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ROUMANIAN CONTRIBUTION TO THE STUDY OF LATENT INFECTIONS INDUCE--ETC(U)  
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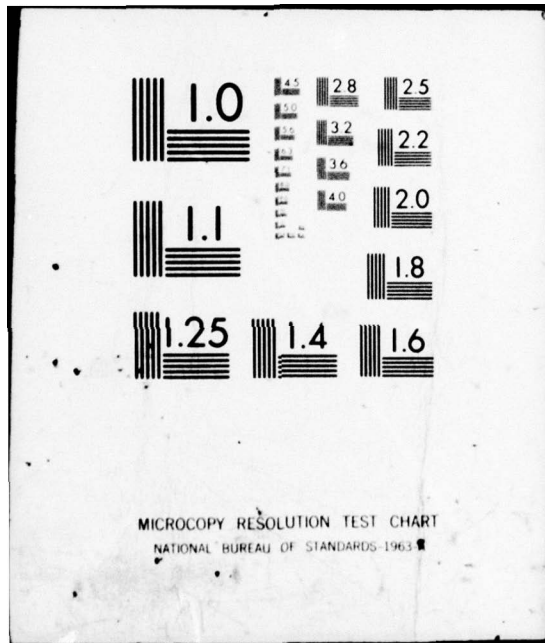
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LA CONTRIBUTION ROUMAINE A L'ÉTUDE DES INFECTIONS LATENTES  
PROVOQUÉES CHEZ L'HOMME PAR LES RICKETTSIES ET LES PARARICKETTSIES  
(Affections cardio-vasculaires; dermatoses vasculaires;  
ophtalmopathies; certains aspects de la pathologie de la grossesse)

[ROMANIAN CONTRIBUTION TO THE STUDY OF LATENT INFECTIONS INDUCED  
IN MAN BY RICKETTSIAE AND PARARICKETTSIAE  
(Cardio-vascular; vascular dermatoses; ophthalmopathies; some  
aspects of the gross pathology)]

C. T. SURDAN\*

Bull. Soc. Pathol. Exot. 61:5:737-752, 1968

(Translated by P. W. Summers)

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3. Vascular dermatoses with: St. G. Nicolau, Gh. Noaghea, A. Badanoiu, G. Bucur.
4. Certain aspects of gross pathology with: P. Sirbu, E. Macarie, A. Cioltei-Mihaila (Hôpital Clinique Giulessti), I. Filipescu et al. (Maternité Grivitzza).
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MUL 0518

The considerable increase in the frequency of cardiovascular diseases in the world, over the last 25 years has brought about study in many countries of the etiopathology of these afflictions.

From new epidemic elements, such as the occasional endemic or epidemic aspect, the matter is affecting young persons more and more frequently, the febrile or sub-febrile evolution in certain cases, sometimes the character of the general illness, the favorable effect of broad spectrum antibiotic treatment, argue in favor of intervention by an infectious factor in the etiopathology of a large number of cases of this type.

The classic work of Burger (6), Brill (5), Parkes-Weber (77), Perla (79), Dawidowsky (16), Abrikosov (1), Goodman (42-44) Zinssen (87) and others has demonstrated rickettsial etiology of some angiopathies affecting older patients with exanthematous typhus, in the same way as the vasculotropism manifested by R. prowazeki.

The latent character of rickettsial infections, the relapses and the resurgences, the large number of mild even inapparent forms, in the same way as the marked angiotropism of these organisms, have been eminently shown by Nicolle (76), Zinssen (87), Sergent (80), Parrot (78), Ciuca et al. (12), Zdrodowski (86), Giroud et al. (21, 41).

At the same time the discovery of new pathogenic species of rickettsiae and pararickettsiae (Bedsonia, Miyagawanella, Neorickettsia) have brought up some important epidemiologic problems and have explained, in part, the incidence actually of increased cardiovascular illness.

The studies carried out in recent decades by Giroud et al. (20-41), Bernard (4), Bernard et al. (3), Derby et al. (17), Michon et al. (46-50), Comte and Ouradou (14), and Comte et al. (13), Donzelot et al.



(18), Catan et al. (11), Faure et al. (19), Marmion (51), Andrews and Marmion (2), Grist (45), Nicolau St. S. et al. (52-72), Surdan et al. (81-85), Kristinson (15), and others have furnished very important data on the role of rickettsiae and pararickettsiae in the etiology of the different cardiovascular affections.

From the works cited, there is unanimous agreement that R. prowazeki is the example of the etiological agent of vasculopathies, of all the organisms in the Rickettsia and Pararickettsia group present similar pathogenic characteristics and can run the entire gamut of illnesses of cardiovascular appearance or of other organs, and be marked by great clinical polymorphism.

The new chapter of infectious pathology opened by Giroud on this problem, has taken on impressive proportions and great importance.

After 1960, encouraged by Giroud and with his concurrence, a number of Romanian virology specialists, under the direction of our late master Stefan S. Nicolau, studied this problem, reporting significant contributions.

Numerous reports and papers have been presented at different international scientific meetings: Union Medical Balkanique, Bucarest (May 1962); 3rd International Congress of Infectious Pathology of the Medical Sciences of the USSR, Leningrad (February 1963); the International Meeting on Information on Rickettsiases and their Vascular Complications, Paris (May 1963); International Congress of Angiology, Paris (August 1964); 4th Congress of the Association of Hungarian Microbiologists, Budapest (October 1964); 3rd Latin-American Congress of Microbiology, Bogota (December 1964); National Congress of Medical Microbiology, Bucarest (September 1965); 8th Argentine Congress of Ophthalmology,

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Mendoza (April 1966); International Congress of Ophthalmology, Munich (August 1967); 1st International Symposium on Rickettsiae and Rickettsial illnesses, Smolence (September 1967); 6th World Congress on Fertility and Sterility, Tel-Aviv (May 1968), as well as others. The abundant material has contributed to the demonstration of directly and indirectly latent rickettsial or pararickettsial infections in the etiopathology of some illnesses which have evolved on a vascular basis: coronary diseases, thrombosing vasculopathies (arteritis and phlebitis), cerebrovascular diseases, some ocular problems, different aspects in the pathology of pregnancy, ulcers, rheumatism (arthrosis or spondyloses), chronic obstructive pneumopathies, some dermatologic or neurologic illness, etc.

Aside from our results obtained from 1960-1966, published in different reviews of the specialty, we propose to present results of studies carried out from 1966-1968.

By repeated serologic, virologic, anatomo- and histopathologic, and specific therapy studies <sup>the authors</sup> we have tried to prove the role of latent infections by rickettsiae or pararickettsiae in the establishment or aggravation of diseases such as:

1. Cardiopathies or vasculopathies (carried out with several health units of the country).
2. Vascular dermatoses (carried out with the Center of Dermato-Venereology of the Minister of Health).
3. Ophthalmopathies (in collaboration with the Institute of Normal and Pathologic Physiology "D. Danielopolu" of the Academy of R. S. Roumania).
4. Different pathologic aspects of the pregnancy of women (in collaboration with Hospital for Women of Giulesti and the Hospital of Obstetrics and Gynecology Grivita).



1. Cardiopathies and vasculopathies.

From 1966-1968, we studied 471 sick people selected from cardiovascular cases; 140 presented different cardiopathies (106 coronaries; 20 myocarditis; 2 endocarditis; 5 pericarditis and 7 valvulopathies) and 331 different vasculopathies (41 peripheral circulatory problems; 191 obliterating arteritis; 75 thrombophlebitis; 7 cerebrovascular problems; 9 pan-angeitis and 9 malignant arterial hypertensions).

Results of the serologic studies for rickettsioses or pararickettsioses are shown in Table 1. The data demonstrate that the proportion of seropositive reactions is 57.1% for cardiopathies and 53.3% for vasculopathies. The distribution of the cases serologically positive in relation to the type of rickettsiae or pararickettsiae relative to the reaction obtained, registered almost equal mean values: 10.11% for R. prowazekii, 27.23%, R. mooseri, 26.44%, R. conori, 18.67%, R. burneti and 17.51%, Pararickettsia. In several cases positive reactions were obtained for 2 or more rickettsial antigens.

Histopathologic study of 15 arterial fragments, 44 biopsies of veins and pieces taken from the heart in 20 fatal cases of myocardial infarcts, has shown in the majority of the cases, lesions of panvasculature and the presence in the stained zone of the cells of reticulohistiocytic type which contain numerous rickettsia-form bodies in their cytoplasm.

Treatment in the specialty clinics, for some of the cases were antibiotics of the cycline group, administered orally or intravenously, in several treatment schedules for 10 days, repeated at 15-30 days, had gradually favorable action, curing or relieving the clinical state.

TABLEAU I  
 Résultats des recherches sérologiques pour les rickettsioses et pararickettsioses  
 chez des malades atteints de différentes maladies cardio-vasculaires.

Affection	Nombre de malades	Résultats de l'examen sérologique	Distribution des cas sérologiquement positifs en rapport avec le type antigénique de rickettsies ou pararickettsies					
			<i>R. prowazeki</i>	<i>R. mooseri</i>	<i>R. coneri</i>	<i>R. karwaki</i>	Pararickettsies Q <sub>u</sub>	
<b>Maladies coronariennes</b>	109	—	—	—	—	—	—	—
Myocardite	40	140	11	22	11	11	11	11
Endocardite	20	—	—	2	3	1	1	2
Pericardite	2	1	—	—	—	—	—	—
Valvulopathie	5	3	1	2	—	—	—	—
Valvulopathie	1	4	1	2	—	—	—	—
<b>Total</b>	149	160	12	28	16	13	16	16
		32,8 0/0	8,7 0/0	34,1 0/0	20,0 0/0	16,2 0/0	20,0 0/0	20,0 0/0
<b>Maladies vasculaires</b>	47	—	—	—	—	—	—	—
Arterite oblitérante	100	26	2	11	8	5	2	2
Thromboangiopathie	75	68	11	18	35	17	12	12
Érythème noueux	2	10	6	11	9	1	1	1
Érythème noueux	2	3	—	2	—	—	—	—
Érythème noueux	2	3	—	2	—	—	—	—
Érythème noueux	2	6	—	1	—	—	—	—
<b>Total</b>	271	177	10	42	52	35	29	29
		65,3 0/0	10,7 0/0	23,7 0/0	20,1 0/0	19,7 0/0	11,1 0/0	11,1 0/0
<b>Total général</b>	421	337	20	70	68	48	45	45
		79,8 0/0	10,3 0/0	27,2 0/0	20,1 0/0	18,6 0/0	17,2 0/0	17,2 0/0



After therapy, there was a lowering of antibodies, which eventually reached negative values.

These results confirm and complete the more extensive studies by us during 1960-1965, and give evidence of the important role of latent rickettsial infections as primary or secondary in the etiopathology of certain cardiovascular diseases.

## 2. Vascular dermatoses.

Serologic studies carried out on 317 cases of dermatologic illness gave positive results in 196 cases (61.82%), doubtful in 23 (7.25%) and negative in 98 cases (30.9%).

From these we selected all in which the etiology could be related to rickettsial or pararickettsial infections.

Results are shown in Table II.

TABLEAU II

*Résultats des recherches sérologiques  
pour rickettsioses et pararickettsioses  
chez les malades à angiodermatoses.*

No. ord.	Affection	Nombre de cas	Résultats de l'examen sérologique (microagglutination)					
			Positif	Douteux	Négatif	Total		
1	Ulceure chronique de la jambe post-phlébotique . . .	77	51	66,2 0/0	4	5,2 0/0	22	28,5 0/0
2	Capillarite osseuse . . .	25	10	64,0 0/0	3	12,0 0/0	6	24,0 0/0
3	Purpura anémopathique . . .	41	26	63,4 0/0	3	7,3 0/0	12	29,2 0/0
4	Grauculome annulaire . . .	3	2	66,6 0/0	—	—	1	33,3 0/0
5	Triade Gougerot . . .	2	2	100 0/0	—	—	—	—
6	Phlébite migrante . . .	5	3	60,0 0/0	1	20,0 0/0	1	20,0 0/0
7	Artérite juvénile . . .	17	10	58,8 0/0	2	11,8 0/0	5	29,4 0/0
	Total . . .	170	110	64,7 0/0	13	7,6 0/0	47	27,6 0/0

Of these 170 cases studied, 110 (64.7%) had positive reactions and 13 (7.6%) doubtful.

In the group with chronic ulcers of the leg, the majority appeared to be the result of thrombophlebitis in an area of varicosity; the proportion of positives is 66.2%, which corresponds to the data presented before by Nicolau et al. (65) and Surdan et al. (82).

It is interesting to note that the other types of angiodermatoses, which follow exclusively from vascular permeability problems, have appeared among the young without visceral damage, the proportion of positives being 64% in cases of purpuric capillaritis; 63.4% in cases of anhemopathic purpura; 2 of 3 cases of annular granuloma and 2 of 2 cases of Gougerot triad (? possibly Osler's triad). Generally, a large proportion of seroreactions are positive for R. mooseri and R. burneti and low for R. prowazeki, R. conori and Pararickettsia.

The proportion of 60% positives in migratory phlebitis and 58% of juvenile arteritis in short reports presented earlier by us (62, 82).

The good results or improvements obtained with tetracycline therapy of angiodermatoses patients open new perspectives in therapy and elucidation of the nature of these illnesses, as established by the work of Nicolau et al. (73).

### 3. Ophthalmopathies.

The serologic study in 50 cases of ocular illnesses (iridocyclitis, chorioretinitis, uveitis, retinal arterioclerosis, conjunctivitis, etc.), has given positive reactions in 31 cases (62%). In order of the frequency the reactions were positive for R. burneti, R. conori, R. mooseri, R. prowazeki and Pararickettsiae.



Study of the polymorphism of the ocular physiopathology in these diseases of possible rickettsial or pararickettsial etiology, gave evidence of endo- and exo-ocular aspects which could be considered almost characteristic. In arteritis of the spastic and scleral type, the clearing up of the center of infection permits the arterial wall to regain normal pliancy, which demonstrates that the direct action of the pathogen as infiltrative (spastic) and slightly infiltrative (sclerosing), is reversible in these 2 cases. In numerous cases, retinal arteritis was accompanied by a complex process, micropolyadenitis, optic neuritis, macular or pigmentary chorioretinitis, chorioretinitis and periphlebitis, chorioretinitis and neuritis, or neuritis.

Among exo-ocular problems seen in seropositive patients, there were torpid, nonexudative conjunctivitis; trachoma with secondary localization; nodular conjunctivitis and spontaneous conjunctival ecchymoses.

By treatment with antibiotics of the tetracycline group of favorable effects were obtained, seronegative results or slight improvement by nonspecific symptomatic therapy (10).

The efficacy of antibiotics was marked by relief of ocular symptoms and decreases in antibody levels.

#### 4. Pathologic aspects of pregnancy of women.

Studies on the role of latency in examination of pregnancy was carried out simultaneously in 2 hospitals of obstetrics and gynecology by a group of specialists.

There were selected from the 2 units, by repeated serologic examination, 176 women who had had previously pathologic aspects of pregnancy and who presented with only positive reactions to rickettsiae

and pararickettsiae. All cases seropositive for toxoplasmosis, listeriosis, leptospirosis or brucellosis were eliminated; in the same way, were cases of anatomic or Rh incompatibility.

For comparison, we present separately results obtained from the 2 groups.

At the hospital for women at Giulisti 126 pregnant women were observed. Data are shown in Table III and IV.

TABLEAU III

Nombre total des cas	Antécédents pathologiques de la grossesse			
	Avortements spontanés répétés (1-11)	Nés, morts (autés, intra, et post-partum)	Fœtus malformés	Fœtus prématurés
126	94	14	7	11
	74,6 0/0	11,1 0/0	5,5 0/0	8,7 0/0

TABLEAU IV

Nombre total des cas	Distribution des cas sérologiquement positifs d'après l'antigène agglutiné					
	<i>R. prowazeki</i>	<i>R. mousleri</i>	<i>R. coheni</i>	<i>R. burneti</i>	Pararickettsies	Deux ou plusieurs antigènes
126	6	39	39	21	10	11
	4,76 0/0	30,95 0/0	30,8 0/0	16,66 0/0	7,93 0/0	8,73 0/0

Of the 126 positives under observation, 72 were new pregnancies; a part received tetracycline treatment, 2 to 4 courses for 10 days (2 gm/day) during the period between pregnancies and the majority had been treated during pregnancy with 1-2 gm tetracycline/day, for a total of 10-20 gm/month, for 3-5 months. In some cases, tetracycline treatment had been associated with bismuth salts (1 vial at 3 day intervals).



Therapeutic results are shown in Table V.

TABLEAU V

Nombre total des cas traités par la tétracycline avant ou pendant la grossesse	Nombre total des femmes qui sont restées gravides	Naisances à terme d'enfants normaux et viables	Évolution normale de la grossesse après le 6 <sup>e</sup> mois	Accidents pathologiques de la grossesse	
				Avortements	Gravides morts
126	72	49	9	13	1
	57,14 0/0	68,05 0/0	12,50 0/0	18,05 0/0	1,37 0/0
		80,55 0/0		19,44 0/0	

Thus from the table, 72 of 126 women (57.14%) who had been treated with tetracycline remained pregnant. Pregnancy progressed normally and 49 (68.08%) gave birth at term to normal, well developed infants and 9 have passed the first 6 months of pregnancy in normal fashion. Thus, the efficacy of therapy was 80.55%, compared to the same treatment group (table III) in which the proportion of abortions was 74.6%, dead at birth 5.5% and premature 8.7%.

At the Grivita hospital, 50 women were studied and data are presented in Table VI.

TABLEAU VI

Nombre total des cas	Antécédents pathologiques de la grossesse			
	Avortements spontanés (1-10)	Nés morts antès, intra ou post-partum	Fœtus malformés	Fœtus prématurés
50	43 cas sur 128 av.	3	0	1
	81,00 0/0	6,00 0/0	0	2,00 0/0

Serological results are shown in table VII.

TABLEAU VII

Nombre total des cas	Distributions des cas serologiquement positifs d'après l'antigène antigène					
	<i>R. prowazeki</i>	<i>R. mooseri</i>	<i>R. conori</i>	<i>R. burneti</i>	Para-rickettsia	Deux ou plusieurs antigènes
50	2	9	9	7	2	20
	4,00 0/0	18,00 0/0	18,00 0/0	15,00 0/0	4,00 0/0	42,00 0/0

The 50 positive women were treated with tetracycline as already mentioned. Of the 50, 44 remained pregnant; the other 5 have not been pregnant during the 2 years of observation after treatment. Efficacy of treatment on conception and on the evolution of pregnancy is shown in Table VIII.

TABLEAU VIII

Nombre total des cas traités à la tétracycline	Nombre des femmes		Naisances à terme d'enfants normaux et viables	Accidents pathologiques de la grossesse		
	Non gravides	Gravides		Avortements	Enfants nés prématurés	
					en vie	morts
50	6	44	35	4	2	3
	12,00 0/0	88,00 0/0	79,54 0/0	8,00 0/0	4,54 0/0	6,81 0/0
			79,54		20,45 0/0	



Thus, as seen in Table VIII tetracycline therapy was 79.54% with normal evolution of pregnancy and birth at term of a healthy infant which developed normally. If one compares the proportion of pathologic antecedents in this group 86% repeated abortions, 6% born dead, 8% prematures, with the situation obtained after tetracycline therapy (Table VIII), so that 44 (88%) remained pregnant and 35 of the 44 (79.54%) had normal pregnancy with births at term of well developed infants, positive results are obvious and noteworthy.

In this sense, results obtained by the two groups with tetracycline therapy in serological positives are very close (80.55% and 79.54%).

The results of these studies confirm all the findings of previous workers (7, 8, 9, 81).

The result of our research in the realm of latent rickettsial and pararickettsial infections is more and more applicable in the following manner in the clinics of our country and the positive results of therapy with antibiotics of the tetracycline group are noted by numerous reports.

This leads to the fact, that the new problem of latent rickettsial and pararickettsial infections, a problem uncovered above all by Paul Giroud and co-workers, becomes more and more important. Workers at the Institute of Inframicrobiology of Bucarest, in collaboration with other researchers, have assembled a vast collection of about 100 studies; they studied more than 4000 cases of different diseases where rickettsial and pararickettsial organisms played a primary biological or a secondary role as a second infection. Results have been the subject of more than 100 papers published in Roumania or in foreign countries, and thanks to this effort over nearly 9 years, the problem is in perspective and real. At the same time, these findings applied on a large scale in our country,

have succeeded in helping numerous patients, improved or cured their infections, as shown by reduced numbers, attaining the satisfaction of some women who desire to be mothers and who were prevented apparently, by their latent infections of accomplishing this.

Aside from the clinico-therapeutic importance which results from the demonstration of rickettsial or pararickettsial etiology of some diseases, it should be emphasized the large view of opening up prophylaxis for these maladies, thanks to early serologic diagnosis and application of appropriate treatment.