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LECTURES AND SEMINARS

Rickettsioses, para-rickettsioses, and the nervous system

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[Dedication:] I would like to dedicate these pages to the memory of Professor Brenno Babudieri, who inspired them. He had asked me to prepare a lecture explaining in detail the nature of rickettsial conditions and their immediate and longer-term reactions *[sic]* on the nervous system, so that his personal case of professional contamination by *Coxiella burnetii* might serve as both an example and a lesson.

Rickettsioses and para-rickettsioses — conditions that I have been studying for more than 30 years, in Europe as well as in Africa and Asia — are ubiquitous infectious diseases that have the common characteristic of always including profound cardiovascular involvement, with constant repercussions, which are often very severe, on the nervous system [1].

They constitute a group of exanthematous febrile conditions whose bacteria, while differentiated from one another, all display the same fundamental pathogenic properties. Referred to for a long time as “large viruses,” and today classified among the bacteria, these microorganisms are living, toxic, infectious, episodic; infra-microbes with a clearly defined morphology. They are also especially sensitive to broad-spectrum antibiotics.

The entire group of these bacteria initially constituted the order of Rickettsiales, which consisted of the following two superfamilies:

- The *Rickettsiaceae*, or rickettsias; and
- The *Chlamydiaceae*, or para-rickettsias.

However, these superfamilies subsequently acquired increasing importance, and recently were promoted to the level of orders, thanks to the efforts of Leslie Page, who is an authority on the subject [2]:

- The *Rickettsiaceae* became the order of Rickettsiales; and
- The *Chlamydiaceae* became the order of Chlamydiales.

The detection of these various pathogenic agents includes, on the one hand, a search for their antibodies in the serum of patients, and, on the other hand, the isolation of their strain in animals and the culture of the strain on the vitelline membranes of the egg.

The order of Rickettsiales

Rickettsias

The name “rickettsia” was given to these bacteria in memory of the American scholar H.T. Ricketts, who, after having discovered their existence in 1906, succumbed a few years later during his research on Rocky Mountain spotted fever.

Table 1 below lists the principle types, in a classification established in accordance with the antigenic specificity of the pathogenic agents themselves [3].

Table 1. — The major rickettsiosis antigens.

I.	<i>Rickettsia prowazekii</i>	Epidemic typhus
II.	<i>Rickettsia mooserii</i>	Murine typhus
III.	<i>Rickettsia</i>	<i>Rickettsia rickettsii</i> : Rocky Mountain spotted fever <i>Rickettsia acarii</i> : Rickettsial pox
IV.	<i>Coxiella burnetii</i>	Q fever
V.	<i>Rickettsia tsutsugamushi</i>	Tropical typhus
VI.	<i>Rickettsia quintana</i>	Trench fever

Rickettsia prowazekii is the pathogenic agent of epidemic typhus, which is a severe condition transmitted to humans by the droppings of the louse, which infect the bite of this insect.

This discovery, made in 1909 by Charles Nicolle, won him the Nobel Prize in 1928 [4].

Rickettsia mooserii is the pathogenic agent of murine typhus. This essentially murine condition is transmitted to humans by the droppings and urine of the rats that taint the food.

There are two types of murine typhus:

- The first type (“shop typhus” or “nautical typhus”), which is usually encountered in port cities, warehouses, and along navigable waterways, is transmitted by rats that are commensal with humans. It is always benign.
- The other type, which is transmitted by wild rodents, is always very serious. Its severity is identical to that of epidemic typhus, with a high and often startling mortality rate.

I determined its existence in Central Africa in 1939 (confirmed in 1951 by the isolation of the specific strain I), and named it “savannah typhus,” because it is found in all of the savannah regions of black Africa, during the period in which brush fires were used in hunting the rodents [5] [6] [7] [8] [9].

Rickettsia conorii is the pathogenic agent of Mediterranean exanthematous spotted fever. Transmitted by the bite of the *Rhipicephalus sanguineus* tick, it is the leading member of the louse and spotted–fever group, which (as indicated in Table 1) also includes *Rickettsia rickettsii*, which is the pathogenic agent of Rocky Mountain spotted fever, and *Rickettsia acarii*, which is the pathogenic agent of Rickettsial pox.

Coxiella burnetii (three strains of which I was able to isolate in Central Africa [10]) is the pathogenic agent of Q fever. This condition is manifested in two forms that are completely different, depending on the method of contamination:

- When transmitted via the respiratory, ocular, or digestive pathways, it is usually manifested in the pulmonary form, with no exanthema or adenopathy.
- When transmitted via insect bites [11], the condition is manifested in the exanthomatous form, of which the most striking type is red Congo fever [12], with its constant adenopathies and, above all, its impressive and intensely scarlet exanthema.

Rickettsia tsutsugamushi is the pathogenic agent of the tropical typhi that are more widely known as “scrub typhus.” These conditions, which are always very severe, are found only on the Asian continent and in the Sunda Isles [13].

This rickettsia is transmitted to humans by a *Thrombididae* larva (*Trombicula deliensis*), whose bite always leads to the formation of a small necrosing eschar. This eschar, which is highly specific, is caused by the true digestion of the tissues by the vector. I isolated 4 strains of this rickettsia in South Vietnam in 1954.

Rickettsia quintana is the pathogenic agent of Volhynie [Wolhynia] fever (more commonly known as “trench fever.” The virus reservoir is man, with the louse as the vector.

As shown by Weyer of Hamburg [14], this is the only rickettsiosis that is an anthroozoonosis. All of the others are zoonoses.

The order of Chlamydiales

Para-rickettsias

The term “para-rickettsia” was coined in 1931 by Professor E. Brumpt, and soon afterward was adopted by Professor C. Levaditi as a replacement for the highly non-standard name “*Rickettsia psittaci*,” which had been given to the psittacosis virus by Lillie in 1930, when this researcher presented a number of characteristics of the *Chlamydiaceae* which clearly distinguished this virus from the rickettsias. Thus, the para-rickettsias represent all of the bacteria that belong to the order of *Chlamydiales*, the most recent list of which, as drawn up by Leslie Page, is shown below (Table 2).

This order includes, in particular, the important group known as the “TPL group” (trachoma, psittacosis, and lymphogranulomatosis), which includes the bacteria discovered by J. Jadin in Rwanda-Urundi and known incorrectly since 1955 as “Giroud’s neorickettsia.”

Here, in order to put an end to a regrettable amount of confusion, it should be emphasized that *Bergey’s Manual* (the international authority on microbiological nomenclature) recognizes only a single neorickettsia, i.e., *Neorickettsia helminthoeca*, which is the name given in 1953 by C. Philip and Trib to the pathogenic agent of so-called “salmon-poisoning disease of dog” [*sic*; quoted in English in the original French-language article – Tr.]. Having observed that this bacterium has characteristics reminiscent of the *Rickettsiaceae*, while nevertheless being different from them but without being reminiscent of the *Chlamydiaceae*, they then coined the

term “neorickettsia,” supplementing it with “helminthoeca,” in order to emphasize clearly the fact that this bacterium is transmitted by a trematode.

Table 2. — Classification of the order of *Chlamydiales*.
(after L.A. Page, 1971)

FAMILY	GENUS	SPECIES	Species name in the former classification in <i>Bergey's Manual</i>
	<i>Coicziola</i> <i>Ricolesia</i> <i>Colettsia</i> – Epi- or endo-cellular – Not cultivated – Too little known to be classified – Only the first 2 are pathogens	<i>Conjonctivae</i> <i>Conjonctivae</i> <i>Pecoris</i>	
CHLAMYDIACEAE Visible: 450 – 100 µm RNA + DNA + carbohydrates, lipids, and proteins Enzymatic system Common thermo-stable antigen Division images Sensitivity to anti-bacterial agents Not known to be transmitted by arthropods	<i>Chlamydia</i> – Endocellular – Cultivable in yolk sacs – Pathogen(s)	<i>Trachomatis</i> – Rigid inclusions – Presence of glycogen – Sensitivity to sulfadiazine <i>Psittaci</i> – Diffuse inclusions – Absence of glycogen – Resistance to sulfadiazine	<i>C. trachomatis</i> <i>C. oculogenitale</i> <i>M. lymphogranulomatosis</i> <i>M. bronchopneumoniae</i> <i>M. psittaci</i> <i>M. ornithosis</i> <i>M. felis</i> <i>M. louisianae</i> <i>M. illinii</i> <i>M. opossumi</i> <i>M. ovis</i> <i>M. bovis</i> <i>M. pecoris</i>

(*) In an earlier article on neorickettsias [15] (and in accordance with the generally accepted view), I attributed to Prof. Charles Levaditi the authorship of the term “para-rickettsia.” However, Jean Levaditi later spontaneously informed me that although his father had been the first to use and circulate this term, it had in fact been coined by Emile Brumpt.

Consequently, by right of priority, the term “neorickettsia” cannot be applied to a bacterium that is reminiscent of the *Rickettsiaceae* (i.e., a bacterium that is a member of the order of Rickettsiales and that is transmitted by a trematode).

Properties of rickettsias and para-rickettsias

Although rickettsias and para-rickettsias are different from one another, all of these bacteria have the same pathogenic properties. Specifically, they are characterized by:

First, an elective endotheliotropism, which, regardless of their port of entry, enables them to progress irresistibly, by means of a centripetal movement, toward the vascular walls, such that they reach the adventitia, and from there attach themselves to the endothelial cells of the arterioles and of the pre-capillaries, where they were observed for the first time by Wolbach et al. [16] in 1921.

Nevertheless, it should be kept in mind that, contrary to the view generally held since the work of Wolbach, the tropism of the bacteria in question is “centripetal,” and that their original location therefore must be adventitial, because their fixation to the endothelium is terminal.

This fact, which was detected in a remarkable manner by Francis and Annie Roger [17] in 1958, but which, alas, is still little known, should be kept in mind in all pathogenic interpretations of rickettsial or para-rickettsial conditions, because it conditions and explains the principal clinical and histopathological reactions [18] that are usually observed during the course of these diseases. In point of fact,

- On the one hand, in view of the close anatomical relationships between the adventitia and the sympathetic plexus, any and all adventitial aggression has immediate repercussions on the sympathetic chain, whose reactions to the harmfulness of the toxins can range from simple irritation (e.g., tingling (“pins and needles”), swelling, and more or less painful cramps with contractions of varying intensity) to the most sudden and violent spasms,

which can cause causing coma, hemiplegia, infarction, comitial crises [i.e., epileptic fits or seizures], tetanic seizures, etc.; and

- On the other hand, the adventitial cell — the omnipotent cell endowed with colloidopexic and ultra-phagocytic properties — has been viewed (since the work of Spielmeyer) as a reticulo-histiocytic cerebral factor.

Thus, the foregoing explanation clarifies the pathogenesis of the inflammatory reactions that take place, in the form of typical perivascular nodular formations (known as “Frenkel’s nodules”), in which the following factors are always present: diffuse arteriocapillarity; constant proliferating perivasculitis; and intense lympho-histiocytic infiltration with thrombosing endothelitis, which in most cases is hemorrhagic. This inflammatory reaction is accompanied, in the nervous system, by the proliferation of glial tissue and of the demyelination sites [19].

These nodules represent a typical aspect of rickettsioses. They are found in all of the vessels — the ones in the nervous system and also the ones in the other areas.

During the course of their evolution in the region of the nerve centers, these nodules are known as “Von Prowazek–Popoff nodules.”

They can be observed in the encephalon of subjects who have succumbed to epidemic typhus, to Rocky Mountain spotted fever, or to a scrub typhus, as well as in the encephalon of animals that have been inoculated intracranially with a rickettsia suspension [20].

They thicken the walls of the vessels, whose lumens they obstruct, to a greater or lesser degree, thereby posing a constant obstacle to the nutrient blood flow, leading to gradual hypoxia or even anoxia of the regions involved. The hypoxia is constantly aggravated, in a more or less understated or else sudden and noticeable manner, by the harmfulness of the toxins discharged from the sites of infection.

Why is this so? Because a second fundamental pathogenic property of these bacteria is their ability to release formidable angiotropic toxins whose effect on circulation is inarguable.

Griesman and Wieseman [21] provided a persuasive demonstration of this phenomenon. By injecting an infinitesimally small dose of *Rickettsia mooserii* toxin into a vein of a white rat, they found, in the region of the arterioles and pre-capillaries, a contraction that intensified gradually until the animal died. At autopsy, the capillaries were found to be empty of blood, [as the result of] a true collapsus, of whose potential possibilities in human rickettsioses we are well aware.

The role of these toxins, which is always precocious, is also always predominant. It is invariably accompanied by an obligatory nervous reaction, which (as we have just seen) is a result of the close anatomical relationships that link the adventitia to the sympathetic chain. This is why the sympathico-vascular reactions initially take on a predominant importance, with the angiospastic ischemia constantly aggravating the cytotoxic anoxia.

These toxins, which are vasoconstrictive, allergizing, and demyelinating, and which have a specific antigenic capability, also encourage the formation of pathognomonic adhesions in the serous glands and particularly in the peritoneum, which adhesions can cause, among other things, sudden appendicular pseudo-crises or even intestinal occlusions, especially in cases of attacks by *Coxiella burnetii*.

Last, as a *third fundamental property*, the rickettsias and para-rickettsias are also characterized by their very long survival in the organism, as can be observed with malarial hematozoans during their latency period, i.e., an apparent “sleep” of indeterminate duration, during which the bacteria develop quietly, with no noticeable external manifestations, while releasing their toxins, which cause constant vascular irritation with subacute ischemia in the affected regions.

This hidden development can always be interrupted by more or less frequent recurrences, which can be either overt or latent, as a result of a variety of stimuli, whether seasonal, endogenous, or exogenous, so long as the bacteria have not been totally destroyed.

Latency usually occurs following an acute primary infectious episode. However, initial latencies also exist. In such cases, there are no signs or symptoms that allow the practitioner to suspect the primary invasion by the microorganism, which, being totally unsuspected, may have years in which to continue its quiet development, but always with the possibility of secreting toxins and manifesting itself more or less suddenly, from one day to the next, in an unpredictable manner. These are the so-called “unseen” diseases that Charles Nicolle detected as early as 1919, during his research on exanthematous typhus [22].

Importance of anoxia

Given the three pathognomonic properties of their infectious agents, i.e.:

- Centripetal endotheliotropism;
- Angiotropic toxin; and
- Latency with resurgence,

the rickettsioses and para-rickettsioses appear, above all, as vascular aggressions that lead to instances of vasculitis that generate anoxia. And it is this anoxia which, in the region of the nerve centers, constitutes the *primum mobile* [“prime mover”] of the various neurological manifestations.

Why? Because these bacteria are not neurotropic in the strict sense of the term. They do not attack the nerve cell (as, for example, the poliomyelitis virus does). Rather, they deeply affect the nerve cell, in terms of its vitality, by altering the vessels that nourish it — specifically, by depriving it (through their parasitism and the harmfulness of their toxins) of its vital principles (i.e., oxygen, glucose, mineral salts, etc.). At the same time, the elimination of the catabolic products is no longer assured. Hence the imposition of a more or less insidious form of anoxia, which may be gradual or sudden, but which is always responsible for nervous manifestations, depending on the region involved [23].

Rindfleisch [24] in 1864 was the first to shed light on the leading role played by the disturbance of the nutritional substances supplied to nerve cells in the pathogenic process of multiple sclerosis.

However, the dependence of the nervous system on the cardiovascular system had already been demonstrated, more than three centuries earlier, by Stenon. By connecting the aorta of a dog below the diaphragm, he observed paralysis and anesthesia of the animal's hindquarters within just a few minutes, with a return to normal as soon as the ligature was removed [25].

This experiment was confirmed after Stenon by the work of numerous authors, including Brown-Sequard, Dejerine, and others. In 1869 Schiffer [26] demonstrated that the neurological difficulties that ensued after compression of the aorta in the dog were caused by anoxia of the peripheral nerves if the obstruction was located in the L3 region; and, conversely, that these difficulties could be attributed to anoxia of the medulla if the obstruction was located above this region. These conclusions are all the more significant because of the corollary in adjuvant surgical therapy which they justify, and from which paraplegics may benefit through peripheral anoxia in conjunction with a sympathectomy, in accordance with the principles of Leriche.

Clearly, all the factors that can cause this type of anoxia represent a large number of etiological possibilities. However, their percentage remains low — on the order of 10 to 15% — while that of the rickettsioses and para-rickettsioses is predominant, at 85 to 90%.

Still, as a function of the anoxia, these pathological manifestations are naturally more precocious and of greater magnitude as the aggression affects functionally terminal vessels with essentially no anastomoses. Hence the very high incidence of difficulties with the act of walking; paresis; and paraplegia, due to the fact that the driving medulla, which is a tributary branch of the sole anterior spinal artery (which has virtually no anastomoses and is functionally terminal) remains very vulnerably, while the sensitive medulla, which is fed by several branches of the posterior spinal [artery] and enjoys the benefit of many anastomoses, usually remains unaffected by the anoxia.

For the same reason, the involvement of the gray matter and — above all — of the anterior horns is manifested earlier than the involvement of the white matter. The determining factor is always a vascular one.

Thus, it is essential to be aware that the central, peripheral, or mixed origin of these neurological difficulties is determined by the area within which the impediment to nutritional transport is most specifically organized. Because each vessel is responsible for different functions, these functions will be altered, reduced, or even suppressed altogether, depending on the greater or lesser degree of disturbance of the circulatory transit. The symptomatology of each attack will also vary, depending on the region or regions involved.

The practice of clamping also constitutes a continuing method for experimental confirmation.

Neuro–psycho–pathogenic manifestations

Long before the rickettsias and para–rickettsias were discovered, their nerve–related symptoms already occupied a dominant position in the clinical context of these redoubtable pandemics, which were attributed to the war, to cold, and/or to the famines that decimated entire populations, and that were known as “typhus,” because one of their leading symptoms was the lethargy or torpor that the patients manifested.

Typhus is characterized by a clinical setting whose principal syndromes are encountered more or less often in all of the rickettsioses and para–rickettsioses. Here is an outline that allows the practitioner to grasp, right from the start, the importance and diversity of the nerve–related manifestations that are customarily observed:

- The disease appears suddenly, in much the same way as a flu, with which it is often confused. The fever initially rises as high as 40 or 41° [Celsius].

- Headache is the first symptom that indicates the involvement of the nervous system. Persistent, painful, and overwhelming, it is generalized to the entire brain case, with painful radiations to the eyeballs and equally painful sub–occipital paroxysms.
- The degree of photophobia is intolerable, and insomnia is complete, with a more or less pronounced state of confusion.
- As a rule, delirium (either calm or typhomaniac) includes vocalized delirium, caused by visual hallucinations.
- The neurological examination reveals a certain stiffness at the nape of the neck, with Kernig’s sign and strong contraction of the abdominal wall.
- The reflexes are lively at first, and then gradually slow down until they disappear.
- Rachialgias, arthralgias, and myalgias are always present, and often very severe. Myoclonias and trembling are frequent.
- The facies is purplish or red, and bloated or puffy. The conjunctiva are bloodshot, the lips are dry and cracked, and the patient experiences intense thirst.
- The appearance of the tongue is so characteristic that, once having been viewed, it cannot be forgotten. The center is covered with a creamy, whitish coating, and the tip and edges are dry. The tongue is often animated by a sort of fibrillary trembling, and is more or less globular, due to the contraction of the genioglossi as a result of the paresis of the last cranial pair. The tongue no longer overlaps the edges of the dental arches. The latter condition constitutes the well–known Godelier–Remlinger sign, which is a characteristic manifestation of rickettsial attacks.
- Hypoacusia may be associated, and is often followed by transitory deafness.

- Enanthema of the soft palate is always accompanied (at about Day 6 or Day 7) by the appearance of exanthema.

Usually announced by abundant sweating, this exanthema is present fairly unobtrusively in epidemic typhus, murine typhus, or savannah typhus. However, it dominates the context of the other typho–exanthematous fevers (i.e., hives and spotted fever, red Congo fever, or scrub typhus, indiscriminately).

- Torpor and lethargy appear suddenly, usually toward the end of the first week. At the same time, the presence of myocardia is usually noted, which is always accompanied by pulmonary stasis with more or less pronounced basal congestion, which may be massive, with intense dyspnea and coughing, sometimes accompanied by hemorrhagic expectoration.
- With the onset of torpor and lethargy, the psychopathological symptoms become more pronounced. The patient, who is very weak and indifferent to his surroundings during the entire day, starts to become agitated as night falls.

Close monitoring is necessary, because as the day wanes, the patient’s state of excitation increases, and may be manifested in the form of highly unexpected demential actions and/or ambulatory delirium, with suicide attempts or the so–called “attraction to the abyss.”.

This “attraction to the abyss” is another characteristic of rickettsial attacks. A dramatic demonstration was recorded during the First World War, during the retreat of the Serbian army toward the Adriatic Sea. During this retreat, it was impossible to prevent a number of soldiers, all affected with epidemic typhus, from leaping off the top of the fortress of Corfu, where they had been hospitalized, and falling to their death on the surrounding rocks below. As mentioned by Sikorav and Ventelon, this phenomenon was the result of suddenly invasive cerebral anoxia.

In cases that evolve favorably, a crisis of defervescence usually occurs at about Day 15. Diuresis increases, the patient's temperature returns to normal, the symptoms regress more or less rapidly, and convalescence begins.

Convalescence is usually long and difficult. Depending on the sympathicovascular reactions, it may be complicated by a variety of more or less transitory neuro–psycho–pathological manifestations, such as sudden paraplegia, sensory hypersensitivity (involving vision, hearing, and/or smell), neuritic difficulties, split personality, etc. In any event, continuous monitoring is necessary, because of the cardiac failures with acute myocarditis that can occur dramatically at any given time — failures that represent yet another of the characteristics of these formidable conditions [27].

Such, in abbreviated form, is the clinical setting that characterizes epidemic typhus, and whose broad outlines can be found, with varying degrees of severity, from one case of rickettsiosis to another. Of course, the setting may also vary greatly depending on the vector, the contamination pathway, the virulence of the bacteria, the harmfulness of its toxin, and, lastly, for many patients, the nature of the area attacked.

As we shall now see, the multiplicity, diversity, and intensity of the neurological symptoms are impressive.

This diffusion along the entire length of the cerebrospinal axis, followed by regress within a few weeks or a few months, with full functional restoration, logically can only involve inflammatory lesions of vascular origin, because the transitory but damaging nerve–related phenomena can only be linked to exudative and congestive reactions to instance of acute vasculitis, caused by the parasitism of the infectious bacteria and the harmfulness of the toxins.

The foregoing conclusions are confirmed in full by the autopsies in the most unfortunate cases, in terms of the disproportional relationship between the clinical reactions that were observed and the paucity of macroscopic observations, which (with regard to the nerve centers as well as to the

other affected areas) are limited to inflammatory lesions accompanied by diffuse congestion and serous extravasations.

In hyperacute cases in which death occurs rapidly, there is no perivascular reaction, and the demyelination is replaced by true tissular necrosis. Both the gray matter and the white matter are necrosed, in the manner of an anergic sideration of the defensive forces.

These objective findings attest to the fact that, although the sites of infection act locally, causing lesional reactions by their mere presence, they also have a more remote effect, due to the release of toxins that can spread like a tidal wave and attack the tissues in the manner of an angiospastic poison, against which the tissues react violently — or else succumb before being able to react.

The evolutionary process

Nevertheless, the presence of toxins and bacteria usually leads to the formation of reactive antibodies, which appear toward the end of Week 1, reaching a maximum level on or about Day 20. Thanks to the development of these antibodies, the rickettsial diffusion is limited, and the lesions tend to be resorbed.

Afterward, a proportional restoration of vascular equilibrium takes place, which terminates the anoxia.

When reactional antibodies or specific therapeutic treatment is able to exercise a rickettsiocidal effect (that is, the total destruction of the microorganisms in question), the above-mentioned restoration is definitive, and the patient is cured.

However, if this effect does not go past the rickettsiostatic stage (that is, the neutralizing stage), then the bacteria, which have been temporarily damped down, continue their evolution in a latent manner, with the preservation of the possibility of spreading their toxins and of manifesting themselves more or less noisily in the event of a momentary weakening of the organic defenses,

when the effects of various stimuli encourage the outbreak of a relapse. This can happen even if a very long period of time has passed since the primary infection, because rickettsial strains have been isolated from lymphatic ganglions in subjects who had been contaminated more than 30 years earlier.

Latent evolution (the unseen disease)

During the latency period, the sites of infection, which had been superficial, become cryptogenic. They form “lair” that lie deep within the thickness of the reactional tissues, doing so in areas in which the structure has been modified and/or circulation has been compromised. Accordingly, they become hard to reach, and the chronic nature of subsequent recurrences is thus encouraged.

Each recurrence (that is, each reawakening of the latent site) leads to focal congestion, with a new release of toxins, such that the lesions are aggravated and the anoxia increases (and, along with it, the magnitude of the difficulties). Each such recurrence is less pronounced than the previous one, because of the deeper organization of the reactional lesions.

Consequently, the instances of acute vasculitis that characterized the initial infection turn into instances of chronic vasculitis, with the *vasa vasorum* constantly displaying tumefactions, hyalinizations, and endothelial proliferations.

These instances of chronic vasculitis, which spread in a manner similar to that of obliterating thromboangitis, have repercussions on all of the organs and viscera — especially those with a rich vascular complexion, upon whose metabolism they can have a profound effect, which in turn can lead to insufficiencies and more or less pronounced and often very severe deficiencies. For example, it is easy to see how, as a result of these gradual capillarites, organs that are as heavily vascularized as the brain or the endocrine glands (i.e., the liver, the pancreas, the thyroid, the adrenals, the ovaries, the testes, etc.), can quietly degenerate. It is equally easy to see how physiological imbalances, often accompanied by severe functional difficulties, can ensue [28].

Although rare during the first few months, these deficiencies and insufficiencies conversely are the hallmark of chronic rickettsioses and para-rickettsioses. They should be carefully controlled and corrected, because, if neglected, they can cause the specific treatment to fail.

The above-mentioned deficiencies and insufficiencies cause such organic disturbances that it is not at all unusual (especially when *Coxiella burnetii* is involved) to see true muscular “melting” in the extremities, with no accompanying spasticity. These amyotrophic characteristics of rickettsioses and para-rickettsioses need to be known. They are caused by profound biological deficiencies, which in turn are the result of a metabolic deficiency in an anoxic environment, and need to be distinguished from myelopathic amyotrophias, with which they could initially be confused, if it weren't for the absence of spasticity [29].

Neural histopathogenesis

Repeated attacks by toxins against the nerve centers evoke energetic local defensive reactions, with, among other things, multiplication of the microgliaocytes (in the reticulo-endothelial system described by Horteaga del Rio) [30] and the affluence of granular Gluge bodies, in the form of large mononucleated macrophage cells that phagocytize the cellular and myelinic debris.

For these reasons, the oligodendrocytes, whose functions consist essentially of ensuring the formation, maintenance, and repair of the myelin, constitute the elective points of impact of the demyelinating agents [31].

Myelin, which is a highly labile complex (that disappears and is reproduced, in tissue cultures, in a matter of days) can be disintegrated by numerous factors, of which the toxins and toxic factors are the most formidable.

And this disintegration always takes place in an oxygen-deprived environment.

In the region of the nerve centers, the anoxia process caused by the infectious bacteria and by their toxins is indirectly aggravated by the fact that the progress of the perivasculitis leads to

the complete closure of the space that Davson [32] detected (through the use of an electronic microscope) between the glia and the capillaries. This space contains the plasma filtrate that comes from the vessels, and in which the sucker–feet of the astrocytes (the histo–physiological structures described by Ramon y Cajal [33] pulse the nutrient factors (water, ions, and various solutes) that are essential to the life and functionality of the neurons to which the nutrients are sent. Simultaneously, the astrocytes discharge the catabolic neural products, which under normal conditions are taken up and evacuated by the vessels.

Therefore, the astroglion performs one of the vital mechanical functions discovered by Claude Bernard, i.e., the true homeostatic mechanism located between the capillary and the neuron, which at any given time controls the so–called “hydroelectrolytic” level of the central nervous system, protecting it from any possibilities of edema and performing regulatory, excitatory, or inhibitory functions with regard to the nearby neurons, through constant monitoring of their needs [34] [35].

However, as soon as the intensification of the perivasculitis produces continuity solutions by closing the Davson space, these so–called “nutritional, electrolytic, and eliminative” exchanges are blocked, and complete anoxia occurs. The primary metabolic disturbances that accompany this anoxic process osmotically lead to the onset of an edema that affects the gray matter and the white matter at the neuronal and oligodendroglial levels, while the astrocytes, which are highly sensitive to the lack of oxygen, which interferes with their activity, respond immediately by withdrawing.

The volume of the astrocytes diminishes significantly; their resting membranal potential is transformed into diffusion potential, and their contents are discharged into the intercellular fluid, where the various catabolic products also accumulate.

Consequently, the ionic concentration changes the pH of the medium, such that the pH, which is normally negative, becomes positive.

Thus, the physical equilibrium is reversed. Under the influence of the positive polarities, the normal repelling forces are replaced by attractive forces which, depending on the ambient pH, cause true cellular anarchy, which is manifested in the form of amoeboid deformations, giant multinucleated cells, huge cell nuclei (which continue to expand until they eventually burst), flocculation phenomena, coagulation phenomena, etc. [36] [37].

In this way, for example, in multiple sclerosis of rickettsial or para-rickettsial origin, the ionic concentration and the inversion of polarity trigger a series of interreactions which are propagated excentrically, starting from a vessel but independently of its path, in a centrifugal motion that gradually expands, in much the same way as a spot of ink on a piece of blotting-paper, always in accordance with the pH of the site. Meanwhile, the perivascularitis is attenuated as a result of the action of the reactive antibodies, and the anoxic astrocytes give way to a massive proliferation of astroblasts. This proliferation serves as a trigger for the resumption of the exchanges between the glia and the vessel, in accordance with the re-establishment of the vascular equilibrium and the regression of the anoxia [38].

Diagnostic difficulties

When the neurological or psychiatric symptoms correspond to the epidemiological data, are part of a typically characteristic clinical setting, or appear within that setting as a complication that can easily be correlated with the patient's overall condition, the etiological diagnosis does not pose any problems.

Quite obviously, the manifestations of polyradiculoneuritis, sensitive and sensory polyneuritis, or neuritis accompanied by amyotrophia that appear following a classical instance of Q fever (as encountered so often in cases of attacks by *Coxiella burnetii*) can easily be linked to their true etiology. The same holds true for a posterior [spinal] cord syndrome that follows an instance of meningo-uveo-papillitis or that appears suddenly during a bout of Mediterranean spotted fever, or for a pyramidal or psychiatric syndrome that appears after murine typhus or [Wolhynia] fever.

Here I wish to cite a personal example, i.e., the case of three Europeans who contracted a scrub typhus in South Vietnam. Upon their return to France, one of them presented with amyotrophic lateral sclerosis, and the two others presented with multiple sclerosis. It was from one of these two cases of multiple sclerosis that I was able to obtain the first isolation of *Rickettsia orientalis* that had been achieved in Vietnam [*sic*]. This was the Tuy–Hoa strain, which is currently being stored and utilized at the Pasteur Institute in Paris, under the designation O–14 [39].

Here's another example. This one involves an isolated and primitive psychiatric manifestation that was observed in central Africa. This was the case of a young European man whose behavior had always been extremely quiet and unaggressive. One evening, happening to notice an African passing, the young European man assaulted the African and killed him, acting on an irresistible impulse that the young European was unable to explain. A few hours after the murder, a raging fever forced the young man to take to his bed. Three weeks afterward, a serodiagnosis that was positive for *Rickettsia mooserii* (with a ratio of 1:1250) clarified his action and, in a very timely way, saved his bacon in court.

However, sometimes the epidemiological context is completely missing, or the acute primary infection phase passes completely unnoticed, or the symptoms associated with one of the several localizations dominates the picture, serving as a sort of autonomous disease that masks the true nature of the infection and leads to erroneous diagnoses, which often include the tags that I have seen so many times before, e.g., flu, myocarditis, meningoencephalitis, hepatitis, pneumonia, or dementia.

Moreover, at any stage in the evolution of the condition (e.g., during the primary infection or during a resurgence), purely neurological or psychiatric manifestations may appear. These may include isolated cubital or femoro–cutaneous neuritis (which are fairly common) or episodic fits of schizophrenia, etc., which can all mislead the clinical practitioner, who cannot find any valid explanation for the condition and who has no anamnestic reason to associate these manifestations with a rickettsial or para–rickettsial attack, of whose physiopathology the clinician moreover is usually completely unaware.

Consequently, because the etiology has been neither detected nor treated, the infectious bacteria proceed, as we have seen, along a subacute or undetected evolutionary course, reappearing at a later time, with the help of a resurgence, in the form of an aggravated recurrence of the same sign or symptom, or else in a new location (in addition to the initial one), while the treatment, which remains symptomatic and does not address the underlying physiopathology, can aggravate the tissular disorders and potentially reach a dead end.

Lessons from the laboratory

Bearing in mind all of the foregoing observations, laboratory–based instruction makes it possible to understand objectively, through focus and a sort of crystallization, all of the complexity of the clinical polymorphism and of the histopathological reactions to which the long evolution and the episodic chronicity of these bacteria can lead.

Accordingly, at the autopsy of animals inoculated intraperitoneally with a suspension of *Coxiella burnetii* and sacrificed 15 days later, we made a striking observation. Even though none of the animals appeared to be unwell, the diffuse vascular characteristic described above was present throughout each organism, affecting the liver, spleen, adrenal glands, lungs, endocardium, and meningoencephalon. Put another way, this experiment successfully replicated the initial latency of the disease.

We made equally striking observations at autopsy in several cases of human rickettsioses, noting the presence, in the nerve centers, of parenchymal arterial lesions, which were usually associated with leptomeningitis, even in cases in which no meningeal syndrome was present.

These objective laboratory observations indicate the intense level of pathogenic activity — so unlikely and so unsuspected — that is masked by the silent latency periods during which the organism is in a constant state of hypoxia and subacute ischemia, which state (as we have seen) favors the onset of metabolic disturbances and increasingly aggravating deterioration of the field.

The laboratory observations also attest to the possible participation of all of the components of the nervous system (both central and peripheral) in the endotheliotropic and angiospastic rickettsial and para-rickettsial process. However, none of the bacteria in question has an exclusive relationship with any particular manifestation. Whether the symptom consists of coma, epileptic seizures, tetanic seizures, ictus, hemiplegia, paraplegia, meningoencephalitis, involvement of the central nuclei, peripheral neuritis, or psychiatric manifestations, the basic factor in these rickettsial attacks is still the anoxia conditioned by a vasculopathy that poses an obstacle to the flow of nutrients.

They also attest to the fact that, even when only a single neurological symptom is present, a general (and continually progressive) disease also exists — even if this disease consists only of the discharges of toxins into the circulatory system.

They offer the possibility of actually watching the latent foci manifest themselves openly from one day to the next, in locations that are preferably either “unique or multiple,” or “sequential or concomitant,” in any area of the organism where they happen to be located, and in any part of the cerebrospinal system (hence the unpredictability and diversity of a symptomatology that is still a function of “the” region or regions that are most directly affected).

They allow clinicians to understand that, depending on their preferred locations, neurological syndromes that are currently classified according to a different nomenclature may have the same rickettsial or para-rickettsial etiology, and thus may benefit from the same specific treatment, provided that a valid explanation or an effective therapeutic treatment is not found elsewhere.

Accordingly, the laboratory observations clarify the etiopathology of all of these neuropsychic signs and manifestations for which neuropsychiatric solutions have not yet been found, because the signs and manifestations in question are generally caused by an infectious disease with a vascular location, which disease generates cellular anoxia (as is the case with multiple sclerosis, amyotrophic lateral sclerosis, Parkinson’s disease, epilepsy, schizophrenia, etc.).

Therefore, it is of vital interest to patients that clinicians consider the possibility of a rickettsial or para-rickettsial etiology whenever they face a febrile disease that includes a sympathico-vascular reaction whose nature remains indeterminate, such as (for example) any neurological, psychiatric, or even cardiac manifestation that has not been confirmed. In these cases, the clinician should seek confirmation of the reaction through the various laboratory tests that have been designed to reveal the presence of these infectious bacteria.

One of the most frequently utilized tests is the Weigl microagglutination test, as modified (in accordance with the technique developed by P. and M. Giroud) through the addition of a May-Giemsa stain. Although microagglutination is a valuable guide, its value — we must recall — is purely indicative. Practical experience with patients has demonstrated that although a positive reaction is entirely valid as soon as its level is modified through the effect of broad-spectrum antibiotics, a negative reaction derives its value from the accompanying epidemiological data and clinical signs, which will then determine the course of therapeutic treatment to be prescribed.

In point of fact, the so-called rule for valid or non-valid levels is completely contrary to what is represented *in vivo* by the evolution of these unseen diseases, with their periods of sleeping and waking, during which the serological response remains a function of the organism's defenses, which are more or less capable of producing reactive antibodies. Accordingly, the responses of a serodiagnosis may be negative even in cases that have been confirmed through the isolation of the bacterium in question. Such was the observation made for the male nurse in central Africa, who during a rodent hunt near Boali (formerly known as Ubangi-Chari) contracted an extremely severe case of savannah typhus, whose specific strain (Strain 1) I was able to isolate, despite the fact that the patient's serum consistently refused to agglutinate its proper strain. Only the use of electrophoresis made it possible (by grouping the gamma-globulins together) to confirm a level of positivity which was similar to that of the control, which itself had always displayed a notable reaction [40].

Consequently, a negative serodiagnosis should not be called upon in support of the rejection of an etiology, when this rejection will determine the fate of many patients by depriving them of the only effective treatment.

Whenever a serodiagnosis turns up negative, a reactivation should be performed; a balance sheet of deficiencies and insufficiencies should be drawn up, so that these levels can be adjusted and corrected; and the neutralization and immunofluorescence reactions should be performed (and, if they are also negative, recourse should be made to electrophoresis). Nevertheless, all of these research steps still leave room for a restriction, because we do not possess the complete range of antigens that correspond to all of the Rickettsiales and/or Chlamydiales that are known to exist, let alone the antigens for the bacterial types that still remain to be discovered.

That is why, when clinical or epidemiological indications are present, recourse to a “touchstone” treatment test representing the broad-spectrum antibiotics is absolutely necessary. The bacteria in question are very sensitive to these antibiotics, and the effect of the antibiotics is more rapidly effective and even totally curative when the bacteria are still superficial. Superficial bacteria are very vulnerable and can easily be destroyed, and (as we have seen) the lesions can regress with no complications or sequelae, until healing is achieved. Hence the importance of early diagnosis [41].

However, regarding therapeutic effectiveness, it should also be emphasized that this sensitivity is not random or general. Instead, it is elective, because the bacterial strains react preferentially to one or another of the antibiotics.

Thus, *Rickettsias prowazekii*, *mooserii*, and *orientalis* require the use of typhomycin; *Rickettsia conorii* specifically needs aureomycin; and *Coxiella burnetii* and all of the para-rickettsias are more sensitive to terramycin — with the reservation, however, that certain strains of *Coxiella burnetii* (approximately 10 to 15%) respond only to aureomycin, often doing so in a spectacular manner.

It should also be emphasized that the effect of the antibiotics varies widely, depending on the doses and duration of treatment, ranging from a total lack of response to the most sudden and pronounced reactions. Hence the danger of using antibiotics indiscriminately, without knowing how or why they will act. Because of the reactivations that they can provoke, excessively low

doses are just as dangerous as excessively high doses or excessively long application periods (which involve a toxic overload).

Lastly, it should also be noted that:

- The laboratory–confirmed results of appropriate antibiotic treatment can be extremely eloquent, in terms of their specificity and their therapeutic effectiveness, thus providing proof of the etiopathology in question; and
- This etiopathogenesis is wholly consistent with all of the epidemiological, clinical, biological, and histopathological criteria, and also with the therapeutic corollary that it entails. It is also strikingly consistent with the teachings of Claude Bernard, who, with regard to the study of living fields, unfailingly recommends that researchers seek the unity of physiological and pathological phenomena that lies at the root of the infinite variety of their manifestations [34] [35].

Social prevalence

The widely held and completely erroneous belief that rickettsias and para–rickettsias are rare in Europe is based primarily on the facts that they are very little known and that what is known about them is largely incorrect, because — limited as they are to the excessively narrow field of exotic pathology — they are not taught as they should be.

Indeed, we must acknowledge that they are just as frequent and virulent in Europe as they are in the tropics, and that they in fact exist all around us in nature, inasmuch as the reservoirs of the virus lie in the animals — including family pets, domestic animals, and wild animals — with which we can readily come into contact.

For example, during research done in 1948 along the French Mediterranean coast in connection with exanthematic Mediterranean spotted fever, I was able (in the middle of the Bozon Forest, no

more than ten or so kilometers from human habitation) to capture a wild rabbit (*Oryctolagus cuniculus*) at the entrance to its warren, and to collect some of its fleas (*Spilopsyllus cuniculi*). The pulverized residue of these fleas revealed the presence of epidemic, murine, and spotted [typhus] antibodies. Thus, these wild rabbits were pluri-infected and pluri-infectious [42].

Contamination may take place at any age, in any environment, and at any latitude; however, it is markedly predominant in the temperate zones, with livestock-rearing and -breeding areas naturally being the most heavily affected.

Contamination may take place:

- Via an intermediate host (such as a louse, flea, tick, or hematophagic insect;
- Via secretion products (such as milk) or excretion products (such as urine) that contaminate food products, with the digestive tract as the port of entry; or
- Via dust from contaminated and dried organs, such as the dust present in livestock-breeding regions, particularly when the herds are moved from one grazing area to another. In these cases, the ports of entry are the respiratory and ocular pathways. In this regard it should be noted that the ocular pathway is a particularly propitious one for the location of pathogenic bacteria on the vessels of the cerebrospinal axis, with precocious effects on the papillae, whose temporary discoloration represents a precursor symptom of multiple sclerosis, which may not be openly manifested until much later — up to as long as 10, 20, or 30 years or more after the initial infection.

With this multiplicity of sources, and this perpetual ease of contagion, we can easily grasp the breadth of the domain of the rickettsias and para-rickettsias, and we can easily understand the vast importance of their social prevalence.

Their epidemiology and their singular pathogenesis (which, alas, has been shamefully neglected, through being insufficiently taught) make them the scourge of the century, because they are so little known and all the more dangerous for it.

— Not only because of their striking acute manifestations, but also (and much more so) in their chronic, latent, and unseen forms, which affect too many individuals who are inevitably doomed, through mistaken diagnoses, to dead-end treatment and often to inhuman suffering, from which a better knowledge of the physiopathology in question could protect them.

Consequently, it would appear to be a social obligation (and one of some great urgency) to grant the rickettsioses and para-rickettsioses — not only within the context of ubiquitous infectious diseases but also in general university-level medical education — the prominent position that they in fact so richly deserve.