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ANNEXES TO

CHAGAS' DISEASE IN BRAZIL

A SURVEY OF CLINICAL AND PATHOLOGICAL ASPECTS

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PAN AMERICAN HEALTH ORGANIZATION
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Table of Contents

CHAGAS' DISEASE IN VENEZUELA *

(Annex I to Document RES 4/10)

According to the census for 1961, the population of Venezuela seems very young. 44.6% are below 14 years of age, 31.9% are 15 to 34 years old, and 23.5% are between 35 and 85 years of age. Three quarters of the population is therefore younger than 35 years, and yet cardiovascular diseases are at second place in the general mortality and first in adults above the age of 25. The national program for the campaign against cardiovascular diseases is organized by the Division of Cardiovascular Diseases which belongs - together with the Division of Dermatology (including Leprosy), Cancer, Venerology and Hygiene of Adults - to the Department of Chronic Diseases and Diseases of Adults in the Ministry of Public Health.

The Division of Cardiovascular Diseases was established in 1959 and is responsible for planning, organizing, directing, controlling and evaluating the national program for the control of cardiovascular diseases in Venezuela. It includes the primary and secondary prevention of cardiovascular diseases, and physical, mental, vocational and social rehabilitation of patients disabled by cardiovascular diseases.

Primary prevention is aimed mainly at syphilis, Chagas' disease, streptococcal infections, tuberculosis and other pulmonary diseases. The early detection, diagnosis, treatment and continuous medical supervision and control of patients with cardiovascular diseases is the aim of secondary prevention. In order to assess the extent of the morbidity from cardiovascular diseases, a central registry of subjects with cardiovascular

* Based on site visit by Dr. Z. Fejfar, 11-17 November 1964.

diseases has been established. About 25% of patients hospitalized in the Department of Medicine suffer from diseases of the heart and vessels with an average hospitalization time of about 22 days. Out of 6,000 cards in the registry, 5,552 (i.e. 92.5%) are of subjects suffering from cardiovascular lesions. The distribution, according to etiology was as follows:

Etiology	No.	Percent	
Rheumatic heart disease	249	4.43%	
Atherosclerosis (main diagnosis)	1,876	33.6)	) 56.58
Atherosclerosis (associated with other etiologies)	1,280	22.9)	)
Other cardiovascular diseases	2,147	38.9	

Among other etiologies, congenital malformations were represented by 11.85%, systemic hypertension 12.4%, cardiopathies (Chagas) 5.5% and syphilis 1.52%.

The Registry at the present stage does not cover all diagnosed cardiovascular diseases and data do not indicate prevalence.

Assessment and control of cardiopathies caused by Trypanosoma cruzi has been given particular importance.

The Division of Cardiovascular Diseases takes part in all activities concerning the control of diseases of the heart and vessels: integral medical care (out-patients, clinics, home and hospital care); investigation and localization of suspected cases in the healthy population; epidemiological and clinical assessment of cardiovascular problems; medical,

paramedical and lay education; supervision, control and evaluation of the activities; preparation of norms for prevention, diagnosis, treatment and rehabilitation, from the technical as well as the administrative points of view.

The majority of assistants to the chief physician are employed part-time only and work in hospitals on very specialized subjects. In this way the Division is an administrative as well as a technical center which ensures a good technical level and thus the respect of practising physicians. There are 17 cardiovascular zone centers in rural areas, 10 metropolitan centers and 3 cardiology services in the University Hospital in Caracas, in the Sanatorium Simon Bolivar and El Algodonal, and in the Hospital Vargas.

A pilot study of the cardiopathies caused by T. cruzi in rural areas is an example of the effective work organized and carried out by the Division of Cardiovascular Diseases.

In 1960 it was estimated that about 40% of the Venezuelan population lived in rural areas, many of them in the palm shacks system, and there is an estimate of 600,000 of these dwellings.[1] Estimates based on several serological studies and of ECG examinations indicate that about 20% of the rural population in Venezuela has been infected by T. cruzi which would cover more than half a million people. About half of this number is supposed to suffer from chronic Chagasic cardiopathy. In areas of high endemicity, more than 50% of the population may be infected (e.g. Belén in the State of Carabobo).[2] This contrasts with the island of Margareta where there is no Chagasic infection at all.

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[1] Pifano, F. Arch. Venez. Med. Trop. y Parasit. Med. 1960, Vol. 3, 73-93

[2] Pifano, F. 1963, Bol. de la Ofic. Sanitaria Panamericana, 54, 396-411

The main vector is Rhodnius prolixus; T. cruzi is the main parasite while the role of T. rangelli and all mixed infection has not been entirely clarified. Complement fixation tests (CFT) have been carried out on more than 7,000 people from rural areas at the Institute of Tropical Medicine by Dr. Maekelt. Positivity increased with age.

Age in years	Percent Positivity (CFT)
5-9	20%
10-19	30
20-29	48
30-39	60
40-49	62
50+	65

Frequency of abnormal ECG tracings increased in a similar way.

A small number of blood donors have also been found to have positive complement fixation problems of congenital Chagas' disease. These were reviewed and investigated by Dr. Espinal in 1962.[1] Complement fixation tests were done on the venous blood of 500 mothers and their newborn babies. Blood from the umbilicus was positive in 57 pairs (11.4%). Twenty-three of them were then studied again within two to three months. All 23 newborn with positive CFTs at the time of birth became negative three to four months later. This shows that the antibodies were transmitted from the mother. In one infant three and four months after birth, when the

[1] Arch. Venez. Med. Trop. y Parasit. Med. 1962, 4, 243-264

CFT was negative, the xenodiagnosis was positive. Direct infection through the vector was considered unlikely in this case because of good housing conditions. The transmission of the parasite through maternal milk or through the placenta at the time of birth can be a possible explanation. In the latter case one would have to suppose that maternal antibodies prevented formation of antibodies by the child.

In 1961 the Department of Cardiovascular Diseases of the Ministry of Public Health, in cooperation with the direction of the Division of Malariology of the Ministry and with the Institute of Tropical Medicine, initiated projects to determine:

1. The prevalence and incidence of cardiopathies in rural areas with endemic Chagas' disease
2. The evaluation of clinical and functional features of Chagas' cardiopathy in correlation with the anatomy/pathology picture in longitudinal studies
3. The evaluation of methods and procedures suitable for epidemiological assessment and for clinical diagnosis of Chagasic cardiopathy
4. The medical treatment of the condition

The rural area of Belén with a population of 6,996 and the city of Belén with 2,135 people in the district Carlos Arvelo, State of Carabobo, was chosen on the basis of previous surveys where 518 houses out of 705 examined (73.5%) were found infested with triatomas; out of 1,694 triatomas 294 (25.8%) were infected with T. cruzi or T. cruzi plus T. rangelli; 280 out of 501 people had positive Machado-Guerreiro reactions (60%).

Methods of examination were multiple:

1. CFT for Chagas' infection and for syphilis
2. Cardiovascular examination - history, physical, ECG 12 leads, fluoroscopy, fluorography
3. Hematological and biochemical examination of the blood, medical examination of the urine and examination of the stool
4. Special examination such as radiokymography, vectorcardiography, angiocardiography and cardiac catheterization, phonocardiography, examination of cardiorespiratory function, gastroenterological for determination of the megaorgans, xenodiagnosis, liver and kidney function tests, biochemistry of the blood (protein, cholesterol, lipoproteins, C-reactive protein, and transaminases.)

The population has been examined since June 1961 in the rural health center in Belén by a stationary team composed of one physician (Dr. J.R. Nava), one laboratory technician, a secretary and an auxiliary nurse. Clinical examination, ECG, X-ray and routine blood, urine and stool examinations have been carried out there. The Department of Cardiology in the Central Hospital in Valencia provided hospitalization of selected patients; the cardiovascular center of Barbula and the T.B. Sanatorium S. Bolivar examined cardiopulmonary function, vectorcardiography, phonocardiography, angiocardiography and radiokymography.

The Institute of Tropical Medicine in Caracas has been responsible for serology, xenodiagnosis and parasitological examination. The Department of Pathology in the Central Hospital in Valencia provided macroscopic

and microscopic examination of the heart. The program was prepared and undertaken with the cooperation of the University of Carabobo.

Results of the first examinations performed in 1961 and 1962 showed that 51.5% of the 1,110 subjects had positive CFTs.

Serology	Number	Percent
Negative	521	47%
Positive	572	51.5
Doubtful	17	1.5
Total	1,110	100
Anti-complementary	43	

Cardiovascular Disease Prevalence	Number	Percent
Without cardiovascular diseases	915	75.6%
Clear cardiovascular disease	209	17.3
Doubtful cardiovascular disease	86	7.1
Total examined	1,210	100

17.3% had clear cardiovascular disease with the diagnosis of chronic myocarditis in 92.3% of them.

Distribution of 209 subjects with cardiovascular disease	Percent
Chronic myocarditis	92.3%
Chronic cor pulmonale	1.9
Hypertensive and arteriosclerotic heart disease	1.9
Hypertensive heart disease	0.9
Congenital heart disease without cyanosis	0.9
Syphilitic heart disease	0.5
Other	1.5
Total	100

CFTs were positive in 84.8% of subjects with the diagnosis of chronic myocarditis.

Definite cardiac disease was found in 155 out of 572 subjects with positive CFTs (27%) and in 29 out of 521 subjects with negative CFTs. The great majority of people with positive reaction did not show any, or only doubtful, signs of cardiovascular involvement.

Cardiopathies (N = 1093)	Serology Negative		Serology Positive	
	Number	Percent of N	Number	Percent of N
No	472	43.2%	359	32.8%
Clear	29	2.7	155	14.2
Doubtful	20	1.8	58	5.3
Total	521		572	

In Belén practically all selected subjects were examined yearly, three times altogether. Results of the follow-up study were not yet available, and the Consultant urged Dr. B. Gomez to put it as a high priority because this may be the first systematic follow-up of subjects with Chagas' infection in a population sample.

In order to compare data from Belén (700 meters above sea level) with those of a lower altitude, a sample of 500 people above the age of five years was chosen in El Eneal, altitude 275 meters, total population of about 780, and with about half the rainfall of Belén. The time for examination was not well chosen - rainy season - and only 395 subjects (75%) of the chosen sample participated. Fifty-one (12.9%) showed definite abnormality in the cardiovascular system; 40 of them were diagnosed as chronic myocarditis; CFTs were positive in 52% of examined subjects.

Dr. B. Gomez considers Margareta Island as the third place for examination, where there is no Chagas' disease (no vectors, no trypanosomes).

The program of the Division of Cardiovascular Disease is well planned. In particular, a close link with practical cardiology in the field, in hospitals and with the specialized university departments, is highly commendable.

At the Institute of Tropical Medicine the Consultant was given a general introduction to the problem of trypanosomiasis by Dr. F. Pifano, was acquainted with the serological aspects (Dr. G.A. Maekelt) and discussed problems of experimental Chagas' disease with Dr. A. Anselmi. In Valencia the Consultant was given an opportunity to examine hospitalized patients and to see autopsy material. In the field unit in Belén the Consultant examined more than 40 subjects who had gone there for annual

examination. He had the opportunity to visit several old and new houses. The joint activities - eradication of malaria and control of the vector of trypanosomiasis - were explained to the Consultant by Dr. Gomez - Nuñez at IVIC. The Consultant was also acquainted with some work on the ultrastructure of the trypanosomes.

At the end of the Consultant's visit, Dr. B. Gomez and his coworkers in the Department of Cardiovascular Diseases of the Ministry of Public Health described the organizational structure, functions and achievements of their division. Several aspects of the campaign against Chagas' disease in Venezuela, including the methodology, epidemiology, research and training of personnel, were described in detail by Drs. F. Pifano and L. Guerrero[1] and need not be commented on further in this report.

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[1] Bol. de la Ofic. Sanitaria Panamericana 54, p. 396-411, 1963.

CHAGAS' DISEASE IN CHILE*

(Annex II-A to Document RES 4/10)

The studies in Chagas' disease in Chile between 1938 and 1958 were summarized by Neghme and Schenone.[1] Cases with Chagas' disease reported during that period were 2,480. Xenodiagnosis was done on 21,581 inhabitants in seven provinces in Chile and found positive in 8.4%. The sample represents about 1,200,000 subjects. The CFTs were positive in 15.3% of 14,902 individuals tested. Triatoma infestans captured in the endemic areas numbered 33,708 and 39% of them were found infested with T. cruzi. The endemic areas are between latitude 18°30' to 34°35' S. and the infestation varied between 24.2% to 51.4%. One reported area is in a Southern suburb of Santiago where the carriers were mainly dogs and cats, but also some other domestic and wild animals such as Oryctalagus cuniculus, Capra hircus, Ostodon degus, Dusicyon griseus, Dusicyon culpaeus. T. infestans were not found in sheep, cattle, horses and guinea pigs.

Human cases reported were mostly chronic and with few symptoms; about 100 were acute with typical syndromology and laboratory findings. Megacolon apparently is not frequent either. Thus Atias et al investigated 38 patients with this disease.[2] Xenodiagnosis and complement fixation tests were positive in 13 of them; CFT only in 19 subjects. Seven out of 30 cases showed a variety of ECG abnormalities (RBBB 5 times); radiography of the esophagus was normal in all 29 patients on whom it was carried out. With only one exception all patients were born or lived in the Chagas' disease endemic area.

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* Based on information received by Dr. Z. Fejfar while on a site visit in Chile, 23-27 November 1964.

1 Revista Médica de Chile, 1960, 88, p. 82-93.

2 Revista Médica de Chile, 1960, 88, p. 94-97.

The Chagas' disease cardiopathy has been found similarly infrequent in Hospital Dr. J.J. Aguirre in Santiago. Nine cases were described[1] in the period of over five years 1954-59. They had severe right-side heart failure, often with Adams-Stoke syndrome, with ECG signs of conduction defects (3 total complete A-V blocks, 5 A-V blocks first or second degree, 8 RBBBs, one complete LBBB), extrasystole 3 times, auricular fibrillation 3 times and signs of myocardial necrosis or ischemia 3 times. The course and prognosis look similar to elsewhere and the so-called benignity ascribed to Chilean trypanosomiasis could be explained by the infrequent cardiac disease of infected persons.

Schenone and Niedmann[2] compared the clinical and ECG signs in 240 people with chronic Chagas' infection and 129 non-infected controls. They found a difference in complaints like palpitations, pain, etc; however, there was no marked difference in the incidence of ECG alterations in both groups.

Congenital infection with trypanosoma is not a rare finding in prematurely born babies. Thus out of 2,360 babies with birth weight below 2 kg., 12 had Chagas' disease, 10 syphilis and 1 toxoplasmosis. (Howard, La Enfermedad de Chagas Congenita, University of Chile, Santiago, 1962), and 4 out of 100 mothers with prematurely born babies had positive CFTs. The prognosis of congenital Chagas' disease is severe. Howard described 23 cases out of which 9 died during the acute phase and 3 before the first year of age. Marked hepatosplenomegaly is more often in congenital Chagas' disease than in syphilis or toxoplasma infection. Diagnosis was proved by positive CFTs and by the discovery of parasites in the blood.

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[1] Heitmann et al, 1960, Revista Médica de Chile, 88, 94-104.

[2] Bol. Chileno Parasit. 12, 2, 1957.

Professor G. Dusaillast from the Hospital del Salvador described the results of clinical and autopsy data of patients with hypertensive heart disease without hypertension. Agreement with the autopsy appeared in 80% of cases. The main manifestations were:

1) Rather sudden onset of left-side heart failure which increases and leads in a few weeks to right-sided failure
2) Marked enlargement of the heart contrasting with small aorta and short history of the disease
3) Bed rest and drug treatment lead to striking decrease in heart size
4) Angina pectoris - on effort and at rest, sometimes occurs during heart failure
5) ECG showed marked variability of alterations and in particular different forms of intra-ventricular conduction defects such as wide QRS, low voltage in extremity leads (so-called arborization block) RBBB with picture resembling LBBB in standard extremity leads; necrosis in left precordial leads without signs of injury or ischemia, arrhythmias, A-V blocks, E.S., atrial flutter and fibrillation.

An analysis of 200 cases admitted with heart failure shows the following distribution according to etiology:

Etiology	Number		Percent
Rheumatic heart disease	80		40%
Hypertensive heart disease	25	49	24.5
Coronary and hypertensive heart disease	8		
Coronary heart disease	16		
Myocardiopathy	32		16
Syphilis	15		7.5
Chronic cor pulmonale	4		7
Congenital heart disease	3		7.5
Others	7		3.5
Total	200		100

Cardiopathies were described as:

Chagas' disease	3
Post-partum	1
Senile heart (mild course, atrial fibrillation, good response to digitalis)	19
Alcoholic	5

Necropsy data in this hospital show about 8% of primary myocardial disease of all cardiovascular diseases. Professor Dusaillant stressed that alcoholism and malnutrition were important etiological factors.

Prophylaxis of rheumatic heart disease has been carried out since 1955. December 1964 marked the end of the tenth year and cover of 400 patients. Benzathine penicillin has been used for treatment. Severe

complications to this were death following the injection (noted once) and anaphylactic shock (three times). Following the meeting of the Pan American Health Organization in October 1963, a Chilean Committee for Rheumatic Fever prophylaxis was created. Information of the current state of rheumatic heart disease and rheumatic fever prophylaxis is being collected for WHO by Dr. B. Florenzano. Dr. Rammel Kampf stimulated a genetic study on rheumatic heart disease in conjunction with similar research in the U.S.A. Dr. Vaisman from Aguirre Hospital intends to assemble and follow-up families where both parents suffer from chronic rheumatic valvular damage or had acute rheumatic fever.

There appears to be great interest in studies of cardiovascular disease in Chile. The departments which the Consultant had the opportunity to visit have a very good standard of modern clinical cardiology and perform highly specialized routine examinations such as right and left heart catheterization and angio-cardiography. By chance the Consultant entered one catheterization laboratory at the moment when a patient's circulation suddenly stopped because of ventricular fibrillation. Resuscitation (mouth-to-mouth breathing and external heart massage) started immediately and continued until the arrival of the surgeon who opened the thorax and sustained the circulation by direct hand massage of the heart until the heart could be defibrillated. The hospital had only the usual defibrillator where the electrodes are placed directly on the heart. Within three hours the patient whom the Consultant had seen clinically dead at the beginning was in bed with a reasonable heart function and arterial blood pressure.

The need for more systematic study of cardiovascular diseases and interest from the medical profession and also the Government was evident. A month before the Consultant's arrival there had been a conference in

Santiago with the members of the Committee of the International Cardiology Foundation and several well-known scientists, e.g., M. de Bakey, A.C. Taquini, P.D. White and others had discussed the possibilities of establishing a CV research institute. Dr. L. Bravo, Director-General of the National Health Services, told the Consultant, informally, that the Government intends to create a cardiovascular institute in Santiago and he himself considers the building which was previously a TB sanatorium the best for this purpose. Centralization of cardiovascular research in a country like Chile is necessary. Equipment is expensive and there is need for several highly specialized cardiovascular institutes. Moreover, there appear to be difficulties in importing spare parts, as well as new parts for the existing equipment, and the economic advantages of one well-equipped center against several partly equipped departments is obvious.

CARDIOPATHIES IN CHILE*

(Annex II-B to Document RES 4/10)

Professor E. del Campo and Dr. G. Niedmann, from the Department of Medicine A in the Hospital San Borja showed the Consultant patients suffering from primary myocardial disease. From April to October 1964, out of 452 patients admitted to the department, 80 were diagnosed as having cardiovascular disease, the breakdown being as follows:

Rheumatic heart disease	23
Hypertensive heart disease	16
Arteriosclerotic heart disease	10
Primary myocardial disease (myocardiopathy)	22
Congenital heart disease	9

Reviewing their material over the last 12 years, they found only eight cases of Chagas' cardiopathy out of 45 subjects with myocardiopathy. Six cases with myocardiopathy had a total A-V block and all of them died within three years of its discovery at ages 17, 18, 19, 21 and 48; there were no facilities for implantation of the pacemaker at that time. They pointed out that although there have been several individual studies concerning the parasitology, immunology or clinical aspects of Chagas' disease in Chile, there has not yet been adequate epidemiological study of this disease and therefore no data on mortality and morbidity exist. An integrated approach and team work is badly needed. The scattered information is from various hospitals; e.g., about 5% of apparently healthy blood donors in Santiago were infected,

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* Based on a site visit to Chile on 23-27 November 1964 by Dr. Z. Fejfar.

as judged from positive Machado-Guerreiro reactions. CFTs have been found positive in about 20% of pregnant women in one maternity hospital.

The other myocardiopathies were diagnosed and demonstrated to the Consultant: alcoholic, toxoplasmic, idiopathic (of unknown origin) and in hemochromatosis. Dr. Niedmann has been particularly interested in heart disease caused by Toxoplasma gondii, and published in 1959[1] one of the first descriptions of chronic toxoplasmic cardiopathy. So far he has collected 15 subjects - 7 males and 8 females; all of them were serologically positive. The main symptoms and signs were as follows:

Signs and Symptoms	All Subjects	Those with Heart Failure
Dyspnea	12	6
Palpitation	9	5
Edema	7	5
Precordial pain	5	2
Orthopnea	5	4
Precordial oppression	2	0

The heart on X-ray showed global enlargement in eight cases. The left ventricle was greater in two; normal size was noted in four. The original X-ray diagnosis was myopathy six times, left ventricular dilatation once, normal heart twice, double mitral lesion once, pure mitral stenosis once, and combined mitral and aortic valve disease once. ECG showed:

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1 Niedman et al. Bol. Chil. Parasit. 14, 59-61, 1959.

ECG Changes	Frequency
Extrasystole	11 x
BBB (Bundle Branch Block)*	9 x
A-V block first degree	4 x
Ischemic T waves	3 x
Auricular fibrillation	2 x
Flutter	1 x

* Both right and left are included.

In summary these alterations are similar to the Chagas' cardiopathy. The first case was diagnosed in 1957. The course seems to be acute, subacute or chronic and subjects with heart failure responded to the treatment better than those with Chagas' disease.

Course	Heart Failure		Total	
	With	Without		
Improved	2	7	9	
No change	1	1	2	15
Worse	3	1	4	
Died	4	2	6	

Four of the deceased were autoposied. In two cases the parasites were isolated from the heart. One woman died suddenly in the street and autopsy showed diffuse fibrosis of the myocardium and normal coronary vessels.

Dr. Niedmann may have the largest series of patients with chronic cardiopathy caused by toxoplasma infection, and reported in 1963 one clinical case with laboratory proof.[1] (Another one was described by Cathie in 1955 as idiopathic cardiopathy, and toxoplasmosis was proved in the serological laboratory). All other published cases were acute; thus Pinkerton and Win described one case in 1940, Hakkila in 1958 described one case (with myocarditis and pericarditis); Bachman in 1962 reviewed 14 cases published up to that time (acute and eight already dead) and added three of his own, one with pericarditis, two with slight myocarditis. Paulley in 1954 (Lancet) reported three clinical cases with myocarditis and serological indication for toxoplasmosis.

Serological reactions for toxoplasmosis (Salin-Feldman) were tested on 137 patients in the Hospital San Borja and diagnosed as myocardiopathy.

Serological Reactions for Toxoplasmosis

Reaction SF	Number	Percent
Negative	18	13.1%
Positive:		
1/4	22	16.1
1/16 - 1/64	69	50.4
1/256 and more	28	20.4
Total	137	100

In 69, that is 50%, the titer was 1/16 to 1/64, in 28 (20%) 1/256 or more. The serological reaction was also done on nearly 400 subjects,

[1] Vukasovic et al. Bol. Chil. Parasitol. 18, No.2, 41-42, 1963

apparently normal students and blood donors, and on subjects having other diseases not connected with toxoplasmosis. Titer 1/256 or higher was in 4% of them, 1/64 or below in 40% of them. Three students with high titer had swollen glands which were considered as a manifestation of acute toxoplasmosis. In Dr. Niedmann's experience, treatment of enlarged lymphatic glands (14 subjects) was successful in all, treatment of ocular signs good in half of 44 subjects, while this was so only in one of 10 subjects with myocardiopathy diagnosed as of toxoplasmic etiology.

In the Department of Medicine B, 20 cases with primary myocardial disease were diagnosed in the past few years, 8 as toxoplasmosis, 4 as Chagas' disease and 8 of other, or unknown, etiology. ECG findings can be seen in the table below:

ECG	Toxoplasmosis	Chagas' disease	Other
Alteration of rhythm	8	2	1
Alteration of conduction	8	3*	6
Alteration of depolarization	3	1	0
Change of repolarization	7	1	3
Hypertrophy of ventricles	2	1	10
Total number of subjects	8	4	8

* 1 double A-V block.

X-ray findings can be seen in the Table below:

X-ray	Toxoplasmosis	Chagas' disease	Other
Normal	2x	1x	0x
Enlargement:			
global	3x	0x	1x
auricle	6x	3x	4x
left ventricle	6x	4x	8x
right ventricle	6x	3x	5x
right auricle	3x	0x	3x
aorta	3x	1x	1x
pulmonary artery	4x	1x	2x

The Departments of Medicine A and B performed more complicated cardiovascular examinations such as cardio-angiography in cooperation. In the last four years about 600 such examinations were performed with 25 complications (4%); these included:

Complications*	No.
Complications due to catherization	9
Infiltration of the myocardium by the contrast medium	4
Allergic reactions	5
Complications from anesthesia	4
Embolism with transient hemiplegia	1
Transient blindness (child)	1
Prolonged shock	1

*One patient died.

In both departments there is a group of young physicians who work in various branches of cardiology. Professor E. del Campo, who spent several months with Dr. Miall in Jamaica on a WHO Research Training Grant, is President-Elect of the Chilean Society of Cardiology.

Dr. J.M. Borgoño, Acting Chief of the Division of Epidemiology in the Ministry of Public Health and Professor of Infectious Diseases at the University of Chile told the Consultant that recent epidemics of diphteria provided the opportunity for studying diphtheric myocarditis in 170 cases. Most of the patients were children of 5 to 9 years and only 10-15% were adults. Myocarditis occurred in about 10% of the subjects. Published results include a smaller number of patients (70) but are of a similar character.[1] Early changes that occur before the eighth day of the onset of the disease have a more severe prognosis than if they appear between 9 to 18 days. The most frequent alterations were heart failure and arrhythmias. ECG changes occurred usually before the symptoms started. Treatment with corticoids for 15 days seems to prevent the myocarditis but there was no difference in the clinical and pathological picture of treated and untreated subjects with diphtheric carditis. Usually 1.5 mg/kg body weight of prednisolone for five days is given at the beginning, 1 mg for the next five days and 0.5 mg for the last five days.

Eight cases of typhoid myocarditis were noted. The diagnosis was made usually in the second week when alterations in the heart auscultation were recognized and confirmed by changes in ECG. Alterations of the rhythm and conduction as well as changes in the repolarization phase were registered. In one necropsy case marked fragmentation of muscle fibers was found.

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[1] Donoso, P. Rev. Med. de Chile, 89, No. 4, 281-288, 1961.

There are well organized health services for employees in Chile. The Consultant was most impressed by the possibilities for obtaining morbidity data from the Department of Cardiology in the National Medical Service for Employees. Dr. D. Lamas, cardiologist in this Department, himself checks all patients with cardiovascular diseases and these data might provide valuable material.

Dr. Niedmann who works part-time in the Department of Parasitology, felt strongly that construction of better houses, education and the use of insecticides (gammexane) is the way to control Chagas' disease. Triatoma infestans has been found only in 1-2% of properly sprayed houses.

CARDIOVASCULAR RESEARCH IN ARGENTINA *

(Annex III to Document RES 4/10)

Professor A. C. Taquini showed the Consultant his department of human physiology at the University of Buenos Aires and also the Institute of Cardiovascular Research of which he is the founder and director. The Institute has its own building in the neighborhood of the University, and has well-equipped research laboratories.

The research in experimental hypertension is done by Dr. A.C. Taquini, Jr., Dr. Pedro Blaquiel, Dr. Ignacio de la Riva, Dr. Nidia Basso and Dr. Ricardo Zuberbühler. Studies include nervous control and production of renin, electrolyte content of the arterial wall (elevation of blood pressure by pharmacological agents increases the concentration of sodium and potassium in the smooth muscles of the wall), and changes of the action potential in the hypothalamus of dogs during the development of hypertension.

The group investigating kidney function, extra-cellular fluid and electrolytes (Drs. M. Fernández Villamil, Neamo Yeyati, P. Garrahan and Fort) developed techniques for perfusion of one kidney leaving the other in the general circulation. This technique is being used for studying the effect of substances such as serotonin.

Hemodynamics of the pulmonary circulation is studied by Drs. José D. Fermoso, Pedro Aramendia and Alberto Kauman. They are interested in the reflex regulation of the pulmonary and systemic circulations and in the circulatory effect of exercise in human beings. (The well-known marathon runner Suárez is one of their research subjects). One of the studies concerns the influence of catecholamines produced by exercise on

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*Based on a site visit by Dr. Z. Fejfar to the Centro de Investigaciones Cardiologicas, Buenos Aires, Argentina on 28-29 November 1964.

the strength of the heart contraction.

Dr. Gimeno and Dr. Sabino studied the mechanical and electrical response of the isolated muscle fiber during metabolic changes. The second son of Professor Taquini prepared the technique for research on the regulation of circulation in dogs without anesthesia.

All workers at the Institute are full-time. The Institute belongs to the University. Seven members of the staff are career research investigators paid by the National Research Council (CNICT) of Argentina. The research grant is given partly by NIH/USPHS (two grants) and by a private institution which is called AFIC - Association for Scientific Investigation.

Professor Taquini was one of the first to study hemodynamics in patients with Chagas' disease. In his opinion, Chagas' disease is mainly a medical sanitary problem - to kill the vectors. There are, of course, several interesting scientific questions which should be studied and which concern the parasite, ecology, pathogenesis of the heart and gastrointestinal alterations, etc. Frequency of Chagas' disease in some areas of Argentina resembles that in Brazil and the problemsappear similar.

CARDIOVASCULAR AND ALTITUDE PHYSIOLOGY *

(Annex IV to Document RES 4/10)

The Peruvian University of Medical and Biological Sciences in Lima, Peru, is a private university founded in 1961 when a great percentage of professors left the University of San Marcos. The Faculty of Medicine, with Professor Alberto Hurtado as Dean, was the first to be established, followed more recently by the Faculty of Humanities. There are about 60 students per semester (200 in San Marcos) and the selection apparently is very severe.

In 1961 Professor Hurtado and his group left the Institute of Andean Biology, which is now headed by Dr. M.T. Velasquez and whose laboratory is located in Morococha, and founded the High Altitude Research Institute. The Cardiovascular Laboratory of this Institute is headed by Professor Dante Peñalosa. The High Altitude Research Institute has developed well-equipped laboratories in Cerro de Pasco, which is only 200 meters lower than Morococha (4330 meters above sea level), but is farther from Lima and the population of 20,000 seems more stable.

The cardiovascular laboratory has been very active indeed, utilizing the unique possibilities of comparing cardiopulmonary functions and anatomical changes in healthy people living at sea level (Lima) with those from an altitude above 4,000 meters. They also investigated the mode of acclimatization to high altitude and sea level life and the pattern of cardiovascular diseases in these two areas.

The work to be briefly mentioned is outstanding, probably unique, and PAHO/WHO should consider using the Institute as a center for high

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* Based on a site visit by Dr. Z. Fejfar to Lima, Peru, on 18-22 November 1964.

altitude research. The work on pulmonary hypertension in children and adults born and living at high altitudes was published in 1963,[1] ECG and vectorcardiograms were summarized in 1960 and 1961.[2] Anatomical description of right ventricular hypertrophy in children born at high altitudes was published by J. Arias Stella, head of the Department of Pathology, and Dr. Recavarren,[3] and anatomy of the pulmonary vascular tree by Arias Stella and Saldana in 1963.[4]

The natural acclimatization of humans born and living in high altitudes involves a number of adaptive mechanisms such as hypervolemia, polycythemia, changes in cardiopulmonary function and structure, altered metabolic and enzymatic activity.

The ECG and VCG at birth is similar at sea level and high altitude, and shows right ventricular preponderance, which at sea level is fairly rapidly replaced by the predominant left ventricle. In high altitude subjects, however, the right ventricular preponderance persists. The changes in the weight of the right and left ventricle are in the same direction as ECG. The predominance of the right ventricle in sea level babies is replaced within three to four months by the dominating left ventricle. In residents from high altitudes the right ventricular hypertrophy persists. Measurements of the pressure and flow in the pulmonary circulation demonstrated in children from high altitudes unchanged cardiac output, normal pulmonary wedged pressure but elevated systolic and diastolic pressure in the pulmonary artery. Calculated pulmonary total and pulmonary vascular resistances were elevated as well as the work of the right ventricle.

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[1] Amer. J. Cardiol., 11, 143 and 150

[2] Amer. Heart J. (1961), 61, 101

[3] Amer. J. Path. (1962), 41, 55 and 467

[4] Circulation (1963) 28, 915 and 1094

Anatomical examination of autopsied cases revealed a greater amount of muscle in the distal arteries of people from high altitude; this contributes to the reduction of the cross-sectional lumen area of these vessels. The increased number of muscularized arteries resembles the structure of the fetal arteries in the lungs. It may be inferred that in high altitude people the fetal pattern remains both in the distal arterial tree as well as in the elastic structure of the main arteries.[1]

The above findings, although markedly different from those in humans at sea level, are part of the natural acclimatization. People in high altitudes live in the similarly reduced oxygen tension as the fetus in the uterus and maintain a similar function and structural pattern of the circulation. Men are capable of performing heavy physical work and have no symptoms which are related to the described functional or structural pattern. The level of pulmonary arterial pressure (systolic, diastolic and mean) measured in 58 healthy adult men 17-34 years of age was positively correlated with the altitude of the birthplace; the pressure increased with the altitude and this relation can be expressed mathematically as a curve of parabolic shape. Similar correlation has been found in arterial Hb O_2.

Observations were made on acute pulmonary edema in 36 young healthy subjects born and living at a high altitude who developed this condition within 24 hours after returning home from one or two weeks' stay at low level, usually at sea level[2]. In most instances severe clinical manifestations disappeared within one to two days on breathing oxygen. X-ray of

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[1] Arias Stella and Saldana (1963) Circulation 27, 1094 and 28, 915

[2] Marticorena, E. et al, Dis. of the Chest, 45, 273 (1964).

the thorax shows mottling exudate of varying degree more in the parahilar region than in the periphery. ECG signs of acute overloading of the right ventricle and alterations of repolarization indicating right ventricular ischemia are frequent. Autopsy in two patients demonstrated, apart from edema, alveoli with hyaline membrane and thrombosis of the distal arteries and arterioles. It seems that increased capillary permeability is an important feature of the acute pulmonary edema in high altitudes and increase in cardiac output and pulmonary blood volume as well as ventilatory changes occur during rapid exposure to hypoxia and to low temperature.

Another interesting study was the screening of 5,000 school children of both sexes living in towns between 3,500 and 5,000 meters above sea level.[1] The incidence of patent ductus at that altitude was about 18-30 times greater than the average incidence from several studies at sea level. With the altitude the frequency increased and at 5,000 meters it was 30 times greater than at sea level. Persistence of the fetal and functional and structural characteristics of the pulmonary circulation in high altitudes may be important in maintaining the ductus patent.

Clinical, radiological and ECG features of the patent ductus in high altitude subjects may be markedly different from usual. One hundred subjects (66 females and 34 males, 8 months to 29 years old) have been studied; in 17 the diagnosis was confirmed by cardiac catherization and in 58 by surgery. Only 28% had no symptoms. Others had dyspnea at effort (49), palpitations (30) and cyanosis at exertion or while crying (12 children). Many suffered from repeated respiratory infections. The

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[1] Marticorena, E. et al, Proceedings of the Fourth World Congress of Cardiology, Mexico City I-A 155 (1962)

anomaly was frequently discovered at this time or during the school or pre-school examination.

The machinery-like murmur was found in 59% of cases (see Table 1 below). There was no close correlation between the type of murmur and the pulmonary artery pressure (17 catheterized subjects). Machinery-like murmur was found in some patients with a very high pressure and in others, with relatively small hypertension for the given altitude, there was only a systolic murmur.

TABLE 1

Murmurs in P.D.A. at sea level and high altitude

Type of Murmur	Sea level* (435 cases) percent	High altitude (100 cases) percent
Machinery-like murmur	85%	59%
Systolic and diastolic	6	18
Systolic at pulmonary area	8	21
No murmurs	1	2**

*Krovetz & Warden's series
**Ejection click

Compared to subjects with patent ductus at sea level there was a marked difference in ECG (See Tables 2 and 3). Right axis deviation and hypertrophy of the right ventricle or combined ventricular hypertrophy were found much more frequently at the high altitude.

TABLE 2

QRS axis position in P.D.A. at high altitude and at sea level

QRS Position	Sea level* (383 cases) percent	High altitude (100 cases) percent
Normal	94.7%	35%
Right axis deviation	3.6	53
Left axis deviation	1.5	4
Undetermined and unusual positions	0	8

*Krovetz & Warden

TABLE 3

Hypertrophy on ECG in P.D.A. at high altitude and sea level

ECG	Sea level* (272 cases) percent	High altitude (100 cases) percent
Normal	58.4%	8%
R.V.H. (pure)	2.2	30
L.V.H. (pure)	27.5	17
Combined ventricular hypertrophy	11.3	45
Septal hypertrophy	12.8	4

*Krovetz & Warden

Data on right heart catheterization are in Table 4. Pulmonary total and vascular resistances were similar in children with and without patent ductus. The elevation of pulmonary artery pressure in patent ductus, which was small in children born and living at sea level and marked in those living at high altitude, is therefore caused predominantly by the increased blood flow through the lungs. The great load on the right ventricle (increased pulmonary vascular resistance and high pulmonary flow) is reflected in high right ventricular work and in the frequency of the right ventricular hypertrophy. High pressure in the pulmonary circulation during exercise may explain the cyanosis on effort by a reversal of the shunt. Breathing of 100% oxygen decreased the main pulmonary pressure within two minutes from the onset of the oxygen breathing. This happened in spite of the increased pulmonary flow from greater aorta pulmonary pressure gradient. The marked decrease of the pulmonary vascular resistance demonstrates the functional nature of its elevation.

Data on two subjects catheterized before the operation and one month after showed similar pulmonary artery pressures before and after the operation although the ductus has been closed and the shunt abolished. (see Table 5).

TABLE 4

Cardiac catheterization findings in healthy children and in P.D.A. at sea level and at high altitude

Group	No. of cases	Pulmonary artery pressure mm Hg			Pulmonary flow index Lit/min/M^2	Pulmonary resistance		Right ventricular work Kg/M/min/M^2
		S	D	M		Total	Vascular	
						dynes sec.cm $^{-5}/_{M^2}$		
Sea level Normal children	16	16	5	10	4.71	180	91	0.78
High altitude Normal children	25	41	18	28	4.55	558	459	1.83
Sea level P.D.A.	10	28	11	18	7.04	191	100	1.085
High altitude P.D.A.	17	68	39	54	11.05	567	486	3.7

TABLE 5

Hemodynamic data in basal condition and during O_2 inhalation in 2 patients, before and after division of the Ductus Arteriosus

Case		Pulmonary arterial pressures (mm.Hg.)						Pulm. flow index Lit/min./M^2		Pulmonary resistance dynes sec.cm^{-5}/M^2				A.V.W. kg/M/min/M^2	
		Basal			O_2			Basal	O_2	Total		Vascular		Basal	O_2
		S	D	M	S	D	M			Basal	O_2	Basal	O_2		
1	Pre-op.	80	48	63	68	42	56	12.46	29.32	402	81	370	68	4.2	1.1
	Post-op.	82	30	54	60	15	30	6.62	10.32	653	233	613	213	5.0	4.3
2	Pre-op.	64	48	52	52	30	40	36.45	55.12	120	55	107	51	4.7	2.7
	Post-op.	63	52	56	24	15	19	3.56	4.25	1252	373	1158	280	2.6	1.0

The marked post-operative increase in the total vascular and pulmonary resistance is caused predominantly by vasoconstriction. This may be seen from the decrease of resistance during the oxygen breathing. The alveolar oxygen tension and the oxygen saturation of the arterial blood remained unchanged. It is difficult to explain this high post-operative pulmonary resistance except by the reaction of the pulmonary vessels to acute hypoxia, although the event points to the possible influence of the O_2 and CO_2 tension on the pulmonary arterioli.

Varying degrees of enlargement of the heart and of the pulmonary artery shadow on X-ray was noted in most children. The increased pulmonary vasculature was found in all cases except two where only a small shunt had been found during the operation. In spite of the high pulmonary pressure the patients tolerated the surgical closure of the ductus very well.

A lot of research has been done on the acquired acclimatization to high altitude and to sea level. Eleven soldiers from high altitudes, 22-23 years old, were closely followed for a period of two years during their military service in Lima. Oxygen consumption at rest did not change as well as the co-efficient of oxygen extraction from the arterial blood. Ventilation per minute decreased. Cardiac output increased due to the high stroke volume, while the pulse rate diminished. This was reflected in the higher systolic arterial pressure, lower diastolic pressure and the greater pulse pressure. The heart increased in size on X-ray (difficult to compare because the thorax in high altitude is more expanded than at sea level and looks as it does in emphysema). The total peripheral resistance decreased. All the pressures in the pulmonary circulation decreased

(at rest). The number of red cells, hematocrit and viscosity of the blood also diminished. During the exercise test cardiac output rose in a similar way to that at high altitude. Only systolic pressure rose in the pulmonary artery, while during the stay in high altitude, both systolic and diastolic pressure increased. It thus seems that the rigidity of the wall of the pulmonary artery remains high even during a long stay at sea level, while the peripheral vascular resistance decreases. The hemodynamic picture of soldiers from high altitude at sea level resembles the pattern of well-trained sportsmen at rest, and one may assume that physical activity at high altitudes requires much more circulatory effort than physical activity at sea level. One should now pay more attention to the metabolism of tissue of high altitude subjects, to study the metabolism of their heart muscle (enzymes, catecholamines etc.), obtaining the specimen of the heart through biopsy at surgery or through heart puncture, in order to get information on the adaptation processes at the cellular level.

The data show that people born at high altitudes, compared to sea level, have more developed muscles of the pulmonary vessels, react to anoxia by greater vasoconstriction and a smaller cross-sectional area of the pulmonary circulation. The structural pattern and reactivity remains even after a rather long stay at sea level. On the other hand it has been shown that adaptation to high altitudes also requires several months' stay there.

Dr. R. Garcia from the laboratory of endocrinology measured the amount of testosterone in the urine and in blood by gas chromatography, and found no significant difference between the highlanders and the

lowlanders. The glucose tolerance test in high altitude subjects starts at a lower level than usual at sea level and is also flatter. The lower levels of blood glucose resemble the low systemic blood pressure and it seems worthwhile to look systematically and much deeper into the problem of why the control of regulatory mechanisms is set at the different level on high altitude subjects.