A Fundamental Approach to the Enigmas of Virus and Disease

An Inaugural Lecture

GIVEN IN THE UNIVERSITY COLLEGE
OF RHODESIA

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A FUNDAMENTAL APPROACH TO THE ENIGMAS OF VIRUS AND DISEASE

VIRUSES are microbes and as is the wont of microbes some are or can be pretty unpleasant. Those that are cause infectious disease. Infectious disease is the 'raison d'etre' of medical microbiology and it is therefore right and proper that it should be the essence of this inaugural lecture. I will introduce my subject by telling five short stories.

The village of Melcombe on the Dorset coast was a pleasant spot at the time when this incident took place. It is now called Weymouth and was then as at present a sea port of some importance. Perhaps it is as well that the name has changed because its most sensational import was one best forgotten, but is nevertheless unlikely so to be. It was a rat—a black one—which had embarked somewhere in the middle East. Its only luggage (presumably) was its own fleas. The time was August. Within a very few days men, women and children were going down with a severe acute and tragically dramatic illness. Within a month, the plague, for this is what it was, carried by this creature had spread through the whole of the West Country—thence to London (November 1st) and the rest of Britain. A mere 15 months later one quarter of the population of England, that is some 800,000 people, were dead of the Black Death. The world mortality estimates vary up to 75,000,000. The years were **1348** and **1349.**

Move now to India a few hundred years later. Asiatic cholera, well recognised for many years, had always hitherto remained on the Asian continent, but in 1826, probably through the medium of the movement of British troops, the disease burst its confines spreading both East and West. In the British port of Sunderland, the Medical Officer of Health, one Dr. Clanny diagnosed (in the face of powerful commercially minded opposition) the disease in 60 year old William Sproat—the first case ever seen in the U.K. Over the next forty years three separate waves of the disease each worse than the last occurred building up to a crescendo in which eventually in London 7,000 people a week were dying, 1,200 in one day being the record. That year was **1866.**

And then again one spring in a Spanish village—no-one knows which one—someone went down with influenza and a mild outbreak spread rapidly over Europe and then the rest of the world; then it died out. Come autumn of the same year it began again and reached such proportions of virulence that in some three months it is estimated that 20,000,000 people died. This, the greatest disaster of any sort, atomic holocausts included, to hit mankind over a short period occurred just 50 years ago in **1918** and **1919.**

Again in India, variola major—the virulent form of smallpox—infected about 160,000 people of whom 25 per cent or around 40,000 died. That was **last year.**

And finally there was the time that about 100,000,000 new cases of malaria occurred in just about a year. That is what well informed sources reckon is going on **this year.**

So much for cautionary tales: I have chosen them to bring out certain points:—

There is the popular notion—particularly in more temperate climates—that the study of infectious disease as a speciality is no longer a worthwhile undertaking, that such diseases are under control, that they are uniformly amenable to therapy and that the major devastating type of epidemic of the middle ages is a thing of the past.

That it is true that things are better—much better—is due only to positive action to keep these diseases under control. This is far from easy to do. For example many infectious diseases are primarily diseases of animals—and though bringing human beings under some kind of control is difficult enough, it is child's play in comparison with attempting the same exercise with animals in the wild. Rabies and plague are both diseases mainly of animals and there are at the moment increasing world wide epidemics of both these infections amongst animals. These are 'time bombs' indeed for man. And we have, to be honest, really no idea why they should remain confined as they are. So my first point is that infectious disease even on a grand scale is still a real potential menace.

The second feature illustrated is the wide variety of creatures which come within the purview of the medical microbiologist today. Though all at some stage of their life cycles are 'micro' in the sense that they are difficult or impossible to see with the naked eye, certain of them are at other times very large indeed. Amongst the parasitic metazoa Tapeworms may be a yard or so long and roundworms are often measurable in inches rather than microns (Fig. 1). The protozoa like the Plasmodia of malaria are a

good deal smaller—about the size of one of our red blood corpuscles—and are correspondingly simpler in structure and behaviour (Fig. 2). Smaller still are the fungi. The one illustrated is Aspergillus fumigatus which can cause severe lung disease in the right host (Fig. 3). Further simplification is seen in the bacteria like this staphylococcus (Fig. 4) which nevertheless remains a complex and dangerous creature able in its one twentyfive thousandths or so of an inch to give a good account of itself in terms of disease production in spite of the armamentarium that can now be ranged against it. The most minute (so far) are the viruses some of which are 50 or more times smaller than the staphylococcus.

Of course, only a very small proportion of all micro-organisms do any harm to anyone or anything. One can indeed go further and liken them to men (or wives)—some, a very few, can be killers but we cannot do without the rest. For example, while it has been possible to maintain certain animals entirely free from any bacteria at all for short periods after birth without any harm resulting, all living things, plants and animals alike, are utterly dependent upon micro-organisms for their very existence. Surprisingly science fiction writers have seemingly failed to realise that far more devastating would be the results from *eliminating* all bacteria than from the introduction of even very virulent ones into a population.

However, it can be truly stated that both minor infectious diseases like mumps and scarlet fever, and the more major ones like polio, cholera, plague, and typhoid have been progressively brought under some form of control. This has been due to two groups of

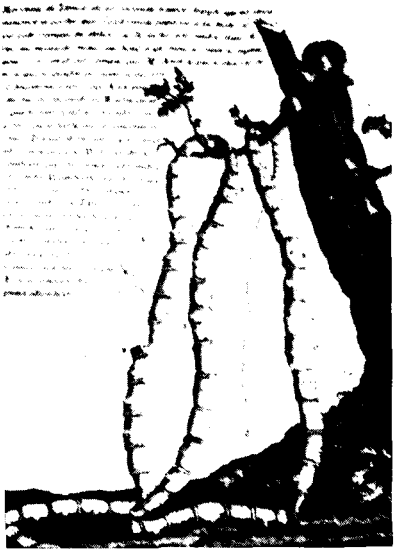

Fig. 1. *Tapeworm. An ancient and somewhat exaggerated representation !*

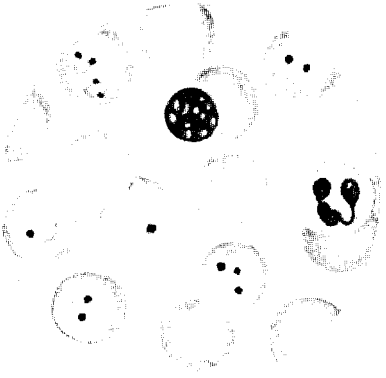

Fig. 2. *Malaria. Plasmodia in human red blood cells.*

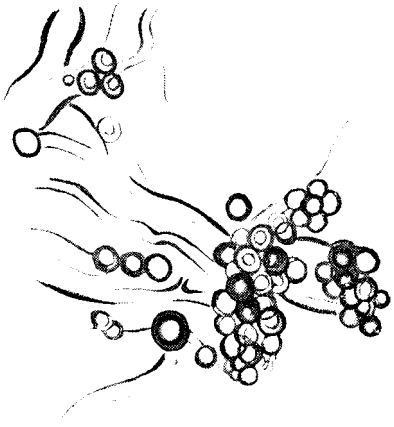

Fig. 3. *Aspergillosis. The conidia of Aspergillus fumigatus — a pathogenic fungus.*

Fig. 4. *Staphylococci.*

things or events—those intangible and those tangible mediated through human agencies.

Anachronistic as it may sound, the intangible factors are real—very real indeed. In some areas involving countries or even continents, pestilences have ravaged the population, sometimes for hundreds of years, when for no good reason at all a major killing disease has just died out. For example, plague suddenly disappeared from Britain in 1666 as an endemic infection, and almost exactly 200 years later, in 1866, Asiatic cholera did just the same thing and just as inexplicably. Explanations are put forward:—that the Great Fire of London destroyed the main focus of plague—not so! it was raging all over the country at the time:—that the black rats died out—they didn't and in any case more recent research shows that other rodents can carry both the bacterium and the fleas to transmit the disease to man. Hygiene had certainly not improved—indeed those times must have been one of the most insanitary in history. The great diarists like Pepys have much to say of this. But the disease, plague, went and has reappeared but rarely in England—last I think in 1918—and never in pandemic form. So whenever one assesses the effects of preventive or therapeutic measures on the incidence of an infectious disease, one must constantly ask oneself if any effects are due to the measures taken, or whether an 'Act of Providence' or whatever one may wish to call it must be invoked. They do happen—all the time and no satisfactory explanations are as yet forthcoming—at least none that has satisfied scientific scrutiny.

Unfortunately such events are unpredictable and cannot be conjured up on request, so we must rely on human intervention.

The active control of an infection depends upon the application of four approaches to the problem, and research and advances in this field today are directed towards one or other of them.

There is firstly the rapidity and accuracy of the recognition of the cause of any new epidemic, i.e. the efficiency of clinical and where necessary (which is nearly always) the laboratory diagnosis. The importance of this cannot be over emphasized because failure in this respect has far reaching consequences both for the medical personnel coping with the situation and for the involved public. A person suspected of a serious disease, say smallpox, may well find himself removed from his home to an isolation hospital, his house disinfected, his family isolated and subject to daily scrutiny, his friends searched for spots and so on. If it turns out after all to be chickenpox and not smallpox, the altered diagnosis being far less dramatic will often gain only slow acceptance and people have become pariahs for a great deal less. In fact the reverse happened in Britain about 40 years ago when it was recognised that what had been thought to be chickenpox was shown to be a mild form of smallpox. This had been going on for three years and some 16,000 cases came to light. The first example illustrates the consequences of delay in diagnosis and the second those of its inaccuracy.

Research in this field has three main facets—the development of new equipment such as the electron microscope 100 or more times more powerful than ordinary instruments,—the practical application of more fundamental research on the nature and behaviour of micro-organisms such as the production of a new medium for growing a bug never before cultivated in the laboratory,—and the careful

assessment of these new methods in the field, a task being performed in nearly every clinical laboratory every day.

An example will emphasize the value of this type of research. Recently investigations showed that the organism causing smallpox was present in sufficiently large numbers in the rash to be seen directly in the electron microscope. The result is that a positive diagnosis can now be made five minutes after getting a small specimen from the rash to the laboratory, and if such facilities are available, no one in whom the diagnosis is in doubt need be inconvenienced until or unless there is positive confirmation.

Then there is, secondly, the knowledge and understanding of the epidemiological pattern of a disease, the epidemiological approach. This approach is concerned with the natural history of a disease—where it comes from, who gets it, and when and how, and how it gets from one victim to another. By taking just such an approach one Dr. John Snow halted a devastating cholera epidemic in the Soho district of London by the simple expedient of removing the handle of the Broad Street water pump because he had deduced after careful observation that all those infected drank water from that pump. There was no knowledge of micro-organisms in those days. Neither was there much when Walter Reed and his co-workers cut the Yellow Fever incidence in Central America by 95 per cent by discovering the sort, nature and habits of the mosquito that transmitted the disease. He and two others died of the disease in the course of their experiments, never I imagine having heard the words virus or vaccine.

The third approach concerns the application of specific preventive measures—vaccination and immunisation. This, as is well known, has been highly successful in a number of cases, but rather less so in others, particularly protozoal disorders like malaria and trypanosomiasis. The problem does not however, end with the production of a successful vaccine. As we know in Africa as big a question is how to get the vaccine to the people.

This leads into the *fourth* approach—the fundamental one—which from a practical point of view leads to rational forms of therapy: that is, measures to stop a disease once it is under way and when preventive action will no longer influence the course of the disease. This approach is concerned with physical, chemical and biological minutae in the life of these micro-organisms in the hope that specific phases in their lives may reveal weakness which may lay them open for therapeutic attack without harming the host.

Though it must be generally accepted that the preventive measures are likely to be the ultimate means of total control and indeed elimination of infectious disease, until this is achieved therapy has possibly an even greater importance. After all, malaria can be prevented but tens of millions of cases require treatment every year.

The development of anti-microbial therapy is one of the success stories of this century, and though it has brought its own problems (and serious ones to boot) there are virtually no protozoal fungal or bacterial infections which do not respond in greater or lesser degree to specific treatment. The beginning of this success story was due to careful observation and deduction rather than the application of knowledge gained through experiment. It is only recently

that an understanding of the mechanisms of action of many of these agents has been arrived at.

This focuses attention on the apparently ever-enlarging group of disease-causing agents for which the rather empirical "try it and see" approach has been singularly fruitless—the viruses. Since this approach has failed, virologists have been forced to look at the situation in a much more rational kind of way, to look hard—very hard at the fundamental nature of viruses in an attempt to find a weakness in their way of life. Then on the basis of what is found rationally to search for or even design means to stop them. It is to indicate how this approach has proved recently so rewarding that, at long last, virus therapy on a rational basis seems imminent, that is my thesis tonight.

The field of viruses is an enormous one and I shall tackle my task by making first a few observations about viruses in general and then discuss the approach or approaches being taken with particular regard to one important disease and virus which has been an interest of mine for some years, smallpox. Finally I shall try to indicate where the information gained from the findings with this agent can be more generally applied.

Viruses came to light as most microbes did and do by causing disease which could not be attributed to bacteria or any other known agent. Interestingly enough the first described were in plants and animals rather than man—tobacco mosaic disease virus and that of foot and mouth disease. Over the years and rather slowly their unique properties began to come to light.

Firstly they are vastly simpler than any other form of life—not as might be expected more complex. Some can be split up and reduced to a

fairly simple molecule of near defined chemical structure capable of initiating the reproduction of itself—the nearest thing to a defined initiater of life and perhaps as such a little frightening.

Secondly they are too small for the ordinary microscope. They are distinctive and in many ways delightful in appearance when looked at under the electron microscope—something only achieved 10 years ago. There is quite an extraordinary but limited variety of shapes. Many though not all have a symmetrical structure and from electron photomicrographs virologists have been able to construct models. Figure 5 is a photograph of an adenovirus and Figure 6 is a model constructed from ping-pong balls from the picture. The structure is an icosahedron—a 20-sided object—and it turns out that most small viruses have this same basic pattern. There is a very good reason why this shape should be and it may be of some interest that it was predicted by Nobel Laureates, Watson and Crick about seven years before it became possible to see the particles clearly in the electron microscope. What one is looking at is the virus coat—molecules of protein which are there to protect the material inside, which is just a length of stuff carrying hereditary characteristics—a message in the form of a chemical substance deoxyribosenucleic acid or DNA. In man it might say red hair, straight nose or big feet. In this virus it says grow and kill cells in the throat and cause cancer in animals because this is an adenovirus which can do just this. Other viruses built on the same basic construction include human warts (Fig. 7) and chickenpox and that of poliomyelitis one of the smallest known (Fig. 8). In contrast the larger viruses do not show this type

Electron photomicrographs—All (except Fig. 6) magnified about 100,000 X.

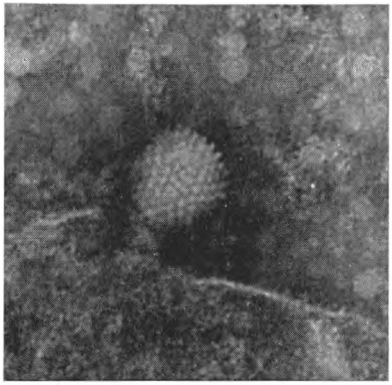

Fig. 5. *Adenovirus.*

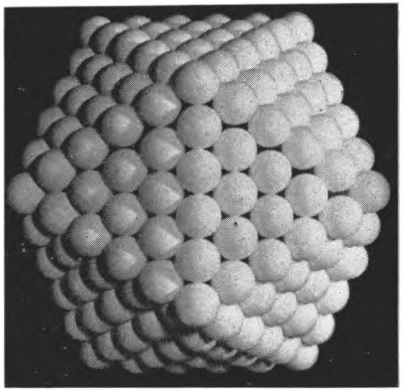

Fig. 6. *Adenovirus model.*

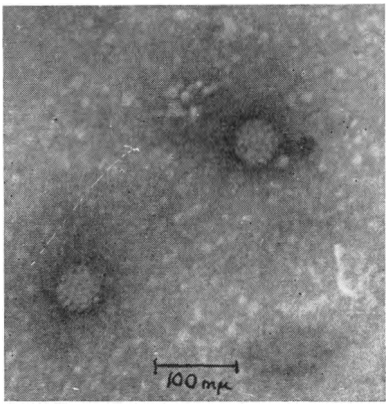

Fig. 7. *Human warts virus.*

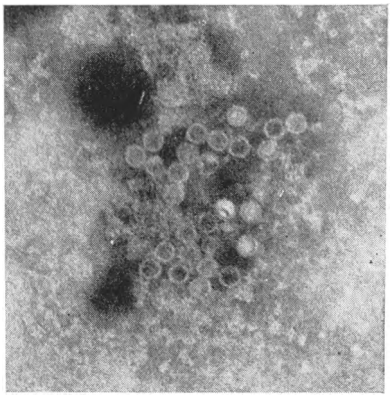

Fig. 8. *Poliomyelitis virus.*

of symmetry but nevertheless exhibit characteristic shapes (Figs. 9 and 10).

Now, even before technical advances allowed these structures to be defined, it was known that when viruses were in this particular form they were quite inert, and if they could be kept like this they could do no harm and be as innocuous as chalk. This is because unlike bacteria, viruses have no independent metabolic activities which amongst other things means that viruses produce no toxins.

The reason for the failure to respond to anti-bacterial drugs lies in this incredible inertness and simplicity. It is the complex metabolic processes necessary to maintain bacteria and higher organisms alive and growing that are hit by antibiotics, and if they are not there, "you might as well try pea soup", as a former colleague used to say.

Viruses only *do* anything when they actually get into the cells of the tissues of the body. When they do, they break up, lose their characteristic appearance and identity and may apparently disappear altogether. It is when they achieve this relationship with their host that they can exert their full potential and induce one of a quite extraordinary variety of results.

Now it is rather surprising that when it became apparent that viruses were merely rather special pieces of genetic material, it did not occur to more people that destruction of tissues and cells and disease was only one of a number of things which *might* happen when a virus infected a cell.

In fact on investigation the range of virus induced activities recognised so far is considerable. Plant viruses as already mentioned were amongst the first

looked at. This tulip has these attractive red slashes down its petals (Fig. 11). This is due to the presence of a virus—which does not apparently harm the plants which live and breed as well as any others. The characteristic called tulip break was known to be naturally transmissable long before microbes were thought of and is considered to be first recognised plant virus affection. Other flowers having colour and colour pattern variants can be shown to be carrying up to six different viruses. By selective breeding and crossing, different combinations of viruses can be obtained and each of these is associated with different colours and patterns. The causative relationship requires further establishment but most workers have little doubt that it will be in due course. On the other hand in contrast, the infection of the tobacco plant by tobacco mosaic virus (Fig. 12) results in death and destruction and this can happen on a vast agricultural scale.

Even bacteria have their own viruses—known as phages (Fig. 13)—which may destroy their host cells but which may sometimes disappear into the substance of their host altering its hereditable characteristics—a real Dr. Jekyll and Mr. Hyde phenomenon. Phages may act on the other hand as carriers of information and may transfer from one bacterium to another markers such as sensitivity or resistance to antibiotics which may have profound clinical consequences. Diphtheria bacilli are only virulent when they carry bacteriophages. If they lose them, they are no longer virulent and infection of an avirulent strain turns it into a virulent one. There is also evidence that the factors determining the sex of certain bacteria is viral in nature, and the fact that this factor can be transferred to an organism not

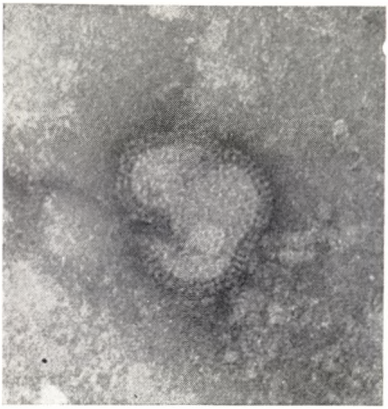

Fig. 9. *Influenza virus.*

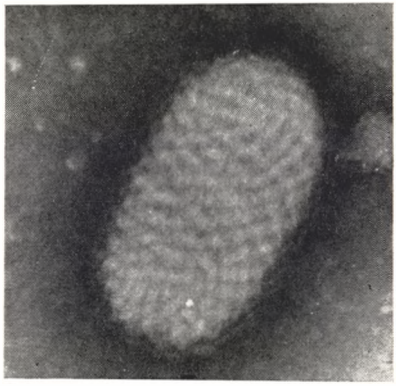

Fig. 10. *Orf virus.*

Fig. 11. *Tulip break disease.*

Fig. 12. *Tobacco mosaic disease.*

possessing it only goes to show what enormous potential may lie within these tiny particles.

In the higher animal sphere viruses do one of two things—kill by the destruction of cells or kill by the proliferation of cells, i.e. by causing the formation of malignant tumours. Man seems by contrast to other creatures to be the least versatile of responders —infection resulting only in destruction of tissues and disease.

Thus far then the activities of these minute creatures include induction of mutations, colour change association, resistance to drugs, carriage of virulence, sex change, destruction of tissues and the induction of tumours.

There have been suggestions but no proof as yet of any other kinds of activities resulting from virus infection in man. It is now, however, uncommon for virologists to speculate on the possible consequences, financial and otherwise, that would result were it to be discovered tomorrow that James Bond's craggy looks or the Beatles' skill with their guitars were commercially exploitable virus infections.

What I have tried to indicate so far is that viruses pose quite unique problems in terms essentially of fundamental biology and that this may have many consequences in many fields. As medical virologists our concern lies particularly in their disease producing capacity.

So the task is to see what there is to go on in the relationship between virus and disease.

If in the course of a disease caused by a bacterium (say bubonic plague) the organs and tissues of the patient are examined at various times after the onset, the organism or its toxins will be found generally disseminated throughout the body. These organisms and toxins in isolation will produce (or

are) substances which destroy a wide range of tissues. It can immediately be seen that the basis of such a disease lies in the virulence of the organism and the toxicity of its products.

Looking at the same aspects of a virus disease like influenza, it is found first that the virus particles like those shown earlier are not themselves toxic. All that can be found is that the particle gets into a cell, multiplies and when the progeny are mature, the cell ruptures and dies. We are therefore forced to the conclusion that viruses cause disease purely by growing inside cells as a result of which sooner or later they die.

At once attention is directed to the level of the cell rather than at the whole animal or its liver or brain. The problem all resolves round how the virus multiplies in the cell. The solution of that enigma should indicate how the virus kills cells, and hence how it causes disease.

The problem then seems, at face value, to be a simple one. Stopping the virus from growing should be all that is necessary as there should be no question of having to mop up toxins and other such products. And it is to the solution of the problem of virus growth that the fundamental approach is directed.

What happens when a virus infects a cell is illustrated in Fig. 14. The particle enters the cytoplasm and then apparently disappears—a phase in the cycle known as the eclipse. After an interval which varies from 1 to 24 or more hours according to the virus involved, from 50 to 5,000 progeny are produced with concomitant cell death—an enviable production list in some respects.

Successful therapy implies the irreversible halting of virus development *once the infection is under way,*

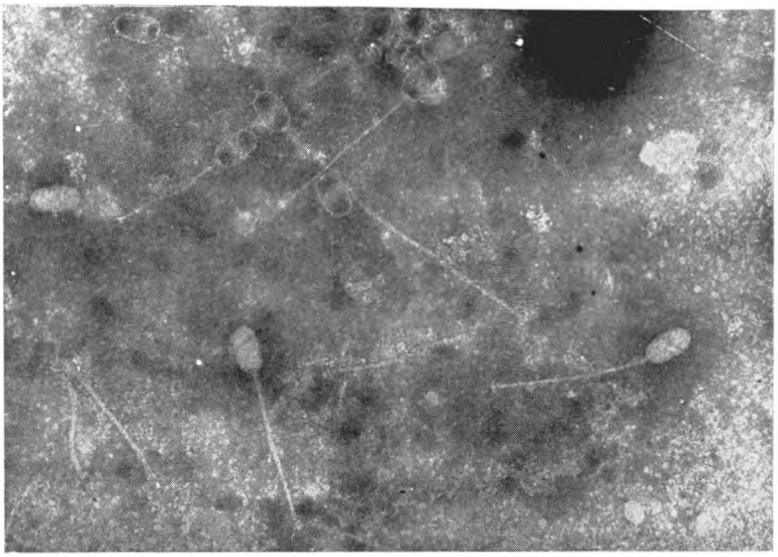

Fig. 13. *Staphylococcal bacteriophages x* 100,000.

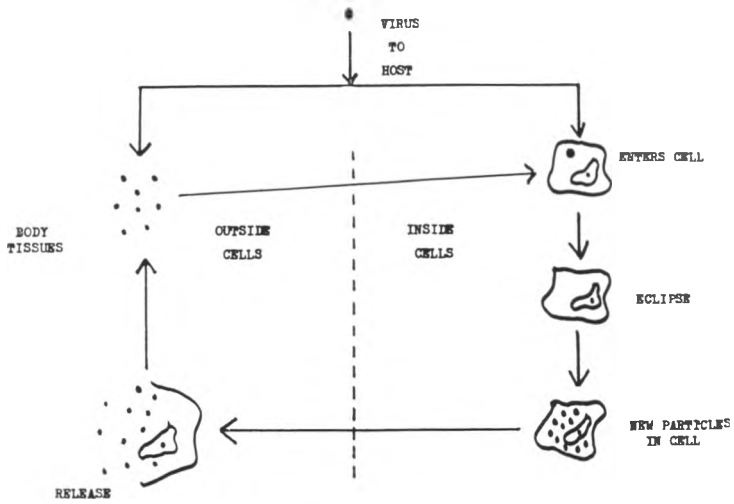

Fig. 14. *Virus Growth Cycle.*

i.e. during the eclipse. In fact it is true to say that this stage *is* virology. When it is successfully elucidated the enigmas will no longer be there.

Fig. 15 depicts the events that take place during this period. In essence it is all very orderly and logical. What must happen is that the virus must make copies of itself and this it does rapidly and efficiently. First it makes its core of genetic material and then its protein coat. The two are put together, new particles are released, and the cell dies.

It seems all very straightforward but on analysis the real problem has only just been stated. This is that the very cell in which the virus is growing, and every other cell in the body (liver, heart, gut and so on) is also continually making both these materials. Both these synthetic processes *can* be stopped but the result is not selective—the host suffers as well as the parasite. A rather gloomy state of affairs.

Obviously the situation must be examined further and in greater depth to see *not what* happened but *how* it was all caused to happen, i.e. the mechanisms involved. And here is where the complexities of virus replication now begin to emerge.

Taken step by step, the virus must get into the cell, which involves the processes of attachment and penetration. Then the particle must be opened releasing the core of genetic material from its protective covering. This is a vital process and must be completed before the business of manufacture can be initiated.

The process of manufacture involves the formation of a number of compounds necessary for the synthesis of virus genetic material. These compounds which are enzymes are made in large quantity at this stage. The idea was put forward that though in principle the making of the genetic material of the

virus was likely to be pretty similar to that of the cell, there might be differences in the enzymes if they were formed specially to do the job on behalf of the virus. If this turned out to be the case, here at least would be a stage potentially exploitable—where the virus might be affected but not the cell. As I will elaborate later this idea has proved to be correct.

Once the synthesis of new viral material is complete, the various parts of the particle are assembled together and the newly matured progeny released ready to initiate another cycle of growth and destruction. Analysis of these stages indicates that they too are sufficiently specific to be worth looking into.

However, it is a valid point that by the time these late stages have been reached, the cell is inevitably doomed, while a block at the early stages will allow a cell to return to normal. This is very significant in circumstances where cells do not regenerate—as in polio when once an infected nerve cell is irreversibly damaged, some paralysis is inevitable.

The point then that I wish to make is that careful analysis of the fundamental biology of virus infection has indicated where it would be worthwhile to attack in a rational kind of way. This is the first step in the achievement of successful therapy. Has it in fact helped?

There are those who would have it that the results of effort in the scientific world can be divided into two categories—useless and useful knowledge. The time has come to indicate that what has been sketched here is turning out to be of the useful variety, and I shall now illustrate this with particular reference to a long term interest of mine, smallpox.

Smallpox is a disease with a long and ghastly

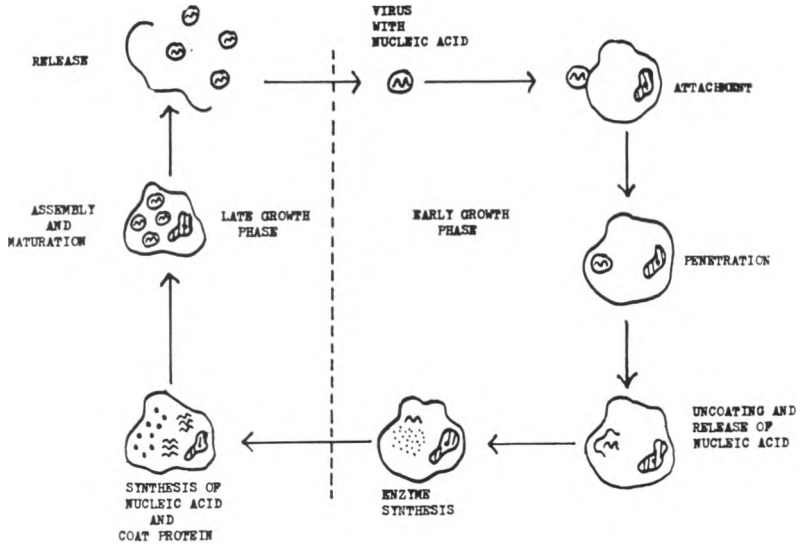

Fig. 15. *Analysis of Virus Growth Cycle.*

Fig. 16. *Rameses V Death from Smallpox?*

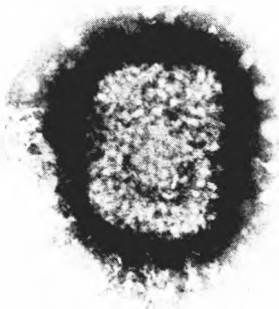

Fig. 17. *Electron photomicrograph. Smallpox virus.*

history. Probably originally confined to India and China, there is evidence to suggest its presence in Egypt and the middle East since Pharoahan times. The mummified body of Rameses V is reckoned to bear testament to this (Fig. 16). The high susceptibility of the Central and Southern African has been taken to imply a fairly recent introduction but that some tribes in Southern Africa practise a form of immunisation called variolation (i.e. protection by inoculation with material from a smallpox case) may indicate otherwise. The disease reached the New World only recently in 1520, when a Spanish adventurer brought over a slave from Africa suffering from the disease. (Incidentally, yellow fever is another disease introduced to the Americas via the slave trade). By the later Middle Ages the whole of Europe was an endemic area and in the 18th century smallpox was as common as measles is now. Overall mortality was about 20 per cent and that in infants and children rose occasionally up to 50 per cent. So common in fact was the infection that amongst the few to benefit from it were those portrait painters most adept at imagining what his subject had looked like before he was left pock marked and scarred by the disease. In the late 1700s Benjamin Jesty and Edward Jenner improved on variolation by using cowpox instead of smallpox in the vaccination process and slowly the disease came under control.

It is now found endemically in three areas in one of two forms; smallpox major, in the Far East and India, smallpox minor in South America—Brazil in particular, and in Africa in both forms. Elsewhere the disease is imported from time to time by travellers and may or may not set up an epidemic. Since even today smallpox major (i.e. the Indian

variety) carries a 20-25 per cent average mortality during epidemics and smallpox minor is fatal in less than 1 in 1,000 cases, the distinction must be considered obviously an important one. A third and very similar member of this virus group is vaccinia virus, which is used to vaccinate and protect us from smallpox. The origin of this virus is obscure.

Vaccination began when Jenner noticed that dairymaids who had acquired cowpox, a mild local infection, were immune from attacks of smallpox. They acquired cowpox through milking infected udders. Jenner grew this agent on the side of a cow and when the rash came up scraped it off and used it on people and very good it was too. It is thought that vaccinia arose when by mistake smallpox was inoculated onto a cow already suffering from cowpox. The two agents combined to form a hybrid—and this was vaccinia. This virus, which is not found in the wild, is literally a man made invention. By its low virulence and high immunity induction it has saved countless millions of lives.

The smallpoxes, vaccinia and for that matter cowpox, all look exactly the same in electron microscope pictures (Fig. 17). Further chemically, immunologically and by nearly every other test they appear to be identical. This seems ridiculous and is an admission of our own limitations in the laboratory. The only thing one can demonstrate at the moment for certain is a difference in their propensity to kill. This digression indicates a further enigma and emphasises that in these circumstances too the approach which seems most likely to yield useful information lies in what a virus *does* rather than what it seems to be in isolation.

In practical terms this disease is utterly preventable but as already pointed out still kills in India up to 40,000 people each year. Therapy remains therefore a prime requirement.

There has been no dearth of treatments suggested for smallpox. Quite early on it seems to have been accepted that in the laps of the Gods alone lay the decision whether the final outcome would be life or death, and so most thought and energy was directed towards amelioration of the long term effects of the rash; that is, the deeply pitted scars by which even today a former sufferer can be generally recognised. Dixon in his authoritative work on the disease refers to the hanging of red curtains around the bed and to the opening of the vesicles with a golden needle as two experimental approaches that failed. Drugs, potions and other forms of physic likewise failed to influence the course of the disease and but for one discovery, which will be enlarged upon later, it was apparent that empirical trials were unlikely to provide a solution. It must be emphasised that the earlier workers had not the advantages of modern equipment, knowledge and technique and the studies of many of them were and are still eminently praiseworthy.

There remained a careful and fundamental analysis along the lines already indicated.

The cycle of growth in Figure 18 can be seen to follow in principle the same basic sequence and stages outlined in general terms early on.

It is unnecessary to consider the complex events step by step and I shall confine the discussion to those which have proved to be particularly relevant to this thesis.

This virus is a big and complex one and removal

of the coat is a multistage process which in experimental systems can be selectively stopped. At the moment this has not been possible in patients though it may come.

At the rather late stage when virus coat proteins are being made a drug known commonly as Marboran (isatin B-thiosemi-carbazone) does stop further virus development before it is finally assembled and matured. Fig. 19 is an electron photomicrograph of a cell in tissue culture and which has been infected with smallpox. The virus is developing in two areas but maturation has been frustrated by treatment with Marboran and these particles are quite non-infectious. This drug is successfully used in man—provided and only provided it is given very early on in the incubation period of the disease. It has saved many lives in India but is still not quite what one is looking for, i.e. something that can arrest the infective process at an early stage. Cells damaged to the extent shown in the micrograph will not recover.

So the earlier stages came under close scrutiny. The reasoning went thus:—in the infected cell are two sorts of genetic material—one from the host, the other from the virus. The enzymes necessary for virus development could be controlled by one or the other or both. If it turned out that they were solely under virus control, then they would almost certainly differ from those in the normal host. Should this be so, there is a chance at least of selectively affecting one of the enzymes only and hence that stage of development.

The techniques necessary to determine these things took some time to be perfected, but when they were, the efforts were rewarded—the enzymes

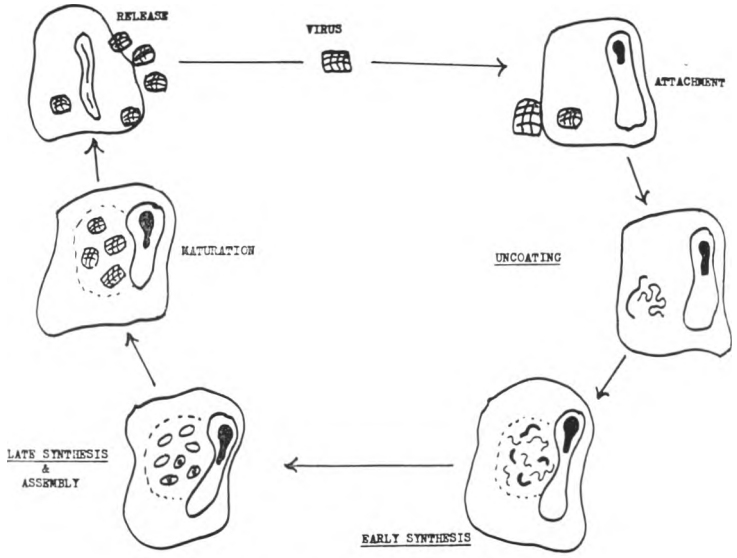

Fig. 18. *Growth of Smallpox virus.*

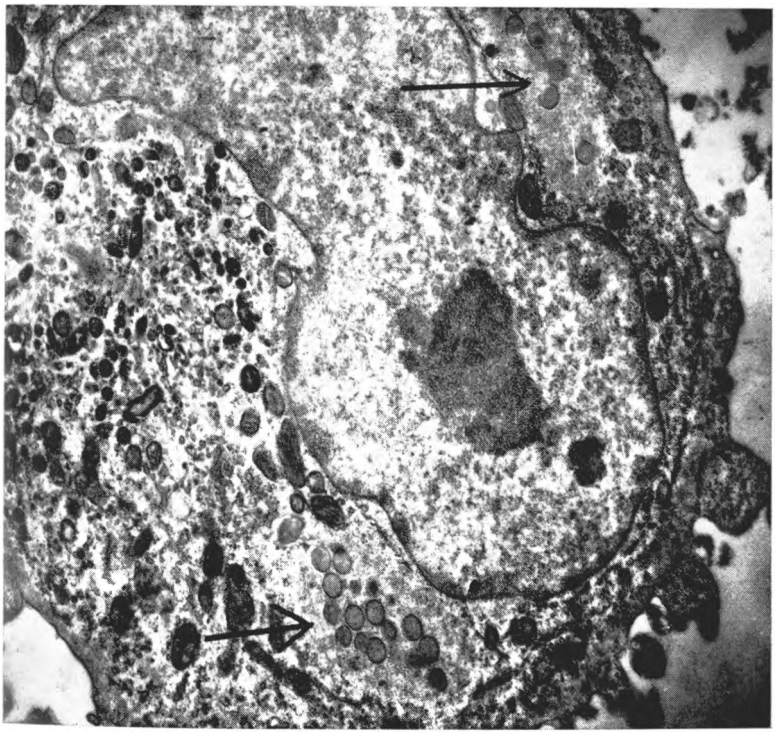

Fig. 19. *Electron photomicrograph of a cell in which Smallpox virus is growing (arrows).* x 30,000.

were different. It seemed that it was now known just where and how a suitable drug would have to act and search began for such a compound. Not many months ago the first usable one turned up—an antibiotic—which inhibits specifically certain virus mechanisms leaving even very closely related ones intact. Much more data is needed before a final evaluation can be made, but the prospects are better than ever before that a *cure* for some virus infections is near to hand. The potential is further enhanced by the fact that the activity of this drug has been shown to extend against at least three groups of viruses other than that of smallpox.

Here is a situation in which a fundamental approach may have paid off in a truly rational form of therapy. This way of tackling the problem is, however, totally dependent upon technical advances and it is only when new methods are developed that the investigation of features hitherto quite outside the range of the experimenter become possible. New techniques also bring their heartaches for virologists. In no other discipline have so many so-called proven facts proved subsequently to be incorrect when newer and more definitive methods have been developed.

But it is fair to look at the place of this type of research in the context of Rhodesia and its needs at the moment. From the point of view of infectious disease there is a mixture of the poorly developed and well developed environments. The more urban parts of the community are such that many of the problems are similar to those in other countries. The range of disease is well enough recognised and the methods of control, tried and proven satisfactorily elsewhere, can be adapted in principle at

least to the habits and way of life of that section of the population. What is different is the vast reservoir of disease which is continually and continuously feeding this more sophisticated part of the population. This reservoir occupies geographically most of the country and consists both of people and animals. The ultimate aim is to eliminate these diseases completely—a process involving a series of steps and carried out in phases. What has been achieved so far has been a greater or lesser degree of control whereby the incidence of many important diseases has progressively decreased and whereby widespread outbreaks are largely avoided or contained. The difficulties in this respect with regard to parasitic infections like bilharzia are only too well known to require further elaboration here and I will confine myself to special problems with viruses.

First, there is the problem of the reservoir and the unresolved situations are of two sorts. Those in which we know what the nature of the reservoir is and apparently cannot do much about it, and those in which we do not know what it is and obviously cannot do much about it. An example of the former is yellow fever which we know is maintained in vast quantity in the apes and monkeys of the African and South American jungles. It seems that at the moment we must accept that because of this inexhaustable and to all practical intents untouchable reservoir, this disease will always be with us on our doorstep, and we must plan accordingly. The second sort is much more common and even more baffling. Where does influenza go in the summer time and where does poliomyelitis go in the winter? Indeed in the case of certain particularly unpleasant strains of influenza virus it may well be asked what they were

doing between 1896 and when they apparently returned like the prodigal son in 1957.

Then there is the problem of prevention by vaccination. Success or failure depends upon three factors. First the adequacy of the vaccine—does it work? How well does it work? What degree of protection does it give and for how long? Secondly, with the best of them even, it must reach, for ultimate control, not just a proportion of the population but everyone—probably not just once but a number of times. And as is only too obvious here everyone tomorrow is some hundreds more than everyone today. The third factor concerns what to vaccinate against—which takes me into the third sort of problem.

What infections are there to be brought under control? Some we are well aware of—measles, polio and so on. However, here in Central and Southern Africa is a problem which is possibly unique. Many virus diseases are carried and transmitted by insects —mosquitoes, fleas, ticks and the like. It is becoming increasingly apparent that the circumstances necessary for these creatures to transmit their viruses and hence cause disease in many are very delicately balanced by such things as climate, movement of animals, the success or failure of crops, the availability and condition of water and other environmental conditions. If the balance moves one way—the bugs die or won't bite or move away—if the other, infection results. Thus when a variety of factors combine to provide a favourable environment, a community may become ripe for an epidemic. As an outbreak gains momentum more and more people become involved but this in itself begins to alter the balance by decreasing the susceptible in the population. This together with other

changes in local circumstances will continually slow down both the rate of dissemination of the infection and, usually, its severity. In time it will disappear altogether perhaps after a long period of endemicity but perhaps with dramatic suddenness as did the plague in Britain.

Of the many implications of this pattern there are two which are perhaps amongst the less obvious but which are particularly relevant to this thesis.

First there is little doubt that not only is there a continually changing pattern of disease but also a continually changing spectrum. Some infections have disappeared altogether presumably when the animal or human host or the vector are no longer able to maintain the virus owing to altered environmental circumstances. It is quite likely that in many cases the viruses may have completely died out. Secondly, it seems on the other hand equally likely that new diseases could arise and there is evidence to suggest that this is in fact so. A number of new diseases, frequently of a rather mild nature, have been reported in recent years. They appear suddenly often in epidemic form, reach a crescendo and then may either become endemic or die out. They are all insect transmitted and it would therefore be reasonable to conclude that there exists a vast resource of hitherto unknown viruses in a variety of different hosts just waiting for the right conditions to cause overt infections. Many are unpleasant rather than dangerous but who is to say when something with the devastating severity of Yellow Fever or even West Nile could turn up? It is, of course, impossible to prevent them at the time of their first appearance and to be prepared at the moment is a reflection of Public Health organisation rather than specific attack on the disease.

The point is then that despite the many methods available to prevent certain virus diseases, the ability to treat such conditions remains the bulwark around which the ultimate conquest of these diseases lies. That it looks as though this might be possible is a reflection of the fundamental experimental approach. On the brighter side results so far suggest that success against one organism seems likely to imply success against a wide range of other viruses—a particular advantage when new agents appear as they do from the jungle.

Here then is the enemy, the arch-exponent of the simple life—the one we like to consider at the bottom end of the scale of life. But is it: I wonder. We have evolved bodies of great complexity to live a life of great complexity and in return accept that existence is limited to our three score years and ten —in spite of extensive searches for the elixir. The final figure (20) shows on top a reiteration of what a

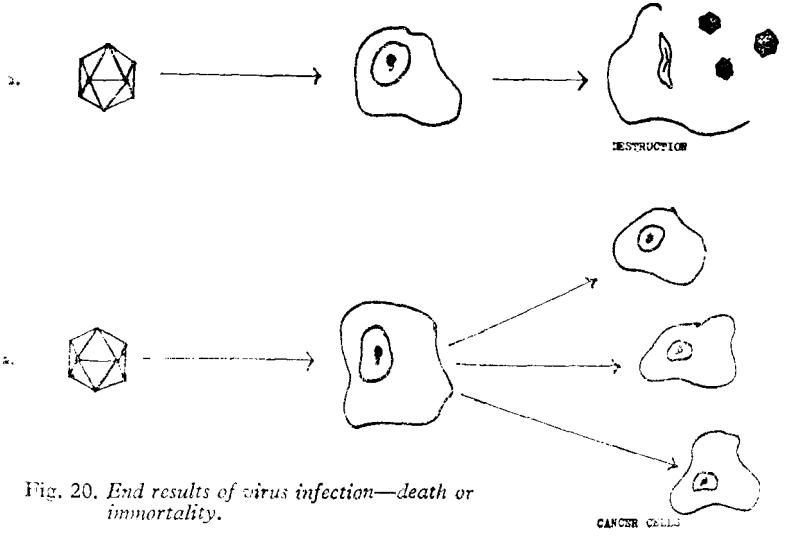

Fig. 20. *End results of virus infection—death or immortality.*

virus usually does—the bottom shows what some may do. It enters a cell and becomes part of that cell—living with it, dividing with it but nevertheless a distinct part of it. In return it converts the cell to a cancer cell—and a cancer cell in the laboratory may apparently be cultured indefinitely. The virus has traded a brief span of independent existence for immortality for itself and its host. A perfect symbiotic relationship never achieved by any other living thing.

I wonder who are really more successful they or us!

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