LATENT INFECTIONS

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In the contemporary literature which deals with the infectious diseases, the designation "symptomless infection" is used with increasing frequency. The question immediately arises: Do recent observations, experimental and clinical, and new epidemiologic experiences justify the creation of this term? Is it not likely that a new word has been coined to describe the well-known state of "latent infections"? No one will deny that the usual signs of an infectious malady—the manifest and latent stages—may be readily bridged by the so called rudimentary or "abortive" forms of the disease. In other words, the symptomatology of an infection oscillates between the frank, clinically typical disease and the unrecognizable reaction. The persistence of a disease agent from the time of its entry into a host or the "symptomless" state of infection, which may follow clinical recovery, has been described, since the discovery of the tubercle bacillus by R. Koch in the tissues of apparently healthy individuals, as a "latent infection." Furthermore, one was satisfied to characterize certain atypical forms of a disease as "abortive" when it was believed that the disease-producing virus multiplied only to a moderate extent and consequently induced feeble reactions or no symptoms at all. The recognition of the "abortive" cases has gradually led to a broader conception of the infectious maladies. Since a disease is generally considered from an etiologic point of view, it is not surprising to note the descriptions of scarlet fever without a rash and poliomyelitis without paralysis. Whether or not the variant types of a disease are truly "abortive" forms has certainly not been determined for a great many infections. In fact, the

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recent intriguing studies by Paul, Salinger and Trask and others amply illustrate the difficulties which may be encountered in the interpretation of the minor illnesses which are observed in association with clinical poliomyelitis. Moreover, it must be reserved for future experimental studies to furnish proof that the attenuated clinical course of an infection, which cannot be recognized without the most searching medical examination, is truly the result of a supposedly diminished multiplication of the disease agent. Observations to be discussed later indicate that a number of additional factors are of equal if not of greater importance.

What is the proper concept of a "symptomless infection?" An observation made by Charles Nicolle in 1912 in connection with certain studies on typhus lead to its precise definition by Nicolle and Lebaillly in 1919. These investigators had noted that, occasionally, in a series of guinea pigs experimentally infected with typhus blood, one or several would fail to show a characteristic febrile reaction. The blood or organs of such animals transferred to other guinea pigs would, however, induce the typical fever and thus prove the existence of the virus in the animals which had shown no symptoms. This peculiar behavior probably conditioned by a particular constitutional state of the guinea pig was designated by Nicolle as "une infection inapparente ou silencieuse." In recent years, this phenomenon has been intensively studied and amply confirmed by numerous investigators (Doerr, Breinl and others). Thus, Breinl showed that the simultaneous but separate injection of virus and serum in proper dosage produces an afebrile infection with regularity. Under the influence of the immune serum the virus multiplies and reaches the same concentration in the blood as in the non-treated animals with the only difference that the onset of the virus propagation may be delayed for a few days. The virus growth curve, except for a slight shift in time, is the same in both animals, irrespective of the fact that the serum-treated guinea pigs remain permanently afebrile. That this type of infection leaves a permanent immunity was anticipated and experimentally proven. A further analysis of these interesting observations by Breinl and Singer demonstrated that not only the fever but the
other typical symptoms such as the perivascular infiltrations, the blood monocytosis, and the loss in weight were equally absent. Only the polymorphonuclear leucocytes and the lymphocytes were slightly but temporarily increased for a period of time which ordinarily corresponds to the febrile state of the typically reacting animal. Obviously, this peculiar type of infection is not absolutely "symptomless" but it deviates so markedly from what is generally recognized as the norm that the formulation of a new term appeared justified. The deciding criterion of the "symptomless infection" is a rise and fall of the virus growth curve. Under normal conditions this proliferation of the virus induces the well-known symptoms. However, under certain conditions—individual disposition of the animal (Nicolle), influence of immune serum (Weil and Breinl), infection with louse-passage virus (Breinl) or shifts in the electrolytes of the body (Breinl and John)—the symptom complex fails to materialize though the typical virus multiplication curve remains unchanged. The parasite increases in the macroorganism to the characteristic saturation point \(10^{-6}\) M.L.D. in the brain) without provoking a noticeable defense reaction, other than a completely "symptomless" process of immunization. This phenomenon should be considered for the time being as a condition decidedly different from that which is generally described as "latent infection." The term "symptomless" or "inapparente infection" should be applied only to those maladies in which the virus is distributed with respect to location, time and quantity in a manner characteristic for the usual course without, however, causing the appearance of clinical or anatomical signs of disease. As late as 1933 Nicolle declares himself opposed to the recognition of this type of infection as a "latent process." He defines a "latent infection" as a subacute or chronic state of disease without evident symptoms in which the carrier harbors the disease agent. The microbe may have been acquired through a preceding disease; it may regain its infectiousness and thus affect the carrier or may serve as a source of an infection to other individuals.

Nicolle warns against the error of describing a disease as "inapparente" should the pathogenic agent escape detection by the
examiner. Non-visibility is not synonymous with "inapparence." Finally, the exponent of the term "inapparente" vigorously demands that it be limited to the infectious disease, but not to deficiencies or dystrophies as already proposed by Moriquand, Velu and Balozet.

True "symptomless infections" may be expected to develop when agents similar to the spotted fever virus are involved. According to Nicolle, this type of infection is observed in the following diseases and species of animals:

- Epidemic European spotted fever in man, rats and mice
- Endemic rat typhus in guinea pigs, monkeys, mice and rats
- Kala-azar in the spermophiles (Citellus citellus) and in dogs
- Weil's disease in rodents and guinea pigs
- Treponema pallidum infections in mice, rabbits, possibly man
- Variola in the rabbit, dog and cat
- Yellow fever in man and monkeys
- Poliomyelitis
- Herpes and encephalitis in man
- Lymphogranulomatosis in the monkey
- Malaria in man and probably in Anopheles
- Spirochaeta recurrentis in the gondi and other animals (Ctenodactylus gondi)
- Infectious anemia of horses, rodents and ticks
- Dourine
- Fowl plague
- Brucella infections, not infrequently in man, constantly in goats

This brief compilation merely suggests that the world may be flooded by a sea of disease agents which, as a rule, produce merely a "symptomless infection." In order to emphasize the significance of the problems involved, additional examples are herewith presented.

In 1929 Blanc, Caminopetros and Manoussakis injected a human being intravenously with 3.5 cc. of serum collected from a patient with dengue fever. He remained clinically well but the blood removed from him on the third day after the administration

of the serum and reinoculated in an amount of 7 cc. into a third person proved to be infectious. A typical dengue infection was produced. Subsequently, the person with the "inapparente infection" was found to possess a specific immunity towards the dengue virus. Nine cubic centimeters of whole virulent blood, which proved virulent in a control experiment induced neither manifest symptoms nor did the blood of the person reacquire infectious properties. The same investigators found in 2 out of 6 experiments that guinea pigs injected with dengue blood may yield no febrile reactions while their blood transferred to human beings may prove infectious. Transfers to guinea pigs were not successful, doubtless on account of the very marked variability of their individual susceptibility. Similarly, experiments conducted by Blanc, Caminopetros, Dumas and Saenz on monkeys (Macacus cynomolgus and Cercopithecus callitrichus) have shown that these species of animals pass through "inapparente infections" when injected with virulent dengue blood. They are neither visibly ill nor is their temperature elevated. However, their blood, avirulent 24 hours after the injection, becomes infectious for man on the 5th, remains so until the 8th but loses its pathogenicity on the 12th day. It is of interest that the infectiousness can be proven only by transfer experiments to man. Reinoculations on species of monkeys that react quite regularly with an "inapparente infection" to an injection of dengue blood invariably failed. These observations, provided they are confirmed, would indicate that the extinction of an "inapparente infection" in its first generation in certain animal species may be a phenomenon of greatest general biologic significance.

Under the influence of a potent immune serum, the course of a cattle plague or hog cholera infection may be so modified that "symptomless infections" are by no means infrequent. Doubtless, the combined influence of an inherent natural resistance enhanced by the immune serum is responsible for these results. That the virus increases in the hog, which has been treated with serum and then injected with virulent blood, may be readily proven by systematic transfer inoculations to susceptible young pigs. As an aftermath of this infection, which passes through an
afebrile course, a permanent active immunity is produced. Aside from the “inapparente infection,” a hog cholera virus invasion may be followed by a typical “latent infection.” The virus may persist for 3 weeks in the blood and up to 103 days in the lymph-nodes (McBryde, David); it may even be discharged irregularly in the urine for a much longer time.

A measles infection under the influence of convalescent serum may be modified to an unrecognizable condition, absence of fever or Koplik’s spots with an indefinite rise in temperature. Yet, it is well-known that these so called “mitigated forms” of measles are highly infectious and not infrequently the nodal centers for large epidemics.

In connection with the studies on herpes occasional “inapparente infections” have been noted. Levaditi has produced in the rabbit encephalitides without symptoms; their existence was placed in evidence after death through the demonstration of the neuropathologic changes. Other workers have demonstrated the virus in considerable quantity in the nervous system, irrespective of the fact that the clinical signs of the brain infection were rudimentary or entirely absent. Olitzky and Long noted virus propagation in the brain of guinea pigs without encephalitis and Remlinger and Lebailly found the herpes virus “non-pathogenic” for the turtle (Testudo mauretanica) although the infective agent was demonstrable for a long time by transfer of the brain tissue into the susceptible rabbit. Virus increase in the central nervous system and the pathogenic effect are apparently two entirely different processes. In fact, no one is in a position to-day to explain the reason why an increase in the virus is followed in one instance by an acute fatal disease while manifesting itself in another experiment as a “symptomless infection.”

It is the merit of the late Professor Kolle to have applied the term “symptomless infection” to certain observations which he and his associates, Evers and Prigge, had made in connection with the experimental study of syphilis. Rabbits treated with bismuth preparations and subsequently injected with syphilitic material are apparently protected against a luetic infection. Although a chancre formation and the enlargement of the lymph-
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nodes—the usual criteria of a “take”—are missing, the spirochaetes remain viable without producing lesions. Since it had been shown by Pearce and Brown that the popliteal lymph-nodes of rabbits recovered from a syphilitic infection retain the spirochaetes, it occurred to Kolle and Evers to extirpate various nodes of the bismuth-treated and clinically unaffected animals, and transfer them into the testis of normal rabbits. In numerous instances typical chancre were produced. Thus, it was shown that the bismuth preparation failed to sterilize and although it prevented the development of local and general syphilitic lesions, it permitted the general distribution of the spirochaetes. Since this phenomenon was discovered under more or less artificial conditions, it was at first believed to be of little or no general significance. However, within a short time the field of “inapparente” spirochaetal infection was broadened. It was noted that rats and mice may be readily infected by placing pieces of gummatous tissues under the skin of the back or the testes. The local lesions healed without the formation of a chancre. After a lapse of many months the subinoculation of the lymph-nodes, spleen or brain of the infected muridae produced in rabbits typical chancre. Furthermore, the transfer of organ particles removed from mice with “inapparente infections” again created in this species a “symptomless infection.” The mice became hosts for the Treponema pallidum without showing clinical or anatomical manifestations. Comparative studies on rabbits leave no doubt that the distribution and the degree of the spirochaetal increase within the tissues correspond in every respect with that established for the manifest infections. Inflammatory reactions are not histologically demonstrable in the animals which are not visibly sick. For the latter the designation “residual brain infection” and for the former “symptomless infection” would be correct.

In many ways analogous, but not identical, are the observations dealing with the Spirochaeta recurrentis infections of burrowing rodents and other animals. Experiments carried out in California indicate that chipmunks and tamarack squirrels may harbor spirochaetes in their tissues. Particularly late in the fall
these findings are by no means infrequent. Since anatomical lesions are invariably absent and the presence of the spirochaetes is established by subinoculation into mice, the majority opinion of investigators is that these rodent infections are "symptomless." A few carefully controlled tests, however, have shown that this chronic state is preceded by an acute infection which has conferred a certain degree of immunity on these carriers. These rodents serve as a reservoir for the spirochaete and continue to furnish the parasites which, through the agency of Ornithodorus Hermis, a newly discovered vector are accidentally transmitted to man. With this incomplete evidence at hand one would prefer to designate the process in the rodents as a "latent," though in some other animal species and the tick as an "inapparente," or according to Nicolle as an "invisible" infection.

These and similar reflections now logically demand an analysis of the term "latent microbismus," "silent or resting infection" introduced during the war by surgeons to characterize the delayed appearance of tetanus and gas gangrene infections. It is well-known through the animal experiments of Vaillard and Rouget (1892), Tarozzi (1906), Canfora (1908) and Koser and McClelland (1918) that spores of the tetanus bacillus may remain at the site of the inoculation or may be carried by phagocytosis to various parts of the animal body where they persist for long periods. Although it is as yet unknown whether such persisting spores are free in the tissues or inclosed in phagocytes, the fact remains that they may be activated by various chemicals, bacterial products, etc. and thus induce typical tetanus. For example, Schneider demonstrated tetanus spores in the liver, spleen and even the blood of rabbits 43 days after their injection with detoxified spores. Every process, which results in tissue necrosis, spontaneous bacterial infections or artificially induced disease, may lead to an attack of tetanus in these animals which harbor the spores. This peculiar "latency" has been experimentally established for many other toxicogenic anaerobes. In fact, it is well-known that anaerobic spores introduced into the human body by traumatic injuries and gunshot wounds, especially shrapnel splinters, may remain within the wound or scar tissue without
causing the least reaction. These spores, whether deposited with or without a foreign body, are a constant source of danger as numerous observations collected between 1914 and 1919 have definitely shown. An aseptic operation as, for example, the removal of shot fragments performed weeks, months or years after the original injury may lead either to a local or general tetanus (Courtois, Suffit and Giroux) or a rapidly fatal gas gangrene infection (Penhallow, 1916, Lesne, 1916, Phocas, 1915, Plant and Roedelius, 1918). There is no doubt that an individual, who, in the interval between the injury and the subsequent operations, carries the seeds of tetanus or gangrene, is in a state of "latent infection." However, it is equally obvious that these forms are by no means comparable with the classical "symptomless infection" as illustrated by certain Rickettsia and virus infections. What are the differences? A multiplication of the microbe in the scar may with considerable certainty be excluded. Furthermore, this lack of vegetation of the spores is not due to any active immunological effort on the part of the host, but is probably conditioned by factors which influence the growth phases of the microorganism. What are the factors which temporarily inhibit and later activate the vegetation of disease agents? Through a series of brilliantly conceived experiments Fildes (1927) came to the conclusion that the normal positive oxygen tension of the healthy tissues is sufficient to account for the lack of germination. This may be reduced in various ways: A slight inflammatory process may cause through capillary thrombosis a hindrance of oxygen diffusion or the leucocytes may place an increased demand on the oxygen; perhaps the presence of foreign particles induces local asphyxia and favorable respiratory requirements for the germination of the spores. There is no regulated incubation, generalization through the blood stream, no critical disappearance of the disease agent and no subsequent immunity. It is not the host per se but certain environmental factors influencing the vegetative phases of the microbe which are of importance. Although Fildes' experiments offer a reasonable explanation for an understanding of the factors which initiate the germination of the spores, they fail to elucidate the primary inhibition after
they have gained entrance to the tissues. Whether phagocytosis (Vaillard and collaborators) or the fortuitous absence of contaminating microorganisms of the Clostridium Welchii or Clostridium sporogenes varieties may have something to do with this apparent inhibition deserves further experimental scrutiny. How far the so-called dormancy of spores as observed in the test-tube has a bearing on this problem has not as yet been investigated. In any event it is advisable to define this intriguing state of non-reactive persistence of anaerobic spores in the tissues of man and animals as "silent or resting microbismus."

Promptly the question arises: Are the well-known diseases with "long incubation times" as, for example, tuberculosis, Brucella infections, leprosy, fungoidal disease, processes due to cocci, perhaps rabies, psittacosis, etc., analogous to the conditions just reviewed? In no instance has an absolute or complete inhibition of the growth activities of the implanted microorganism been demonstrated. Moreover, systematic investigations, as far as they have been carried out, have always revealed a definite though occult primary focus. It is supposed that within this focus, growth of the disease agent may be very slight and frequently retarded or completely arrested by factors which are as shrouded in mystery as the primary inhibitory influences on the spores. The experimental studies by Rous and Jones on the protection of bacterial cells from the action of destructive substances suggest one of the factors which may be operative. In any event, all the evidence available marks these conditions as "quiescent infections" in contradistinction from the "silent microbismus."

It has already been mentioned that Nicolle presented sufficient evidence to exclude from consideration as "symptomless infections" those conditions in which the persistence of pathogenic microorganisms on the surfaces of the mucus membrane or even in the blood has been recognized. This differentiation has not been followed. In fact, under the influence of the newer trends to analyze medical bacteriologic phenomena from a general biologic point of view, an interesting terminology has appeared. The word saprophytism is suddenly replaced by symbioses (Rim-
pau). Kolle and Prigge in their monograph on "symptomless infection" list as "symbionts" (a misnomer for the Greek word "symbiote" = companion or partner) of the mucous membranes or the blood the following disease agents and their hosts.

Man. *Lamblia intestinalis*, pneumococci, anaerobic spore-bearing bacteria such as *Clostridium tetani* and *Clostridium Welchii*; diphtheria, influenza and Ducrey bacillus, fungi and various species of filaria.

Mammals. *Pasteurella pestis* in rats, fowl cholera bacillus in chickens, various spirochaetes in rodents; *Trypanosoma Lewisi* in rats; *Brucella melitensis* in goats.

Insects. *Plasmodia* in the *Anopheles*; trypanosomes in *Glossina*, yellow fever virus in *Aedes Aegypti*, pappataci virus in the *Phlebotomus* flies; spotted fever *Rickettsia* in lice; Rocky Mountain spotted fever in the tick, tsutsugamushi virus in mites, etc.

The list could be readily enlarged; one could include the Bar-tonelloses of rats, the anaplasmoses and gonderioses, the finding of plague bacilli in the inguinal glands of natives at Dakar by Leger and Baury, etc.

On the other hand, certain corrections and limitations must be pointed out. The *Brucella* infections in goats, particularly the elimination of the organism in the urine or its presence in the milk ducts, is always associated with definite anatomical lesions and is certainly not a state comparable with true symbiosis. Many years ago Carter had shown that the massive ingestion of gametocytes by the *Anopheles* may lead to profound disturbances, even death of the mosquito. The flea tolerates an invasion with the *Rickettsia* of endemic typhus while the louse succumbs (Nicolle). More important in this connection, however, is the pertinent inquiry as to whether such a terminology as "symbionts" and its implication are truly justified.

The presence of a disease incitant on a mucous membrane merely attests that the microorganism has found conditions suitable for its vegetative development. However, it may lack the ability to penetrate and thus be transformed from a potential to a true disease-producing agent. For the infections without symptoms it has been proven that the agent has the power to invade, and that the immunity mechanism of the subclinically
infected macroorganism neither neutralizes its action, if any, nor destroys it more readily than in the visibly diseased. Already Vaughn recognized such a state of affairs when he applied the term syssitic to the organisms living commensally on the surfaces of the mucous membranes without production of evident disease. Topley believes that they possess inherently the power of multiplication on mucous membranes or so called supragliscence. Under these circumstances, it is quite reasonable to assume that the microorganism has not as yet adapted itself to the macroorganism. The residence on the membranes or in the blood is merely the first act, the beginning of an interplay which may lead from the invisible to the visible disease form.

In the light of modern biologic thinking which gradually permeates the utilitarian concepts of medical bacteriology, it is believed, although by no means proven, that the infection without symptoms is the sequel and not its precursor. Such reasoning outlines the problems still to be solved. By taking into consideration the newer knowledge on symbiosis, one may perhaps define the paths along which future inquiries may be directed. Furthermore, a discussion of this important and significant relationship between various microorganisms and their hosts may in part help to clarify such unfamiliar words as Epilo- and Endosymbiosi (Rimpau) as applied to the microbic behavior under consideration.

During my early training as a zoologist, the phylogenesis of parasitism was always presented as an evolution of the parasitic from non-parasitic types and it was assumed that the pathogenic ascended from the non-pathogenic. With increasing insight it became clear that the reverse may also be true. Benign parasites evolve from harmful ones. Although it is obviously impossible to observe this phylogenesis, a brief insight into certain families of Diptera connected with myiasis offers many convincing observations relative to the correctness of the deductions (Martini). The mode of nutrition of certain species clearly sketches the evolution from true to facultative parasites. The larvae of muscae are rarely found in suppurative wounds, while those of the Fannia group may live on wound secretions, although they prefer decomposing plant material. Representatives of the
sarcophaginae generally found in feces and dead flesh may invade wounds and destroy even healthy tissues. The genus Wohlfahrtia causes severe destruction in the healthy tissues of man and animals which may be the victim of these flies. Lucilia caesar and Calliphora vomitoria now used to cleanse wounds (Baer and others) unquestionably destroy the dying tissue fragments. Chrysomyia may extend its activities from wounds and pus cavities to healthy tissues. In fact, in Australia a great many Calliphorae deposit their larvae in the wool of sheep. They not only live on the wool but they attack the skin and cause extensive destruction. The larvae of Cordylobia, which bore into the skin of dogs and occasionally of man in Senegambia, are primary parasites. They form the transition stage to the obligatory parasites belonging to the subfamilies of Cuterebrinae and Hypodermina. Their advanced stage of parasitism is indicated by a retrograde formation of the mouth parts, and it is interesting that many of these forms are living at the expense of the wound secretions which accumulate within the boil. They avoid invasive feeding in the healthy tissues. Polyhagism of certain species of Dermatobia is replaced by a specific adaptation of the genus Hypoderma for certain ungulatae. It appears that the gradual and more intimate adaptation to a host and to its mode of living more or less improves the existence of the parasitic species. Simultaneously with this adaptation, the ability to invade other hosts is progressively lost.

Quite generally, it seems that the less violent action of a parasite on its vertebrate host, the monophagic tendencies and the difficulty of growing on artificial media are signs of a progressive and phylogenetically old parasitism. Viewed from this angle, it is obvious that the slowly fatal or chronic illness of the host is of greater advantage to the parasite than the rapidly deadly or rapidly cured malady. The highest type of adaptation is recognized as a life-long infection of the host (herpes-virus) and, in order to insure persistence of the parasite, a more or less fully developed pseudoheredity. The final stage is reached with the state of symbiosis in which the host becomes infected early during its development and receives no injury through the presence of
the "parasite." In fact, the physiology or mode of living of the host may be so adjusted that it cannot exist without its "symbionts." This master-servant relationship has doubtless reached its highest development in the insects. Of interest in this discussion, however, are the conditions in which the adaptations of the parasite to the host are as yet incomplete and the equilibrium between host and invader is quite labile.

The fields of helminthology, protozoology and botany offer many examples of harmless and highly adapted parasitism. Unfortunately, these balanced infections have aroused little general interest in the workshops of medical bacteriologists. The microbiologist, who intentionally administers huge doses of microorganisms in order to decide the pathogenicity of a disease agent for certain animals, has doubtless drawn and continues to draw erroneous conclusions. Fortunately, in recent years it has been appreciated that the massive infections, only too often supplemented by procedures which paralyze and deaden the resistance, have in no way imitated the natural conditions. Exposure experiments or the herd studies of Webster, Topley, Greenwood and Wilson more readily harmonize with the concepts of the parasitologist. This type of experimentation will answer more definitely the pertinent question as to which vertebrate or plant is the true host for a microbe or virus. To repeat, it is the animal or plant which assures the parasite a satisfactory permanent existence and since the physiology of the host harmonizes with that of the invader, the transmission to a new host of the same species is simple and permanently assured. Viewed biologically, an infection would pass phylogenetically through the following phases: from a free existence, the microbe, through an unequal symbiosis—parasitism _sensu strictu_—would reach the balanced and adjusted symbiosis.

The term symbiosis as originally used by the botanist, Anton de Bary (1879), denotes a condition of conjoint life existing between different organisms which are benefited in a varying degree by the partnership. As Nuttall has pointed out, the term symbiont, strictly speaking, applies equally to the partners. It has, however, come to be used also in a restricted sense as meaning the
microscopic, perhaps invisible member or members of the partnership in contradistinction to physically larger partners which in conformity with parasitological usage are conveniently termed the "hosts." On the other hand, symbiosis must be regarded as a condition of life balancing between two extremes—complete immunity and deadly infective disease. To be sure, it has been shown by botanists (N. Bernard, Magrou and others), whose theories are similar, that the factors governing immunity from parasites or symbionts are essentially the same for each partner. The struggle between the two partners had led in the course of time to a form of mutual adaptation. The symbiotic relationship of orchids and fungi has been experimentally investigated from this point of view, and it has been shown by N. Bernard that tuberisation is a sequel or a manifestation of an advanced adaptation of the plants to a communal life with fungi. It is worth considering that such structures as the mycetocytes, bacteriocytes and mycetomes in the insects are survivals of previous profound pathologic changes. How far this knowledge has any bearing on the various symbiotic stages which one observes in man and animals has not as yet been investigated.

It seems advantageous to discuss various other aspects of the problem of symbiosis as far as they pertain to the subject under discussion. Of particular interest are the important studies by Oehler, Pringsheim, Goetsch and others on the separation and recreation of algae symbiosis in paramecia, hydra, rhizopoda, etc. Dependent on whether their habitat is in fresh or in sea water, the endoplasm of these organisms may become occupied by Chlorella or Zooxanthella. An analysis of the factors involved in this type of symbiosis has shown that a separation of the partners may be achieved and that each may be cultivated independently of the other. However, this separation is no easy task and the many painstaking experiments which have been carried on attest to the striking tenacity with which the algae may adhere to the host. Various gradations of intimacy may be noted in one and the same species. Far more important than the separation of the plant from the animal is the causation of the symbiosis. There is absolutely no question that the immunity of the Algae against
the enzymes of the digestive vacuoles is of prime importance. As Pringsheim has demonstrated, it may be an inherent property of the Algae or it may be acquired within a few weeks. Certain Algae, despite systematic exposure to the invertebrate, remain susceptible. Equally important in the restoration of the symbiosis is the regulatory mechanism of the animal partner which controls the growth rate of the invaded Algae. Without this factor, the immune plant would readily overwhelm the animal as a parasite. Aside from this mechanism, one encounters as another host factor the disposition to accept the Algae as "symbionts." Certain species of Hydra freed from Algae, receive the plants and become green but within 10–14 days expel them just like ordinary food particles. In other cases the fresh water polyps are injured but following a massive and stormy multiplication and expulsion of clouds of Algae they ultimately recover. This form of elementary parasitism shows a remarkable analogy with the invasion of man and animals by unicellular plants. Further experiments indicate that the animal partner is, in a manner as yet unknown, profoundly impressed by a preceding symbiotic relationship. This property manifests itself in a greater receptivity; thus the customary partnership is rapidly renewed and balanced. Finally, the operation of the host-symbiont factors are rendered complex by the formation of physiologic races or types, morphologically indistinguishable but non-acceptable to the actinizoon or protozoon.

In connection with the study of a bacterial intracellular symbiosis in mollusks, the idea was expressed that this condition had its origin in true parasitism, probably disease. The same thought probably applies to the many and exceedingly complex symbioses observed among insects, irrespective of the doubts which have been voiced by Buchner, Reichenow, Florence and others. The comparative pathologist cannot recognize anything in the mycetocytes and mycetomes other than the survival of profound lesions induced by highly parasitic organisms. Such reasoning casts doubt on the widely expressed idea that the intracellular microorganisms are in a mutualistic relationship with their hosts. Until some of these forms have been cultivated
—an extensive new field for the bacteriologist acquainted with tissue culture technique—little can be said concerning their taxonomic position and their biologic significance. In fact, it is exceedingly doubtful whether a true state of symbiosis has been established. However, in order to avoid further confusion, it is advisable to retain the term “symbiosis” for the time being. Glaser, who critically compared the symbionts of the insects with the rickettsiae, correctly concludes that each of these intracellular elements originated among the invertebrates in the form of a disease, and that some of them are still in process of adaptation to higher animals in which they may produce definite diseases. The many examples of “inapparente infections” amply support his contention. Furthermore, he proposes a novel concept to explain the parasitic tendencies of *Rickettsia melophagi*. A gradual loss of characters adaptive to the invertebrate may be accompanied by a progressive modification leading to parasitism in the higher animals, particularly the mammals. His views are in harmony with present-day biological concepts and have numerous analogies as, for example, the evolution of the life cycle of the malarial plasmodium from a parasitic “symbiotic” state in the *Anopheles* to an advanced form of parasitism in man or birds. Finally, the biologically minded must agree with him when he casts doubt on the common belief that all new diseases may arise through sudden permanent modifications or variations of a disease agent instead of through a slow, orderly, evolutionary adaptation to the new hosts. It is not the purpose of this analysis to express an opinion relative to the importance of the “symbionts” as sources of growth-accessory factors, hormones, etc. That the “symbiosis” has a diversified function throughout the animal kingdom is fully recognized in all the speculative interpretations which have been published. However, Carter recently suggested that the phytotoxic secretions of certain coccids transmitting the spotting of pineapple leaves may be conditioned by the activities of the mycetome and its included symbionts. What bearing this hypothesis may have on the solution of certain insect borne diseases must remain a matter of conjecture.

Many of the facts briefly considered in the foregoing para-
graphs have prompted a number of bacteriologists to propound well sounding hypotheses and far reaching analogy deductions. For example, the commensalism of protozoa, ciliates in particular, in the rumen or stomach and in the coecum of herbivora has been designated as an endosymbiosis, which is active in the digestion of cellulose. This and the "symbiotes" themselves are thought to serve as nitrogen sources (for the horse it is estimated to be a quarter to one-third of the daily protein requirements) for the host. The implantation of bacteria into the buccal cavity and the intestinal tubes is compared with similar conditions in the insects and is known as episymbiosis. It has even been suggested that the early seeding of the mucosa of the mouth may be comparable with the bacterial contamination of the eggs of *Lagria hirta* while passing the smear glands of the urogenital tract of the insect. The new-born, passing through the vaginal canal, thus becomes the recipient of the maternal "symbionts." Additional examples of visionary comparisons could be cited but the few chosen emphasize again the unfortunate tendency to generalizations. From what has been outlined concerning symbiosis, it should be obvious that not one of the examples listed by Kolle and Prigge conforms to the fundamental definitions of a symbiosis. One could hardly support the idea that any one of the bacteria—pneumococcus, diphtheria bacillus, meningococcus, etc.—is in a mutualistic relation with the human host or that the gray rat is benefited by a partnership with *Trypanosoma Lewisi.* Since a true state of symbiosis has not been established, it is only proper to describe the organisms present on the mucous membranes or in the blood and tissues without evident disease as *commensals* and not as symbionts.

It is quite evident that such terms as "inapparente," silent infections or latent microbismus and commensalism describe a variety of processes. Since not infrequently the terminology has been applied without the necessary degree of care, an unfortunate state of confusion and contradictions has arisen. It is to the lasting credit of R. Doerr (1931 and 1934) to have clarified the problem, not only by proposing a tentative system in which the various independent processes or phases of an infectious disease
previously discussed may be arranged, but by listing some of the
factors responsible for infections without disease. He clearly
states that the principal criterion is the absence of *manifestations*
of the disease which may be recognized either by direct obser-
vation or may find expression in man by a feeling of malaise. The
opposite to manifest is latent; consequently the nomenclature
will be greatly simplified if the various terms are classed under
the collective designation "latent infection." Since "latency" is
merely a clinical concept, it is quite permissible to use this term
even when anatomical lesions inaccessible to direct observation
or immunological and allergic reactions are recorded. Under
certain circumstances one may even go further and describe a
human being as "latent-infected" when general symptoms are
absent and local reactions so exceptionally mild that the condi-
tion is recognized only by bacteriological procedures (for example
a mild pharyngitis with diphtheria bacilli). Equally significant
and applicable to a better understanding are the concepts with
respect to the phases of an infectious disease. The state of a
typhoid carrier is a latent one and not a manifest chronic infection
irrespective of the fact that the presence of the typhoid bacillus
may reveal itself clinically and anatomically (cholecystitis, focal
nephritis). In clinical circles typhoid fever is defined as an acute,
three-phased process which terminates with the restoration of the
temperature to normal. With the onset of recovery, the clinical
syndrome "typhoid fever" is passed and the ensuing carrier stage
represents an entirely different condition which remains mostly
latent and may only be recognized through a bacteriological
examination.

In his latest discussion of the subject Nicolle (1935) now defines
the "inapparente infection" as an infectious disease without
symptoms. Its existence may be placed in evidence by direct or
indirect laboratory methods, inoculation tests or serologic,
immunologic procedures. He says, "L'infection inapparente
perdra une part de son domaine au bénéfice de l'infection à
symptômes. Réduites, elle demeurera la forme mineure des
infections, celles qui échappe à la pratique usuelle du clinicien.
L'inapparence n'a de sens que par rapport à la clinique."
From what has been said, it is obvious that "latent infections" may be either independent processes or phases of an infectious disease. This is clearly set forth in a descriptive system proposed by Doerr (1934) which makes no claim for completeness but merely outlines the main characteristics, their occurrence and their relationship to the clinically manifest processes.

**SYSTEM OF LATENT INFECTIONS**

1. **Infections latent during their entire existence**

   (a) **Cyclical processes.** This group covers the "infections inapparentes" of Nicolle.

   (b) **Acyclical or chronic processes.** It is advisable to subdivide the group into (aa) the "silent microbismus" (tetanus, anaerobes, etc.) and (bb) the "quiescent infections" (tuberculosis, leprosy, etc.) irrespective of the fact that a clear distinction between the two forms is sometimes impossible.

2. **Latency as a phase of an infectious disease**

   (a) **As a precursor of the malady.** In the majority of infectious diseases, this period of latency may have a remarkably regular and consequently normal value while in others it may be either unknown or it may be exceptionally long—certain chronic infections, tuberculosis, actinomycosis, undulant fever, malaria (primary latency), rabies, etc. Diseases with pronounced tendency to latency rarely reveal regular incubation times. Undulant fever offers a great many striking examples in support of this statement: A young man has a febrile attack of one day duration; his blood yields a culture of *Brucella melitensis* but a frank clinical attack of undulant fever develops but 3 months later. In typhoid, cerebrospinal fever and diphtheria these so called *incubationary* (Nicholls) or *precocious* carriers may play an important rôle in the epidemiology of these diseases.

   (b) **As a sequel of an infectious disease.** The state of latency in these so called "shedders" may be temporary and be terminated by spontaneous recovery or they may last for years or even during the entire life of the host. The word "shedder" has been employed since the proliferating microbes are, as a rule, eliminated.
in the excreta and secreta. However, a carrier of "malarial gametocytes" is not a "shedder." Furthermore, distinctions have been attempted by designating as a "germ carrier" an animal or a human being who contracted the latent stage as an independent process without a previous visible disease. This confusing nomenclature is properly replaced by the significant designations "healthy" and "convalescent" carriers. Certain observers (Sacquepêe and Doerr) believe that this differentiation is particularly valuable in diphtheria since they found the bacilli to persist longer in the convalescent than in those who had no recognizable clinical signs of the disease.

(c) As an intermediary stage. In the course of certain diseases with an intermittent or undulatory clinical course, periods of latency alternate with those of obvious disease. Dependent on the length of time which elapses between the manifest attacks, it is customary to speak of exacerbations or relapses, provided a reinfection may with certainty be excluded. In malaria, relapsing fever and certain septic processes, occasionally in Brucella infections, the sequence and duration of the latent and manifest phases follow with striking precision and are well regulated according to time. Malarial fevers offer an opportunity to analyze some of the factors which guide the latency. The febrile attacks coincide with the schizogony of the merozoites or agamonts and develop only provided the asexual forms reach a certain threshold which is in part dependent on the type of the malarial parasite (according to Ross, at least 140 quartan, 200 to 300 tertian and 600 to 3,000 tropical parasites per 1 cc. must be present before a febrile attack is induced). In vaccination malaria, not less than 14,000 tertian parasites per cubic centimeter cause fever. From the many speculative hypotheses, which have been advanced in order to explain the febrile paroxysms as an aftermath of the schizogony, the concept of poison formation by the interaction of agamonts and cellular detritus on the blood plasma (Doerr), and the phagocytosis of the parasites by the reticulo-endothelial cells (Taliaferro) deserve serious consideration. The investigations of Cannon and Taliaferro on the cellular basis of resistance to both avian and simian malaria suggestively
illuminate the role of the macrophage-lymphocyte system in the mechanism of latency. These superb studies have shown that in the course of these infections a certain percentage of the parasitized red blood cells are phagocytized by the "hemophages" of Kyes and rendered inert. Peculiarly, this function is not continuous but synchronizes with the development of each new generation of parasites. The periodicity of malarial fever may well be intimately connected with this mechanism. During latency against plasmodia, the host acquires some factor or factors which specifically cause the macrophages to ingest the parasites. Whether this altered reactivity of the reticulocytes is supported by a humoral factor in form of a tropin is not as yet settled. Similar in many ways is the mechanism in relapsing fever. Autopsies on children (Bykowa, 1926) or animals infected with *Spirochaeta recurrentis* show a marked hypertrophy of the reticulo-endothelial apparatus. An interplay between lytic antibodies and the mesenchyme cells guides the periodicity of the fever attacks. Protection of the spirochaetes within the cells and development of antibody-fast variants may lead to latency. In many septic diseases (undulant fever, various streptococcic infections, etc.), it has been noted that, as a rule, the causative microbes are less likely to be isolated from the blood during an afebrile than a febrile period. Then again, in certain animal diseases, the phenomenon of "microbial showers," by no means explained, merely indicates that in all probability the bacteria multiply irregularly. Some clinicians, by analogy with protozoan infections, attribute this behavior to growth cycles. However, the evidence, which gradually accumulates, involves the cellular activity of the host and not of the parasites.

The diverse experimental studies to convert a latent infection into a manifest process and *vice versa* offer many suggestions relative to the causes of latency. By splenectomy, latent plasmodial infections of apes (Gonder and Rodenwald) and piroplasmoses (dog, sheep and horses) have been changed into severe, even fatal infections. The entire *Bartonella* problem received a great impetus from the systematically planned removal of the spleen in rodents. The same principle applied to other latent protozoan infection has been even more fruitful. A *Trypanosoma Lewisi*
infection of the gray rat runs, as a rule, a benign and clinically latent course. Regendanz and Kikuth (1927) showed that in splenectomized rats the multiplication of the trypanosomes was frequently not retarded. In fact, the infection was thus transformed into a manifest process and frequently terminated fatally. Similarly, the extirpation of the adrenal by Marmorston, Gotterm and associates was followed by a like result in approximately 70 per cent of the experiments.

To the disappointment of many a worker, latent bacterial or virus infections in laboratory animals have been recognizable by the injection of diverse agents. Carriers of Bacterium leptisep-ticum may be made recognizable by placing silver nitrate or dyes into the nostrils of the suspected rabbits. The microbian associations (Microbio de salida or Microbes de sortie of Maurice Nicolle) with protozoa in virus diseases belong to this group. With increasing frequency, “latent infections” are converted into visible diseases by transferring organ material of various animals to new hosts. One recalls the discovery of the virus III of rabbits, the encephalitis virus of mice and the protozoon Encephali-tozoon cuniculi. Saprophytic viruses are discovered in cultures (Barnard). Vice versa, as already detailed, manifest infections on a large scale and quite successfully have been transformed into latent stages by shifting the field of action from one host to another species. Although theoretically of greatest interest and subject to extensive investigation, these experimental metamorphoses contribute little to the understanding of the problem of latency in man.

Concerning the mechanism or the cause or causes of latency, the available knowledge is exceedingly fragmentary. For a few cases, a satisfactory explanation may be offered. The localization of the infectious process may condition the latency. A small tuberculous or fungoidal focus in a lymph-node frequently does not provoke clinical signs. The commensalistic existence of meningo- and pneumococci on the mucosa of the respiratory tract remains “symptomless” until the invasion of certain organs is followed by the typical clinical syndromes of cerebrospinal fever or lobar pneumonia.

Certain forms of latency are, in part at least, influenced by the
behavior of the disease-producing agent. The mechanism of the resting tetanus or gas gangrene infection has been explained as a phenomenon of growth inhibition which takes place at the moment the microbe is transmitted. In contrast to this primary lack of vegetation of the spores, a secondary retardation in the growth of bacteria in encapsulated abscesses, scarred or calcified tissues may be equally responsible for the absence of symptoms. A small number of infective agents, in part inhibited, may never multiply to a level which incites the clinical reactions. Under the circumstances, the infection may remain latent either through a long incubation time or for variable periods between primary attacks and relapses. In the considerations which are given to the carrier problems, one meets not infrequently the hypothesis that the latency was the result of a microbe of low or even non-pathogenicity. It is easy to assume fluctuations in virulence of the causative organism but its relationship to latency can rarely be proved. When the pathogenicity is associated with a specific toxin, successful correlations have been established. Thus, occasionally healthy diphtheria carriers may harbor organisms of relatively low toxicity. In fact, in rare instances, non-toxic strains have been isolated. However, as a whole there is no evidence that a true Corynebacterium diphtheriae loses completely its ability to produce toxin, and as such becomes an organism particularly endowed to create carriers. On the other hand, there are authenticated reports in the field of latent microbial and virus infections which conclusively prove a persistent and uniformly high pathogenicity during a very long sojourn of the disease agent in the tissues of the host. Under the influence of increasing but incomplete knowledge on the variability of bacteria, it is by no means surprising to note that latency is believed to be the result of a transformation from a pathogenic to a non-pathogenic variety. The frequent demonstration of rough variants in the excreta of typhoid-paratyphoid carriers lends support to these hypotheses. In fact, certain groups encourage the concept that these variants are stages of a continuous adaptive process leading ultimately to a harmless symbiont. Others, making use of the unsolved problems of life cycles, suspect
changed facultative invisible forms of the disease agents to be factors responsible for the latency in tuberculosis and syphilis. The effort is thus made to incriminate only the microbes. Despite the ubiquity of certain bacteria and the disease induced by them, not everybody becomes a carrier or acquires a latent infection. Without more precise information relative to such vague terms as "infectiousness" or pathogenicity, little progress will be made in the understanding of latency.

The mechanism known as "organotropism" by which is selected the tissues in which the parasites localize themselves and the many factors which control their growth and multiplication have been analyzed. Technical difficulties have prevented studies with plant parasites and viruses, but for certain macroparasites, *Trichina spiralis* and protozoa (malaria), the selective organ localization has been proven. Equally encouraging are the preliminary investigations on the influence of a trypanosome infection on the protein, carbohydrate and fat metabolism of certain rodents. It is assumed that the parasites disturb the metabolism and that, in turn, the abnormalities affect the nutrition and multiplication of the protozoa living in such a milieu. A study of *Pasteurella pestis* infections in hibernating rodents with profoundly changed metabolism discloses interesting and important facts which may help to explain certain causes of latency.

In the course of an infection, the environment to which the parasite is exposed changes continuously. It is certain that the disease agent is subjected to influences of varying intensities during the incubation time, the onset, the peak and the healing of the infection. Adaptations are suspected and newer studies attempt to demonstrate all kinds of transformations although for technical reasons, it is usually impossible to prove conclusively their existence in the living host. The solution of such intricate problems requires expert knowledge of modern experimental-pathological methods, and should not be attempted by those who merely know the "test-tube" and not the "animal" phases of a microbe.

Infectiousness and pathogenicity are relative conditions which are not dependent on the parasite alone, but in more important
degree, on the individual, racial and species characteristics of the host. Aside from a disposition for a manifest disease, the host in all probability possesses an equally important yet independent susceptibility for infections without pathological consequences. *Latency is conditioned by the behavior of the infected macroorganism.* For the sake of completeness, the various possibilities may be briefly noted. The possession of one factor or factors, which antagonize or neutralize the injurious effect of the microbe, for example, antitoxin content of the blood in a diphtheria carrier, may be important. Or a preceding infection of like etiology or phases of the disease may change the reactivity of the organism to such an extent that a reinfection or persistent infection may appear or remain in a clinically latent state. Since these modifications in the clinical course are the result of immunity reactions, Doerr has proposed the term "immunosatoric latency." Why the defensive mechanism remains incomplete and then suddenly ceases to function so that the disease becomes manifest as a relapse or is so intensified that a carrier state after months and years is promptly healed has not been explained. It must be frankly admitted that the method by which the host participates in these reactions is not known. These resistance variations should be correlated with phagocytic activity. Studies in this direction are obviously indicated. Latency is rather frequent in the infections in which the phagocytic mononuclear cells actively participate in the defense, or furnish the environment most conducive toward a favorable development of the infective agent. Extensive studies on the histopathology of *Brucella* infections and psittacosis suggest an experimental approach to a clearer understanding of the immunosatoric latency.

Dependent on certain conditions of the host are those forms of latency which already as primary infections remain free from clinical signs. The latent yellow fever and typhus fever of children, dengue in adults, typhoid bacilli in the blood of healthy persons and various *Rickettisia* infections in laboratory animals belong to this group. Since the effects of active or passive immunity can with certainty be excluded in the typhus infections of laboratory animals, it is strange that this state of individual
tendency to "latent infection" has not been correlated with the operation of genetic factors. Even the immunosatoric latency is in part influenced by these forces. Competent observers have in recent years pointed out that focalization and chronicity of a microbian disease process is not merely conditioned by individual immunizing subinfections but ultimately may be traced to the selection of resistant generations (Hirzfeld). Though the analysis of constitutional immunity is in its infancy, the data thus far available suggest that latency is often the expression of the host's inheritance rather than the variability of the disease agent. However, it must be stated with frankness that it will be impossible to list or discern more in detail the causes of latency until accurate information concerning the factors which promote or suppress symptoms of an infectious disease is available. The problem of "inapparente infections" is a part of the unsolved problem of pathogenicity. In its broader aspects it is the key to the understanding of latent epidemization and as an evolutionary phase participates in the rise and decline of certain diseases. The results of the scientific investigations of this important problem will doubtless furnish a rationale for the natural fluctuations of epidemics which now cannot be completely explained either through the frequency of the manifest infections or by the variability of the causative agent. Finally, this analysis has shown that a comprehension of mass disposition is intimately dependent on a clearer understanding of individual disposition and disease symptomatology.