THE CARRIER PROBLEM

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That it is always hazardous to generalize may sound like a truism, yet the tendency to indulge in generalization is so strong that it even outweighs experiment itself. This is especially true in Biology, and, unfortunately at the present time certain phases of this science, Hygiene among others, are based almost entirely upon generalizations.

What is a carrier? In the broad sense of the word a carrier is an individual who serves as the medium for the growth of a given bacterium. In order that this person may be infectious it is necessary that the bacteria which are multiplying within his body be subject to dissemination more or less readily and widely throughout his environment.

Within the host the point of bacterial multiplication may be the blood, as in plague and malaria, and in such cases dissemination can only be effected through the intervention of an insect vector. Lacking such a vector the bearer of the organism is not infectious. In other cases bacterial growth may take place on the skin, as is the condition in many of the mycoses, and here contagion may be effected through either direct or indirect contact. In another type of case the point of bacterial growth may be within the tissues of an organ communicating with the respiratory tract, as is true in tuberculosis, and here the infecting material is an exudate which is distributed by the sputum, the saliva, or the feces after ingestion of the exudate. Finally, the locus of bacterial growth may be the tissues of some organ associated with the digestive tract or the intestinal contents themselves. In such cases the feces is the infectious material and contamination is effected by the ingestion of water or foods polluted through any agency with such excreta. This type of carrier and this mode of dissemination of the infectious agent are operative in the two diseases, typhoid fever and cholera, to which particular attention will here be drawn.

If we define the carrier, as we have above, as "a person who serves as the culture medium for a given bacterium", it would seem that the whole problem should be simple; that it resolves itself solely into the possibilities of transferring this culture to another susceptible organism. In reality, however, many other factors come into play,

and that we may the better understand them, let us consider the different categories of carriers.

When a pathogenic organism becomes implanted in a susceptible host it grows in a selective tissue* and after a variable incubation period the distinctive symptoms of disease appear. After a time, also of variable duration, the individual either dies or recovers, and in the latter case the multiplication of the pathogen may continue without leading to any appreciable symptoms. (These facts are merely stated as such, with no discussion as to the mechanisms involved.) Thus, we already have four types of carrier: 1) the "incubating carrier" from the moment of infection until the appearance of the first symptoms, 2) the "sick carrier" during the period when the symptoms of disease are manifest, 3) the "convalescent carrier" throughout the period of convalescence if the pathogen continues to grow in the body, and 4) the "recovered carrier" in whom, as is sometimes the case in typhoid fever and often in cholera to mention only these two diseases, the growth of the bacterium continues for months or even for years.

But there are still other types of carrier. Let us consider the pharyngeal exudate of persons who have been in contact with a case of cerebrospinal meningitis. In many of them we will find meningococci, and repeated examination will show that the organisms there found are not simply latent cocci but that these organisms must actually multiply in the mucous secretions, for they often persist for several weeks. Nevertheless, the majority, often all, of these carriers remain free from the disease, although experience shows that they are infectious and are often a source of contamination.

Let us consider also the stools of individuals living in contact with cases of cholera. In a certain number of such persons we find that the cholera vibrio grows in the intestinal contents, sometimes so abundantly that they are found in almost pure culture. Among these "carriers" some contract cholera, but the majority manifest no symptoms of the disease, while some develop a simple diarrhea which persists for a few days and does not interfere with their ordinary activities. How shall we class these "contact carriers"? In

*Let us recall our definition of virulence: "The ability of a bacterium to secrete ferments capable of breaking down the constituents of a given living tissue". This problem is discussed more fully in The Bacteriophage and Its Clinical Applications.

the case of cholera, which I have more particularly studied, they are certainly "incubating carriers" in whom the disease either becomes manifest quickly or becomes aborted before the appearance of cholera symptoms. One further case remains to be considered, a situation very common as regards cholera. A recovered carrier or a contact carrier may disseminate his vibrios throughout an uncontaminated population and as the result many individuals became in turn contact carriers, who, in turn, also disseminate vibrios. This condition, which I have personally observed in the case of cholera, can hardly be limited to this disease.

Carriers may also be divided into two categories upon the basis of the duration of the carrier state; those in whom the growth of the pathogenic organism stops after a short time, the "temporary carriers", and those who harbor the organism for months or even for years, the "chronic carriers".

Are all of these different types of carrier infectious? In other words, do the organisms present in these different carriers retain their virulence in all cases? From the point of view of epidemiology this is a fundamental consideration in the problem of the carrier.

It is unnecessary to list here the diverse diseases for which the existence of the carrier is recognized. Discussion will be limited to two typical diseases, typhoid fever and cholera which, better than all others, exhibit the dangers of generalization. Here are two diseases with intestinal manifestations. For one as for the other the contamination is always of alimentary origin. In both cases after complete recovery the pathogenic organisms may continue to grow in the intestinal tract or in the gall-bladder. It would seem then that from the point of view of etiology and that of epidemiology as well the two diseases should be entirely comparable and that what is true for one should be equally true for the other. Let us see if this is the case.

Typhoid fever was the first disease in which the presence of carriers was actually proved. That incubating or sick carriers may be infectious has been unquestioned since the days of Pasteur. As for healthy carriers, either recovered or contact, there is abundant proof that they remain infectious as long as the typhoid bacilli continue to grow within the body, and it has been demonstrated that such growth may persist for a long time, more than 20 years in certain cases. All epidemiological textbooks record observations con-

clusive in this respect. It is only necessary to mention the epidemic of 1927 in Montreal, where several thousand persons contracted typhoid fever after the ingestion of milk derived from a dairy contaminated by a chronic carrier. Therefore, in so far as this disease is concerned, chronic carriers, recovered or contact, may remain for many years just as infectious as are patients with the disease.

The problem of the typhoid carrier is, however, not completely solved; one unknown remains. Are all chronic carriers infectious and to the same degree? This part of the problem has, up to the present, received no attention, for since it has been known that epidemics of typhoid usually originate in a chronic carrier we have generalized and have concluded that all chronic carriers were infectious.

The many studies which I have carried out* show that in infectious disease the bacteriophage intervenes *in vivo* and the course of this very complex phenomenon regulates the progress and the outcome of the infection. But bacteriophagy, whether it takes place *in vitro* or *in vivo*, is not simply a phenomenon of bacterial dissolution; lysis is but the visible macroscopic manifestation of a group of phenomena. Among these phenomena the mutations which the bacteria undergo through the action of bacteriophage offer a major interest from the point of view of the carrier. The bacterium does not remain passive before the attack of the bacteriophage. When acted upon by a powerful bacteriophage it succumbs, attacked by a bacteriophage of less virulence it defends itself and is capable of acquiring a certain degree of resistance and of contracting a true chronic disease. There is formed a bacterium-bacteriophage symbiosis, in which case the characters of the bacterium may become modified; a character may become more pronounced, it may persist unchanged, or it may disappear. Each character varies as a distinct entity. For example, the morphology may not become modified while the power of fermenting a given sugar may disappear, or the form of the bacterium may be completely changed, a bacillus assuming the coccus form, while the agglutinability by a specific serum may remain. All combinations are possible.

Among the variable characters virulence is, from the point of view which now concerns us, the most important. In the bacterium-bacteriophage symbiosis the virulence of the bacterium may be in-

*The Bacteriophage and Its Behavior; The Bacteriophage and Its Clinical Applications.

creased, a change which is indeed rare, it may be maintained, attenuated, or, as is the most frequent condition with the bacteria thus far studied, it may be suppressed. Within the body of the chronic carrier there is a culture, not of a normal bacterium but, without exception, of a bacterium-bacteriophage symbiosis, as may be readily shown by bacteriological examination of strains isolated from these carriers. In other words, the organisms developing in carriers are not typhoid bacilli, but are bacilli which have survived bacteriophagy because of a resistance which they have acquired. They have contracted a true chronic disease and remain "carriers" of bacteriophage, and because of this they are mutating bacilli*.

It is impossible to verify experimentally the variations of virulence in typhoid bacilli which are carrying bacteriophage, since an experimental animal naturally susceptible to these organisims is lacking†. To the end of ascertaining the possible variations of virulence in the typhoid bacillus I have recently made a study of a related disease—mouse typhoid, caused by a bacillus of the same group, *B. typhi-murium* of Loeffler. Among eight of the mutants experimentally obtained six were totally avirulent, in one the virulence was greatly attenuated, and with another it was maintained. This would imply that mice carrying any of the first six mutants would not have been infectious, while a mouse carrying the eighth mutation would have been as infectious as a sick mouse.

Since each character of the bacterium varies independently, it is impossible to predict the degree of virulence by variations in the other characters. However, it appears from many experiments with many bacterial species that the loss in agglutinability accompanies the loss in virulence, although the reciprocal of this is not true. A mutating bacterium inagglutinable by a specific serum is

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*I must adhere to discussion of observed facts; for the explanation of the mechanism of these phenomena and for their demonstration consult the different texts which I have published during the past 15 years, particularly The Bacteriophage and Its Behavior, The Bacteriophage and Its Clinical Applications, Studies on Cholera.

†An experiment of this type carried out on a refractory animal, such as the guinea pig or rabbit, is without value and can only lead to erroneous conclusions. In so far as typhoid is concerned the only susceptible animal is the anthropoid ape, and unfortunately the funds available for laboratory studies do not permit of their utilization.

avirulent, but a bacterium normally agglutinable may also lack virulence.

Although it is not permissible to compare the two diseases, the experiments carried out in mouse typhoid show that bacilli which grow in carriers may not be equally virulent, while studies made of the typhoid bacillus show, at least, that none of the mutations are fixed, that the characters may evolve, and that in the mutating bacilli the virulence may fluctuate, disappearing from a virulent mutant or reappearing in an avirulent one.

If, and this is only a possibility, the typhoid bacillus of man and *B. typhi-murium* of the mouse behave in the same manner it may be that all chronic carriers are not uniformly infectious and that the infectiousness of each one of them may vary with time. Let us note, moreover, although this has been known for a long time, that the specific serum agglutinability of bacilli isolated from chronic carriers varies, and may even disappear to reappear later.

In brief, then, in so far as typhoid fever is concerned, the incubating carrier and the sick carrier are certainly infectious while of the healthy carrier (recovered or contact) only a certain number, but not all, are infectious. In these the infectious state persists as long as the growth of typhoid bacilli continues within the body, that is, during a variable period of time which, in certain cases, may extend for more than 20 years.

Let us turn to cholera. We may first ask if there are in this disease carriers of each of the types described. It is essential in the first place to recognize that individuals in the incubation period may differ. The incubation period may pass without the person exhibiting outward symptoms of any kind, or it may be accompanied by a simple diarrhea, the *so-called* premonitory diarrhea. Both types are certainly contagious to the same degree, but it is important to be better informed concerning the actual duration of the maximum incubation period in both cases. Those who have dealt with this subject say nothing upon this point, and, indeed, except for rare exceptions it is very difficult to determine precisely the incubation period, for during an epidemic or in an epidemic region it is generally impossible to establish the actual time of the infection.

In France during the epidemic of 1892 it seemed that in one case the incubation period was definitely established at six days. A soldier left the city of Calais where cholera was present and went to

Cette. Six days after departure from Calais he presented the first symptoms. One might obviously object that possibly virulent vibrios were transported on soiled linen and that he was infected during the voyage. We do not know, moreover, that he did not suffer from diarrhea during the voyage. In Indo-China I have observed a vibrio diarrhea some seven days preceding a fatal attack of cholera. We do know, however, judging from facts based upon quarantine procedures, that the incubation period in cholera is never greater than nine days.

Many observations have shown that the "incubating carrier" is particularly infectious. He is likewise the most dangerous, for being able to move about and to follow his habitual occupations he can disseminate pathogenic vibrios over a wide area.

For cholera, as for typhoid fever, the progress of the disease and its termination are under the direct control of *in vivo* bacteriophagy, as I have shown by the study of a large number of cholera cases. In this disease one of three situations develops: 1. Bacteriophagy does not take place, the symptoms develop and the individual dies within 48 hours. 2. Bacteriophagy takes place quickly, before symptoms appear, and the disease is aborted. 3. Bacteriophagy occurrs more slowly and progressively. The characteristic symptoms appear and the course of the disease is strictly related to the intensity of bacteriophagic action. Convalescence begins at the moment when the phenomenon reaches an intensity sufficient to bring about a destruction of the vibrios.

Up until the time when complete bacteriophagy is effected or, in other words, until convalescence begins, patients are, like incubating carriers, potentially infectious. All studies made of cholera epidemics show this clearly.

The question of the infectiousness of recovered carriers remains to be considered. It must be understood, that it is necessary to include in recovered carriers both those who have actually had the disease and became convalescent through effective bacteriophagy, and those in whom the disease became aborted before the symptoms appeared because the bacteriophagic phenomenon took place early at the beginning of the infection.

During the studies made in India in 1927 I was able to discover the mechanism leading to the development of recovered carriers. Recovery is the direct consequence of bacteriophagy *in vivo*, but in

all individuals the phenomenon does not take place with the same intensity. In certain patients (about one-third of the cases studied) bacteriophagy developed suddenly and intensely within 24 hours of the first symptoms. In these cases the vibrios disappeared from the intestine. These individuals did not become recovered carriers. In other patients the virulence of the bacteriophage developed more slowly, with the number of vibrios diminishing gradually, disappearing completely between the second and fifth days. Vibrios remained absent from the stools during a period which varied from a few hours to three days and then they reappeared, sometimes in considerable numbers. Study showed that here a "secondary culture" had developed. The phenomenon of bacteriophagy *in vivo* resembles in all respects bacteriophagy *in vitro*, and the vibrios which reappear thus in the stools are no longer normal vibrios but are mutants. They represent a vibrio-bacteriophage symbiosis, that is, the vibrios are carriers of the bacteriophage. This reappearance of vibrios, however, has no influence on the course of convalescence which continues in a normal fashion whether such vibrios are present or absent.

The vibrio-bacteriophage symbiosis which develops *in vivo* behaves exactly like the symbiosis which can be produced at will *in vitro*. According to the conditions present at the time of its formation one of three things may occur. 1. The resistance of the vibrios increases and they succeed in effecting a destruction of the bacteriophage. In this case the symptoms of cholera reappear and a relapse, generally fatal, takes place. Such cases are rare and occur in only about one per cent of patients. This phenomenon develops some six days after the beginning of convalescence, that is to say, at the time the symbiotic relationship appears. 2. The virulence of the bacteriophage increases and it succeeds in overcoming the resistance of the vibrios. The latter are completely destroyed. It is this type of behavior which occurs most frequently and it generally takes place during the early days of convalescence. These individuals cease being carriers at this time. 3. Sometimes the resistance of the vibrio and the virulence of the bacteriophage balance. A symbiotic culture then develops within the intestine and persists until the virulence of the bacteriophage removes it. This usually takes place during the course of the first weeks following convalescence, but it may, in certain cases, be retarded for several years.

Up until this time the individual remains a carrier and he disseminates his vibrio-bacteriophage complex which may become implanted in others with whom he comes in contact, whereupon they also become carriers of the symbiosis and disseminate it.

In brief, up to this point the situation in cholera is completely comparable to that in typhoid fever. In both cases the decisive phenomenon is bacteriophagy and the formation of carriers is determined by the appearance of a secondary culture *in vivo*. In typhoid fever the contaminating bacilli constituting this secondary culture may retain their virulence. Is this likewise true for cholera? In other words, and this has been the subject of many controversies for the past 15 years, are chronic carriers of the cholera vibrio infectious or are they not?

It is pertinent to observe that the epidemiology of the two diseases is essentially different. Typhoid fever is a disease which is endemic throughout the entire world and what is called an epidemic of typhoid fever is in reality but a local recrudescence of a perpetual pandemic. We know the reason of this persistence, for since a certain number of patients remain infectious carriers for a long time there exist, therefore, among the population reservoirs of virulent bacilli and these disseminate the organisms throughout their surroundings, and according to the conditions governing this dissemination either sporadic cases occur (dissemination by direct contact), or more or less extended epidemics (dissemination through contamination of some agency, such as a well, dairy, etc.) Because chronic infectious carriers exist a pandemic of unlimited duration, with accidental local outbreaks, is inevitable.

The epidemiology of cholera is different. There are in the world two strictly limited regions where cholera persists in a perpetual endemic state with seasonal recrudescences. These are in the Bengal portion of India, and in Indo-China and the adjacent Chinese province of Yunan. Outside of these two regions cholera is the epidemic disease par excellence. In Europe and in America several epidemics have occurred during recent centuries, and the course has always been the same. At the beginning of each epidemic the cholera vibrio is brought in from one of the two endemic regions (usually from Bengal because of the greater facility of communication) *always by a patient*, and it has been possible in all cases to discover the route followed. With the vibrios once imported into a region hitherto

free of the disease the epidemic of cholera extends gradually and continues to spread during one, two, or at most three years, and then it completely disappears. For a new epidemic to occur the virulent vibrio must again be imported by a patient from one of the two endemic regions.

This distinctive epidemiology of cholera proves that infectious chronic carriers do not exist, for if chronic carriers were infectious, instead of disappearing completely the epidemic would be transformed into the endemic state. We are, then, forced to conclude that the vibrios which are present in the intestines of chronic carriers are always completely avirulent. Observations, indeed, directly confirm this conclusion. Let us cite a few facts.

At the quarantine station at Tor, in 1897, Ruffer encountered five pilgrims returning from Mecca who exhibited symptoms of dysentery, and from them he isolated organisms which morphologically and serologically were typical vibrios, but in no instance did cholera appear in these pilgrims. Indeed, during 1897 the Hejas was entirely free of cholera. In the same way, in 1905, Gottschlich also isolated, under the same conditions, typical vibrios from the stools of five pilgrims. Analogous observations, always in the absence of an epidemic of cholera, have been made at different times by Krauss, Kolle and Meinicke, Muhlens and Raven, and others.

Greig has reported that he found cholera vibrios in the drinking water of Calcutta throughout a period of several months, and he was unable to discover the cause until he found out that an employee of the laboratory engaged in making the examinations was a chronic carrier who, by means of his soiled hands, contaminated the water supplies. There was, nevertheless, no increase in the number of cases of cholera during the period of contamination (Calcutta, the capital of Bengal, is in the endemic region).

In 1892, when cholera appeared in Hamburg, vibrios could be isolated from the water of the Spree at Berlin, but no cases of cholera were noted in this latter city. These vibrios could only have been derived from carriers.

During an epidemic of cholera in Algeria in 1912, Sergent demonstrated that the drinking water of a city of 5,000 inhabitants in the province of Oran was contaminated throughout several weeks by the vibrios, but no cases of cholera developed. From whence came these vibrios? Unquestionably from carriers.

Two years after an epidemic which had occurred in Paris in 1892 Metchnikoff isolated cholera vibrios from the water of the Seine. He also isolated them at different times from the drinking water of Versailles, which was taken from the Seine from below Paris. Nevertheless, for the two years no case of cholera had occurred in Paris, and Versailles, had never had an epidemic of cholera in spite of the presence of vibrios in the drinking water.

It would be easy to multiply such examples. All of them show that vibrios derived from carriers are not pathogenic. They are completely avirulent.

We are, therefore, forced to conclude that there is an important difference between the epidemiology of cholera and that of typhoid fever. In the latter disease chronic carriers may be infectious for an unlimited period, at least for more than 20 years, while in cholera both epidemiology and direct observation show that the chronic carriers are never infectious.

But here we must ask a question. Since a chronic carrier is necessarily at one time a recovered carrier or a contact carrier and since in the disease the vibrios are infectious, at what moment do they cease to be so? Through what mechanisms do the vibrios pass from the virulent to the avirulent state and at what moment is this transformation effected?

Let us first examine the data of those authors who have considered carriers as the origin of epidemics. Throughout the whole literature of the past fifty years, that is to say, since the discovery of the cholera vibrio by Koch, only two such observations have been recorded in spite of the fact that thousands of papers have been published. The first observation is that of Greig (Indian Medical Gazette, 1908, *48*, 10) who attributed a localized epidemic in the prison at Puri (Bengal) to the admission of a carrier. Such an example is of questionable value, for cholera is endemic in Puri where it has occurred for some centuries without interruption throughout the entire year. It is manifestly impossible under such conditions to exclude other sources of contamination. In order to be valid such an event must take place in a known uninfected region where if an epidemic develops through the arrival of a carrier only this carrier can be incriminated. Furthermore, did not Greig himself demonstrate that in this town of Puri contamination takes place chiefly through the intermediary of flies? Could not an infected fly have

entered the prison and contaminated the rice used as food for the prisoners? MacRae (Indian Medical Gazette, 1908, *43*, 61) had earlier noted the spread of cholera in a prison by flies, and Haffkine, a member of the investigating commission, provided bacteriological proof for this mode of transfer. In a town like Puri, a center of infection, the causes of contamination by direct or indirect contact are so many that it is impossible to regard the carrier as the sole possibility.

The second observation is that of Sergent, who stated that during an epidemic in Algeria in 1912, three cases of cholera developed in one house in a village which up to that time had been free of the disease. These cases followed the arrival of an old woman who was later shown to be a carrier. This observation is also subject to discussion, for it was not demonstrated that the infecting organisms were derived from the stools of this woman. In India it has been possible very frequently to demonstrate a distant transfer of virulent vibrios on fruit or on linen soiled through contact with patients. It has been possible to trace the origin of a very extensive epidemic in the Sudan to a flask of water brought from Zemzem, the sacred well of Mecca, by a pilgrim. In the epidemic region the possible causes of contamination are many.

In the face of these two isolated cases, the one of doubtful value, the other open to discussion, there are thousands of observations which show that the carrier, even the recent one, is never a cause of contamination.

It is significant that in the course of cholera epidemics the number of carriers is extremely large. In Russia, after the epidemic of 1910, it was shown that 6.7 per cent of the adults in the infected regions became carriers, and that the figure reached 20 per cent in infants. While studying cholera at Rostov, Barrikine and Zaccharoff (Centralbl. f. Bakt. 1.0 1924, *92*, 201) found that in March, at the beginning of the epidemic, the number of carriers was practically zero, in June they represented 6.5 per cent of the total population, and at the end of the epidemic in October, 72 per cent, almost three-fourths of the population, were carriers.

Babès records that at the end of an epidemic in Roumania 30 per cent of the individuals exposed to contagion were carriers of the cholera vibrio.

It is needless to add further examples, but it may be pointed out, and to this we will return shortly, that it is at the time when an epidemic definitely ceases that the number of carriers reaches its maximum. This in itself warrants the assumption that the vibrios thus being harbored can not be virulent. Obviously, one might object in accordance with the theories which are still current, that when the epidemic ceases it is simply because the population becomes "immunized" during the course of the epidemic. Let us consider then, the case of the transfer of carriers into disease-free regions where the inhabitants are certainly not immune to cholera.

For centuries cholera has been endemic in Bengal. At Calcutta, its capital, there is not a single day throughout the year without the development of a case. Thousands of travellers embark each day at this port for diverse destinations, most of them countries which have been free of cholera for many years, such as Australia, America, and Europe. For those whose destination is Europe a sanitary examination takes place at Suez under the direction of the Conseil Sanitaire, Maritime et Quarantenaire d' Egypte. This examination consists of a simple visual inspection, and even this is waived in the case of first class passengers. There can be no doubt, in view of the recognized presence of many carriers in Bengal, that transient carriers debark frequently in Europe but that such a carrier has ever caused an epidemic of cholera has never been observed.

Cholera broke out in Russia during the first decade of this century. Beginning with the 15th of August, 1910, the sanitary service at Amsterdam undertook the bacteriological examination of the crews (not the passengers) of ships, coming from Russia and considered as free of the disease, in order to determine if vibrio carriers were present. Such carriers were found, from which it was logical to infer that carriers were being admitted to the country, for if carriers were found among the crews which made but short stays in the ports of call they must have been still more numerous among those passengers coming from the infected regions. But during the years when cholera raged throughout Russia not a single case of cholera in Europe was reported which could be attributed to the admission of carriers. Observations of this nature enabled the International Conference on Cholera, Paris, 1911, to conclude that proof of the transmission of vibrios for a long distance by the intermediary of carriers was lacking.

Let us cite a still more typical fact which in value is equivalent to an experimental demonstration. The Conseil Sanitaire, Maritime et Quarantenaire d'Egypte which administers the station at Tor has felt obliged to deny that cholera vibrio carriers pass through that station. Let me present the figures extracted from the official publications of the Conseil itself.

Each year the Mohammedans make pilgrimage to the holy cities of Islam, Mecca and Medina, located in the Hedjaz. In the course of this pilgrimage those pilgrims coming from the Mediterranean basin mingle with those coming from India, who bring with them the cholera vibrio from Bengal and who frequently cause thus epidemics in the Hedjaz. To the end of assuring the protection of Europe an International Conference established the Conseils Sanitaires, Maritimes et Quarantenaire of Constantinople and of Egypt (the first has been inoperative since the Great War) which were charged with the application of defense measures established by the International Conference of Venice.

Before the war the pilgrims returned by two routes, by the Hedjaz railroad or by sea. The Conseil at Constantinople supervised the pilgrims returning by rail by means of a quarantine station located at Tebouk. The Conseil at Egypt had charge of the ship transport, and the quarantine station was located, and is still, at Tor, on the shore of the Red Sea on the peninsula of Sinai.

Cholera has occurred with violence in the Hedjaz among the pilgrims on several occasions, particularly in the years 1908, 1910, 1911, and 1912. During these four epidemic years 65,487 pilgrims passed through the station at Tebouk. As may be gathered from reading the reports published at this time, in the Bulletin of the Committee of International Hygiene, no bacteriological examinations for carriers were made. The sole effort was directed toward restraining patients affected with clinical cholera. All of these pilgrims became distributed throughout Asia Minor, Turkey, Persia, and the Balkans, and in spite of the presence among them of carriers (a presence certain in view of the findings made at the station at Tor, which we will consider later) no case of cholera occurred which could be attributed to them.

The second group of pilgrims returned to their native countries by sea, and their examination was directed by the Conseil Sanitaire of Egypt which operated for this purpose a large quarantine station

at Tor where all of the pilgrims debarked and were treated according to the rules of the sanitary police. Article 55 of these rules reads: "If plague or cholera is present in the Hedjaz or in the port from which the ship sailed, or has occurred in the Hedjaz during the period of the pilgrimage, the ship is to be subjected at El Tor to the following measures. Persons affected with plague or cholera are to be debarked and isolated at the hospital. The other pilgrims are to be debarked and isolated in small groups in such manner that the entire number shall not be allocated to a particular group. . . . All pilgrims are to be subjected to observation for a full seven days for plague or for cholera. If a case of plague or cholera develops in a given group the seven-day period of observation for this group shall begin on the day when the last case was noted."

The regulations governing the Conseil make no mention of the search for carriers (Bulletin of the Committee International d'Hygiene Publique 1911, 3, 1724) and, in fact, during the epidemics which we have mentioned this investigation has never been made on non-Egyptian pilgrims. Only with those of Egyptian derivation, with whom the jurisdiction of the Conseil of Egypt is absolute in matters of hygiene, has this study been carried out and then only in the epidemic of 1911-12. Figures presented in the official report published by the Conseil are available and, as I have stated above, the experience at Tor is as valid as an experiment and shows that carriers are never infectious and that a simple segregation of patients, with a quarantine of seven days for contacts, suffices to establish a barrier against the diffusion of cholera.

The report of Dr. Gottschlich, bacteriologist of the Conseil, shows that during the pilgrimage of 1908 only the stools of patients entering the hospital at Tor were examined. Four cases of cholera developed at Tor. All of the pilgrims, Egyptians and non-Egyptians, their quarantine terminated, reembarked and were distributed throughout the countries bordering on the Mediterranean with no case of cholera being noted, either on the ships which carried them from Tor to their port of landing or in the countries of their origin.

In the course of the pilgrimage in 1910-11, when a new epidemic occurred in the Hedjaz, 25,550 pilgrims debarked at Tor. There were 45 cases of cholera, with 23 deaths, in the hospital. Dr. Gottschlich made 1160 stool examinations of pilgrims without cholera, finding agglutinable vibrios in 31, non-agglutinating vibrios in 23.

In view of these results, it is obvious that among the 24,390 pilgrims not subjected to bacteriological examination there must certainly have been many carriers. Nevertheless, these continued their passage when the quarantine period expired, but no case of cholera referable to them developed either on the ships or in their native lands.

The station at Tor received 11,880 pilgrims in 1911-12. Of these 29 contracted the disease after their arrival and 21 died. Bacteriological examinations were carried out on 1454 healthy pilgrims (of which 1384 were Egyptians) and on 365 persons with diseases other than cholera. Thirty-two carriers were found (one remained a carrier for 53 days after debarkation). In this year then, 10,426 pilgrims were passed without examination after having undergone the period of quarantine. None caused a case of cholera.

And, finally, in the campaign of 1912-13, 16,551 pilgrims (13,373 Egyptians and 3,178 from countries bordering the Mediterranean) debarked at Tor. Thirty-two cases of cholera were recorded, 11 among the Egyptians, 21 among the others. In this year all of the Egyptian pilgrims were examined and 40 healthy carriers were detected together with 33 more among the patients in the hospital with diseases other than cholera. This number of carriers is certainly far below the true number, for it is well known that a single examination is inadequate to detect all carriers. The 3178 non-Egyptian pilgrims underwent no bacteriological examination. Among them the incidence of carriers were certainly greater than among the Egyptians since, as evidenced by the morbidity, this group was more strongly infected with cholera. They became distributed, like the pilgrims of preceding years, throughout the Mediterranean Basin without leading to a single case of cholera.

The experience at Tor, added to the other facts mentioned, seems to be conclusive. Carriers of the cholera vibrio, other than incubating and sick carriers, are not infectious. This conclusion had been reached by Dr. Zachariadis, one-time director of the quarantine station at Tor. In his report for 1911-12 he wrote: "The author is convinced that the rôle played by carriers in the dissemination of cholera is practically negligible, and only patients assure the propagation of the disease." This report was published under the jurisdiction of the Conseil Quarantenaire d'Egypte which, it would seem, must have approved of such a conclusion.

There only remains a last question, namely, at what moment does the carrier cease to be infectious?

We have seen above that in cholera, as in other infectious diseases, recovery takes place as a result of *in vivo* bacteriophagy, and that in those patients (as is the case with direct or indirect contacts) who remain carriers the intestinal flora no longer contains a culture of pure cholera vibrios but a culture of vibrios in symbiosis with bacteriophage. As may be shown, it is possible to demonstrate that the loss of virulence is coincident with the occurrence of bacteriophagy, from which it follows that only incubating carriers and sick carriers are infectious. In the convalescent carrier bacteriophagy has taken place and he is no more infectious.

A study of cholera epidemics in India has revealed the nature of the phenomenon which leads to the cessation of epidemics. It is the dissemination by convalescents of bacteriophage adapted to the cholera vibrio. That this is true is shown by the fact that it has been possible to check epidemics promptly by disseminating cultures of experimentally adapted bacteriophage through the intermediary of drinking water. These experiments have since been confirmed by those, also carried out in India, of Asheshov (d'Herelle, Studies on Cholera, published by the Conseil Quarantenaire d'Egypte in 1929; Asheshov, Indian Journal for Medical Research, 1929). We have seen that within the enteric tract of the carrier there is a symbiotic culture. These carriers distribute with their excreta not only avirulent vibrios, but also bacteriophage races antagonistic to the infection.

In the epidemics of cholera which took place in Paris at the end of the last and at the beginning of the present centuries Metchnikoff was greatly intrigued by the fact that no cases of cholera were observed at Versailles, in spite of the constant presence of vibrios in the drinking water of this city. These must have been symbiotic vibrios.

While studying cholera at Rostov in 1923, Barikine and Zaccharoff saw that the epidemic ceased when the number of carriers reached the maximum, 72 per cent of the population. And Babès, in Roumania, in the 1913 epidemic records that more than 10,000 persons had been in contact with patients and for this reason were placed in isolation camps after examination of the stools. Nevertheless, none of these carriers contracted cholera. In none of the contacts which had been affected had he found vibrios when previously examined.

The explanation of these apparently contradictory facts is that these contact carriers are in reality infected individuals in whom the disease does not develop because bacteriophagy takes place before the appearance of symptoms. They, like convalescents, remain carriers of a vibrio-bacteriophage symbiosis. They are the source of a new contamination and distribute about them the symbiosis containing the antagonistic bacteriophage.

I have recently made an experiment conclusive in this respect. It was not possible to utilize the cholera vibrio, for there is, for this organism, no susceptible experimental animal. As we know, the mouse is naturally susceptible to the experimental disease provoked by the ingestion of minimal doses (0.001 cc.) of cultures of *B. typhi-murium*. First experimentally producing *B. typhi-murium-bacteriophage* symbioses, I have shown that the ingestion of such a completely avirulent symbiosis by mice protects them against the ingestion of several times the fatal dose of virulent culture of *B. typhi-murium**.

From all of these facts, both of experiment and of observation, it seems permissible to conclude:

1. In typhoid fever there are certainly chronic infectious carriers, but it is possible that there are also carriers who are not infectious and that the latter propagate an adapted bacteriophage, an agent antagonistic to the infection.

2. In cholera the carrier is never infectious. The transformation of the vibrio from the virulent to the avirulent form takes place at the time of bacteriophagy. These carriers are thenceforth protected from infection, and remain so as long as they remain carriers of the symbiosis. Furthermore, other individuals become "contaminated" by them.

The sole agents in the propagation of cholera are the "incubating" carriers and those sick with the disease. Moreover, bacteriological examination renders it possible to distinguish the infectious incubating carrier from the recovered or non-contagious contact carrier. In the first, the intestine contains a culture of pure vibrios, in the latter, there is a symbiotic culture, from which it is easy to isolate a bacteriophage competent to induce *in vitro* bacteriophagy of the cholera vibrio.

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*The details of these experiments will be published later.