Drugs in the service of Man

by Adrien Albert

Throughout the countless millenia of evolution and under the strong pressure of natural selection, Nature has evolved many small, highly selective molecules to do the work of the cell. They govern its nutrition, growth, and reproduction. They are the vitamins and coenzymes, hormones and neurotransmitters, inorganic ions (some light, some heavy), metabolic fragments (such as acetyl), and the pigments (respiratory and photosynthetic). Even more remarkably selected are the polyaza-heterocycles; firstly, adenosine triphosphate which, in every kind of living cell, stores the energy provided by the breakdown of nutrients and releases it on demand. Then secondly, the purine and pyrimidine bases of DNA, which encode all needed information for regulating the cell's moment-by-moment metabolism, and also define its character and heredity. These small molecules interact with their complementary biopolymers to generate every response needed for the cell's continuity both as an individual and as a species. Collectively they may be referred to as the natural agonists.

1.0 What is 'Selectivity'?

A remedy is said to have selectivity if it can influence one kind of living cell without affecting others, even when these cells are close neighbours. Man has found many selective agents for treating his diseases and those of his farm animals, and field crops. Most of the chemical substances than Man uses in therapy differ from those evolved by Nature, and yet are often related to them because both kinds may act on the same receptors. The substances employed by Man are called drugs when used for

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relaxants, and (but less rapidly) the antagonists of histamine and of neurotransmitters. Antiparastic agents, on the other hand, although they must be selective against the parasite and sparing to the host, are preferable irreversible.

It is an achievement of prime importance for Man that selectively toxic agents have been found not only for many of his ills, but also for use in his animal husbandry, fields, and forests. The continuance and even expansion of these benefits requires continuous discovery of improved selectively toxic agents.

Whereas the task of chemotherapy is to rid the host of bacteria, viruses, fungi, protozoa, worms, and insects, pharmacodynamics has a more difficult programme because (a) the uneconomic cells are part of the organism of the economic species. For example, the uneconomic form may be an endocrine gland that has hypertrophied and upset the balance of metabolism of an otherwise healthy body; it may simply be some part of the nervous system which has become overactive and has disrupted the harmony in which bodily functions normally work. Moreover all selectively toxic agents for pharmacodynamic use are required to have a graded and temporary action. For instance, the abolition of the ability to feel pain in a circumscribed area is one of the great triumphs of pharmacodynamic practice; but it would be no triumph if the local anaesthesia were to persist throughout the remainder of the patient's life.

Chemotherapy and pharmacodynamics together constitute the science of pharmacology.

Selective drugs are usually synthetic and of low molecular weight (<500). Sometimes, however, they are of natural origin, but used outside their natural context (examples, alkaloids, antibiotics, overdoses of steroids). Immunochemicals, as in vaccine and sera, are separated from our subject by their enormous molecular weight.

Overdoses of Vitamin C, so popular at the present time, should not blind us to the fact that replacement substances can be toxic in excess, either through a side-effect, or by exerting their normal action more strongly. Thus calciferol (vitamin D) in excess causes calcification of arteries and kidneys, and an excess of vitamin A has repeatedly proved lethal. A small dose of ferrous sulphate has often killed young

the treatment of human beings or farm animals, and agricultural agents when designed to suppress weeds, insects, or fungi in crops. Collectively they are known as biologically active agents, or simply agents, and the principles governing their actions are identical. Most of what is written about drugs in this book is applicable to agents generally.

Man's therapeutic agents are of three kinds. A few, such as vitamins, hormones, and minerals, are simply used for replacement when depletion has taken place. The replenishment of phosphorus and calcium during pregnancy provides an example. The second kind is the agonist, one of Nature's controlling substances modified, either to form depots for longer action, or to be less susceptible to wastage, or to act locally rather than generally. The therapeutic steroids furnish several examples of these agonistic drugs. Most agonists are made by effecting a change, usually a very small one, in hormones and neurotransmitters.

The vast majority of drugs, however, are antagonists, designed either to eliminate invading organisms (this is chemotherapy) or to suppress sensations of pain or to counter metabolic events when these have gone out of balance (pharmacodynamics). Antagonism, provided it is selective, enlists toxicity into the service of man, and provides the benefits of 'Selective Toxicity'. Selective toxicity means the injury of one kind of living matter without harming another kind with which the first is in intimate contact. Either reversible or permanent injury may be chosen to suit the problem in hand. The living matter which is to be injured is conveniently referred to as the uneconomic species, and the matter which is to remain unaltered is the economic species. These may be related to one another as parasite and host; alternatively uneconomic and economic cells may be two tissues in the one organism.

General anaesthetics admirably illustrate the selective use of toxicity. The more toxic the anaesthetic, the more valuable it is, but only if the toxicity is selective for the central nervous system and completely reversible with time. Morton's success with ether as a general anaesthetic in 1846 was an early and convincing demonstration of selective toxicity. The accepted general anaesthetics combine a high toxicity for the central nervous system with negligible toxicity to other tissues; all toxicity rapidly and completely disappears when administration is halted. So, too, with local anaesthetics, muscle

It is most unfortunate that, for the most part, the search for biological controls has been very expensive of time and money, and has not often yielded a practical result. Selective toxicity, on the other hand, is solving a high proportion of the problems of disease in plants, domestic animals, and human beings.

At the present time, the most successful examples of biological control are those effected with selectively toxic agents. Thus trypanosomiasis, a protozoal disease of man and cattle, is controlled by chemical defoliation of those areas of the African jungle where tsetse flies breed, and then spraying organophosphorus insecticides on the exposed breeding sites. In this way, by attacking the insect vectors, which transfer trypanosomes to their mammalian hosts with every bite, the biological life-cycle of these parasites is broken. For the same reason, houses in malarious areas and swampy grounds which harbour anopheline mosquitoes are regularly sprayed with insecticides to kill these insect vectors of plasmodia (the protozoa which, transmitted to humans by the mosquito's bite, produce the disease malaria). Needless to say, drainage of the swamps where practicable has helped to control this disease. Another example of the use of selectively toxic agents to break a life-cycle is the spraying of streams with molluscicides to kill snails that are the intermediate host to the worm that causes bilharziasis in man. Although these three examples are of tropical diseases, the principle of exterminating the vectors of disease by selectively toxic agents is fundamental to maintaining good health in temperate climates also. Two universally dreaded diseases are kept in check only by constant vigilance over rats and insects: typhus (rat → louse → man) and bubonic plague (rat → flea → man).

Another way of combining biological and toxic methods is to use pheromones (the natural insect sex-attractants) as lures to bring insects to poisoned baits. This method, not yet very successful, looks promising. Another contemporary search is for substances which could make crops unattractive to insects, or impair their appetites.

children. A slight overdosage of the pituitary antidiuretic factor increases the blood-pressure unpleasantly; thyroid hormones in small excess cause muscular tremor; and adrenaline, injected before a dental extraction, can precipitate tachycardia. Steroid hormones are often used in unphysiologically large doses; e.g. oestrogens and progestogens for the prevention of conception, and cortisone for arthritis and the atopic diseases. While it has not been thought necessary to review all replacement substances in this , their borderline character has earned them a place in many of the discussions.

Food, too, is not free from toxicity. Through millenia of enforced experimentation, Man has gradually learnt to avoid eating acutely toxic species. However, choice or necessity, can restrict the diet to foods whose feeble toxicity may not otherwise be apparent. Chronic toxicity can then arise, as from the natural goitrogens of cabbage and cauliflower, the liver-injuring pigment lycopene in tomatoes, the convulsant alkaloid in yams, the biotin-depleting whites of eggs, and calcium deprivation from the phytic acid of oatmeal. For many other hazardous factors in common foods, see National Academy of Sciences (1967).

A much discussed alternative to selective toxicity is biological control. Thus economic species can be bred, or trained, to become more disease-resistant. Also, specific parasites can occasionally be found for the uneconomic species. For example, the cactus known as prickly pear, which deprived Australian farmers of great areas of valuable pasture, was eliminated in the 1930s by the release of a beetle (Cactoblastis) which attacked no other form of life. Again the Japanese beetle, which became a serious pest to crops on the Atlantic seaboard of the U.S.A. about 1916, has been kept in check by the introduction of a parasitic wasp (Tiphia vernalis) from China and a bacterium (Bacillus popilliae), both of which are harmless to earthworms, birds, mammals, and plants.

which later burst the corpuscles and escape into the host's blood stream (this erythrocytic cycle usually takes about 48 hours). Most of the escaped schizonts migrate to other erythrocytes and repeat the cycle, but a few become gametocytes. Only partial immunity is acquired after repeated attacks.

Malaria has been eliminated from Europe and the U.S.A. within living memory. For example Italy had 8407 deaths from this disease in 1919, but none since 1948. WHO's worldwide programme, begun in the late 1940's, had, by 1976, eradicated malaria from about 20 countries with the result that about 436 million people are now freed from the risk of infection. Moreover, the incidence of the disease has been greatly reduced in areas inhabited by another 1260 million. Unfortunately, 350 million other people live in areas where malaria is still freely transmitted, and there are countries which at first had the disease under good control but have since lost ground through diminished vigilance. In 1966, WHO estimated the world's annual death rate from malaria as one million. Thanks to adequate spraying and drainage, to widespread prophylaxis with daraprim tablets, and the high rate of cure with chloroquine, deaths are now quite rare in developed and developing countries; in undeveloped countries there still seem to be many deaths, but exact figures are hard to obtain.

After malaria, trypanosomiasis, leishmaniasis (kala-azar), and ameobiasis (amoebic dysentery) are the most serious of the diseases caused by protozoa.

Whereas malaria is endemic in the majority of tropical countries, trypanosomiasis is confined to Africa (in a wide belt between latitudes 10°N and 25°S) and Latin America. In Africa, trypanosomes are transmitted during bites of the tsetse fly to Man in whom the smaller crithidial form becomes the elongated trypanosomal form, which reverts to the crithidial when taken up by flies in subsequent bites. The Rhodesian species of this protozoon often causes death within one year, but the Gambian species produces chronic infection lasting many years. In both types, the central nervous system is affected giving rise to extreme lassitude, hence the popular name 'sleeping sickness'. About 50 million Africans are infected, and their horses, cattle, and camels die of related trypanosomal infections. Although there is some drug-resistance, several effective remedies are known (see Section 6.3 c). The factors which prevent the wider use of these selectively toxic agents, and the control of the vector flies, are largely economic, and the incidence is not decreasing.

1.1 Beneficial results from the use of selectively toxic agents

Ability to resist change is inherent in even the simplest physical system, such as a cup of water, as Le Chatelier showed in 1880. Any external effect, such as heat or pressure, always displaces the equilibrium in the direction that tends to restore the original state. Small wonder, then, that living organisms resist change, particularly as they have stores of energy to apply to the task. This homeostasis of living cells enables them to fight Man's best efforts to control them, and though he has won some notable victories, some of these have been only temporary. This is not surprising because even the humblest species of prokaryote has been in existence much longer than Man and, in the course of that time, has built into its genome much information on how to survive almost every imaginable type of catastrophe. The real surprise, then, is that Man has, in many cases, discovered how to influence, injure, or even eliminate a pathological form of life without endangering his own. These remarks are particularly applicable to selective toxicity.

An annual record of what selectively toxic agents have accomplished, have lost ground, or have yet to do, can be found in the Annual Report of the Director-General to the World Health Assembly and to the United Nations, issued separately or bound annually in The Work of WHO, and abstracted and supplemented in the monthly WHO Chronicle (all are published in Geneva, Switzerland). The following account owes much to this source (World Health Organization, 1976, 1977).

Infectious diseases. Malaria is still the disease that causes the greatest amount of debility, illness, and death in the whole world. WHO has long given top priority to advising nations on the elimination of this disease by draining and spraying to eliminate the insect vector, and by medication, both prophylactic and curative. WHO also labours constantly to find improvements in all these approaches. Projects approved for a country by WHO can expect to be funded internationally.

Malaria is a chronic illness characterized by periodic attacks of high fever. It is caused by various species of protozoa of the genus Plasmodium. The complex life cycle of the parasite begins when a biting female mosquito ingests human blood containing the sexual form (gametocytes) of the parasite. These mate inside the mosquito, and the progeny (sporozoites) reside in the salivary glands and so enter Man when he is bitten. The sporozoites multiply in the human liver and their progeny (merozoites) enter red blood corpuscles where they mature to schizonts,

sufferers exceeds the nursing resources. Trachoma, which is simply infection of the eyes by a minute bacterium of the psittacosis group, has 400 million sufferers at the present time, as reported by WHO, and is the greatest cause of blindness in the world. It readily yields to the local use of antibiotics, but reinfection is common because this disease occurs mainly in lands where water is scarce and hygiene poor.

The WHO estimate of the number of lepers in the world is 12 million, many of whom have no access to treatment. The most effective remedy is dapsone (diaphenylsulphone), but recovery is slow and this drug can cause haemolysis.

It is amazing that such a well understood and readily prevented (and cured) disease as tuberculosis should still be rampant in Latin America, Africa, Asia, and the Western Pacific, but in these countries it is a public health problem of the first order. WHO reports: 7 million infectious cases in the World, and half a million deaths annually.

Brucellosis is a very worrying disease in all countries. Cattle, sheep, pigs, and goats are commonly infected and in turn infect the men who handle them; also whole families can be stricken through drinking the unsterilized milk of an infected animal. Treatment with tetracycline is effective in man, but prophylaxis still presents a problem. This disease is a typical zoonosis, i.e. a disease transmitted to man by animals (there are many of these zoonoses). The incidence of gonorrhoea (about 1% where health facilities are good and up to 20% elsewhere in the developed countries) is rapidly increasing, and highly drug-resistant strains are emerging. The main cause of the increase is failure to seek treatment, rapid and painless though this is. Fifty per cent of all cases occur in the age-group 15 to 24. Of the treponematoses, syphilis (about 40 times less prevalent than gonorrhoea) is slightly increasing, and yaws (mainly affecting children in the less hygienic of the tropical countries) is diminishing; pencillin remains the best treatment for both diseases. Louse-born typhus, caused by a very small bacterium called a rickettsia, has declined greatly through the use of DDT and rodenticides: two African countries (Ethiopia and Burundi) have 95 per cent of the world's cases, according to WHO.

Of virus-caused diseases smallpox, formerly the most prevalent and damaging, has been wiped out through the widespread use of vaccination as a prophylactic. Only in very recent years have promising clues been found for drugs against viral diseases, and a few of them (notably herpes) are being successfully treated with

In America, from Mexico down to the Argentine, a different species (T. cruzi) is transmitted by a face-biting nocturnal bug. The result, Chagas' disease is caused by trypanosomes lodging in the heart muscle, leading often to sudden heart failure, especially in children. About 12 million cases a year occur and no completely effective drug has yet been found. Chagas' disease is confined to under-developed areas, and is complicated by under-nutrition. In fact nutrition must always be considered alongside medication as a prime requirement for health in countries where food is not adequate.

Amoebiasis, common in many tropical countries but not confined to them, responds well to drugs, particularly metronidazole (Section 6.3 c).

Concerning bacterial diseases, it is interesting to contrast conditions today in the developed countries with those encountered by a medical student in the 1930s. The medical wards always had several patients severely ill, and others dying, with pneumonia; there were special wards for patients with tuberculosis, and at the outskirts of the city there were special TB hospitals. In the surgical wards, severe and disabling bacterial infections of the hands and limbs were common and difficult to treat, bacterial infection of the bladder was almost inevitable in elderly men with prostatic enlargement, and peritonitis was a dreaded complication of abdominal surgery for which little could be done. Mothers, in childbirth, often acquired septicaemia from which very many died. In the children's wards osteomyelitis was an intractable disease, and there were always cases of severe middle ear infection. After the discovery and application of sulphonamides, penicillin, the tetracyclines, and isoniazid, these severe bacterial infections almost completely disappeared because chemotherapy either prevented or cured them. Bacterial epidemics are now less dreaded; children are no longer immunized against scarlet fever (a streptococcal infection) because penicillin so rapidly cures it. Similarly, although travellers can be immunized against typhoid and paratyphoid fevers, treatment of the non-immune with chloramphenicol is simple and rapid.

The least-controlled bacterial diseases in the world today are cholera, trachoma, leprosy, tuberculosis, brucellosis, gonorrhoea, and the treponematoses. Indonesia, North Africa and (especially) the Indian Subcontinent are most severely afflicted with cholera, but thanks to the aeroplane, no part of the world is safe. Cholera is easily cured with chloramphenicol and intravenous saline. Cholera epidemics begin through poor hygiene, and spread explosively where the number of

with elephantiasis (grossly enlarged limbs). Onchocerciasis, a worm disease transmitted by biting flies in tropical Africa, often leads to a total loss of sight known as 'river blindness', sometimes affecting 20% of the population. Drugs are available for treatment but not for prophylaxis, and a new lead is required. Meanwhile spraying with DDT is eliminating the larvae of the insect vector. Hookworm, which penetrates the skin in about 500 million agricultural workers in the tropics, is grossly debilitating. The worms become attached to the host's intestinal wall, from which they suck his blood. Common in Africa, Asia, and South America, children are most often the victims. Fortunately, it responds well to drugs.

Roundworms, common in the tropics, with about 650 million sufferers, have an interesting life-cycle shared between intestine and lungs. They are easily killed by anthelmintic drugs, and so are the universally occurring tapeworms and threadworms. Difficult to treat worm infestations of temperate climates are trichinellosis, which starts in undercooked pork and ends up in the sufferer's muscles, and hydatid disease, which often follows the course sheep → dog → man; promising drugs are available.

Many farm animals suffer from severe worm diseases which sap their vitality and decrease their market value. In most cases, effective anthelmintics are known, but many good ones are too uneconomic to use. This state of affairs illustrates the well-known fact that veterinary remedies have to be inexpensive or they cannot be afforded.

Over and over, in the above account, it can be seen that even more important than good selective agents to prevent infectious diseases is a good water supply and waste-disposal system. At present about three-quarters of the world's population lacks an adequate and safe water supply and are depending on the most primitive methods for sewage disposal.

In March 1977, the United Nations Water Conference, meeting in Mar del Plata (Argentina), proposed an international drinking water and sanitation decade, commencing 1980. It was agreed that the health problems of undeveloped, and even of many developing, countries cannot be solved until their water resources are efficiently managed (Falkenmark and Lindh, 1977). The cost of providing an adequate and pure supply of drinking water to all nations who lack it has been estimated at sixty thousand million dollars.

selectively toxic agents. Meanwhile immunotherapy remains the cornerstone of prevention, and is seldom successful for treatment. Hence selectively toxic agents are needed aginst hepatitis, yellow fever, rabies, dengue fever, mumps, influenza, and the common cold.

Fungal diseases of man, even when superficial, are being treated more successfully than before by internal medication. There is still great scope for improved remedies.

The position regarding diseases caused by worms is as follows. Of parasitic diseases in Man, schistosomiasis is second only to malaria in causing prolonged, debilitating illness and economic loss. Of the 600 million people at risk in Egypt, China, and their neighbouring countries, about 200 million are severely infected. The disease occurs also in Brasil, Venezuela, and the Caribbean. Schistosomiasis is caused by the parasitic flatworm Schistosoma mansoni in hot, dry countries wherever sanitation is poor. New irrigation schemes, population growth, and poverty all increase the prevalence of infection. The life cycle begins with a larval stage, in freshwater snails, which penetrates the skin of anyone working or bathing in the same stream. The larvae mate, then lay eggs in the victim's intestinal veins. The eggs, due to an immunochemical effect, are intensely irritating and cause large, painful swellings. Eggs, passing out in the faeces, hatch in the streams, releasing embryos called miracidia. Magnesium ions, emitted by the snail, attract these embryos which enter the snail's liver where they give rise to larvae. Bilharziasis, a genito-urinary form of the disease, is caused by S. haemotobium which has a similar life cycle.

In worms, as in most protozoal diseases, the host's immune response is not only ineffective, but sometimes counterproductive. Moreover, adult schistosomes attract enough host material to their surfaces to become immunologically undetectable. Selectively toxic drugs for treatment of schistosomiasis are now available, although better prophylactic drugs are needed. The use of molluscicides against the infected snails is helping. Greatly improved hygiene would work wonders, but is hard to enforce in those parts of a hot country where the population is large relative to the amount of water available.

Filariasis, a tropical mosquito-borne worm infection, responds well to mass medication with diethylcarbamazine combined with spraying against larvae. WHO estimates that there are 100 million sufferers, many

treated

The last 20 years has seen severe mental illness far better by medication than by psychological treatment; many otherwise hopeless cases have been able to return to their homes, and to employment, on maintenance doses of new drugs. More and more, biochemical research on mental illness is suggesting that many cases are caused by purely biochemical changes in the central nervous system (schizophrenia by over-methylation, for example). Hence the hope for more specific drug-based treatments is very bright.

Cancer, a collective name for about 100 diseases characterized by unrestrained growth, began in 1942 to yield more and more to medication. Cancers are of two major kinds, (a) solid tumours and (b) the leukaemias and lymphomas of the blood and lymphatic systems respectively. In the Western nations, lung cancer is the largest cause of cancer-related death, followed by colonic and rectal cancer, whereas breast cancer comes third. At any time in the U.S.A., with its population of a little over 200 million, about 650,000 new cases of cancer are diagnosed each year (for the whole world, WHO estimates 5 million new cases each year). No correlation between human cancer and viruses has ever been demonstrated, although well known in other mammals.

Usually some 50% of malignant tumours in Man initiate colonies in remote sites. Hence chemotherapy, which used to be reserved for terminal cases, is now introduced at the beginning of treatment, as soon as the mass of a solid tumour has been removed by surgery or radiation. This is done because drugs can reach out, far beyond the surgeon's knife and radiotherapist's rays, to destroy metastatic colonies of cancer cells anywhere in the body. Some 50 anticancer drugs have now been established as clinically useful.

Chemotherapy is effective against Burkitt's lymphoma, testicular carcinoma, muscle cancer, bone cancer, histiocytic lymphoma, and melanoma. Moreover, choriocarcinoma, a womb tumour of young, pregnant women which used to be 90% fatal within a year, now has a 90% chance of complete cure, thanks to two selectively toxic drugs. The leukaemia of childhood, which until recently was almost always fatal within two years, now yields to a combination of selective drugs, and more than half the children who have received this therapy are alive and well 5 or more years later.

Both Hodgkin's disease (a lymphoma) and lymphosarcoma are responding well to a combination of radiation and chemotherapy. In early cases of Hodgkin's disease there is now an 80%

Meanwhile the fight against infections must be waged with selectively toxic agents. In 1976, WHO's World Health Assembly, meeting in Geneva, resolved to intensify the attack on the following tropical diseases: malaria, schistosomiasis, trypanosomiasis (both African and American), leishmaniasis, leprosy, and filariasis. With resistant strains in mind, they urged the search for new chemotherapeutic agents against malaria, trypanosomiasis, leprosy, and schistosomiasis.

Non-infectious diseases. Whereas in under-developed countries most cases of illness stem from infectious diseases which require chemotherapeutic agents, most of the illness in the more prosperous countries is metabolic in origin and hence requires pharmacodynamic agents. In the latter countries, the principal causes of death are (in decreasing order of frequency): heart disease, cancer, and stroke. Altogether these form 70 per cent of all deaths. In most of these highly industrialized countries, the mortality from arteriosclerotic and degenerative heart disease is continually rising. Mental ill-health and rheumatoid diseases account for a high percentage of incapacitating illness. Common diseases in industrialized countries, but almost unknown in communities untouched by Western urbanization and Western dietary habits are: coronary heart disease, cancer of the large bowel, diabetes, gallstones, obesity.

For each of these diseases some pharmacodynamic agents are available, but still more effective ones are sought.

Yet the versatility of pharmacodynamic medication is remarkable. Patients can be relieved of pain of all types and degrees of severity, put to sleep or made more alert, prevented from having convulsions or caused to have them for their therapeutic value. All of these things can be done with simple selectively toxic agents. Similarly, the patient's temperature can be raised or lowered, his sympathetic or his parasympathetic nervous system can be selectively stimulated or depressed, his basal metabolic rate raised or lowered, and the clotting power of his blood can be made greater or less. Moreover, deficiency or hyperactivity in the action of muscles (including the heart) has come under control, and so have the activities of several of the endocrine glands. Excessive secretion of histamine, the cause of so many distressing symptoms, can be counteracted, and Parkinson's disease (an error of brain metabolism arising in middle age) now yields to medication.

blood level found effective in laboratory animals. From kinetic data, obtained from the analysis of blood and urine samples as described, a safe and effective probable dose for patients can be calculated.

The next step, provided that the drug is unquestionably more promising than any existing remedy, is to introduce it to a selected group of volunteer patients, using the necessary precautions of placebos and crossover tests. Where any element of risk exists, much can be done on (a) human post-mortem material, (b) excised samples (biopsy, or necessary surgery), and (c) tissue cultures. However, human trials, where possible are preferable, and should be conducted within the strict ethical framework laid down by the Declaration of Helsinki made by the World Medical Association in 1964.

chance of cure. Wilms' disease, a kidney cancer of children, is being cured in 80% of cases by using a combination of surgery, radiation, and chemotherapy. Several other solid tumours of children can be similarly cured. The foregoing information was obtained from the American Cancer Society in 1977, and reflects American practice.

About 20% of cases of advanced breast cancer respond to hormone therapy and another 48% to antimetabolites such as 5-fluorouracil and cyclophosphamide (Brulé, et al., 1973). But here, as in the chemotherapy of ovarian cancer, the figures refer to survival time rather than cure. Current interest centers on prevention of the recurrence of postoperative breast cancer with a combination of methotrexate, fluorouracil, and cyclophosphamide, and in the clinical trials now being conducted on this and other epitheliomas, most dreaded of all solid tumours, with adriamycin and the retinoids (see Sections 4.0 and 5.0 respectively).

Clinical trials. As soon as a substance has shown it is both promising and harmless in two laboratory species, nothing short of its administration to man can give useful new information. Many a seemingly specific and potentially useful substance, chosen on the basis of animal trials, has had to be rejected in the clinic for such reasons as: too brief an action, not absorbed from the gut, or serious side-effects not shown earlier. (Parenthetically, the member of a series of new compounds that turned out best in man has not always been the member that excelled in laboratory experiments.) The following study is illustrative.

Six much-used drugs, with different pharmacological actions, were tested for toxic side-effects during several months on dogs and rats. The results were compared with the case records of 500 patients for each drug. It was found that, when the rat was used as a basis for predictions, only 18 out of 53 (i.e. 34 per cent) of the physical signs observed in man were predicted correctly, and even dogs gave only 53 per cent agreement. These figures indicate that one should not expect too much from animal experiments as a guide to clinical trials. The latter are indispensable (Litchfield, 1961).

When different test-species are compared, little connection can be found between dosage and activity, but activity is usually well correlated with blood level. Hence the first task of a clinical unit is cautiously to find what dose in healthy human beings will produce the