I am deeply honored by your kind invitation to participate in this meeting of the Japanese Society of Tropical Medicine and feel privileged to have the opportunity to address this distinguished group. Your hospitality has been most gracious. It is a pleasure to visit Japan again and to renew acquaintances with colleagues.

I should like to discuss with you today an important and growing problem, to talk about the need to alter entrenched concepts and to explore solutions to some of the problems through application of modern field, laboratory and data processing and retrieval systems operated on an international basis.

To many of us living in the temperate zones, tropical medicine has often implied a sense of remoteness. It has traditionally involved diseases of people situated a great distance away, diseases which were of no immediate concern to anyone except those who were going to travel in the tropics. This is an outmoded concept. Many so-called tropical or exotic diseases of various kinds may be of direct concern to almost any part of the world, demanding a global perspective of medicine. The tropics still retain a certain degree of uniqueness because of their high population density, often low level of sanitation and the fact that climate, prevalence of arthropods and vertebrate reservoir hosts may permit year-round transmission of certain viral agents. In this way, these regions may serve as reservoirs for certain kinds of infection which can spread to other parts of the world.

This shift in perspective has been brought about in part through the great technical advances in air travel in recent years which have permitted large numbers of people from any one part of the world to go to any other part of the world rapidly—within the incubation period of most infectious diseases and within the survival time of many vectors of disease, just as I have done in the past two days! Every international airport, even those situated in the middle of large continental land masses, are potential ports of entry for infectious diseases from any part of the world, even the most remote and medically unexplored. We can no longer rely upon a disease making its appearance and being recognized during transit before it reaches a port, as we could with the slower modes of surface transportation. Sea-port cities traditionally had specialists who were trained to recognize disease and to impose quarantine, where necessary. Now every international airport must attempt to do this under the most trying conditions.

Control of the spread of disease will require the evolution of appropriate
methods applied on an international scale as never before. This, of course, is already done fairly effectively, but not completely, with a number of the great pestilences of man-smallpox, cholera, plague, yellow fever. With some other well-known diseases, such as influenza, no effective means has been found to limit global spread. Finally, some newly recognized diseases are showing capacity for spread over great distances.

Some prerequisites for control or prevention are: (1) knowledge of the disease agents which exist, their mode of spread, prevalence, geographic distribution, potential for causing epidemic disease or establishing new endemic foci, etc.; and (2) current, up-to-date information on the activity and spread of the individual disease at any given time.

The first represents the basic investigation about the nature of the disease; the second requires some kind of effective surveillance, reporting and alerting system on an international basis. It is evident that our knowledge about the disease agents which exist in many parts of the world, especially in tropical areas, is far from complete. This state of affairs forms the main basis for my discussion today. I will confine myself to selected topics on the arthropod-borne viruses, a field with which I am somewhat more familiar than many others and in which there has been a great deal of activity in the past few years. Even with this restriction, I cannot hope to be fully comprehensive.

New viruses, especially arboviruses, are being discovered at a frightening pace. In many instances we know little about their capacity to produce human disease, their vectors and ecologies and their potential to be transported from place to place and to establish themselves in new areas. As virological work proceeds, each geographic region appears to produce a new array of arboviruses, new potential vectors and peculiar ecologies. There still remain in the world vast regions which are medically and virologically unexplored. Some of these remain relatively undeveloped economically and are still isolated from usual channels of communication. However, as new settlements are made, new areas are brought under cultivation and large numbers of people enter and work in previously uninhabited or undeveloped areas, two things might be expected to happen: (1) the people developing the areas may contract diseases, some known and some new and never before encountered; and (2) some of these diseases, under the newly created conditions and improved communications, may spread from their original sites of endemicity to new areas.

Another situation involves the appearance of new, or at least never before recognized, diseases in settled areas. And, finally, there are old diseases which reappear from time to time. I would like to illustrate several of these situations with a few selected examples drawn from among the described episodes of recent years.

1. New diseases appearing in people entering and developing previously unsettled or virgin territories was illustrated by the experience of immigrants from Okinawa to the forests of the Amazon headwaters in Bolivia a few years ago. These people came from a totally different geographic region and, of course, would be expected to be susceptible to viral agents peculiar to the new area. Reports by Gajdusek, Schaeffer, and others\(^1\)\(^2\) have revealed an interesting sequence of events. As these people established a new settle-
ment or colony in 1955 and began to clear the rain-forest jungle, almost half of the 400 pioneers developed acute, febrile illnesses, some of which were fatal. The general term, “jungle fever” was applied to the outbreak. Virological studies were limited, because of the remoteness of the region. Despite this, a new Group A arbovirus, the Uruma virus, related to the Mayaro and chikungunya viruses was isolated from a patient late in the outbreak. This virus was found by serological means, however, to account for only 10—15% of the cases of “jungle fever”.

It is apparent that the outbreak was complex in origin, probably involving other agents whose nature is still not defined. Here, then, is an example of a non-immune population entering a virgin, medically unexplored area and contracting new diseases which were presumably silently endemic and totally unsuspected on the basis of previous knowledge. Extremely difficult communications may have played a role in preventing one or more of these from spreading to other areas.

2. Several examples of newly recognized diseases in old, long-settled areas have appeared in recent years. One of the most fascinating examples is the account of the recognition of the chikungunya virus in East Africa and its subsequent recognition in widely separated areas in the world—an excellent example of the potential global importance of such new agents.

In 1952 an explosive outbreak of a dengue-like disease occurred in Tanganyika Territory in Africa\(^8\). A new arbovirus belonging to Group A—the chikungunya virus—was isolated and was shown to be largely responsible for the epidemic.\(^4\) Subsequently, this virus was shown to be present in various other parts of Africa where it also caused a dengue-like disease in man\(^6,9\).

Then in 1958 a large outbreak of hemorrhagic fevers and dengue-like fevers occurred in and near Bangkok, Thailand, a point a long way from Africa\(^10,11\). In addition to Group B dengue viruses, viruses similar to, if not identical with, the chikungunya virus originally found in Africa were isolated from some sick persons.

Then, in 1963 an epidemic of a dengue-like disease, with some cases showing hemorrhagic manifestations, occurred in Calcutta, India\(^12\). While several viruses apparently were involved in this outbreak. The chikungunya virus was again found to cause some of the cases of dengue-like diseases.

The occurrence of the relatively “new” chikungunya virus as a component of serious epidemic disease at different times in widely separated areas over the surface of the earth attests to its great public health importance and suggests one or the other of two alternative hypotheses: (1) chikungunya viruses have long been widely distributed over several continents or subcontinents and are just now being recognized in different areas; or (2) chikungunya virus has spread from its original focus to widely separated geographic regions in the course of a very few years.

Very little is known about the ecology of chikungunya virus infections or about the existence of mammalian or bird reservoirs. Neither of these two hypotheses can be excluded categorically with the present limited knowledge. The fact that the last two mentioned appearances of the virus occurred in large population centers which were also major international air travel centers is compatible with the spread of the virus by modern rapid air communi-
cation systems. If this is the case, then the chikungunya virus story illustrates dramatically the fact that what happens in East Africa may be of vital concern to large populations in the rest of the world. On the other hand, some serological work suggests that chikungunya virus or one closely related to it had been present in Calcutta previously.

The large epidemics of dengue-like disease and hemorrhagic fevers which have occurred in recent years in the densely populated, warm areas of Manila, Bangkok and Calcutta have clearly established another important point—namely, that when conditions are right for arbovirus transmission and propagation in a human population, more than one virus, sometimes several, if present, can be transmitted during the same epidemic season. Hence, defining the etiology of an epidemic involves a virological study effort of considerable proportions. One can no longer be satisfied with the isolation and characterization of one or two virus strains from an outbreak and then assume that the cause has been discovered. Multiple strains taken at different times and places during the epidemic are now required.

3. Old diseases reappearing in old areas after apparent prolonged absence is amply illustrated with dengue fever. Dengue fevers in the Western hemisphere make an interesting story with unsolved problems and a number of side-issues. Prior to 1940, dengue fever epidemics had occurred sporadically along the West Indian island chain in the Caribbean Sea, even extending to the Southern United States within this century. From these earlier years, detailed data are not readily available. However, in the early 1940's dengue fever epidemics are recorded or remembered in several widely scattered areas along this tropical island chain-Puerto Rico, Martinique and in the Central American country of Panama. The serological surveys conducted by Dr. Downs and his collaborators in many other Caribbean islands have since confirmed the fact that dengue had probably been widespread up until the early 1940's. Then clinically recognized epidemics seemed to disappear. Various fevers of unknown origin, of course, continued to occur sporadically, but nothing happened in the way of the classical, widespread epidemics of dengue. Serological surveys have suggested that perhaps there was some dengue activity on some islands but, because of the complex serological overlap among Group B arboviruses, it is impossible to state with certainty that it was dengue which gave rise to the antibodies.

Up until recently, the only dengue viruses which had been isolated in the Western Hemisphere were type 2 viruses from Trinidad in the 1950's, indicating the presence of a dengue virus there even though a large-scale epidemic was not in progress. Serological surveys have indicated that some islands have been relatively or entirely free of dengue since the widespread occurrence in the early 1940's.

Our own unpublished studies with sera collected from Puerto Rico indicated that, prior to 1960 at least, there had been little or no dengue infection since the middle 1940's when the last recognized outbreak occurred. The story of dengue on Puerto Rico is a particularly interesting one in view of recent events. In the middle 1940's, an intensive anti-malarial campaign with residual DDT was instituted in Puerto Rico. This was eminently successful and malaria virtually disappeared. As a by-
product of the anti-malarial campaign, the *Aedes aegypti* mosquito population was also reduced to a very low level, but it was not eradicated. This decline in *Aedes aegypti* population coincides fairly closely with the decline in the Group B arborivus sero-positive rate in Puerto Rico. Presumably, dengue transmission had been almost or entirely stopped.

After several years of effective malaria control, measures were relaxed. There is a hiatus in our knowledge here, but presumably with the cessation of widespread residual spraying with DDT the *Aedes aegypti* population began to increase. At least we know that by 1963, the *Aedes aegypti* rates in households were over 80% in some areas.

Meanwhile, since the middle 1940’s, in the absence of widespread dengue infection, a large non-immune population had grown up. Presumably, all that was required now for a largescale dengue epidemic was the introduction of a virus. Island communities, such as Puerto Rico, are geographically and biologically relatively isolated so that, once a virus like dengue disappears, the island would tend to remain free until it is reintroduced again by man.

We do not know for certain that dengue had disappeared completely from Puerto Rico but the chances are good that it may have. We do know, however, that a disease diagnosed as dengue began to appear in appreciable numbers, sufficient to attract the attention of physicians, on the neighboring island of Jamaica in the spring or early summer of 1963. There is good communication between Jamaica and Puerto Rico, both by sea and by air. It is not absolutely certain that dengue was introduced into Puerto Rico from Jamaica, but it may not be merely coincidental that in the summer of 1963, not long after dengue had reached epidemic proportions in Jamaica, cases of dengue were recognized on the northern coast of Puerto Rico. This spread rapidly and swelled into an island-wide epidemic of very great proportions in the late summer and fall of 1963 and began to decline towards the end of the year, presumably in part because the susceptible population was nearing exhaustion.

The story does not end here, however. Later, it was learned that an epidemic of dengue had occurred on the island of Martinique, which is administered by another government. This illustrates the fact that widespread disease of international importance can occur without being generally known. Also, at about the same time, an outbreak of “influenza” had occurred in the Virgin Islands close to Puerto Rico. This was probably also dengue. In this last case, the majority of inhabitants have pigmented skin on which the typical dengue rash is difficult to see—a problem in the differential diagnosis when modern laboratory methods are not applied. The epidemic apparently spread further and by 1964 the disease was occurring on the Venezuelan coast of South America.

Island-hopping of dengue over great expanses of water could only occur through the efficient human communication systems between points where proper conditions for transmission exist. This point is emphasized by the known experiences in the United States during the fall and winter of 1963.

Puerto Rico is a favorite vacation spot and many tourists fly there from the United States. Transportation by air is only a matter of a few hours from New York, Baltimore, or Miami. There are perhaps
18 or 20 known instances, and probably many more, in which people became infected with dengue in Puerto Rico, returned to the United States by air during the incubation period, and subsequently developed dengue fever. Nevertheless, a dengue outbreak did not occur in the United States. There are probably several reasons for this. The only known vector of dengue in the United States is *Aedes aegypti*. Its distribution is limited to several of the southern states. Even in these states, the activity of *Aedes aegypti* is diminished or absent during the winter. Thus, some of the dengue cases were introduced into parts of the country where there is no dengue vector and, even in those areas where vectors might occur, the disease was introduced at the wrong season of the year.

Needless to say, this whole episode has spurred the campaign to eradicate *Aedes aegypti* from the United States mainland and from the island of Puerto Rico.

The form of dengue which was epidemic was mild. It produced no deaths as far as could be determined. This was fortunate. Had the virus, which was introduced, been that of yellow fever instead of dengue, the results could have been disastrous.

This epidemic, which occurred in areas where mosquito control has supposedly been going on for some time and where good public health programs are in effect, dramatizes the need for a mechanism of constant surveillance, an adequate reporting system and improved control measures against international spread of arbovirus diseases.

These few illustrations of recent origin, drawn from a much larger store of new knowledge in the rather specialized field of arthropod-borne virus virology, amply support three main general points of my thesis, points which are applicable to other diseases as well—namely.

1. Tropical diseases are at our doorstep. A global perspective is essential under conditions prevailing today.

2. There is much still to be learned about "old" diseases and about "new" or unrecognized agents of disease which undoubtedly exist in the great medically unexplored areas.

3. There is need to make what knowledge is available, or becomes available, known as rapidly as possible to all concerned—and this would appear to include potentially almost all countries.

Now, I should like to turn to a consideration of the methods at hand for obtaining information, especially from the medically unexplored areas of the world.

There are several methods for gathering information about the arboviruses in unexplored areas, each with certain strong points and each with certain disadvantages.

1. The oldest method, and perhaps in many ways the most rewarding, is the study of an epidemic or outbreak of human disease. Here, most of the essential features related to human disease are present and concentrated at a given place within a relatively short period of time. Human cases are plentiful; material for virological, serological and clinical studies is abundant and easily obtained. Obviously vectors important for transmission to man must also be present and available for study. It is often relatively easy, but not always so, to relate viruses isolated from patients or vectors to the clinical disease or diseases which are prevalent through established methods. Studies of epidemics have continued to yield an abundance of valuable
information over the years.

Certain problems, however, do exist with this approach. First, epidemics tend to occur at unpredictable times and places. If the areas involved are remote, or are located in different political areas, word may not reach interested scientists at all. Or, as is very often the case, notice comes only late in the epidemic when opportunities for adequate study are diminishing.

Then, a team of appropriately qualified specialists, properly equipped, must be ready to speed to the site of an outbreak when notification is received. Often, early reports may be misleading. Moreover, clinical diagnoses may be erroneous. A team of arbovirus experts may find that what has been reported as a dengue-like disease is in reality an enterovirus infection, influenza or measles; or a yellow fever outbreak is really hepatitis or leptospirosis; or an outbreak of encephalitis is due to the ingestion of toxic food adulterants, or poliomyelitis.

Even when it is reasonably certain that an arthropod-borne virus is involved, the clinical manifestations may not permit a very accurate guess specifically as to which, if any, of the known viruses is involved. Information which has been accumulating strongly suggests that man may respond to arbovirus infections in the form of certain general classes of clinical patterns. We now know that several serologically unrelated viruses may elicit similar clinical diseases or that a single virus may be found associated with more than one kind of clinical response.

There are other disadvantages from relying upon the study of epidemic disease. For example, in highly endemic areas where transmission is almost constant or occurs at frequent short intervals, infection may be limited to sporadic cases in the young. Large epidemics might not occur under these circumstances and an area which in reality possesses a high degree of endemicity may superficially give the impression that there is no disease problem.

Finally, conditions which are optimal for transmission to man may be unusual and fail to give a clue to the cycle of infection which maintains the agent during inter-epidemic period.

2. Long-term studies of fevers of unknown origin in an area of interest have constituted another approach. Here, a semi-permanent clinical-virological team establishes itself in an area and studies in detail the human infections which occur in that area over a period of time. This approach requires a relatively large and sustained effort. It theoretically should yield a good sample of the causes of human disease in the area. Programs of this kind have been carried out in a number of places in the world. In some instances, this approach has yielded a moderate number of agents. In others, the reward has been discouragingly sparse. Note, again, that the screening device for study material in this approach, as in the study of epidemics, is the occurrence of human disease in the area. Programs of this kind have been carried out in a number of places in the world. In some instances, this approach has yielded a moderate number of agents. In others, the reward has been discouragingly sparse. Note, again, that the screening device for study material in this approach, as in the study of epidemics, is the occurrence of human disease in the area. Programs of this kind have been carried out in a number of places in the world. In some instances, this approach has yielded a moderate number of agents. In others, the reward has been discouragingly sparse. Note, again, that the screening device for study material in this approach, as in the study of epidemics, is the occurrence of human disease in the area.
considerable effort which has gone into this general approach in the past few years. In general, two kinds of methods have been emphasized: (a) the systematic trapping or collection of arthropods, such as mosquitoes, ticks or sandflies, from different kinds of habitat and attempting to isolate viruses from pools of these arthropods; and (b) the use of sentinel animals, such as suckling mice, to attract mosquitoes which feed and transmit viruses to the sentinels.

This approach has been profoundly productive of arthropodborne viruses. A few years ago, only a handful of arboviruses were recognized. Now the number is probably in excess of 150. The systematic screening of arthropods has contributed very heavily to this phenomenal increase.

Unlike the other methods of approach which have been described, this method is not selective of viruses which cause human disease. The only selective factors at work here are: (a) that the virus was present in the arthropod and (b) that it grew in the host system employed, be it the suckling mouse, or a tissue culture. The result is that we now have on hand a very large number of viruses, presumably carried by arthropods, whose potential, if any, to produce human disease is unknown. Some may be capable of producing significant, or even serious, diseases in man under natural conditions; others may constitute no problem at all.

Thus, in the wake of all this activity has been left undone a task of immense proportions for the clinician and epidemiologist amply supported with proper laboratory facilities, a task which will require years of painstaking effort. It is clear that we, as a scientific and medical community, must now logically begin to place relatively greater emphasis upon the evaluation of the new viral agents as potential human or domestic animal pathogens. As in most fields of scientific endeavor, nature provides many more problems than man can expect to solve in the foreseeable future. Value judgements, then, other than more unbridled curiosity must enter into the direction of available effort. Over the years, the value judgements which have had the greatest impact have been those related to the welfare of man himself.

4. The last general method of approach which I shall mention is that of serological epidemiology. This method has enjoyed widespread use on the one hand and has engendered considerable criticism on the other. Therefore, it is worthwhile to examine its strong points and its limitations in order to define more clearly under what conditions it can be expected to yield useful results and just what kind of results might be expected.

On the positive side, one can list several highly significant advantages:

(a) Within certain limits, which must be defined in each instance, the serum of an individual serves as a cumulative record of his past arbovirus experiences. If we can learn to decipher and interpret accurately the information coded into the antibody patterns, we can learn a great deal about past arbovirus infections in that individual.

(b) Despite the great advances in rapid transportation, very large numbers of people still reside all of their lives within very restricted geographical areas. If the areas is defined and documented, these people then can serve as sentinels for arbovirus infections of man for that area.

(c) There is built in a selecting mechanism for viruses which infect man, thus excluding many agents which are of no
(d) Sampling of a population can be done in such a way that the pattern of past experiences of individuals comprising the group can yield a great deal of qualitative and quantitative epidemiological information, such as infection rates, endemicity versus single wave epidemic, recent or past activity, sex and occupational predisposition, etc. One may be able to reconstruct past experience and assess current activity.

(e) Much information can be obtained when these data are correlated with ecological and anthropological factors, such as climate, terrain, vegetation, agricultural practices, prevalence of certain arthropods and vertebrates, etc.

(f) Serum specimens can often be obtained under conditions in which it is impossible for various reasons to carry out detailed virological studies.

(g) The results of serological surveys properly performed can aid in the selection of sites for the more laborious and expensive detailed virological studies, thereby improving the efficiency of the overall effort.

(h) Through the use of broadly reactive antigens, one may detect the activity of even new, antigenically related viruses which have not yet been isolated and identified.

(i) With properly documented banks of sera on hand, it is possible at times to learn something of the geographic distribution, prevalence and ecology of a newly discovered virus simply by testing carefully selected sets of sera for the presence of antibodies.

(j) Finally, it may permit a prediction of the susceptibility of populations threatened with an introduced viral agent.

This is an impressive array of points in favor of the serological survey technique. Unfortunately, however, there is also an impressive array of disadvantages or weak points. In order to help define the limitations of the method and to place it in its proper perspective, we must give equal attention to the things that it will not tell us.

(a) While the presence of antibodies in man is strong evidence for past infection, it tells us nothing about the nature of the disease. This could range all the way from an inapparent infection of no clinical significance to a severe, incapacitating or even fatal disease. Elucidation of the clinical manifestations of the infection still requires careful clinical observation of laboratory-confirmed infections.

(b) While serological overlap among viruses has some advantages, as we have just pointed out, it also imposes serious limitations upon the specific identification of the particular virus or viruses that have been present. One often can only say that viruses antigenically related to the test viruses have been present. To attempt to incriminate a specific virus strain or type without additional information is hazardous. It becomes increasingly difficult as the numbers of related agents causing multiple infections in a given individual broaden the antibody pattern, as occurs so notoriously among the Group B arboviruses.

(c) Viruses, new or old, not represented in a set of test antigens and not related serologically to components of the tests system, will not be detected by this method. This is a particularly serious drawback when one is studying new or previously unexplored areas where the indigenous viruses are unknown.

(d) Antibodies to different viral
agents may persist in detectable amounts for variable periods of time.

Despite these and other limitations, the serological survey technique can give a great deal of useful information when appropriate restrictions are placed upon the interpretation. It is especially useful as the initial examination of a new or unexplored area and can help direct the more laborious and expensive definitive approaches mentioned earlier. It is no substitute for definitive virological studies. All of the approaches mentioned should be considered as interdependent components of the overall investigative effort.

Since individual laboratories can seldom mount a comprehensive program which embraces in depth all of the approaches, it is essential that separate groups maintain a reasonable perspective or their contributions to the overall problem and that information uncovered by one group is made freely available to all interested groups in order that a well-rounded, efficient study will result from the cumulative efforts of all participants.

The handling of data obtained with many different antigens from thousands of serum specimens constitutes a major problem which we are just beginning to resolve. This is being accomplished through modern data processing and computer techniques. We have devised special forms onto which serological and pertinent epidemiological data are recorded. With recently developed optical reader equipment, IBM cards are automatically punched by machine directly from the data sheets. The information on the cards can be transcribed to tape and then be fed into an electronic computer for analysis. Dr. Helbig of the Communicable Disease Center working in my laboratories is now in the process of devising a program for the computer by which the initial analyses can be carried out in a few minutes instead of the weeks and months of painstaking labor required for analyses carried out by hand.

Since there are probably many different groups faced with similar problems and attempting to solve them by the same general methods, there is great need to establish a uniform system for collecting and recording epidemiological data pertinent to such surveys so that data collected by one field group can be compared with data collected by other groups in the same or different areas. It should logically be in such a form that would permit ready coding for computer analysis. The system required would need the expert advice from many different disciplines and should be drawn up with the help of international authorities in such fields as anthropology, climatology, botany, geology, entomology and zoology, ecology, etc. The objective would be to devise classification systems which would be generally acceptable throughout the world as guidelines for field workers and data analysts alike.

Finally, if we are to achieve any degree of effectiveness in developing a global system of surveillance and control, the information obtained by all of the different groups of investigators in various parts of the world must be readily available in a rapidly retrievable form at some central location.

I have been pleased to learn that serious proposals along these general lines are being made. Hopefully, in the not-too-distant future, a truly global sense of medical and public health responsibility which transcends political differences will develop and will enjoy world-wide participation and acceptance. Perhaps the joint
medical program prepared by your Prime Minister and our President can serve to further this data.

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