how the drug works. During the past 10 years we have obtained answers to the first two objectives for a wide range of antibiotics and have gone a long way to providing answers to the third—though it is probably true to say that we cannot as yet give final answers for any one antibiotic. The question is whether understanding is necessary for the proper use of a drug. If we had understood how penicillin worked and how resistance to it arose before it was put into clinical use we should have prevented many mistakes and penicillin would be a more effective drug today than it has become in practice. But many thousands of lives that have been saved by penicillin would presumably have been lost; perhaps it was fortunate in one way that our experience was gained at the expense of a relatively harmless drug. Certainly if we had waited until we fully understood the action of thalidomide before it was used, several thousand personal tragedies would have been averted. The knowledge gained in the investigation of the first three objectives serves as the basis for development and exploitation under the last two objectives. Ehrlich's ideas were based on the belief that the efficiency of partially selective drugs could be improved by suitable chemical modification, but he did not have the experience now at our disposal as a guide to what constituted "suitable chemical modification," and I hope to illustrate this point below.

Bases of Selective Action

Possibly the most important knowledge we have gained from a study of antibiotics relates to the second objective—the targets that can be attacked in a parasitic cell so that selection can be achieved. Once such targets have been identified and the rules of chemical attack discovered in the investigation of the third objective, the way should be open for the production of selective drugs to order, and this is the main aim and drive behind present research in this field.

At a simple level we can set out three bases for selective attack designed to knock out one cell without effect on another. For the moment we shall concern ourselves with two unspecified cells A and B; though no one is going to get very excited about a drug which knocks out the host while allowing the parasite to go happily about its business. These three bases are: (*a*) the presence in cell A of a component essential to the continued existence or growth of that cell but which is missing in cell B; (*b*) the presence of an essential component in both cells but which is synthesized in cell A by a pathway different from that in cell B, so that the synthesis in one can be inhibited without effect on synthesis in the other; and (*c*) the presence in both cells of a component whose function is essential but whose properties in cell A differ from those of the homologous component in cell B.

Penicillin is an example of a drug acting in the first way. The bacterial cell possesses a rigid cell wall whose function is to protect the delicate cell membrane from osmotic damage in a hypotonic environment. One of the components of this cell wall, peptidoglycan, is unique to the bacterial cell and contains chemical structures not present in mammalian cells. Penicillin inhibits a step in the synthesis of peptidoglycan and so renders the bacterial cell vulnerable to osmotic damage and lysis while having no action on the host mammalian cell.[1] Drugs acting in this way, attacking a component unique to the sensitive cell, provide the best examples of selective toxicity.

The possibility of preventing the synthesis of an essential component in one cell by attacking a synthetic pathway specific to that cell has often been postulated as a basis for selective inhibition but has seldom been realised in practice. The sulphonamide drugs represent a special case of this nature. Sulphonamides act, as shown by my late colleague Professor D. D. Woods,[2] by inhibiting the synthesis of folic acid, which is a metabolite forming an essential part of the enzymic machinery of all cells. Folic acid is synthesized by a complex reaction involving the condensation of a pteridine with *p*-aminobenzoic acid; Woods pointed out the chemical similarity of the *p*-aminobenzoic acid and the sulphanilamide molecules and suggested that they compete for the surface of an enzyme involved in folic acid synthesis. Since folic acid is essential for all cells, however, why should this action in bacteria be selective? The first suggestion put forward was that since mammalian cells have lost the ability to synthesize folic acid and consequently must have it provided in the diet, where it is classed as a vitamin, they are not troubled by inhibition of its synthesis. But this clearly cannot be the answer; we are concerned with the disinfection of a host possessing bacteria growing in the blood stream. Sulphanilamide prevents the synthesis of folic acid in the bacteria but the blood of the host contains dietary folic acid, so why does not the inhibited bacterial cell make use of the host's supply of folic acid? If this were the case then the action of sulphonamide would be bypassed.

The answer was discovered by Hitchings,[3] who found that in general pathogenic bacteria are not able to take up folic acid from their environment while mammalian cells possess a specific transport mechanism carrying folic acid across the membrane into those cells. In the absence of such a transport mechanism bacteria are dependent on synthesis of folic acid and so can be knocked out by sulphonamide drugs. This is then a special case whereby an essential component is provided by two pathways—though one of those pathways is a transport mechanism and not a separate, different synthetic pathway.

Wood's demonstration of the chemical analogy between sulphanilamide and *p*-aminobenzoic acid led to a spate of syntheses of analogues of other cell components and metabolites, but with very few exceptions these have not proved to be selective drugs. This is partly because the mechanism of the selective action of sulphonamides was not understood and it was not realized that chemical analogy alone is not sufficient to produce an effective drug. Among the analogues that have proved useful are substances related to further modification of the folic acid structure. The first condensation product of pteridine and *p*-aminobenzoic acid is pteroic acid. Pteroic acid has to undergo reduction before it is finally effective as a component of the enzyme mechanisms; a two-stage reduction is involved—firstly, to dihydrofolic acid and then to tetrahydrofolic acid—and the enzyme involved in reduction, folic acid reductase, is common to all cells. Hitchings[4] discovered an effective inhibitor of folic acid reductase, and this was the analogue diaminobenzylpyrimidine. The interesting thing was that this inhibitor proved to be selective, being noticeably more effective against certain parasites and pathogenic bacteria than the mammalian hosts.

Hitchings[4] proceeded to investigate the selective nature of diaminobenzylpyrimidine by testing its inhibitory action against cell-free preparations of folic acid reductase isolated on the one hand from a bacterium, *Escherichia coli*, and on the other from rat liver cells. Fig. 1 shows that the concentration of diaminobenzylpyrimidine which will produce 50% inhibition of the bacterial enzyme is 44 times smaller that the amount of the analogue which will produce the same inhibition in the rat liver enzyme. Hitchings then prepared a series of derivatives of the basic structure, and results for three of these are set out in fig 1. It is shown that progressive substitution of methoxy groups for H in the benzyl moiety not only increases the effectiveness against the bacterial enzyme but has a most marked effect on the ratio of the sensitivities of the bacterial and mammalian enzymes. In the case of the trimethoxy derivative (trimethoprim) the bacterial enzyme is 52,000 times more sensitive than the mammalian

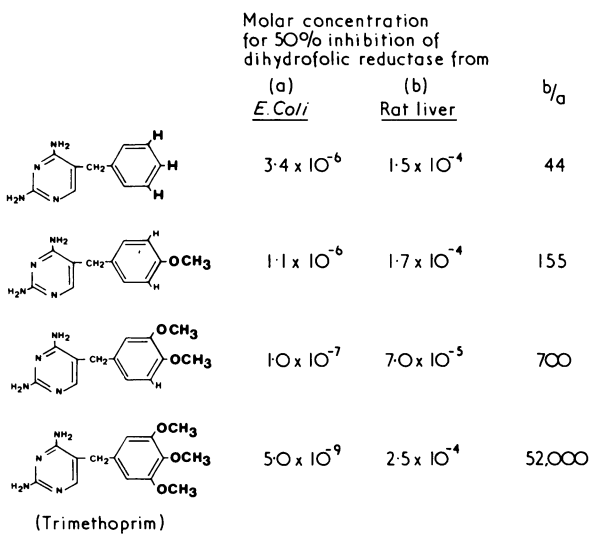

FIG. 1—Inhibitory effects of derivatives of diaminobenzylpyrimidine on folic acid reductase preparations from *Escherichia coli* and rat liver (Hitchings, 1969[1]).

enzyme. I quote this investigation because it illustrates two points—firstly, that chemical modification of a drug can greatly increase its effectiveness as an inhibitor, and, secondly, that homologous enzymes—that is, enzymes catalyzing the same reaction—in different cells may display widely different affinities for a drug.

In the case of folic acid reductase we have an example of a component whose function is essential for both bacterial and mammalian cells but whose properties in the two types of cell are sufficiently different to enable a chemical attack to be made that will differentiate between the activities in the two cells. Folic acid reductase is, in fact, an example of the third basis for selective action set out above—homologous components with different properties in the two cells. Present experience indicates this is probably the most common form of difference between cells which can be exploited by selectively toxic antibiotics. Thus both chloramphenicol and streptomycin inhibit protein synthesis in bacteria but not in mammalian cells since they react with components, the ribosomes, which have different compositions in the two types of cell.[1]

Fungal Infections

Having thus briefly summarized the aims and some of the results of research in antimicrobial chemotherapy, I shall spend the rest of this lecture discussing a modern instance where we hope to be able to exploit differences in properties of structures —namely, membranes—common to mammalian and fungal cells and to apply knowledge so far obtained to improve the efficiency and selectivity of drugs which are at present only partially effective as antifungal agents.

Fungal infections have not assumed great importance in the past since, though difficult to treat, they have not occurred with high frequency and have generally been more of a nuisance than a serious danger. It is common experience, however, that as we learn to combat one group of parasites others take their place and assume increased importance as pathogenic agents. Fungi are not sensitive to the antibiotics in common use against bacterial infection—penicillin, tetracycline, chloramphenicol, streptomycin—and so survive such antibiotic treatment. The matter becomes of importance when the defence mechanisms of the body are impaired and of dramatic importance in transplant surgery when the immune response is cut down by immunosuppressive drugs and bacterial infection is kept at bay by antibiotics. Under such conditions certain fungi are able to establish serious and possibly lethal infections, the so-called "opportunistic fungal infections."

The question is whether we can find or devise drugs to combat such fungal infections. There is a group of antibiotics, called the polyenes, which kill fungi. Polyenes have an interesting selectivity; they have no action on bacteria but are toxic to all eukaryotic cells, including those of man. Some polyenes, however, display a degree of selectivity between mammalian and fungal cells which makes it possible to use them under strictly controlled conditions for the treatment of fungal infections. Here we have a situation where if we can discover the mode of action of these antibiotics, find out the basis of their selective action, and determine the chemical nature of the toxic reaction—in other words, investigate objectives 1 to 3 set out above—it should be possible to design chemical modifications of the drugs which would improve their action and selectivity so that their use in mycotic infections would be safer and more effective.

Mode of Action of Polyene Antibiotics

Polyenes react with, and damage, the membranes of sensitive cells. I shall discuss their action on *Candida albicans*, one of the organisms commonly found in opportunistic infections. *C. albicans* is carried harmlessly by many people, but in conditions. where the defence mechanisms are impaired or not fully developed it can set up an infection such as thrush in children or candidiasis in adults and is one of the organisms producing post-transplant mycoses. The organism is dimorphic and exists in both yeast-like and mycelial forms, the mycelial form being the more common in infected tissues.

Electron micrographs of the cell, whether in mycelial or yeast form, show that the cytoplasm is contained within a typical cytoplasmic membrane lying beneath the cell wall. This membrane places an osmotic barrier between the inside and the outside of the cell. It is a lipoprotein structure and effectively encloses the cell contents within a lipid layer that controls the passage of substances in and out of the cell. The membrane is semipermeable and enables the cell to retain essential substances at concentrations above those in the environment—that is, at concentrations suitable for the rapid promotion of metabolic and biosynthetic processes—and also prevents the inward diffusion of many substances which would otherwise be harmful to the cell. It is necessary, of course, for the cell to take up a number of essential nutrients and metabolites which cannot normally diffuse through the lipid layer, and in the course of evolution cells have acquired active transport mechanisms for this purpose. In this discussion we shall be concerned only with the properties of the membrane as a permeability barrier preventing the outward diffusion of essential cell materials such as cations, amino-acids, sugars, etc. The properties of the membrane impose order on the contents of the cell, so that they are more than a simple mixture of chemicals. Impairment of the function of the membrane can have drastic effects on the continued existence of the cell, and alteration of membrane permeability may produce a degree of mixing with the environment that prevents further growth of the cells.

Polyene antibiotics form a range of related substances; they are all large cyclic lactones with one segment consisting of all *trans*-, conjugated double bonds (poly-enes) and another segment with many hydroxyl groups. All the polyenes damage eukaryotic cell membranes, but Lampen[5] and his colleagues found that the smaller molecules, such as filipin (see fig. 3) with molecular weight 660 and containing 35 carbon atoms per molecule, produce more damage than larger ones, such as amphotericin (see fig. 2) with molecular weight 960 and containing 46 carbon atoms to the molecule. Cells treated with filipin were found to leak many of the small molecular weight substances (up to a molecular weight of 160-180) normally retained within the cell; cells treated with amphotericin were found to leak only potassuim

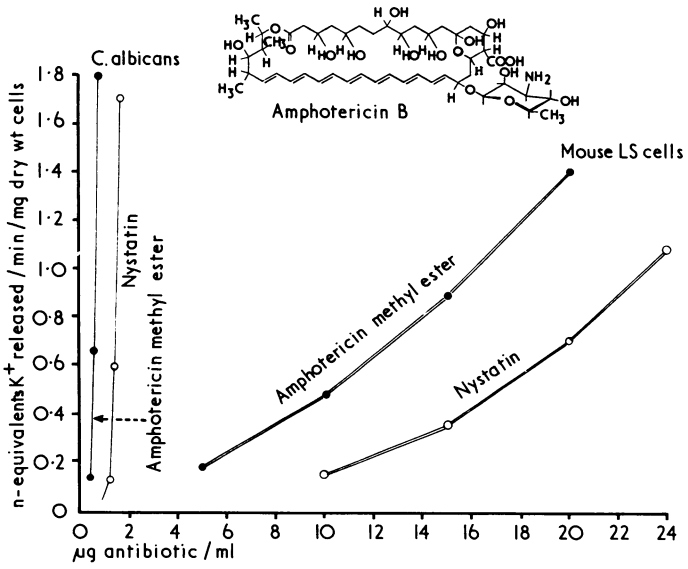

FIG. 2—Effect of amphotericin and nystatin on release of potassium ions from *Candida albicans* and mouse fibroblast suspensions (from Gale[6]).

and phosphate ions. Filipin is generally toxic whereas amphotericin is sufficiently selective to be of use in the treatment of mycotic infections.

Treatment with any of the polyenes results in the loss of potassium ions from sensitive cells, and this can be used for studying the reaction of the antibiotic with the cell membranes.[6] Potassium ions are essential for protein synthesis and are normally retained at a high concentration within the cell, so that if they leak out into the medium their concentration falls to a point where protein synthesis, and hence growth, stops.

Selective Action of Polyene Antibiotics

The concentration of amphotericin methyl ester[7] required to release potassium from *C. albicans* is compared in fig. 2 with that required to produce a similar release from mammalian cells—that is, mouse fibroblast cells grown in suspension culture.[6] In the experimental system adopted the concentration of amphotericin required to release potassium at a given rate is some 20 times greater than that required for a similar result with *C. albicans*, so that the drug has this degree of selectivity for the fungal cells. Fig. 2 also shows results for nystatin, a polyene of structure and size similar to that of amphototericin. On the other hand, fig. 3 gives a similar comparison for filipin and shows that in this case the yeast cells are less sensitive than the mouse cells, and it is clear that filipin could not be used for the treatment of candidiasis in mice.

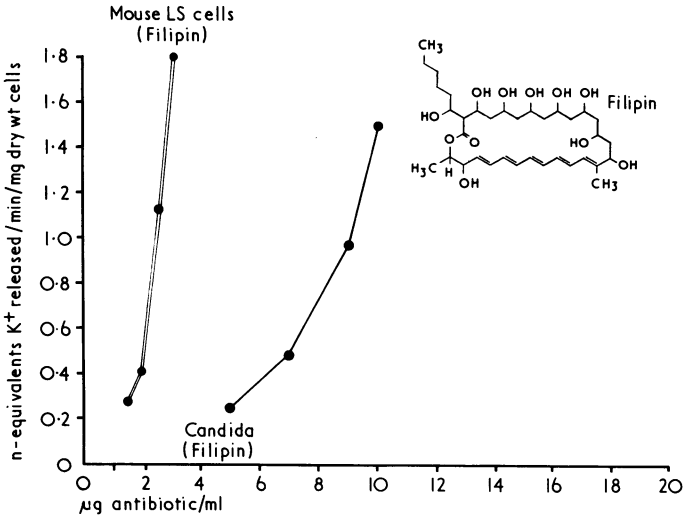

FIG. 3—Effect of filipin on release of potassium ions from *Candida albicans* and mouse fibroblast suspensions.

What is the basis of this selectivity and how do the drugs work to make membranes permeable to potassium?

Polyenes undergo hydrophobic interaction with sterols to form complexes, and sterols are essential structural components of both fungal and mammalian cell membranes. Bacterial membranes do not contain sterol and bacteria are completely insensitive to polyenes. Certain types of mycoplasma, the *Acholeplasmas*, can grow either in the presence or in the absence of sterol. When grown in the absence of sterol they are insensitive to polyenes; when grown in the presence of sterol the organisms then become sensitive to the action of polyenes in general.[8] It appears, therefore, that the reaction which occurs between sterols and polyenes could be the basis of a change in sterol-containing membranes which results in alteration of their permeability. The main sterol in mammalian cell membranes is cholesterol (fig. 4) while that in fungal and yeast membranes is ergosterol, and our present preliminary studies indicate that amphotericin has a higher affinity for ergosterol than cholesterol,[6] while filipin has a higher affinity for cholesterol than ergosterol. The selective effects are thus based on the relative affinities of the antibiotics for the main sterols. The possibility of using amphotericin as a drug in the treatment of mycotic infections in man therefore rests on the greater affinity of that drug for the fungal ergosterol than for the mammalian cholesterol.

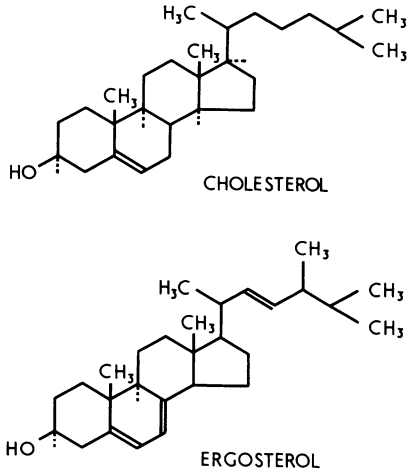

FIG. 4—Structures of cholesterol and ergosterol.

Molecular Basis of Polyene Action

The conventional formulae of the polyenes, as shown in fig. 2 and 3, show that they have a hydrophobic polyene section and a hydrophilic hydroxylated section, and we appreciate the full significance of these sections when we construct molecular models based on *x*-ray diffraction studies recently made by Professor Schaffner[9] and his colleagues at Rutgers Unversity (see fig. 5). Then we find that the molecule is not an open ring but has a finger-like structure. The polyene portion is straight and rigid; the hydroxylated portion lies directly alongside,

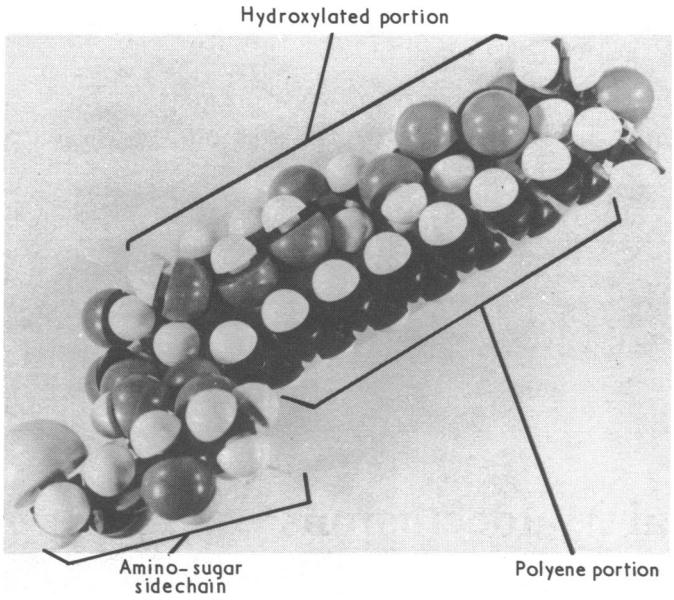

FIG. 5—Molecular model of amphotericin (Schaffner[9]).

close-packed to the polyene section, so that the molecule has the form of a rod with the hydroxyl groups orientated in one sector down one side. The molecule as a whole presents a hydrophilic face and a hydrophobic face and would be expected to position itself in the interface between hydrophobic and hydrophilic media such as at the surface of a membrane. Sterol molecules are strongly hydrophobic and could interact in a number of ways with the hydrophobic portions of a polyene molecule, and it may well be that more than one sterol molecule can complex with one polyene molecule.

A diagrammatic representation of half of a biological membrane is given in fig. 6. The lipid consists mainly of phospholipids which will be orientated with their hydrophilic phosphate groups lying in the interface and their hydrocarbon chains orientated to form the hydrophobic core of the membrane. Eukaryotic membranes will also contain sterol molecules; these will orientate with the hydroxyl group in the interface. If polyene molecules are added they will at first tend to lie in the interface as described above. But the presence of a sterol molecule will give rise to the possibility of a hydrophobic interaction which would bring the polyene down into the surface of the membrane as shown in fig. 6. This would, however, be an unstable arrangement, since the hydrophilic part of the drug would now be in a hydrophobic environment. We should therefore expect other sterols or sterol-polyene complexes to come together to form a micelle with the hydrophilic segments of the drug molecules arranged in the centre, surrounded by hydrophobic molecules. There could be two consequences of such micelle formation; the bringing together of sterol molecules into the micelle might itself disorganize the membrane to an extent that it would no longer be an effective barrier to small molecule diffusion, or the micelle arrangement might (as shown in fig. 6) result in the formation of an aqueous pore through which small ions such as potassium could diffuse.

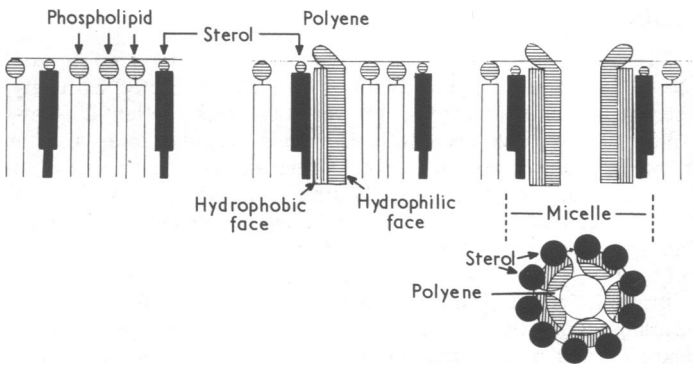

FIG. 6—Representation of possible interaction between amphotericin and sterols in half of a biological membrane.

The reality of such micelles has recently been shown by Verkleij *et al.*, who have grown acholeplasmas in the presence and in the absence of cholesterol, treated the cells with filipin, and then examined the resulting membranes under the electron microscope by the freeze-etch technique. The micrographs show the presence of aggregates 150-200 Å in diameter in the membranes of the acholeplasma grown in the presence of cholesterol and then treated with filipin, whereas no such aggregates can be seen in the controls grown in the absence of sterols. The degree of resolution of the image is not yet sufficient to show whether the aggregates have holes down the middle or not. Finkelstein and his colleagues,[11 12] using physical methods, have obtained results suggesting the formation of aqueous pores through artificial membranes treated with polyenes. They found, however, that the formation of such pores was increased when polyene was added to both sides of the artificial membrane. The electron micrographs produced by Verkleij *et al.*, seem to show that the aggregates in acholeplasma membrane treated with filipin occur on the outer surface only. The detailed structure of the natural aggregate thus has still to be resolved, but the molecular basis of the attack on membrane structure is becoming clear.

Prospect for Improvement

The key to polyene action lies in the hydrophobic interaction between the drug molecule and a sterol molecule, and the key to selectivity lies in a greater binding affinity between polyene and ergosterol interaction than between polyene and cholesterol. The affinity of the hydrophobic interaction depends on the closeness of fit of the hydrophobic surfaces of the two molecules. At the moment we have a series of polyene structures—of which amphotericin and filipin seem to be examples of extremes—and a series of sterol structures of different biological distribution. The important finding is that not only does the affinity of the drug molecule for a sterol differ with the structure of the sterol but that the order in which the sterols fall in this respect differs with different polyene structures. We can do little about the nature of the sterol in a natural membrane but it appears that by appropriate modification of the structure of the polyene molecule it should be possible to increase the affinity to a given sterol and so alter the selectivity of the drug.

The next step is to determine the precise nature of the interaction between polyene and sterol, to discover what part of the surface of the sterol molecule fits what part of the surface of the polyene molecule, and to show the way in which the differences between ergosterol and cholesterol affect the hydrophobic interaction. Once this information has been obtained it should not be beyond the wit of the chemist to introduce such modifications into, say, the amphotericin molecule that will increase its affinity for ergosterol and decrease that for cholesterol so that a drug more effective against fungi and more selective between fungus and man may be produced.

In this survey I have endeavoured to summarize what we have learned about the selective action of certain antimicrobial drugs and to suggest how we might apply our understanding to a modern problem. A quotation from Galen supplies a fitting conclusion: "I always teach that, in the art of medicine, reasoning may easily find an explanation; belief comes from experience."

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Hospital Topics

Trigeminal Neuralgia and Dental Malocclusions

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Summary

Out of 39 patients with intractable trigeminal neuralgia seven have had continuing relief for over three years after dental treatment. Five out of six recent consecutive edentulous patients had immediate improvement. More radical treatment, such as ganglion injection or nerve root section, has been at least postponed.

Introduction

Trigeminal neuralgia is a severe paroxysmal pain occurring in one or more divisions of the trigeminal nerve. The patient describes a stabbing or electric shock sensation lasting usually less than one minute. Initially the attacks are relatively mild and remissions of some months are common. Later, remissions become shorter and the pain becomes more severe until attacks occur daily for many months.

Pain is precipitated or "triggered" by a variety of stimuli including eating, talking, tongue and lip movements, yawning, touching the skin of the face, draughts, sudden movements of the head, and, occasionally, walking, loud noise, or bright light. It affects women more often than men; the onset is usually after the 45th year.

As its fundamental cause remains unknown the condition is usually referred to as idiopathic trigeminal neuralgia. A few cases have been attributed to multiple sclerosis. Harris[1] noted that the pain sometimes starts after dental extraction or sepsis. Dott[2] suggested that the basic mechanism is the conversion of innocuous stimuli into intense paroxysmal pain by a short-circuiting mechanism in the brain stem. Gardner[3] thought that deficient insulation between touch and pain fibres in the preganglionic root of the trigeminal nerve would allow the development of a short-circuiting mechanism. On the rare occasions when an identifiable lesion is present, it lies in the cerebellopontine angle—for example, acoustic neurinoma.

The relation between dental malocclusions and paroxysmal craniofacial pain was first described by Costen.[4] Henderson[5] pointed out that a trigger point in a masticatory muscle may be the single precipitating factor. The muscle is often tender.

The classical treatment of trigeminal neuralgia was alcohol injection of the Gasserian ganglion and its branches or operative section of the preganglionic root of the trigeminal nerve. More recent treatment includes carbamazepine (Tegretol) and phenoliophendylate injections. Injection or operation may be complicated by painful numbness, (anaesthesia dolorosa); prolonged carbamazepine therapy can have side effects.

A favourable short-term response to dental treatment in patients with trigeminal neuralgia was reported by Lindsay.[6] Adjustment of dental malocclusion can benefit various forms of craniofacial pain; migraine and trigeminal neuralgia have responded to the elimination of occlusal dysharmonies.[7]

This paper describes dental abnormalities, chiefly malocclusions, found in patients with trigeminal neuralgia. The value of dental treatment is discussed.

Patients

Thirty-nine patients (30 women and 9 men) referred to the Royal Victoria Hospital Belfast, in 1969 and 1970 with trigeminal neuralgia were given various forms of dental treatment. They have been followed up at regular intervals for three to four years (see table). The short-term response to dental treatment of six consecutive patients seen recently is also described (Cases 9-14, see table). Each patient fulfilled all the diagnostic criteria for trigeminal neuralgia; these included the identification of the character of the pain, its duration, its distribution, onset, periods and patterns of remission, and the triggering factors. A complete neurological examination was carried out in the department of neurology or neurosurgery to eliminate primary disorders like multiple sclerosis or intracranial tumour.

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