TWENTY YEARS OF YELLOW FEVER CONTROL THROUGH PREVENTIVE VACCINATION

by

Dr. Jean Laigret
Membre Correspondant de l'Académie de Médecine
Directeur de l'Institut d'Hygiène
et de Bactériologie de Strasbourg (France)
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Epidemiological, economic and social results of vaccination

The first trials of yellow fever vaccination were made a little more than 20 years ago. Next year will mark the twentieth anniversary of the first large-scale applications of the vaccine in West Africa. Progressively thereafter a large part of tropical and equatorial Africa was immunized. Next came the vaccination campaigns of the Rockefeller Institute in America, the vaccination of numerous contingents of allied troops during the war and the vaccination of the crew and passengers of aircraft and ships. Nowadays, subjects vaccinated against yellow fever can be counted in millions. When the present position is compared with that 20 years ago it can easily be seen that considerable progress has been made. Yellow fever has fallen to the level of a rare disease. No longer do epidemics occur such as those which periodically returned to sow panic in Africa and America, making it necessary to close ports, quarantine ships and stop trade, thus adding commercial ruin to the heavy loss in human life. The disasters which yellow fever so often caused in the past are being forgotten. It is as well to recall them, so that the importance of the change brought about and the resulting advantages for the modern world may be realized.

Among the economic consequences of vaccination, there is one which should be stressed, namely, that involving aviation. When the first intercontinental airlines were set up there was grave disquiet; it was feared that aircraft would transport yellow fever to India, the Far East and the Pacific. There, it would have found populations untouched by the disease among whom the ravages it would have caused may well be imagined. By a fortunate coincidence, at the very moment when such concern arose, vaccination commenced to be applied; its powerful preventive action was soon recognized and made use of for the immunization of the crew and passengers of aircraft. In this way, air transport succeeded in developing its network of communications from one country to another without the threat of the development of new foci ever materializing. Since that time the number of human lives safeguarded by the yellow fever vaccine, the material and financial benefits to trade, as well as to sea and air transport, have greatly exceeded the hopes of the most optimistic workers during the period of the first trials. The change observed in 20 years can best be compared to
the upheaval caused in the epidemiological situation of the period by Jenner's vaccine;  
the yellow fever vaccine occupies the same place in the prevention of yellow fever as  
Jenner's vaccine does in the prevention of smallpox. As early as 1934, Charles  
Nicolle prophesied that yellow fever would be vanquished. Today the World Health  
Organization affirms that vaccination is absolutely reliable; there is no longer any  
risk that the effectiveness of the vaccine will be doubted.

**Previous criticisms of vaccination**

Nevertheless, doubts voiced in this connexion were long included among the  
criticisms levelled against vaccination. There was of course Max Theiler's sero-  
protection test which revealed the humoral signs of acquired immunity in the blood of  
vaccinated subjects, but opponents of the vaccine rejected this test as being non-specific.  
They spread the tale, which now can only raise a smile, of a cow in India whose blood was  
said to be positive to the Max Theiler test, clear evidence that the latter was worthless!  
Yellow fever cases were discovered among vaccinated subjects; a woman had contracted  
the disease two years after vaccination. Enquiry showed that she had received only the  
first injection of vaccine; this was at a time when vaccination was carried out, for  
reasons of safety, in three injections of which the first had a very low virus content  
and was insufficient to bring about immunization.

Much more serious, the accusation was made that vaccinated persons represented a  
danger to those about them.

Experiments, in particular those of Roubaud in France, had proved that the vaccine  
virus is not transmitted by mosquitoes. Despite this, attacks such as the following  
were made against vaccination; in a railway station on the Dakar - St.Louis line, lived  
a stationmaster with his wife and daughter; the stationmaster alone had himself  
vaccinated, feeling that he was the most exposed by reason of his night duty. However,  
the daughter who was visiting friends at Rufisque followed their example and was also  
vaccinated, so that in the family there were two vaccinated persons. Only the mother  
was unvaccinated, and she contracted yellow fever and died. Could there be a better  
proof of the effectiveness of the vaccine? An official report put matters differently,  
however; according to the report it was the vaccine circulating in the bloodstream of  
the father and daughter which had infected the mother and killed her. The author of
this report published articles written in the same vein, articles which are still consulted in good faith by those studying vaccination. What has been said above shows how much confidence can be placed in such reports. The literature concerning yellow fever vaccination is full of publications of this nature which mislead the uninformed reader. Having made this point clear, it must nevertheless be recognized that everything is not perfect in yellow fever vaccination. It is sometimes followed by reactions which it would be very desirable to avoid. In the following we shall study them, commencing with the simplest and most harmless, namely, the febrile reaction on the 6th to 7th day.

The febrile reaction on the 6th to 7th day

Reactions were only to be expected since every form of vaccination produces them, above all those employing a living vaccine, as is used for yellow fever immunization. It is well known that the vaccine used is the original yellow fever virus which, in the hands of Sollards and Max Theiler, underwent a mutation involving the loss of the power to bring about yellow fever.

It paralyzes the mouse when inoculated intracerebrally so that it is called "neurotropic" yellow fever virus. It immunizes man by causing an asymptomatic infection during which it multiplies in the human body, and this infection leads to immunity comparable in every way with that following recovery from the natural disease.

Charles Nicolle said that, for effective vaccination with a living virus, the aim should be always to remain on "the borderline between asymptomatic infection and disease". In practice there is always an involuntary deviation one way or the other, either above or below this limit; when it is below, immunity is not produced or is inadequate; when it is above, reactions are caused which come within the field of clinical infection but which, nevertheless, do not forbid the use of the vaccine in the case of symptoms which are really mild and of short duration. This is the case with the febrile reactions which are observed during yellow fever vaccination six or seven days after the inoculation.

I noted these reactions during our first trials at the Tunis Pasteur Institute and subsequently observed them again in West Africa. Since then everyone who has carried
out vaccination against yellow fever has seen them. They involve an attack of fever resembling a mild malaria attack and terminating at latest on the following day or the day after that. Vaccinated subjects, provided they have been warned, never become alarmed.

The incidence of these reactions is difficult to define precisely. In my experience they are always rare in children, rare or very rare in women and distinctly more frequent in adult men, although never exceeding 25 per cent of those vaccinated.

I attempted to find a connexion between these febrile reactions on the 6th day and the virulence of the vaccine, the latter being evaluated in mouse units, i.e. minimal lethal doses for the mouse. I could not find any relationship; a very small amount of virus, less than one unit, is all that is required to bring about the febrile reaction in one subject, whereas other subjects receiving 100 or 500 units do not react. I also looked for a connexion between the febrile reaction and the development of immunity. Again, there is none; vaccinated subjects who do not react are as strongly immunized as the others and within the same period of time.

One thing is certain, namely, that those reacting are always subjects vaccinated for the first time; the febrile reaction is never seen in revaccinated persons. When we carried out vaccination in three steps, using first, less than one mouse unit, next, two units and then 20 units, with an interval of two or three weeks, a small number of febrile reactions occurred after the first injection. They were particularly frequent after the second and exceptional after the third injection, because all or almost all subjects were already immunized by the first two injections, as confirmed by serological tests.

Some workers have wondered whether there is not a relationship between the febrile reaction on the 6th day and the late meningeal reactions which we shall discuss later on. I can answer this point straight away; the 6th day fever in no way indicates that a neural reaction will subsequently appear; conversely, the neural reaction, when it does occur, may equally well have been preceded or not preceded by a 6th day fever; the two reactions are quite independent of one another.

Disquiet has also been caused by the presence of the virus in the blood during the
febrile reaction. To this we have already given the answer in defining vaccination as "an infection, usually asymptomatic, during which the virus multiplies in the body". The virus is found in the blood of non-febrile vaccinated subjects just as it is in that of febrile vaccinated subjects. In the study of viral, rickettsial and spirochetal infections, this virulence of the blood is frequently observed both in man and animals, even in the absence of any symptom, and this is all the more so when a feverish stage occurs. The presence of the virus in the blood can have no pathogenic or prognostic significance any more than can the fever itself; it is merely a sign of the in vivo multiplication of the virus, a multiplication necessary for the development of immunity.

Cases are cited of what some authors called "prolonged" 6th day reactions. These occur in vaccinated subjects who develop fever, digestive upsets and generally an enlarged liver and remain in this state for one, two or sometimes three weeks. I have seen cases of this kind in West Africa and mentioned them in my 1934 report. I found that these patients were always old colonial residents, tired by a long period spent in the colonies; several had already suffered from troubles of the same kind before vaccination. Everything seemed to point to hepatitis of a type fairly common in hot countries and, indeed, during the thousands of vaccinations which I have carried out in temperate zones, I have never seen similar cases. Colleagues in charge of yellow fever vaccination centres in France have also never reported such cases. Consequently, something other than a vaccinal reaction is involved. It would seem certain that vaccination favours the outbreak of such disturbances in persons whose liver is more or less impaired, but other types of vaccination would have the same effect. Thus, there are no grounds for speaking of "prolonged 6th day febrile reactions" as some workers have done.

Post-vaccinal jaundice

I have intentionally left the question of jaundice on one side in the last chapter, although it is implicitly included, since the hepatitis seen in hot countries which has sometimes been taken to be a vaccinal reaction, is usually accompanied by jaundice or mild jaundice. Indeed, this is precisely the cause of the error which some authors have made. It seemed natural to them that the vaccine should bring about in certain
subjects a mild jaundice, a kind of "miniature yellow fever" (this expression has actually been employed) appearing as a clinical proof of the potency of the vaccine. Unfortunately, this reasoning does not hold and I feel that it is worth while devoting a little time to giving the reason for this.

It is known that natural yellow fever has benign forms. Formerly it was not known how to diagnose them but today they can readily be identified, thanks to serological tests. Numerous cases were seen during the surveys carried out to delineate the endemic zones; they are short-term fevers without jaundice.

The absence of jaundice in these mild forms can readily be understood. Jaundice is a symptom which appears only in the second phase of yellow fever, associated with haemorrhage, together with which it constitutes the grave syndrome of the terminal period. Before this, there is the initial period which during the first three or four days is simple fever without jaundice. The benign forms of yellow fever are abortive, truncated forms and recovery commences immediately after the first phase, before the syndrome of the second phase has developed. Thus such forms never involve jaundice nor are they ever serious.

When it is not completely asymptomatic, vaccination takes a form similar to a benign natural infection but still more reduced, being limited to an attack of fever on the 6th-7th day which cannot include jaundice among its symptoms any more than can a natural mild attack.

It is thus an error to attribute jaundice to the vaccine and to believe it capable of causing "miniature yellow fever", taking the form of benign jaundice. When jaundice develops following vaccination, some other factor is involved and in hot countries this is frequently long-standing hepatitis, either known or unknown, which becomes active following vaccination.

However, an associated virus may also be responsible. To this category belong the cases of jaundice which followed, first of all, Findlay's sero-vaccination experiments in Gambia and then, during the war, the inoculations with vaccine 17D which was recognized to be contaminated with the virus of epidemic hepatitis.

In the same connexion, I may mention two personal cases which greatly disturbed me
in Tunis during our first trials. Two grave cases of jaundice appeared among a group of vaccinated subjects. The neurotropic virus had at that time only undergone a relatively small number of mouse passages so that the return of its original pathogenic power was to be feared and was naturally my first idea. However, these cases seemed to differ from yellow fever in several details, i.e. jaundice appeared at an early stage, almost at the same time as the fever; the intense colour was neither that of jaundice nor of yellow fever; the patients did not vomit but they spat blood, which came from pulmonary hepatization foci detectable on auscultation. Finally, the disease was found to be leptospirosis. The blood, urine and sputa contained spirochaetes; this diagnosis was confirmed by inoculation of guinea pigs. Both patients belonged to a community living in deplorable conditions, in contact with rats, dogs and other animals.

These two cases have often made me think of Noguchi's mistake. The patients Noguchi encountered at Guayaquil and believed infected with yellow fever were certainly of this type. Perhaps they were indeed suffering from this disease at the same time as leptospirosis. Sellards found leptospiros in the blood and urine of a monkey inoculated with yellow fever. As regards the two vaccinated Tunisians, they were infected both with Leptospira and with the neurotropic yellow fever virus with which they had been inoculated for purposes of immunization.

These are facts which unmistakably indicate an association of viruses and there is no doubt that they warrant our attention. Nevertheless, it should be mentioned that since that time, out of millions of subjects vaccinated with the French neurotropic strain, no further cases of such grave jaundice have ever occurred. The two cases in Tunis were therefore isolated ones and consequently care should be taken to avoid drawing general conclusions from them. However, it should be noted that when faced with these cases the first idea to arise was that the nature of the vaccine had changed, for it must be admitted that there were serious reasons for believing this. Nevertheless, nothing of the kind had occurred and it was a concomitant pathogenic agent which had caused these accidents. The intruder was relatively easy to detect and identify, but it might have been an unknown or little known virus which we would have been unable to detect and we should then have continued to hold the vaccine responsible
for what had happened. We must be careful not to conclude too hastily that the virulence of the vaccine has changed; this is doubtless the most useful lesson to be learnt from this chapter on post-vaccinal jaundice.

**Post-vaccinal meningitis or meningo-encephalitis**

As compared with the 6th-7th day fever, the neural reactions are always late. They appear most often between the 11th and 15th day, sometimes a little earlier, sometimes a little later, the longest incubation period seeming to have been 23 days.

As mentioned above, they may or may not have been preceded by fever on the 6th-7th day. When the two reactions follow one another, the temperature curve repeats itself, i.e. an initial peak is followed by an apyrexic interval, then there is renewed fever, accompanied this time by meningo-encephalitic symptoms. These symptoms, it may briefly be recalled are: headache, photophobia, a more or less marked stiffness in the nape of the neck, Kernig's sign fairly often only slight, paresia of the limbs, obnubilation and somnolence. In addition, the reaction commences with convulsions in children, which are alarming for the family. Lumbar puncture yields a clear, hyperlymphocytic, hypertensive liquid. This state continues for four-five days; exceptionally it may last ten-twelve days.

Until recent years the general view was that such accidents are always curable. The neural symptoms disappear as suddenly as they come, the fever falls and recovery ensues without sequelae. The cases observed in French West Africa (including the first two which I reported in 1934) recovered in this way as well as cases observed subsequently in France and in North Africa, whether they developed following the use of the French vaccine or of vaccine 17D, as in the recent cases of Professor P. Lépine.*

Following the events which occurred in 1951, the same confidence is no longer felt as regards prognosis. There were fatal cases in Costa Rica and Nigeria. The conditions under which these accidents appeared were appreciably the same, but they took a different course and were fatal in a proportion reaching, and in Nigeria even exceeding, a third of the cases. Thus we are faced no longer with benign neural reactions but with grave accidents, at least in the circumstances which we have just mentioned.

* See document WHO/YF/7
In the past, as at the present time, post-vaccinal meningitis has happily always been rare. In his report Dr. G. Stuart has brought together data published concerning the number of such cases. I do not wish to add anything to this excellent report other than a simple personal statistical detail, the absence of which from my earlier publications was noted by Dr. Stuart and which I wish to give him:

Between 1934 and 1946, twelve cases of meningitis came to my knowledge out of a total of 25,000 vaccinations carried out by myself or by colleagues to whom I sent vaccine and who kept me accurately informed of the results of their inoculations. I carried out, or made it possible to carry out by supplying vaccine, many other vaccinations, but I have only taken into consideration the above total, all of which were supervised in a more or less experimental manner. Thus, out of 25,000 vaccinated persons there were twelve cases of meningitis, i.e. 0.50 per thousand.

Of these, 9,000 had been vaccinated in three steps, this being our initial method. Five of these cases developed meningitis, i.e. 0.55 per thousand.

The vaccine enclosed in egg yolk was administered in a single inoculation to 16,000 subjects. These developed meningitis in seven cases, i.e. 0.44 per thousand.

The difference in favour of the second vaccine is extremely small. Above all, it should be noted that the overall proportion indicates, in round figures, a frequency of one case out of every 2,000 persons vaccinated. This is the proportion which is found to recur with little variation in other statistics, provided that the averages have been calculated on a sufficient number of persons and over a sufficient length of time. Thus, to take the example of Nigeria where fatal accidents occurred, the 1951 reports for this country give a total of 142,000 persons vaccinated among whom there were 85 cases of meningo-encephalitis, i.e. 0.59 per thousand. As can be seen, this figure is pretty close to our own.

However, all this only makes it possible to state that, on the whole, the proportion of neural reactions is low. It is much more instructive to consider the statistics from the viewpoint of age, as has been done by Dr. Stuart in his important paper and, in addition, by Professor Lépine in a note which he was kind enough to communicate to us.
Indeed, my personal statistics showed 3 adults and 9 children out of 12 cases, but as we had vaccinated many more adults (21,000) than children (4,000), the respective frequencies were: 0.14 per thousand among adults and 2.25 per thousand among children, i.e. 16 times more children than adults for the same number of vaccinated subjects.

I should mention, on the one hand that we counted adolescents up to the age of 15 as children and, on the other hand, that at this early stage very small children were not vaccinated. Now that the regulations prescribe vaccination from birth, the sensitivity of children is even more noticeable, so that Professor P. Lépine found using vaccine 17D in Paris, a proportion of 4 cases of meningitis per thousand infants vaccinated between 0 and 6 months of age. Dr. Stuart's report indicates the high proportion of young children affected in Costa Rica; in Nigeria, only children and above all infants were attacked.

Consequently, although meningitis may follow vaccination at any age, it is much more frequent among children, the frequency increasing the younger the child. This point can be regarded as definitely established.

There is another factor, not affected by any question of age, namely the existence of a definite tendency for such cases to be grouped together. In countries such as French West Africa, it seemed at certain times that the neural reactions had disappeared and then one, two or more cases developed over a short period of time and in one and the same place, whereas elsewhere the after-effects of vaccination continued to take their normal course. In France Professor Lépine and myself use the same vaccine 17D prepared at the Pasteur Institute for vaccination. In two years Professor Lépine has observed five cases of meningitis in Paris whereas in Strasbourg none have come to our notice.

The fact that post-vaccinal meningitis which is benign in France, North Africa and French West Africa, has caused deaths in Brazil, Costa Rica and Nigeria is apparently due to conditions of localization and time which are appreciably the same.

* Doc. WHO/YF/6
Exactly similar phenomena have been observed to follow smallpox vaccination. There have been veritable outbreaks of encephalitis in certain countries at a given period, the cases varying in number and in seriousness, whereas similar vaccination carried out in neighbouring countries and even in neighbouring localities, has continued to be without incident.

It has been necessary to suspend smallpox vaccination in several situations of this kind and similarly we have seen the authorities in Costa Rica and Nigeria interrupt their yellow-fever vaccination campaigns, so that not only loss of human life is to be deplored but also the very future of yellow-fever prophylaxis, which we believed finally assured, is compromised to some extent.

The necessity for research on the international level to determine the cause of such meningitis

The position is serious. We are faced with a dilemma whose solution cannot be seen at present, and either vaccination can be continued and further accidents will certainly occur, or the fear of such accidents will lead to a falling off in vaccination, yellow fever will regain the upper hand and we know only too well what epidemiological disasters this may lead to.

Our difficulty is due solely to the fact that we do not know the cause of the neural accidents. However, there has been no lack of opportunity to study this during the period of almost 20 years since the first cases were reported. Unfortunately, instead of these neural reactions being studied, they were cited against the method, the first used on a large scale, which was held responsible for them. An attempt was made thereby to substitute other procedures, which were stated in advance to be incapable of causing meningitis. The first of these was sero-vaccination. I stated that it would be unsuccessful; that the addition of an immune serum may neutralize part of the virus but does not change the nature of the remainder; moreover, sero-vaccination was not practical, being ill-adapted to the immunization of large population masses. Nevertheless, it was applied. As a result, cases of virus jaundice occurred, without any improvement as regards the meningeal reactions. Indeed, the most severe reaction of this kind seen at the Paris Pasteur Institute followed on sero-vaccination.
Later the culture vaccines were tried. Their method of preparation was to eliminate everything thought capable of maintaining the "neurotropism" of the strain. True, these vaccines produced encephalitis in monkeys, but their harmlessness for man was guaranteed. The deceptive but fairly long periods during which neural reaction may not appear led to the belief that this time the aim had really been attained and many were deceived in this way. At the present time we know that culture vaccines cause meningitis in the same way as vaccine prepared from mouse brain. Thus, during 20 years, no progress was made as concerns this question of meningitis. All that was done was to repeat the mistake of believing that by modifying the technique empirically, it would be possible to prevent an accident of whose origin, nature and conditions of appearance we have no definite knowledge.

Laboratories have been lacking in the spirit of co-operation necessary to solve this essential problem. If workers in the different countries would share their knowledge, their facilities and their efforts, I have no doubt that they would rapidly be able to give vaccination the one improvement necessary to make it perfectly satisfactory. Yellow-fever vaccination reached at the very outset a degree of effectiveness almost unknown in such a field; an equal certainty of innocuity is lacking, above all as concerns immunization of children. There is no doubt that we could succeed in giving such a guarantee of harmlessness, but this goal will only be reached after we have discovered exactly what should be avoided.

We should have learnt from the cases of meningitis which have occurred in various places throughout the world; there have been enquiries, even experimental research, but neither one nor the other seems to have been carried on under the conditions necessary for useful interpretation of the results. Among other things, as far as possible, the same observers should have compared what happened in one region with what happened in another, but this was not done. Finally, more objectivity should have been shown. Faced with a danger of as international a nature as yellow fever, there can be no progress, at the point where we now are, without the international co-operation of research workers.
The lines to be followed by research

No attempt will be made here to lay down or even outline a research programme, since this can be done only after joint conversations and discussions among specialists. Moreover, laboratory experts would not suffice, since the epidemiologists have also something to say on a certain number of points.

We have stated, and this will have been generally approved, I feel, that yellow-fever vaccination is a procedure which is perfect and beyond any criticism, except as concerns neural reactions and, more particularly, neural reactions in children. This already defines the field in which efforts should be concentrated.

Another point should be made clear and will greatly simplify the work, namely, that there is no longer any reason to distinguish between the two methods of preparing vaccine, i.e. in vivo culture of the virus in the mouse brain, and culture in the embryonnated chicken's egg give the same results, ensure the same protective power and unfortunately spring the same surprises as concerns neural reactions. The advantages of one or the other technique on the more or less industrial level of manufacture have become of secondary interest; the problem concerning us is above such details.

Having cleared the ground in this way, we are thus left with a vaccine which sometimes causes simple febrile reactions which can be neglected in practice, since they cause no inconvenience, but also, although more rarely, serious meningo-encephalitic symptoms which are sometimes fatal and which should be prevented at all costs. This meningo-encephalitis is certainly infectious; it is caused by a virus (using the word in its widest sense) which is either the virus constituting the vaccine itself or a virus foreign to the vaccine. In the latter case, the foreign virus may either be introduced by the vaccine on inoculation or may be pre-existent in the body of the vaccinated person. Such are, in my opinion, the three essential ideas upon which work should be concentrated.

There are data for and against each of them which should be checked and made use of. It is here, above all, that the present report cannot claim to be complete,
since we are obliged to limit the details given. Here is one indication based on a clinical finding previously noted: the febrile reaction on the 6th day and the neural reaction occur as two phenomena independent of one another, they may follow one another or may exist separately. The first in point of time, i.e. the febrile attack on the 6th day, is certainly due to the vaccine virus. This is proved by the fact that it is never seen in cases of re-vaccination. This seems to indicate that the neural reaction is connected with another factor, but this argument would be weak if there were nothing more to support it.

It is however supported and considerably strengthened by the fact that the neural reaction can develop when the blood already exercises a protective function; this is very important. One example has been reported by Sawyer, and I myself have observed a second such case. The two vaccinated persons in question were serologically immune to yellow fever when the meningitis developed.

It is understandable why there are not a large number of examples to quote, since normally the neural reaction appears before the body has had the time to manufacture antibodies. Special cases are necessary, where the antibodies appear very early and the meningitis at a relatively very late stage. But the very fact that two duly authenticated cases have already been observed warrants serious attention. Further examples should be sought for in man and brought about experimentally, if possible, in monkeys.

In connexion with experiments on monkeys, some comment is called for. Is it not true to say that the results given by intracerebral inoculation of monkeys have sometimes been misleading? Theiler's virus, when directly injected into the brain, paralyses and kills mice and, in general, guinea pigs also; there is nothing surprising to find that it acts in the same way on monkeys. These are experimental conditions so remote from those of human vaccination that it appears very difficult to draw any lesson from them; how many of the other common vaccines would be found harmless if they were tested in this way?
On the contrary, subcutaneous inoculation of monkeys or inoculation by scarification of the skin is of the greatest interest. This exactly reproduces the process of human vaccination: either the animals become immunized without incident, or curable neural reactions are seen, or, finally, fatal encephalitis develops. But the question then arises, with the monkey as with man, as to whether, when encephalitis occurs, it is caused by the vaccine itself, by a virus contaminating the vaccine, or by virus already present in the animal? Perhaps the experiments on monkeys have not been sufficiently studied from this point of view, but rather on the basis of the vague concept, today a little obsolete, of neurotropism. Such experiments should be taken up again with the aim of supplying an answer to the question which has just been raised and in the exact terms in which it has been stated; I feel that this would be an important part of the research programme which should be established.

What significance should be attributed to the presence of vaccinal yellow-fever virus in the brain of the monkey or of man in the event of death followed by autopsy? Dr. Macnamara performed five autopsies in Nigeria after death from encephalitis and in four cases found Max Theiler's virus living and active in the brain matter of the corpses. This interesting information is given in Dr. Stuart's well-documented report.

However, it is not permissible to conclude as does Dr. Macnamara, that in such cases the vaccine virus certainly caused the encephalitis. Vaccinated monkeys not suffering from encephalitis which are sacrificed in the second week following vaccination have also the virus in their brains. This is in no way surprising since the vaccine virus multiplies in the organism of all vaccinated subjects; this is the very principle of immunization by means of living vaccine virus.

This point may, perhaps, be better understood if I quote an example which I myself observed, quite outside the question of yellow-fever vaccination. A person who had been bitten was undergoing preventive treatment against rabies by the classic Pasteur method; on leaving the Institute, where he came every day for treatment, he was killed in a motor cycle accident. I performed the autopsy and removed a fragment of the brain which I inoculated into rabbits; these developed the usual paralysis caused by the fixed rabies virus. If the same man had been vaccinated against
yellow fever one or two weeks before his accident it would certainly have been possible to find Theiler's virus in his brain in the same way. However, it would doubtless not have been found at a later date after the appearance of the antibodies. Nevertheless, this does not prevent encephalitis making its appearance at such a late period and this is probably why Dr. Macnamara failed to find the virus in one of the five autopsies he carried out, thus indirectly confirming both Sawyer's observation and my own.

Some years ago I reported a case of meningitis following on yellow-fever vaccination* where the cerebro-spinal fluid did not contain Theiler's virus but another virus which was pathogenic for the guinea pig. At the time chorio-meningitis had hardly commenced to be discussed and moreover I was influenced by the fairly general view that meningeal accidents were caused by the vaccine, so that the case was not properly studied. Thus I wrote that the mice bred by us were certainly free from chorio-meningitis. Today I have a better knowledge of asymptomatic infections and would not make the same assertion so readily. I also reported, without being able to interpret it, a fact which seemed curious to me: guinea pigs which had recovered from typhus were resistant to the virus of meningitis but, on the other hand, guinea pigs which had recovered from the latter disease were not immune to typhus, i.e. the immunity applied in one direction and not in the other. I subsequently discovered the reason for this anomaly: our typhus strain had been passaged on mice, like most typhus strains at that time moreover, since we were accustomed to make use of mice in exchanging exanthematic typhus viruses between laboratories. In this way, on inoculating the guinea pigs with typhus we had simultaneously inoculated them with the virus of chorio-meningitis; they were thus immunized against both diseases without our knowing it.

However this may be, it is certain that the vaccinated subject in question, suffering from curable meningitis (like all our other cases in North Africa and France) carried a chorio-meningitis virus of the Armstrong type or a related type in his cerebro-spinal fluid. On seeing the clinical similarity existing between lymphocytic meningitis, generally benign, caused by Armstrong's virus and the neural reactions, also benign, at least so far in our part of the world, following yellow-fever vaccination, one is struck by the fact that a virus identical to Armstrong's virus has been isolated from the cerebro-spinal fluid of a vaccinated person suffering from post-vaccinal meningitis. This is a solitary case, but if it were confirmed, it would be of almost decisive significance.

Our vaccines prepared with mouse brain may be contaminated with the virus of chorio-meningitis. On one occasion I also isolated this virus from the chick embryo. Since then I have made it a rule to check the anti-yellow-fever vaccines which we produce, by means of inoculation into the guinea pig peritoneum. Any vaccine causing fever in the guinea pig should be considered as possibly contaminated with the virus of chorio-meningitis and should be rejected.

In one of the preceding chapters, entitled "Post-vaccinal jaundice", we have drawn the attention of the reader to a certain number of cases of virus association concerning yellow fever and vaccination against yellow fever. We are now brought to this question of virus association in connexion with the case which we have just cited of the infection of a vaccinated subject by the chorio-meningitis virus and we are much inclined to believe that associated viruses constitute the principal element in the problem of meningo-encephalitic accidents. We do not deny a priori that the yellow fever vaccine virus by itself may have caused cases of meningitis; in the present state of our knowledge such a denial would be baseless. No experimental fact could be cited in support of it, no more, moreover, than it could in favour of the opposing view attributing these meningeal accidents to "neurotropism". The myth of neurotropism directed against the vaccine of the Pasteur Institute at Tunis and Dakar, collapses when confronted with the fact that the culture vaccine causes the same reactions in the nervous system. Together with this myth disappears an almost senseless phraseology where the words "organotropism", "viscerotropism" and "pantropism" claim to explain
everything. There is no experimental fact showing whether or not the vaccine alone is capable of causing neural accidents and against this view must be placed the fact that these accidents are rarely seen and that the immense majority of vaccinated subjects undergo vaccination without reaction.

In favour of the associated viruses theory, on the contrary, there is definite evidence which although limited is unmistakably positive. Thus, in two cases the duly confirmed intrusion of *Leptospira* brought about severe jaundice following vaccination and this is all the more significant in that laboratory investigation has now revealed the unsuspected frequency of leptospiral meningo-encephalitis without jaundice. There is also the definite presence of a chorio-meningitis virus in the cerebrospinal fluid during a curable meningo-lymphocytic reaction following vaccination.

Finally, although I cannot go into it here in detail, there is the research which I was encouraged to take up by Charles Nicolle and have continued since his death, with mixtures of different viruses. Owing to circumstances, and, in particular, distance from yellow-fever zones, and also the lack of monkeys, my investigations have been directed towards virus associations other than those which might concern the neural accidents following yellow-fever vaccination. The experiments under way at present on this subject are too incomplete for any details to be given. However, in other fields of virology, experimental study of virus associations has revealed facts of considerable general significance. The most important is the following: on associating two viruses whose action taken separately generally results (for a given animal species) in an asymptomatic infection, clinical disease is brought about. Thus, ectromelia is usually asymptomatic or takes the form of mild lesions in the mouse; the same animal becomes infected with murine typhus only in an asymptomatic form. On associating both viruses in the mouse, however, severe typhus is provoked, with intense multiplication of the rickettsias and paralysis, regularly ending in death. The rat, which is resistant to ectromelia, on being inoculated with the same mixture succumbs to a fatal paralysis; here experimental ectromelia in the rat is an entirely new disease which a virus association has created from
first to last. From this can be drawn, not conclusions (which would not be permissible) as regards the aetiology of neural accidents following yellow-fever vaccination, but an idea for research capable of solving this problem which is so disturbing in the present circumstances.

There can be no doubt that the chorio-meningitis virus already exists in certain subjects, since we see spontaneous cases of meningitis brought about by its action. It attacks children above all. Does this not indicate that yellow-fever vaccination may bring about meningitis by association of the two viruses in children with asymptomatic chorio-meningitis? On the other hand, as the child becomes older the chances increase that it will be spontaneously immunized against chorio-meningitis, rendering neural accidents following the vaccination of older children and adults more and more rare.

However, viruses other than that of chorio-meningitis are certainly able to play a part in the same circumstances and in the same way. This raises the question of the existence of related but different encephalitis viruses, which are endemic in the various regions, and whose study, already undertaken for other reasons, should be taken up anew from the viewpoint of the relationship which these viruses may have to yellow-fever vaccination. If, as appears probable, some of these viruses are maintained by murine enzootics, the variability of their potency, combined with their geographic distribution, would only confirm what we already know of other groups of diseases having the rodents as natural reservoirs. The variability in virulence towards man in particular would explain the differences in the severity of cases of meningo-encephalitis following vaccination occurring in different countries, without it being necessary to attribute these differences to changes in the virulence of the vaccine.

There is no need to add, since the reader will realize this himself, that such research also concerns the sometimes dangerous cases of encephalitis following smallpox vaccination. This only serves to stress the need for the international co-operation of research workers in the solution of these two grave problems, which finally we may well be led to regard as one and the same problem, common to the two great forms of vaccination which represent part of our armament in the fight against the quarantine diseases, namely yellow-fever vaccination and smallpox vaccination.
Temporary measures which should be taken in connexion with the vaccination of children

I feel that in the meantime certain measures should be taken as regards the vaccination of very young children. This is called for by certain centres in Europe empowered to vaccinate passengers travelling to overseas territories. These centres are disturbed by the increase in the number of cases of meningitis since it became obligatory to vaccinate infants before embarkation, without any lower age limit.

The French Academy of Medicine dealt a few years ago with this question of the vaccination of children against yellow fever but, confident in the reported harmlessness of culture vaccines, it recommended that only vaccine 17D should be used. However, as is known, nothing was gained from this.

The persistence of meningeal reactions thus progressively led vaccinators to inoculate children only with very small doses of vaccine, thus creating an illusory security, which was nevertheless guaranteed by a certificate valid for six years. It would be infinitely better as Professor Lépine has remarked, to delay vaccination somewhat, but to make it certain.

Professor Lépine adds that, according to his observations, young children respond poorly to the vaccine from the viewpoint of antibody production. I have not had the opportunity of verifying this, since I have not carried out many serological tests on vaccination subjects of this age. But there is nothing surprising in what Professor Lépine says, since it is a general rule that immunity against most antigens is difficult to impart before one year of age. This is why, as concerns smallpox vaccination for example, French law does not require that vaccination be carried out from birth, but only during the first year of life, except in the event of an epidemic. Similarly, vaccination against diphtheria and tetanus is only compulsory in many countries during the second or even third year, which is a little late.

In my opinion there would be no drawback, on departure from non-endemic zones, in vaccinating only children more than one year of age against yellow fever; it would then be for the authorities in the endemic countries to take those measures
called for by the local sanitary conditions with respect to these infants. This would reduce to a considerable extent the number of meningitis cases until such time as accurate knowledge of the cause of these accidents makes it possible to avoid them completely which, I repeat, is not beyond our powers provided that these are properly employed.

SUMMARY

Vaccination against yellow fever has had the most happy effects on the health and economic position of the regions concerned; the resulting advantages of all kinds are considerable. The effectiveness of this vaccine is now beyond doubt, but it has the drawback of causing certain reactions in the nervous system; these take the form of meningitis or meningo-encephalitis.

These accidents are rare. They affect children above all. For a long time they were invariably followed by recovery; however for about two years fatal cases have been reported in certain countries. The culture vaccine, although said to be incapable of causing such accidents, actually does so.

There is nothing making it possible to say whether or not the vaccine virus alone is involved. There are cases where meningitis has appeared when neutralizing antibodies were already present in quantity in the blood of the vaccinated subject; this is very important and should be confirmed.

In one case the author isolated from cerebrospinal fluid, a virus identical or closely related to that of chorio-meningitis. Such a virus may be derived from the brains of mice or the chick-embryos used in preparing the vaccine. It is fairly easy to detect this contamination by intraperitoneal inoculation of the guinea pig.

However, this virus may already be present in the organism of the vaccinated subject, since there are spontaneous cases of chorio-meningitis in man and particularly in children. Other types of meningitis or meningo-encephalitis virus can certainly
exist in man as asymptomatic infections and may cause accidents following vaccination, by association with the vaccine virus. Differences in the nature of these viruses, according to the endemic zones where they are prevalent, would explain the varying severity of the attacks from one country to another.

Finally, the problem seems to be fundamentally one of virus association, but this should be verified. These neural accidents are compromising the future of yellow-fever prophylaxis by means of vaccination; the establishment of a research programme is a matter of urgency so as to find out the cause of the meningitis and how to avoid it. Such a programme can only be successfully carried out on the international level by co-operation between research workers in the different countries.

In the meanwhile, as concerns vaccination on leaving zones free from the disease, it would be sufficient to require the vaccination of children from one year of age onwards, which would avoid a relatively high number of accidents occurring during the first months of life.