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INAPPARENT, CHRONIC, INFRAMICROBIC INFECTIONS

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INAPPARENT, CHRONIC, INFRAMICROBIC INFECTIONS
I. LATENT VIROSES[(1)]*

Pierrette Athanasiu, Al. Petrescu

Viral disease depends on the multiplication of the virus in the cell, while the lesions and symptoms produced represent the result of cellular injury and deterioration. The clinical manifestation of viroses is extremely varied; it can range over a spectrum of forms, from confluent variola to the common cold.

The different results of the infections depend, in the first place, on the sensitivity of the cells of the organism toward the virus, on the medium of the surroundings, and on the localized foci in the organism; on the circulation of the virus in the organism and its liberation from the infected cells.

Man or animal, and even florae, can have virus infections without any external symptomology whatever, which we designate as inapparent infections. In some of these inapparent infections the virus in the tissues is in a torpid state until external causes, reducing the resistance of the organism, permit the virus to multiply vigorously, and to cause the appearance of some evident disturbances. There are more situations in which the host organism can be infected with a virus without presenting any usual signs of the infection for certain periods of time.

Footnote (1) is on page 29.

* Translator's Note: distinction must be made between virosis and virus in this article. Virosis designates infection with a virus; virus is an infectious agent.

An infection of this kind, designated as a subclinical inapparent infection, encompasses many possibilities, namely: the virus can be present in the organism only for a limited period and disappears when immunity is established; the inframicrobe* can exist in the tissues for a long time simultaneously with the presence of immunologic response. The virus can persist in a certain cell for a protracted period without giving any indication of its existence in the interval before clinical manifestation.

Burnet [20] considers that the long incubation of some diseases can be regarded as the period of latent, subclinical infection which should probably include the phase of active multiplication of the virus. The virus remains latent until characteristic signs and symptoms appear and indicate the end of the incubation period.

Andrewes [7] uses the term *latent infection to indicate chronic inapparent infection in which a state of equilibrium has been established between host and parasite.* The detection of some viruses that cause inapparent infections has succeeded by the use of blind passages** in animals and in cell cultures. It has been shown that parasitism without clinical manifestation is more extensive than was believed.

In certain cases, latent diseases cause the formation of cellular inclusions and antibodies. However, infective attacks may occur in which no specific immunologic reaction can be uncovered.

In order to illustrate somewhat more precisely certain possibilities, we shall present briefly a series of better known virus diseases which, apart from acute clinical form, can encompass a varied spectrum of latent states.

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* Translator's note: inframicrobe = filter-passing virus

** Translator's note: "serial blind passages"

Lymphocytic Choriomeningitis. The virus was isolated from naturally infected mice which did not show clinical symptoms [125, 126]. In 1933 Traub and Schaeffer [127] studied a colony of mice which they did not find infected. However, in December 1934 they found the presence of infection in about 50% of their offsprings. Most of the mice were born apparently healthy, although all their tissues contained virus in relatively large quantities. The infection in the latter persisted throughout their lives, since it had been transmitted to them *in utero*. The mice infected *in utero* remain lifetime carriers of the virus, and eliminate it in urine, feces, and nasal secretions. [127]

Subclinical infections with lymphocytic choriomeningitis have been observed in man; they have been diagnosed by the serological reaction of seroneutralization.

Encephalitis Transmitted by Means of Ticks. It has been found that, upon administration of the virus through the nasal passages, rats develop an inapparent infection, in the course of which the virus multiplies in the nasal mucus, in the olfactory buds, in the lymphatic ganglia, and in the lungs.

Dengue. In many tropical regions, where there are several species of monkeys, dengue is endemic in man. By means of a species of mosquito *(Aedes aegypti (Stegomya fasciata)*, the virus thus passes from monkey to monkey, and from monkey to man [37].

Equine Encephalitis. The virus of equine encephalitis can cause subclinical infection in man. This symptomless infection determines the formation of antibodies. Reeves et al [108] have found that birds infected with the equine encephalitis virus remained infected for long periods of time. In some of the birds, the virus persisted for 10 months after inoculation. The authors subscribe to the possibility that the existence of apparently healthy vectors of this type is responsible for the persistence of diseases during winter in temperate climate regions.

Nicolau et al [87] have observed horses and sheep, after experimental infection with auto-sterilizing neuro-infections, resulting in survival of the animals with slight histological deterioration in the nervous system, presence of nuclear inclusions and specific immunity. It appears, nevertheless, that the sterilization of tissues is not total; probably, virulent units remain in the cells which have not succeeded in reaching a refractory condition. In soil there is little that is favorable for the culture of the virus; the latter can nevertheless subsist for a time in symbiosis with unusual, incompletely immunized cells, but is blocked by antibodies present in the neighboring tissues. It is at this time that the virus can be demonstrated either by cataphoresis [99] [100] or by the technique employed by Perdraux [102], Levaditi and Nicolau [71], etc.

Van Economo Encephalitis. There exist some apparently benign cases that sometimes lead to mild angina, or are totally inapparent. In these cases the defense reaction of the organism is too weak to destroy the pathogenic agent. The parasite continues to vegetate in the cell, where it finds insufficient metabolism for rapid and abundant multiplication, which must determine the reaction of the whole organism, but is consistent with torpid, insidious, pathogenic activity with the slow multiplication of inframicrobes. The course of the development of infections is expressed in the insidious progress of the disease, in the torpid evolution of the disease, manifesting itself clinically as post encephalic parkinsonism which leads to death in 5-10-20 years [96].

Virus of Encephalitis B. (Japanese Summer Encephalitis). Rats and horses in Malaysia have subclinical infections, constituting an important reservoir of this virus. Antibodies are found in the subclinical forms of the disease.

Virus of St. Louis Encephalitis. Sherman and Casey have found in regions of Florida that this virus has caused subclinical infections in man, with positive immunological response of 4% (4291 out of 100,000), clinical cases representing 0.1% [117].

Virus of Murray Valley Encephalitis. This can likewise cause inapparent infections.

Pappataci Fever. The Neapolitan strain of the pappataci fever virus, after adaptation in the brains of new born mice, when inoculated subcutaneously does not cause illness, but only a subclinical effect and the appearance of specific neutralizing antibodies in the blood. [38]

Hemorrhagic Fever. In hemorrhagic fever, among the typical cases there are also numerous subdued and immunizing inapparent cases.

Spontaneous Encephalitis of Mice with Theiler Virus. The virus is found usually in a non-pathogenic state in the intestinal track of white mice. The virus vectors do not show antibodies; however, the latter develop in mice which survive the intercerebral inoculation of the virus [124].

Rabies. In this disease one can speak of occult inapparent immunizing infections which take place when the virus dosages are small or when the strain of the virus is attenuated. Nicolau et al [90], [91] have performed experimental and histopathological investigations which have proved the existence of "inapparent rabic infections". It is known that immunity to rabies is determined after vaccination by just this non-lethal, inapparent infection with the virus vaccine attenuated but alive, which produces lesions in the neuraxis [88]. In man, rabies cases are known with extremely long incubation periods during which time the virus is latent [42], [89], [92].

In a series of technical reports to the World Health Organization [107], problems of the "silent vector" in rabies infection are discussed and, besides the bat, mention is made of the skunk, for example. Such problems of the "symptomless vector" are discussed also by Andral [4], Kantorovich [63], Nicolau [90], [91], Ionescu [59], Burns et al. [21].

Caruntu [31] emphasizes the role of vectors and symptomless excreters of the virus, such as bats, probably some dogs and other animals, as well as reservoirs constituted by other wild carnivores (wolf, jackal, hyena, mongoose) and various rodents. In animals, the susceptibility to rabies disappears in a large part during hibernation, only to return after awakening. Numerous authors have investigated and described the conditions in which animals or humans have developed rabies after they were bitten by non-hemophagic bats, insectivores or apparently healthy vampire bats, but infected with rabies [60], [85], [120], [129], [130], [136]. Frogs and turtles inoculated in the brain with rabies virus suspension do not show a single particular symptom, but it has been found that in the brain of the turtle *Testudo mauritanica* the inoculated rabic virus is retained for a period of 303 days, and in the brain of the turtle *Clemmis leprosa* for 150 days [84], [109], [110], [111].

Yellow fever. In the specialized literature, great emphasis is laid on the slightly characteristic, sometimes asymptomatic, aspects in infections caused by the yellow fever arbovirus in Central America and in South America. In Africa there are communities in which the seroprotection test is positive, although clinical cases of the disease have never been found. Apparently healthy monkeys play an active role in the dissemination and maintainance of the arbovirus yellow fever, constituting, besides man, a reservoir of the virus.

Poliomyelitis. Compared with the many people paralyzed by the disease, much more numerous are those who have been affected, showing or not showing symptoms, but without involvement of the neuraxis [95]. Ianconescu et al [58], Cajal et al [29] have shown that in rural areas, as well as in urban areas,[28] the degree of immunization by inapparent infections is greatly increased. A 100% increase in the virus was found in persons exposed without seral antibodies, without the development of symptomatic disease in the large majority.

Similarly interesting observations of Howe and Bodian [55] have demonstrated poliomyelitis virus in the feces of two normal chimpanzees, whose keepers handles apes ill with the experimental disease.

Coxsackie Viruses. In the literature attention is called to infections simultaneously possible with Coxsackie and poliomyeletic viruses, and their dissemination among apparently healthy persons. [83]. Duca [39], investigating an epidemic outbreak in a rural area, emphasized the presence of clinically inapparent forms. Johnson [62] and Kenyon [64] have shown the existence of subclinical forms, especially in contacts infected with strain A.

Enteroviruses. In connection with age grouping and socio-economic grouping, variuos percentages of ECHO virus vectors have been established: namely, 5.2% in age group 1 - 4 years, 2.6% in age group 5 - 9 years, and 0.2% in age group 10 - 14 years. [106].

Inoculation of the viruses into monkeys per os or intercerebrally causes an inapparent infection with the possibility of reisolating the viruses in the pharyngeal and fecal discharge in 13 days.

Herpes. It is well known that the herpes virus can be present in tissues which do not show signs of pathogenic activity and in afflictions whose etiology differs entirely from that of herpes [105]. The virus can be present in the saliva of people who have never had herpetic lesions [36], [70]. Usually the primary infection occurs in childhood and can take the form of an aphthous stomatitis, the aphthoid of Pospishill-Feyrter [10], [73] eczema herpetica, or can affect the skin in zones contaminated by saliva. In most of the cases, it is not externalized by primary lesions [3]. During the intervals between acute manifestations, there is no single aspect which might differentiate between the normal skin and the herpetic skin. From this zone, the herpesvirus could not be successfully isolated. However, it was possible to show evidence of seral, neutralizing antibodies and complement fixation, leading to the conclusion that people without circulating antibodies are not susceptible to the given recurrent herpes, however strong the stimulus [14].

Investigation of the antibody distribution in children and adults after infection with herpesvirus suggests that, (a) antibodies remain in the blood throughout the lifetime; (b) the individual is

exposed to recurrent herpes whenever he is subjected to adequate stimulus.

Recurrent herpes is characterized by the repeated appearance of blisters after certain intervals —— weeks, months or years — most often in regions of the skin or mucus membranes with varied localizations.

An unusual form of recurrent herpes is the herpes *simplex menstrualis* which in some cases may last from puberty to menopause.

Aujeski's Disease. In man, in many apparent cases, the existence of inapparent forms is also presumed.

In nature, rats are considered to be vectors of the virus with latent infection [75].

Sabin Virus B. (*Simian herpes*). Cases have been noted in which laboratory workers died or suffered grave illness which appeared to be like an acute infection of the nervous system resulting from the bites of healthy monkeys. Isolated by Savin [114] from the nervous system of healthy monkeys, the virus had many of the qualities of the herpesvirus, among them: antigenic (serologic) qualities and internuclear inclusion products of type A in infected cells. Burnet [15] found that some colonies of Rhesus and Cynomolgus monkeys, apparently healthy, had antibodies against the virus.

Cytomegalic Inclusions. This infection is known to be very widespread in view of numerous positive reactions of complement fixation obtained from persons who have not had clinical signs of the disease. Two aspects of the disease in children are apparent: a latent symptomless form, with strict localization of the virus in the salivary glands, and a generalized clinical form which frequently leads to fatal illness. In the form with localization in the salivary glands in the absence of clinical symptoms, diagnosis is made by necropsy following death caused by the affliction.

In adults the disease is generally latent without clinical manifestations. In subclinical infections of humans, it has been found that the virus is eliminated in the saliva and in the urine — even those of the children who had antibodies of compliment fixation two to four months before or after clinical recovery in general form.

Adenoviroses. Of special importance in the pathology of adenoviroses is the frequency, in particular, of inapparent infection [59,61, 86]. The increased frequency of infections with adenoviruses is proven by the large percentage of people evidencing antibodies [77], [79].

Epidemiologic study of the population of our country concerning ailments due to adenoviruses and syncytial viruses has shown the existence of 86% healthy vectors with antibodies against adenoviruses, and 63% against the syncytial virus. [81], [82].

Hubner et al [57] consider that more than 50% of the surgically removed tonsils and adenoids are infected with adenoviruses and that the virus is masked or kept in equilibrium by specific types of antibodies. They believe it can be demonstrated by changing the host factors and by protracted cultivation of the tissues in artificial media leading to deterioration of cell metabolism and of cellular growth, with disappearance of antibodies [57], [112], [113].

Hannoun [52] and Kjellen et al [65,] [66] indicate the possibility of several latent infections in the mesenteric lymphatic ganglia.

In experimental animals, the sole criterion for demonstrating the infection was considered to be antibody production. However, Bronitchi et al [13] have shown that in the lungs of adult white mice, inoculated with adenovirus, there are morphologic modifications without the animals' showing clinical disturbances. Petrescu [103] has described biochemical, histochemical, subcellular and cellular modifications which, in animals vaccinated with live virus attenuated with formol, did not lead to clinically discernible symptoms.

Keratoconjunctivitis with Inclusions. In the pathogeny of these diseases, Cockburn [32] discusses the possibility of reactivating some latent infections, such as is observed in herpetic infection. During interepidemic periods, these inapparent forms are closely connected with the circulation of the virus, and can even become apparent under the influence of vaious factors [8].

Reoviruses. Presumably the number of inapparent infections with these diseases is large [34]. Among 60% of sucklings, Lerner et al [69] have demonstrated antibodies of maternal origin.

Inframicrobic Hepatitis. Numerous investigators have demonstrated the transmission of inframicrobic hepatitis by *blood* or by such products as originate from apparently healthy persons, obtained during the period of asymptomatic incubation [45], [46], [68].

Cajal et al [22], [24] and Mateescu [78] have shown that the hepatitis virus can always be eliminated in feces, rarely in urine, and very rarely in nasopharyngeal discharge. Continuation of virus elimination even after clinical recovery demonstrated the existence of some asymptomatic, torpid diseases, and of virus vectors of great epidemiologic significance.

Cajal et al [23], [24], by means of hemagglutination inhibition reactions, have found in the serum of healthy persons, who had been in contact with clinical hepatitis cases, positive results in a proportion of 42.8%. In the 382 healthy persons, the proportion was 21.82%; the subjects probably acquired immunity as a result of clinically inapparent disease. In homologous seric hepatitis, which constitutes one of the most important problems in medicine, the virus can persist in the blood of some persons even much longer than three years [119].

Burnet [18] considers that the virus of seric hepatitis is a variant of the infectious hepatitis virus transmitted to the fetus *in utero*. Sometimes the result is congenital hepatitis, but more frequently it is an inapparent fetal infection, the consequence of

a specific immunologic tolerance. Thus, from the beginning the child becomes a "silent" carrier during the entire life of the seric hepatitis virus.

Nicolau et al [95] emphasize the importance of cases of inframicrobic inapparent hepatitis and of carriers of virus.

Ward et al [133] consider that, in general, the incidence of healthy carriers is 2 - 3% in the population.

In recent years it has been found that the use of enzymatic tests in dosage activities of serum glutamic oxaloacetic transaminase (SGO-T) [9], [35] leads to the detection of some carriers.

Cajal et al [25], [26], [27], [30] have found that the use of the seric aldolase tests permits the diagnosis of inapparent forms of epidemic hepatitis, demonstrating an early and sensitive diagnostic test

Mumps. (Epidemic Parotitis) Mumps exemplifies a similarly subdued and inapparent form [67], [116]. The problem of the virus carriers is much disputed. Alongside of some authors, who deny the existence of healthy carriers [49], [135], others admit the existence of carriers as well as the transmission of the disease by means of the carriers [104].

In times of epidemics, the forms of occult or inapparent mumps, without any clinical manifestation, represent an important source of contagion. The frequent presence of the virus in the saliva of the latter persons indicates a parotid contact, with multiplication of the virus at the gland level [50].

Influenza. A large number of cases of influenza are asymptomatic. Experimentally, among four young adult subjects who did not have anti-influenza antibodies, upon inoculation with influenza virus, three developed a clinical disease. The fourth, through free from any symptom of disease, ultimately showed an increased titer of neutralising antibodies, like the other three [16].

Bronitchi [11] isolated a strain of the influenza virus A/PR-8 from the nasopharynx of some apparently healthy persons in whom he did not observe the presence of anti-influenza antibodies.

The Parainfluenza Viruses. In regard to these viruses, observation of the increases in the antibody titer of children hospitalized for non-infectious ailments should argue for the existence of some subdued or inapparent forms of the disease [12].

The Common Cold. After many years of research on voluntary test subjects, Andrewes [6] affirms that "common colds are due to a virus which is always passed form one person to another in the community, usually without causing any symptomatology, frequently causing only a very much reduced symptomatology, and causing a true common cold only when the local resistance of the host has been very much lowered". A great number of people are carrier hosts of this virus for a protracted time [51].

Measles. It has been found that in communities with a great number of immunized persons, the development of epidemics is impeded. The persons with natural or artificial partial immunity can, nevertheless, acquire an attenuated, subdued, abortive or inapparent form of the disease, whereby the virus is maintained in the community. Symptomatic disease is observed in only 80 - 90% of the population, the remainder being immunized by a subdued or clinically inapparent form without eruptions [33].

In the problem of immunity, this disease presents very many aspects which influence discussions of ultimately relating the conditions of specific resistance to the persistence of some latent infections with an inapparent virus.

Variolo Vaccinia. Persons who present a weak immunity, due to much earlier vaccinations, on approaching the limit of complete effectiveness, can develop either a benign form of variola, or a clinically inapparent form, with massive elimination of the virus (97). An interesting case noted in the literature is that of a

twelve year old girl, vaccinated six years before an epidemic, who was in contact with a sick family and did not show any clinical sign of the disease, but transmitted the virus to twenty-one persons.

Infectious Lymphocytosis. In the epidemiology of this disease, the cases of inapparent infection are of unusual interest. Like apparent diseases, they constitute a source of infection and are discovered only by hematologic examination.

Most of the cases of the disease have been observed in different medical institutes of a sanatorial type, in which, due to protracted hospitalization, accidental hematological findings have become possible (80).

Lou and Yeh [74] have described an epidemic with 469 diseased cases along with 1673 cases of inapparent infections diagnosed by serologic and hematologic means.

In times of some epidemics, Watson et al [134] have found hematological and serological modifications in 55% of 102 apparently healthy students.

Rubella. In rubella, experimental transmission of the disease to monkeys has led to a similar verification of the existence of clinically inapparent infections in man.

DISCUSSION OF INAPPARENT, CHRONIC, VIRAL, PATHOGENIC INFECTIONS

What we consider the classical sequence of the actions of the virus on cells - penetration, active multiplication and necrosis of the cells - is in fact a phenomenon which is realized extremely rarely in nature. Thus, in such a complex problem of the pathogenic viruses, we must keep in mind simultaneously the susceptibility of some cells and the relative or complete resistance of other cells. In the susceptible animal organism, the process of viral infection meets a succession of obstacles which may interrupt the infection at a number of points.

The infection can be initiated if viral particles have the possibility of entering, and of multiplying, in the initially infected cell, and if from this cell sufficient viruses are liberated to establish a continuing sequence of infections from cell to cell, which will eventually produce lesions or symptoms.

Some of the cases in which lesions are not developed can be due to the failure of the virus to penetrate the cell, but others result from the impossibility of multiplying or of liberating sufficient quantities of virus from the infected cells in the first phase of the infection.

The nature of the interaction between the virus and the host cell appears in the following possibilities:

1) the viral particle *does not give evidence* of its existence;

2) the viral particle initiates the infection process *and gives evidence in this sense*;

3) *the cell can be injured*, but the virus does not reproduce sufficiently to spread the infection to other cells of this type;

4) viral multiplication is produced, but the virus is liberated from the cell *without* coexisting with *cellular lesions*;

5) the virus multiplies, is liberated, and progressive modifications appear in the cell, with or without the formation of inclusions.

For any group of viruses, one must keep in mind their access to the cell, the physiological susceptibility of the latter to the infection, and localization of the sensitive cells in the host organism. The reaction of the host can be manifested in the infected cell, in neighboring cells or in those at a distance, by antibodies, interferon, etc.

Any interpretation of the pathogenesis of viral infections must keep in view these possibilities, as well as the fact that most viral infections in nature are subclinical.

The infecting virus must be able to persist by multiplying in a small number of susceptible cells in the tissues in which the majority

of the cells are susceptible, or by propagating in cells which support viral synthesis but are not damaged by the viral infection. In the first case, the spreading of the infecting virus to the susceptible cells must be limited by non-specific neutralizing antibodies, or the latter are made partially resistant by non-infectious viral material which may interfere with the subsequent infection.

An aggressive virulent inframicrobic *parasite* provokes a more or less severe, acute disease, and immunizes strongly, leading to the exclusion of the parasite from the organism. However, such parasites, in but slightly aggressive form, provoke a light primary infection, occasionally inapparent and non-immunizing, leading to the persistence of the virus in the organism with more or less grave consequences, even being capable of leading to death (parkinsonism, etc.).

The fact that the symptoms do not appear when the inflammatory reaction is impeded by the intervention of certain factors (cortisone, X-rays) represents a distinct tolerance of the immunological tolerance in which we know that no antibodies are formed. Among these conditions one can mention acquired specific non-susceptibility. Likewise, it is presumed that in pre-natal infection such a state of non-immunologic reactivity can be established, which makes possible the persistence of infection without symptoms through the whole life span. Such an example is offered by lymphocytic choriomeningitis in mice, and seric hepatitis in man and others.

Burnet [19] emphasizes that, within the framework of immunological reactions, in explaining the pathogeneses of latent infections we must take into account the importance of injurious effects of the antigen-antibody reactions which take place on the surface of some or all of the mesenchymal cells, for example in seric hepatitis.

Cases of subclinical grippe must probably be due to partial inactivation of the virus liberated on the surface of the respiratory epithelium. This inactivation is sufficient for interrupting the diffusion of the infection from cell to cell, and permits, during this time, the growth of local concentrations of antibodies.

Duca [40] has found that in cases of inapparent Coxsackie infection, the persistence of the virus in the organism for an extended time coincides with the absence of specific antibodies or with their presence in titer greatly reduced.

In connection with the role played by immunity, it has been shown that in herpes, soon after the development of inflammatory modifications in a region, the latter is inundated by antibodies, which prevents the extension of the process, and probably becomes responsible for healing the lesions.

In the diseases extensively investigated, a proportion of *subclinical infections* can be recognized by a change in an *immunologic response*. However, the possibility exists of the presence of some infections in which no *antibody production* whatever can be revealed.

A great amount of research must be done to investigate the proportion of subclinical and clinical infections in relation to the *strain* of the virus and the *quantity of the infecting dosage*, on the one hand; and the *age*, *genetic characteristic* and *physiologic state* of the host, animal and man, on the other hand.

Nevertheless, in the final analysis the presence or absence of symptoms must be ascertained on the *cellular level*. In this regard, the manifestations of symptoms appear to depend on: a) *injury to the specific functions* of the cells in the infected organ, such as may be exemplified in particular in poliomyelitis and in encephalitis; b) *secondary effects of the toxic products* liberated by cellular necrosis at the site of the infection.

Non-immunologic factors often play an efficient role in maintaining states of latent infection. A study of the interferon with environmental properties, pressure of O_2, temperature, etc. has led to interesting findings.

Glasgow et al. [47] have found that a decrease of quantities of *interferon* in cell cultures by digestion of trypsin or frequent change

of the medium leads to intense multiplication of vaccine virus, with concomitant destruction of the cells. The maintenance of the interferon by less frquent changes of the medium leads to chronic infection with survival of the cell cultures. However, there are also examples of viral infection in which the interferon does not seem to be associated with the property of inhibiting the lethal effect of the infection.

Studies of chronic lymphocytic choriomeningitis in mice have shown that the interferon cannot be detected, since the infected mice present resistance to the test with heterologous virus (interference) [132]. These findings lead to the conclusion that the resistance associated with recovery can be induced sometimes by factors other than the interferon.

Experimental modification by reduction of the *oxygen* in the air breathed by mice inoculated with street rabic virus has caused a significant increase in the duration of the incubation [5]. On the other hand, a similar situation is found in the animals whose basal metabolism is reduced in a state of hibernation.

Another factor which can contribute to the determination of some latent infections can be the *local tissue acidity*. The infection of the cell with virus causes the production of lactic acid in an increased quantity [44], [72].

It is a known fact that acid pH is damaging to the cultivation of virus. For example, in a culture medium of weak sodium bicarbonate, the multiplication of poliomyelitic viruses is inhibited [41], [131]. This inhibition was attributed to the low concentrations of bicarbonate ions [56].

Similarly, the presence of environmental factors can influence the complex processes which permit the existence of latent infections.

Temperature is another non-immunologic factor which can affect the course of some viral infections. It has been shown that increased temperature has a much greater direct inhibitory effect on the

multiplication of the grippe virus *in vivo* and *in vitro*, than through the effect of temperature on the host [43].

Hyperpyrexia protects some mice inoculated with Coxsackie virus, and poliomyelitic virus of type EE, or transforms clinical disease into latent infection [48], [76], [123].

In discussing the pathogenic mechanism in latent infections, we believe it is necessary to add a few words in connection with *allergies*.

A state of delayed hypersensitivity can participate in the complex process which leads to the existence of some latent viral infections. This precedes the response with antibodies [128] and can represent, although not in all cases, a reaction which causes recovery.

Other authors discuss the influence of *age of the host* on the course of attenuated infections [17], [118]; for example, the increase in the resistance of the organism to infections of poliomyelitis, parotitis, etc. with given age of the organism.

Other non-immunologic factors which can influence the course of diseases and affect qualitatively the latent subclinical forms depend also on the *nutritional state* of the organism, *activity of the reticulo-endothelial system, phagocytes*, etc.

Nicolau [98] developed a special theory of interest in connection with viral nuclei which can become stable and autonomous in the organism in their macromolecular form, yet without becoming complete "virions"; they thus become *infraviruses*. These inframicrobic forms, we believe, can constitute the basis of some subclinical latent infections.

The persistence of some viruses in tissues other than their favorite ones can entertain an asymptomatic and latent infection. Sulkin et al. [121], Allen et al. [2] have shown that rabic virus can be demonstrated in the brown fat in the interscapular region of bats without the latter presenting any symptoms.

Lipotropism has been found also in other viruses, for example in poliomyelitic virosis [115], in infection with Coxsackie virus [101], in Western and Eastern equine encephalitis [1], in Japanese encephalitis and in St. Louis encephalitis [122].

We believe it necessary to add a few words also about *the role of the virus* whose intrinsic *properties can condition the existence of some latent infections*. In connection with this, Nicolau [94] has shown that "in some cases of sclerogenic hepatitis, virus strains of low aggressivity provoke protracted, torpid infections".

Clinical findings support this viewpoint. Thus, Hortopan et al. [54] indicate a large number of hepatic scleroses, appearing after viral hepatitis with subdued or absent symptoms. Mention is made of cases of apparently benign infectious hepatitis, or cases of inapparent disease.

The results show that it is impossible to ignore the biological properties of the agents involved in this type of situation, in which the agents can persist in a few cells for long periods of time. The explanation of the phenomenon which accompanies the end of the incubation period, at the time when the virus changes its behavior, will shed much more light on the nature of the interaction between virus and host cell.

PRACTICAL RESULTS OF THE EXISTENCE OF LATENT FORMS OF VIRAL INFECTIONS

Nicolau [93] emphasizes the subdued and subclinical forms in viruses, because infected persons represent *virus reservoirs* in their respective communities. For the affected persons themselves, these forms are the consequence of *immunity*.

Gruia [50] shows that in recent years in our country there has been a considerable decrease in the cases of epidemic parotitis among recruits. This is explained in the absence of some earlier parotitis by the existence of a large number of inapparent or occult infections, which confer immunity upon the organism.

The poliomyelitic virus prepared with modified Sabin strains by repeated passage in intervals of 24 hours through cell cultures, and administered orally, with elimination in the feces, infects the population of the vaccinated group, but the infection is immunizing, and is totally inapparent. Thus, the subclinical infection can also have a positive character, upon immunization of the respective persons against renewal of the disease of the disease, but the presence of several antibodies permits diagnosis of the existence of virus in the population.

A brief review of some of the best known virus diseases, serving as the framework within which the existence of their latent forms of evolution has been established, is sufficient to sketch some problems to which researchers and practitioners should pay more and more attention. Chronic bacterial diseases have been well known and studied for a long time, a fact about which there is no dispute. The chapter on latent viruses cannot close without a reference to the vast importance of chronic bacterioses in pathology and epidemiology. Viruses are more difficult for experimental study, and have been investigated with more success in the last decade due to perfection of modern work techniques and apparata. Attacking the host-cells in their *interior*, viruses produce much greater modifications than microbes. Further, the quantitative and qualitative adjustment which is established between them and the tissues generates a large variety of clinical factors. This fact causes the symptomatology of latent viruses, in particular, to differ very much from the classical acute forms, and on account of this it most often escapes precise etiologic diagnosis. More and more intensive future studies will bring, perhaps, the most interesting data, and it will not be surprising to find that many of the afflictions in the domain of clinical medical pathology are based on latent viruses.

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13. ABSTRACT

Some of the best known virus diseases are briefly reviewed. The importance of chronic bacterioses in pathology and epidemiology is stressed. Viruses produce much greater modifications than microbes, and the quantitative and qualitative adjustment which is established between them and the tissues generates a great many clinical factors. This causes the symptomatology of latent viruses to differ greatly from classical acute forms. The authors conclude that future studies will furnich interesting data, and it may be found that may afflictions pertaining to clinical medical pathology are based on latent viruses.

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