ACUTE ENDOMYOCARDIAL DISEASE IN INFANTS AND CHILDREN.

The relationship between acute myocarditis and endocardial fibroelastosis.

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DEDICATED TO VIVIENNE, for her all-encompassing love,
LAWRENCE, for his sagacious wit, and
TAMARA, for her enchantment.

'Know then thyself, presume not God to scan;
The proper study of mankind is Man.'

An Essay on Man - Epistle II

'First follow Nature, and your judgement frame
By her just standard which is still the same :'

An Essay on Criticism

Alexander Pope

1688 - 1744

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ABSTRACT

ACUTE ENDOMYOCARDIAL DISEASE IN INFANTS AND CHILDREN.

The relationship between acute myocarditis and endocardial fibroelastosis.

This prospective study of acute myocarditis (AM) and endocardial fibroelastosis (EFE) was prompted by their common occurrence in infants and children in Cape Town, and by the persisting controversy regarding the possible relationship of these two conditions to each other, and to idiopathic, chronic, congestive cardiomyopathy (COCM). Patients with AM and EFE were analysed concurrently and over the long-term.

The following hypotheses were investigated:

A) that AM and EFE represent different phases of a common disease process, and
B) that either AM or EFE evolves into COCM.

From 1st June 1970 to 31st December 1976 (a study period of 6 years 7 months), 140 consecutive patients with AM or EFE were evaluated, and continually observed until 31st March 1979 (a total observation period of 8 years 10 months). Because there is no definitive, non-invasive, in-vivo diagnostic test for AM or EFE, an inclusive diagnosis of acute endomyocardial disease (EMD) was made in 123 patients who fulfilled all 4 rigid clinical criteria, i.e. a short history (<1 month), clinical evidence of myocardial involvement (heart failure, gallop rhythm or shock), radiological cardiomegaly (CTR >0.55), and ST/T wave changes on electrocardiogram (ECG). Acute EMD was confirmed in all 20 patients who came to autopsy. A further 17 patients with insufficient clinical data had EMD at post-mortem.

In the clinical series, patients were separated into AM or EFE categories

according to the absence or presence of LVH on ECG (SV1 and/or RV6 > normal for age). Classification depended on LVH status on admission (92 patients without, 31 with LVH) ; at any stage of the course (71 without, 52 with) ; or at the end of the study-period or death, i.e. terminally (96 without, 27 with). These LVH negative and positive groups were compared statistically in terms of patient data, epidemiological factors, clinical presentation (mode of onset, symptoms and signs), results of investigations (haematological, biochemical, radiological, electrocardiographic, enzymatic and virological), natural history, mortality and pathological findings.

The following results were observed.

Both AM and EFE occurred predominantly in Cape coloured patients. Patients with EFE were younger (mean age $\pm$SEM of 12$\pm$2.7 months) than those with AM (22$\pm$2.6 months), $p < 0.05$.

Epidemiologically, AM manifested seasonal peaks in winter/spring, whereas EFE was non-seasonal, but relatively more common in the ensuing summer months. A marked rise in incidence of EFE occurred in early 1974 following a minor epidemic of AM in 1973, and concurrent with an increased conversion rate from LVH negative to LVH positive status (21 instances throughout the study).

Symptoms, predominantly respiratory, were in keeping with a viral infection, and were remarkably similar in AM and EFE.

Signs of heart failure were more common in AM. This included tachycardia ($p < 0.05$), elevated JVP ($p < 0.01$), oedema ($p < 0.025$) and two or more features ($p < 0.025$). Conversely, radiological cardiomegaly on admission was more marked in EFE ($p < 0.005$). Gallop rhythm was equally prevalent in both conditions, and severe shock almost exclusive to AM. Grunting respiration occurred mainly in EFE ($p < 0.05$), and CNS abnormalities due to shock and/or viraemia predominantly in AM ($p < 0.05$).

Routine investigations revealed more severe anaemia in AM ($p<0.025$), and evidence of renal involvement - uraemia (31%) and urinary abnormalities (11%) - in both conditions. Evidence of concurrent (viral) infection was equally prevalent in AM and EFE.

Detailed review of ECG's on admission and throughout the course, revealed similar incidences in AM and EFE of arrhythmias (11%), conduction abnormalities (19%), left (21%) and right (34%) axis deviation, P wave abnormalities (69%) and pathological Q waves (16%) and infarct patterns. ST segment depression and deep T wave inversion were more frequent in EFE, in keeping with severe LVH.

Serum lactate dehydrogenase (LDH) and hydroxybutyrate dehydrogenase (HBDH) levels were initially higher in AM (means of 1157 ± 147 and 678 ± 114 u/L) than in EFE (850 ± 128 and 499 ± 128 u/L), but differences were not significant. Serum creatine kinase (CPK) elevation was less frequent. All 3 enzymes decreased progressively towards normal levels over 3 weeks.

The yield of virus by direct culture and serology (31% of patients tested) was similar in both conditions. Enteroviruses occurred almost exclusively in AM, whereas a wide range of viruses was detected in both AM and EFE.

Overall mortality was similar in both conditions over the long-term, though AM patients ran a more fulminant course in the first month, as exemplified by actuarial survival rates at 48 hours, 1 month, 3 months and 1 year of 86%, 79%, 75% and 71% respectively in AM, and 96%, 89%, 69% and 63% in EFE patients. Incidence of readmissions was greater in EFE than AM ($p<0.05$).

Of the 123 patients with clinical EMD, 40 (32%) died - all during the first 13 months, 61 (50%) recovered completely, and 22 (18%) have residual clinical, radiological or electrocardiographic abnormalities (including patients lost to follow-up). After observation of all parameters for at least 1 year, only 11 (9%) have residua, and all are improving. This outcome was similar in AM and EFE.

Autopsy data in 37 patients revealed features of AM in 22, of EFE in 7, and of both coexisting in 8, with a histological gradation from extensive inflammatory cell infiltration and gross myocardial cell destruction in patients with severe AM, through milder inflammation and myocardial cell degeneration in those with AM+EFE, to occasional degenerative changes only in patients with EFE. Viral pneumonitis and bronchiolitis (78%) and lymphoid hyperreaction (76%) were equally prevalent in AM and EFE. Despite the paucity of confirmed cases at autopsy (15), the incidence of pathological EFE was significantly greater in LVH positive patients, preterminally, than in LVH negative patients. ($p<0.05$).

These findings favoured the concept that AM and EFE are phases of a common disease process. Both conditions were prevalent in socio-economically deprived communities, were related epidemiologically, and simulated each other in symptomatology, clinical manifestations, evidence of infection, cardiac size and ECG abnormalities - at presentation and throughout the course - serum enzyme responses, yield of viruses, mortality rate and natural history ; and pathological features coexisted in over 20%.

Most significant differences favoured a bimodal form of presentation, with AM being an immediate, often fulminating, expression of a concurrent (causative) viral infection, and EFE a delayed manifestation of a previous sub-clinical infection, often made clinically apparent by a subsequent (precipitating) viral infection. Differences in degree of anaemia and frequency of grunting respiration were probably age-related, as was the special propensity of young infants to develop EFE. Although largely circumstantial, this evidence strongly supports Hypothesis A. Serial endomyocardial biopsy would be required to prove the dynamic nature of EFE.

By contrast, Hypothesis B is rejected because of the very favourable long-term outcome for both AM and EFE, after the high mortality rate in the first year. Complete resolution occurred in most survivors, and not a single patient evolved into COCM.

Although AM is a common precursor of EFE, it is speculated that many other conditions can provoke the fibroelastotic response, pre- or post-natally, through the mechanism of severe dilatation and high mural tension in relatively thin-walled (mainly left-sided) cardiac chambers.

CONTENTS

CHAPTER 1.

INTRODUCTION.

During the late 1960's, the author noted a relatively high incidence of acute myocarditis (AM) and endocardial fibroelastosis (EFE) in Cape Town. As reported by others, [166, 195, 225, 430] the clinical manifestations in the acute phase and the response to therapy in these two conditions were remarkably similar and suggested a common disease process.

A possible relationship between AM and EFE has been a vexed question since these conditions were first described in 1899 [148] and 1740 [447] respectively. Although AM itself is generally accepted as being due to viral infection, [43, 197, 187, 457, 528] the aetiology of EFE remains controversial [157] and suggested causes abound. [467] Yet it appears that AM and EFE have not been evaluated together, prospectively and simultaneously, in a comprehensive clinical, natural history and pathological study over the long-term.

These factors prompted this prospective study of 140 consecutive patients with AM and EFE, i.e. acute onset endomyocardial disease (EMD), presenting to the wards of the Department of Paediatrics and Child Health, University of Cape Town, from June 1970 to December 1976, and observed until March 1979.

The study was designed to test the following hypotheses,

(i) that AM and EFE represent different phases of the same disease process, and

(ii) that either AM or EFE evolves into so-called idiopathic chronic congestive cardiomyopathy (COCM) in children.

These aims were investigated by a detailed comparison of patients with clinical AM and EFE, in terms of

(i) patient data,

(ii) epidemiological factors,

(iii) clinical presentation, i.e. mode of onset, symptomatology and signs,

(iv) results of investigations, i.e. radiological, electrocardiographic, enzymatic and virological,

(v) the natural history, and

(vi) pathological findings.

It was anticipated that similarities and differences would thus be identified and that the relationship, if any, between AM and EFE would be clarified. It was also reasoned that a long-term follow-up of almost 9 years would permit an assessment of the significance, if any, of AM and EFE in the aetiology of COCM.

Although not the primary purpose of the study, it was expected that these investigations would furnish additional information regarding the racial incidence, socio-economic milieu, age and sex distribution, clinical course, radiological, electrocardiographic and enzymatic changes with time, incidence and type of viral infections, prognosis, mortality rate, and cardiac and non-cardiac pathology, in both AM and EFE in Cape Town.

CHAPTER 2.

HISTORICAL REVIEW OF THE LITERATURE

Acute myocarditis (AM) and endocardial fibroelastosis (EFE) have been regarded as distinctive entities by most authorities. They are discussed in separate chapters by different authors in major text books on paediatric cardiology [293, 379, 549] and, with few exceptions, [166, 195, 255, 225, 467] reported as disparate conditions in the medical literature. AM and EFE are thus reviewed independently in this section.

1. ACUTE MYOCARDITIS

The different terms used for this condition from the first description by Fiedler in 1899 [148] until the present [563] exemplify the confusion and doubt regarding its aetiology. Most authors have agreed that the histological features reflect an acute event, [94, 123, 148, 194, 218, 235, 229, 471] though subacute [334] and chronic varieties [287] have been reported. Other terms have been purely descriptive, i.e. "interstitial" to describe the presence of inflammatory cells between the myofibres, [23, 163, 148, 194, 248, 229, 345, 336, 519, 524] "diffuse" to emphasise its distribution throughout the myocardium, [50, 248, 524] though the pathology is frequently patchy and focal, and "isolated"

to denote inflammation in the heart only, and not in other organs or tissues, [50, 94, 89, 123, 218, 235, 266, 471, 461,551, 563] also referred to as "primary". [142] "Pernicious" myocarditis [54] appears to represent a condition in adults with a more prolonged course, and "giant-cell" myocarditis is a different entity. [514, 563] Other authors have emphasised the "idiopathic", [334, 564] or "non-specific" [55] nature of the disease, or the "non-bacterial, aseptic" aetiology. [9]

More recently, however, there has been widespread acceptance that the disease is usually viral in origin, [187, 457, 528, 562, 558, 43, 197] even though isolation of the virus and a cause-and-effect relationship have been difficult to confirm. [164, 163, 310, 43] Experimental induction of myocarditis has been achieved with the Coxsackievirus postnatally, [225] but not prenatally. [303] Myocarditis has been identified as part of generalised acute viral infectious diseases, [149, 365, 338, 411, 416, 441, 457, 462, 542, 524, 171] and ECG abnormalities have been demonstrated in as many as 10 to 33% of patients with common childhood infections. [443, 470, 516, 553] A wide range of viruses has been implicated in the causation of AM, e.g. in measles, [416, 425] rubella, [10, 11, 160] mumps, [38, 434] infectious mononucleosis, [152, 240, 428, 552] varicella, [112, 147, 210, 373, 374] poliomyelitis, [237, 267, 391, 520] infectious hepatitis, [108, 462] influenza, [3, 88, 150, 411, 399] rabies, [83, 442] and psittacosis; [261, 542] in echo-, [36, 85, 280, 316, 355, 371, 360, 464, 449] adeno-, [233] cytomegalo-, [569, 73] arbor-, [398] herpes simplex [576, 558] and respiratory syncitial [175] virus infections; and post-vaccinially. [452, 304] The likelihood of developing myocarditis in these situations appears to correlate with the severity of the infection. [391]

The coxsackie viruses, mainly group B, appear to be particularly cardio-

tropic and have been incriminated in epidemics [60, 230, 262, 372, 386, 501, 534, 171, 283, 506, 482] and in sporadic cases, [35, 69, 110, 155, 196, 186, 219, 246, 224, 280, 309, 396, 420, 339, 486, 542, 570, 575, 197, 485, 454, 507] with the neonate being highly susceptible. [60, 110, 170, 168, 262, 258, 279, 277, 372, 386, 435, 527, 534, 171, 283, 506, 482] (Further examples in infants and children are referred to in the paper by Burch et al. [69])

Apart from viruses, virtually every infective agent has been identified as a cause of acute myocarditis, including bacteria, fungi, Rickettsia, spirochetes and parasites. [187, 222, 461, 558]

It has been suggested that myocardial cells may be destroyed in the initial infectious phase [457], or be sensitised, with signs of cardiac involvement occurring after a latent period of 7 to 10 days following autoimmunisation, [209, 547, 558] the so-called "infectious-allergic" mechanism. [482, 366, 418]

In routine autopsies in children under 4 years, Burch et al [69] detected histological evidence of myocarditis in 58% and antibodies to coxsackie B viruses by immunofluorescent techniques in 24% ; the latter method yielded positive results in 50% of children aged 1 month to 15 years. [68] This suggests that viral myocarditis (and valvulitis) are more common than previously recognised.

Comment

For purposes of this study, AM refers to cases of sporadic or non-epidemic myocarditis with an acute-onset, characteristic clinical picture, and typical pathology (where possible) of diffuse, patchy or focal, inter-

stitial and peri-vascular, mononuclear, inflammatory cell infiltration.

2. ENDOCARDIAL FIBROELASTOSIS

Endocardial fibroelastosis was first described by Lancusi in 1740 (quoted by Rossi [447]) and by Morgagni in 1765, [375] but remains an enigma to pathologists and clinicians alike. [157]

2.1 TERMINOLOGY

As with AM, EFE has been reported under a multiplicity of titles, i.e. "foetal endocarditis" by Kreysig in 1816 [292] (quoted by Gross in 1941 [203] and by others, [295, 416, 555, 177] congenital cardiac hypertrophy, [41, 228, 359, 557, 469] idiopathic cardiac hypertrophy, [41, 99, 295, 317, 359, 423, 544, 557, 177, 502] endocardial fibrosis, [34] idiopathic hypertrophy with endocardial fibrosis, [259, 335] elastic tissue hyperplasia of endocardium, [459] diffuse endocardial thickening, [326] endocardial hyperplasia, [422] and endocardial sclerosis. [95, 93, 124, 242, 543,52, 53]

Endocardial fibroelastosis, the term generally accepted today, was introduced by Weinberg and Himmelfarb in 1943. [555] In 1956, Andersen and Kelly [16, 274] introduced the concept of primary and secondary forms of EFE for those without and with other congenital cardiac anomalies. This was supported by some authors [417, 572] but rejected by many as implying unproven aetiological significance. [49, 48,28, 165, 367, 368] The differentiation into contracted and dilated forms has also proved unhelpful, since the former is rare without associated congenital obstructive anomalies of the left heart, [115, 137] is often non-dilated rather than contracted, [274, 476] and has a totally different clinical presentation. [226, 521]

2.2 AETIOLOGY AND PATHOGENESIS

The aetiology and pathogenesis of EFE [159, 308] remains "in a state of utter confusion as reflected in innumerable past and present hypotheses". [467]

(a) Inherited, familial, congenital.

Several reports of EFE in both twins [307] (of dizygous [274, 422, 532, 342] and monozygous [166, 191, 174, 306, 501] origin), in the monozygous pair only in the case of triplets, [523] and in a parent and child, [390, 559, 369] suggested an inherited disorder. However, others reported EFE in only one of twins, [160] even if monozygous. [84, 275, 376]

Familial EFE has been recorded frequently [253] (in two, [26, 49, 84, 121, 125, 139, 159, 239, 415, 439, 429, 426, 483, 476, 554, 572, 583] three, [244, 468, 84, 390] and six siblings [351]), the overall incidence in siblings varying from "negligible" [467] to 4% of 120 cases [125] and 8% of 119 families.

Autosomal recessive and X-linked recessive [323] inheritance and genetic heterogeneity [567, 306, 340, 532, 572] have been proposed, but the familial pattern does not generally coincide with these or with multifactorial modes of inheritance. [84]

A congenital factor causing endocardial (and myocardial) elastin hyperplasia [48, 113, 203, 367, 332, 422, 33] or proliferation, [118, 424] or endocardial sclerosis, [95, 93, 128] has been suggested, but there is little supportive evidence for this. [99] EFE in association with congenital metabolic defects has been recorded in isolated cases only, [274] e.g. with glycogenosis, [117, 189, 234, 450, 447, 536, 568] leucinosis, [145] and epiloia. [96] Congenital non-cardiac defects have been observed, [174, 239, 572, 583] but there has been no increased incidence of associated anomalies, in patients with EFE or in their siblings. [84, 274]

Hence, although an inherited disorder appears unlikely, a non-genetic prenatal factor cannot be excluded.

(b) Mechanical and haemodynamic.

The association of EFE with congenital cardiac anomalies has prompted various mechanical and haemodynamic theories. Increased intra-cavitary pressure or stagnation due to mechanical obstruction to outflow, mainly of the left heart, [158, 159] was proposed by Dewitski in 1912 [114] and supported by others, [49, 48, 28, 78, 118, 135, 459] but these same anomalies are usually found without EFE, [63, 76, 408, 447] and EFE also occurs in association with decompressing ventricular septal defects. [78, 166, 165, 214] Coexisting mitral incompetence has been assigned a causative role, [368] but is usually considered to be secondary to EFE. Hypoxia of the endocardium [49, 59, 164, 245, 263, 343, 440] following limitation of flow of relatively well oxygenated blood has been incriminated, especially in the left heart following premature closure of the patent foramen ovale. [37, 129, 214, 348, 532] But most patients do not have a closed foramen ovale, and none of these theories account for cases of EFE extending into the right atrium and/or ventricle [48, 95, 116, 126, 164, 165, 214, 239, 259, 297, 301] or being isolated to the right heart. [49, 113, 159, 214, 239, 447]

The mechanical stimuli known to produce focal EFE, such as the jet effect [130] or lift effect (due to changes in blood velocity [226, 354]) do not apply in most cases, but chamber distention with increased endocardial (mural or wall) tension [72] and consequent elastic tissue proliferation [249, 329, 65] would be a mechanism common to most of the above situations. [48, 255, 254] (see page 181).

(c) Myocardial ischaemia.

Myocardial ischaemia has been implicated by the presence of EFE in isolated

cases of anomalous left coronary artery from the pulmonary artery, [212, 393, 456, 581] and of coronary disease and myocardial infarction in children. [545] Furthermore, the myocardial lesion of EFE resembles the bland infarct in adults. [203, 254] A recent report suggests that coronary insufficiency may cause right sided EFE, [137] but there is insufficient evidence of coronary involvement in left sided EFE.

(d) Other theories.

Interference with lymph drainage of the heart was shown experimentally to result in EFE. [288, 362] This has not been demonstrated in humans but may be a secondary effect of chronic myocarditis. [288, 362]

Other poorly substantiated theories include hyperoxia, [272] collagen disease, [238] transfer of maternal toxins [151] or antibodies, [251] and status thymo-lymphaticus. [82]

(e) Myocarditis

During recent years, interest in the historic theory of foetal endocarditis [148, 203, 292, 427, 571] and myocarditis [276] has been revived throughout the world. [5, 136, 166, 164, 165, 173, 170, 248, 220, 260, 410, 414, 501, 500, 550] Supportive evidence has come from clinical and pathological studies. The clinical course and evolution of the ECG in EFE has been claimed to be indistinguishable from AM in many cases. [195, 226, 225] Coexistence of histological features of acute or chronic inflammation and EFE has been demonstrated at post-mortem by Frühling et al [166] in almost all their 28 cases studied histologically, in 41 of 64 cases by Hutchins and Vie, [255] in 20% of 106 cases in Ontario and approximately half of 729 cases collected from the literature by Schryer and Karnauchow, [467] and in other reports. [43, 132, 126, 140, 248, 259, 336, 349, 529, 466, 512] Similar pathological features were noted in the

naturally occurring cardiomyopathy, " round heart disease", in turkeys.[394, 490] These findings tend to negate earlier rejection of this theory on the grounds of insufficient evidence of inflammation,[4, 203, 439] though fail to prove a prenatal origin.[325, 390] Recent evidence, demonstrating the physical fusion of the endocardial and myocardial process[132] and the presence of myocardial scarring subjacent to the EFE,[126] confirmed the close relationship between the myocardial and endocardial elements of the disease.

(f) Viral infection

According to Hastreiter and Fisher,[226] a viral aetiology is supported by the high susceptibility of embryonal heart tissue to virus infection,[498] the isolation of coxsackie B viruses in 13 of 28 infants with EFE,[166] the widespread acceptance of the viral origin of AM,[372] the experimental production of EFE in animals by inoculation with viruses,[67, 496] and the correlation of EFE with coxsackie B epidemics.[41, 46, 166, 501, 500] The latter was also noted by Mitchell et al[367] in a review of 199 cases from 54 reports in the literature (including many referred to above, and others 296, 268, 289, 270, 312, 356, 518, 499, 582, 207, 188, 154, 179, 503). Viral infections in pregnancy have been implicated in the aetiology of congenital heart disease,[67, 62, 42, 98, 143,227, 311, 504, 566] and a seasonal incidence of EFE has been reported.[80]

The viral theory has been rejected on the grounds that only one of twins or triplets may be affected;[241, 500] that there is no consistent association between the incidence of maternal antibodies to coxsackieviruses, or of viral infections in the pregnant mother, and EFE in her child;[367] and that neither congenital anomalies nor EFE could be induced in the progeny[198, 303] of pregnant animals experimentally infected with coxsackieviruses.

Counter-arguments assert that all cases of AM are unlikely to lead to EFE, [387, 409, 447] and that a short interval between onset of AM and death may preclude the evolution of EFE. [44]

(g) Mumps virus

The role of mumps virus in human EFE remains controversial. [380] Noren et al demonstrated a high incidence of skin reactivity to the mumps antigen in children with EFE, [392] but the skin test is notoriously unreliable [247] and these results were not confirmed by others. [172, 352] Some investigators did find a higher than normal rate of skin test positivity in patients, but without maternal mumps infection and without mumps antibodies in maternal [392, 492] or patients' sera. [392, 476, 481, 541] These results raised the possibility of cross-reactivity to the skin test, [481] or of diminished responsiveness of the foetus to the antigen. [180] Nonetheless, a mumps virus aetiology was supported by several authors, [492, 481, 493, 541] and in 1971, St. Geme et al [495] experimentally produced mumps virus embryopathy in the chick, with disappearance of signs of inflammation one week after delivery and persistence of neutralising antibodies for a year, at which stage pathological EFE was identified in 4 of 5 chicks. [496, 497] In the human, however, no instance of EFE was found in the off-spring of 18 mothers with mumps infection in pregnancy (with sero-conversion), [291] or in several other prospective studies, [201, 243, 478, 561, 560] though other cardiac anomalies were observed in one instance. [45] Furthermore, there is no relationship of EFE to mumps in the general population, [84] there are only scanty reports of mumps cardiopathy in the literature, [79, 434] and one infant with EFE and a maternal history of mumps had a negative skin test. [84]

(h) Immunological mechanism

The above factors suggested the existence of a non-autoimmune, delayed

hypersensitivity mechanism [494] operating either as an allergic response to current infection [297, 302, 457] or by earlier sensitization, with EFE being precipitated by subsequent minor infections. [99] The hypersensitivity mechanism has been opposed because of the lack of similar lesions in other endothelial or mesenchymal structures. [467]

(i) Idiopathic

Other authors believe that the etiology remains "idiopathic", [441, 463, 563] or that EFE is a "non-specific structural change rather than a disease entity". [96]

Comment

For purposes of this study, EFE refers to cases of the so-called dilated variety, without evidence of congenital cardiac anomalies, manifesting postnatally with a short history, characteristic clinical and electrocardiographic criteria, and with typical pathological features (where possible) of endocardial thickening due to excessive fibrous and elastic tissue.

3. THE RELATIONSHIP OF AM/EFE AND IDIOPATHIC CONGESTIVE CARDIOMYOPATHY.

Like AM and EFE, chronic cardiomyopathy has been the subject of much confusion and debate, as is evident from terms previously used to describe this condition, e.g. chronic pernicious myocarditis, [287] idiopathic myocardial hypertrophy, [489] idiopathic cardiomegaly, [315] and obscure cardiopathy. [138]

Most authors agree that myocardial disease in adults [397, 421] and children [164, 195, 222] can be separated into an idiopathic (or primary)* group if the

* etymologically incorrect usage: "primary" myocardial disease should mean originating in the myocardium, whether the disease remains localised or not and whether the cause is known or not.

aetiology is unknown and a secondary group for those with a recognised cause. The idiopathic group has been classified by Goodwin into hypertrophic restrictive (obliterative) and congestive cardiomyopathies. [184, 185, 182, 183, 181] The role of AM or EFE in the evolution of the latter, i.e. idiopathic, chronic, congestive cardiomyopathy (COCM) remains conjectural.

Under the umbrella term "primary myocardial disease of infants and children", Freundlich et al [164] and others [402, 106] included patients with a common clinical picture, i.e. congestive failure, cardiac enlargement, absence of significant murmurs, myocardial damage on ECG, and no primary disease elsewhere. However, this approach led to AM and EFE being included in this grouping together with entities of known cause, e.g. glycogen storage disease, anomalous left coronary artery from pulmonary artery, medial necrosis of coronary arteries, [440] and calcification of coronary arteries, and with idiopathic myocardial hypertrophy. [22, 302] More recently, Harris and Nghiem [222] included viral myocarditis in the secondary group, and EFE together with idiopathic (or non-obstructive) cardiomyopathy in the primary group. Greenwood et al [195] classified AM in the secondary group if known to be viral, and in the primary group if idiopathic, together with EFE and non-obstructive cardiomyopathy (isolated or familial). Hence, the precise classification of AM and EFE remains confused.

In the copious literature on cardiomyopathy in adults, EFE receives scant attention, except to be included in the category of COCM [250, 256, 401] or "systolic pump failure". [397] Viral myocarditis, however, was suggested as a cause of COCM by Corvisant in 1811 [92] (quoted by Somerville [488]) and is considered to be of aetiological importance in some cases. [457, 488, 513, 298, 310, 366, 70, 66, 199] Histological "mark-bodies" [58] and virus-like

particles [236] have been described in hearts of patients with COCM. An immunological reaction has been invoked as the likely pathogenetic mechanism, [71, 70, 56, 102, 208, 271, 403, 402, 305] but this is not universally supported. [77, 156]

Permanent myocardial injury has been demonstrated 6 months after coxsackievirus myocarditis in laboratory mice. [567] However, in the long-term follow-up of patients with AM, although 30% showed signs of cardiac involvement (mostly sub-clinical), no patient with progressive hypertrophy or dilatation was identified. [40, 453, 39] In a symposium on cardiomyopathy in 1972, several discussants mentioned the rarity of the transition of myocarditis to myopathy (noted again recently by Waterson), [548] and Olsen described differences in the distribution of fibrosis in these two conditions. [404]

In South Africa COCM is a common form of heart disease, [57, 472] accounting for 62% of cardiomyopathy [31] and 37.5% of heart disease in urban Bantu adults. [32]

The literature on COCM in children is sparse. The condition was first described in children in this country by Stein and colleagues in 1956, [14,491] and subsequently in the USA [269, 221] and elsewhere. [154, 20, 100, 122, 516, 257, 169] Harris and co-workers [222, 223] discuss possible aetiologies of childhood COCM, including infective agents, [436, 437] magnesium and potassium deficiency, [75] genetic factors, [30] malnutrition, [176] and others. [222]

Comment

In order to observe the possible evolution of acute endomyocardial disease (EMD), i.e. the AM/EFE syndrome, [225] into idiopathic, chronic, congestive cardiomyopathy (COCM), patients with long-standing or established

heart muscle disease were excluded from this study at presentation as far as possible. Also excluded from consideration were patients with hypertrophic cardiomyopathy (idiopathic hypertrophic sub aortic stenosis or asymmetric septal hypertrophy) and endomyocardial fibrosis (EMF) which is common in Central Africa, [19, 90, 104, 105, 127, 479, 522] occurs in North[400] and South Africa, [32] South East Asia, [86, 103, 455, 535, 299, 384] Japan [401, 578] and South America, [18, 91, 141, 205,] and is rare in Europe [144] and America, and also in Cape Town. [31]

CHAPTER 3.

CASE SELECTION

1. METHODS

1.1 CLINICAL, RADIOLOGICAL AND ELECTROCARDIOGRAPHIC

Because there is no definitive, non-invasive, pre-mortem diagnostic test for AM or EFE, the in-vivo diagnosis of either condition depends entirely on non-specific clinical, radiological and electrocardiographic features. For this reason, the diagnostic criteria laid down for inclusion of patients in this study were made stringent and strictly applied, in similar fashion to the Jones's criteria for acute rheumatic fever.

It has been claimed that there is considerable clinical overlap between AM and EFE, with no definitive way of differentiating the two conditions [195, 430] short of endomyocardial biopsy. [195, 226, 255] Other authors believe that the clinical presentation of EFE is characteristic and distinctive, [113, 322, 352] though mainly dependent on electrocardiographic LVH [164, 222, 302, 368, 353, 538] and earlier onset. [368, 339] In this study, the same criteria were used for both conditions on the assumption that they reflected two phases of one disease process. The patients were then divided on the basis of electrocardiographic LVH for comparative purposes.

Overdiagnosis is a major problem, especially in patients without LVH on ECG, and in infants and young children - the age-group most susceptible to both AM and EFE. For instance, congestive heart failure may be simulated by primary respiratory disease, such as pneumonia or bronchiolitis. These patients present with tachypnoea, tachycardia due to pyrexia, hypoxia or respiratory failure, and apparent hepatomegaly from depression of the liver edge by excessive ventilatory excursion. The chest x-ray and ECG, however, would show cardiac normality in these circumstances.

Cardiac failure without significant cardiac murmurs may be caused or simulated by volume overloading in acute glomerulonephritis, the nephrotic syndrome, or nutritional oedema, or by severe anaemia. However, the ECG is usually normal, though associated electrolyte disturbances may produce T wave changes, and LVH alone may occur in longstanding chronic anaemia.

On ECG, non-specific T wave changes may occur with electrolyte disorders, i.e. of potassium, [508, 509] sodium, [510, 511] calcium, [111, 510] and magnesium,[285] and with metabolic acidosis or alkalosis, [333, 431,510, 511] hypothermia, [511] hypoxia [511] and dehydration, [510] but the heart is usually normal in other respects. On chest x-ray, pseudocardiomegaly may be due to thymic enlargement in infants, elevated diaphragms from ascites or visceral organomegaly, or to x-rays being exposed during expiration - a common event in crying children.

To avoid false positive diagnoses, patients were admitted to the study only if there was evidence of cardiac involvement at all three levels of assessment, i.e. clinical, radiological and electrocardiographic. It is common cause that this would exclude patients with milder degrees of acute

myocarditis and preclude an accurate estimate of incidence, but a firm diagnosis of AM was considered essential to validate the comparison between AM and EFE.

1.2 OTHER INVESTIGATIONS

There appear to be no reports in the literature regarding the value of serum enzymes in differentiating AM and EFE. Serum lactate dehydrogenase (LDH), hydroxybutyrate dehydrogenase (HBDH) and creatinine kinase (CPK) values were measured in this study to investigate this possibility.

Haemodynamic and angiocardiographic findings in EFE have been comprehensively reported, [12, 15, 4, 27, 190, 195, 226, 302, 294, 329, 321, 353, 368, 352, 532, 363, 539, 533] are non-specific, and do not discriminate between EFE, myocarditis [195, 226] and cardiomyopathy. [182, 183, 216, 419, 580] Furthermore, these results do not influence therapy, which is identical in AM and EFE anyway. [226, 225, 339] An invasive procedure like cardiac catheterisation was therefore considered unjustified in our patients unless anomalous left coronary artery from the pulmonary artery [195, 226, 476] or other specific entities were suspected on clinical grounds.

The role of endomyocardial biopsy [61, 290, 344, 474, 405, 406, 407, 480] in establishing the precise histological diagnosis in acute endomyocardial disease in children is still highly contentious [146, 167, 195, 226, 330, 331] (see page 182). Because histological diagnosis confers no therapeutic advantage, and patients with EFE and especially AM are prone to arrythmias and sudden demise, endomyocardial biopsy was not undertaken in this study. The value of echocardiography, a non-invasive technique, was not widely recognised in paediatric practice when this study commenced in 1970. This

procedure should be helpful in monitoring cardiac function over the long-term but was considered incapable of differentiating AM from EFE. However, a recent report indicates that the thickened endocardium of EFE can be demonstrated by both conventional and two-dimensional echocardiography.[579] There is only one report of scintigraphy being used in EFE.[505]

2. DIAGNOSTIC CRITERIA - next page.

2. DIAGNOSTIC CRITERIA

Based on the above considerations the following diagnostic criteria were regarded as essential for entry of a patient into the study:

Clinical

i) A short history,

ii) + clinical signs of significant myocardial involvement, i.e. any one of the following,

   a) elevated heart rate in the absence of fever,
   b) obvious cardiomegaly on palpation,
   c) systemic or pulmonary venous congestion,
   d) obvious gallop rhythm, or
   e) cardiogenic shock,

iii) + ST/T wave changes on ECG, with or without LVH,

iv) + cardiomegaly on chest x-ray.

Autopsy

Pathological features of either AM or EFE in patients with insufficient clinical data.

2.1 SHORT HISTORY

The duration of symptoms was limited in order to exclude patients with long-standing disease or congestive cardiomyopathy. However, in view of the concept that certain cases of acute myocarditis may develop as an autoimmune process weeks after the initial viral infection, [120, 297, 325, 457] a period of up to one month was accepted.

2.2 CLINICAL SIGNS

a) Elevated heart rate: A heart rate greater than the 95th percentile for

age was considered excessive, using values modified from the normal ranges reported by Liebman and Plonsey [319] (see Key to Appendix D).

b) Cardiomegaly on examination: This was considered positive when the left ventricular apex was displaced laterally and/or downwards from the normal position for age. Because radiological cardiomegaly may be simulated by pseudocardiomegaly (see page 152) or pericardial effusion, clinical cardiomegaly is a significant pointer to true cardiac enlargement and was therefore included as a separate sign.

c) Systemic or pulmonary venous congestion: Because of the difficulties in detection and interpretation of these signs in small children, left and right sided decompensation were combined into a single sign, which was considered positive if

(i) two of the following features were present;
- oedema,
- elevated JVP,
- hepar > 2 cms below the costal margin at the mid-clavicular level,
- crepitations in one or both lung fields (or diffuse wheeze), or

(ii) the hepar was > 3 cms below the costal margin.

d) Gallop rhythm: A physiological 3rd heart sound is common in young children, especially with tachycardia. A pathological gallop rhythm was diagnosed if the diastolic sound was a prominent feature, i.e. of equal or greater intensity than the 1st and 2nd heart sounds, and constant, i.e. not disappearing during expiration.

e) Cardiogenic shock was diagnosed if

(i) there was obvious circulatory collapse, with absent pulses,

unrecordable blood pressure, and poor heart beat, or

(ii) peripheral vasoconstriction with thready pulses, low BP, generalised pallor and clammy, cold skin.

2.3 ECG CHANGES

T wave flattening (< 1 mm) or inversion (to any depth) in leads V5 and V6 and/or significant ST segment elevation or depression in any leads were regarded as essential features.

(i) T wave alterations in V5 and V6:

Definite - any combination of inverted, flattened or biphasic T waves in both leads.

Suggestive - normal in V5 and inverted, flattened or biphasic in V6,

- inverted, flattened or biphasic in V5, and normal in V6.

(ii) Significant ST segment alterations in children have been defined as follows, though original data has not been presented in any of these references.

"Elevation or depression of ST segment of greater than 1.5 mm are probably pathologic" [383]

"(Normal) ST segment change is rarely greater than 1 mm and never greater than 2 mm in standard leads ; may be greater than 4 mm in right praecordial leads" [273]

"Elevation or depression of ST segment of greater than 2 mm in any lead is always abnormal" [293]

"ST segment change greater than 1 mm in limb leads unusual ; 2 mm change within normal limits in left chest leads and even 3 mm change may be seen in lead V4" [440]

Criteria used in this study were:

ST segment elevation or depression,

a) greater than 2 mm in the standard leads and/or 3 mm in the chest

leads, in an otherwise normal ECG, or

b) greater than 1 mm associated with a coved ST-T wave segment, and/or greater than 2 mm in the chest leads, in the presence of other ECG abnormalities (e.g. T wave changes).

(iii) In view of the importance of LVH in differentiating AM from EFE, [222, 368, 476] voltage criteria for LVH were distilled from several sources which are referred to in Table 2.1.

The values used for LVH in this study were,

for RV6	:	under 1 month	-	> 20 mm,
		1 to under 6 months	-	> 25 mm,
		6 months to 12 years	-	> 30 mm,
for SV1	:	0 to under 6 months	-	> 20 mm,
		6 months to 12 years	-	> 25 mm.

These values are more stringent than the 20 mm limit for RV6 and SV1 accepted by Sellers et al [476] for under 2 year olds and by Hastreiter and Fisher [226] for all ages. Other criteria for LVH, such as the R/S ratio in V1, left axis deviation, size of Q wave in lead V6, QRS-T vector angle, ST-T wave depression, intrinsicoid deflection, and other voltage changes, were omitted from consideration because of lack of agreement regarding their validity or levels of significance, or because they conflicted with the indices of myocardial involvement in this study (see Chapter 9).

2.4 RADIOLOGICAL CARDIOMEGALY

This was considered an essential criterion because the chest x-ray affords an objective, reliable and easily measured parameter of cardiac enlargement. For inclusion into the study, a cardio-thoracic ratio (maximum transverse diameter of the heart : diameter of the chest at the height of the diaphragms) of greater than 0.55 was considered positive. Because the normal cardio-

TABLE 2.1. Voltage criteria for LVH in leads V1 and V6 extracted from literature, and values used in present study (final column).

AGE	RV6 (mm) REFERENCE NUMBER							
	319+	206Φ	385o	13+	383o	81o	293o	Study
months								
0 to <1	22	21	20					20
0 to <3	25		25					25
3 to <6	26	20						
6 to <9	28			24				
6 to <12					30	30	35	
9 to <24	30		30					30
years								
1 to <3								
2 to <6	28	24						
3 to <6				28				
6 to 12	33			33				

AGE	SV1 (mm) REFERENCE NUMBER							
	319+	206Φ	-	13+	383o	81o	293o	Study
months								
0 to <1	15	20						
1 to <3	22	18		23				20
3 to <6	17						20	
6 to <9	30							
6 to <12		16			25	20		
9 to <24				22				
years								
1 to <3	25	27						25
2 to <6							25	
3 to <6		30		25				
6 to 12	36	26		27				

\+ - maximum normal values
Φ - upper limits of normal
o - recommended values for hypertrophy

thoracic ratio is somewhat larger in infants than older children, and because films were not always exposed during inspiration, a more stringent requirement was set than the usual 0.50 ratio. [93]

2.5 PATHOLOGY

The criteria for inclusion of patients in the autopsy series are defined and detailed in Chapter 13.

Comment

These diagnostic criteria are similar to those recommended in the literature. The clinical diagnosis of overt AM depends mainly on acute-onset [223] and signs of heart failure, radiological cardiomegaly, or ST-T changes on ECG. [43] These features plus LVH "with strain" [476, 352] are required for the diagnosis of EFE, including other factors such as onset under 2 years, [476] no or variable murmurs of mitral [352] and/or aortic [476] valve involvement, and the exclusion of other specific conditions such as rheumatic carditis, glycogen storage disease, anomalous origin of the left coronary artery and acute myocarditis. [352] Only Greenwood et al have recommended common criteria for so-called primary myocardial disease in children (AM, EFE and non-obstructive cardiomyopathy), including radiological cardiomegaly, ST-T changes and no murmurs louder than grade 3/6. [195]

CHAPTER 4.

PATIENT MATERIAL.

A total of 140 patients was prospectively admitted to the study from 1st June 1970 to 31st December 1976, a period of 6 years 7 months. The presence or absence of diagnostic criteria for each patient is indicated in Appendix A, together with the initials, race, sex and date of presentation in each case. The patients are numbered consecutively in order of increasing age at presentation within each of the following groups. Each case retains this index number for the entire study.

1. CLASSIFICATION - TOTAL SERIES.

A : CLINICAL SERIES

123 patients complying with the clinical diagnostic criteria, and sub-divided into

GROUP 1 - 92 patients with ST-T wave changes, but no LVH on ECG, and

GROUP 2 - 31 patients with ST-T wave changes plus LVH on ECG, and

B : AUTOPSY SERIES

17 patients with insufficient data for inclusion into section A, but with autopsy-confirmed AM or EFE, and divided into

GROUP 3 - 13 patients with acute-onset (comparable with Groups 1 and 2 in this respect), and

GROUP 4 - 4 patients with a long history.

1.1 COMPLIANCE WITH DIAGNOSTIC CRITERIA

The 17 patients in Groups 3 and 4 were included on the basis of post-mortem findings. Of the 123 patients in the clinical series (Groups 1 and 2), all but 7 complied with the strict criteria of short history, ST-T wave changes on ECG, cardiomegaly on chest x-ray, plus 1 or more clinical signs of cardiac involvement (Table 4.1). Each of these 7 patients failed to comply with one criterion only, but were included in the study for the reasons mentioned below.

(i) Patient no. 9 did not have ST-T wave changes on ECG, but presented with frequent episodes of supraventricular tachycardia, and AM was proved at autopsy.

(ii) Patient no. 111 had LVH on ECG at presentation but no ST-T wave changes. However, the latter appeared on a subsequent ECG 12 days later, and both features persisted till his death 5 weeks later. (No post-mortem was performed).

(iii) Patient no. 117 presented without ST-T wave changes but with evidence of biventricular hypertrophy on ECG (Katz-Wachtel phenomenon), which persisted till her death 10 weeks later. Features of both AM and EFE were demonstrated at autopsy.

(iv) Patient no. 39 died within hours of admission before a chest x-ray was performed, but gross cardiomegaly was observed at autopsy, which also confirmed AM. Because all other criteria were met, this patient was included in clinical Group 1 rather than in autopsy Group 3.

(v) Patient no. 95 presented with a characteristic ECG (LVH with T wave inversion in leads V5 and V6) which persisted for 3 years, cardiomegaly on x-ray, and a 2 cm hepatomegaly, but with no obvious clinical cardiomegaly or evidence of heart failure. However, one day after admission, a gallop rhythm and signs of cardiac decompensation appeared.

In the following two patients the long-term course favoured a diagnosis of AM

TABLE 4.1 Patient Compliance with diagnostic criteria - clinical series.
Number of patients with (Group 1) and without (Group 2) LVH on ECG.

DIAGNOSTIC CRITERION	NO. OF PATIENTS		
	GROUP 1 (92)	GROUP 2 (31)	TOTAL (123)
ECG	91	29	120
RADIOLOGICAL	91	31	122
CLINICAL	92	28	120
1 sign	8	4	12
2 signs	22	4	26
3 signs	25	11	36
4 signs	28	9	37
5 signs	9	0	9

Total number of patients in each group appears in parentheses.

or EFE, and they were therefore included in the clinical series (Group 2).

(vi) Patient no. 98 presented with LVH and T-wave inversion on ECG and radiological cardiomegaly, but with no features of heart failure except for pulmonary crepitations (without pneumonia on chest x-ray). Although the ECG changes resolved within 12 days of admission, the radiological cardiomegaly persisted for over 3 years.

(vii) Patient no. 103 presented without clinical signs of cardiac involvement but with radiological cardiomegaly and LVH and T-wave changes on ECG which persisted for over 10 months.

2. CLASSIFICATION - CLINICAL SERIES.

2.1 THE NEED FOR FURTHER CLASSIFICATION

In reviewing the evolutionary changes in the ECG's of patients entered into the clinical series, it became apparent that the use of LVH on admission to identify EFE as distinct from AM may be erroneous. As many as 32 of the 123 patients (26%) changed status at a later stage from LVH positive to LVH negative or visa versa (detailed in Appendix D).

The proponents of the view that LVH is equated with EFE do not point out whether the LVH must be present on admission or terminally, or whether LVH must be a constant feature throughout the course of the illness, or may fluctuate in its presence or degree of severity at different times. Indeed, the variation of the ECG with time is a major argument in this study for the proposal that AM and EFE are inter-related (see Chapter 14).

So as to enable comparison of LVH negative patients (Group 1) with LVH

positive patients (Group 2) in this study, it was decided to allocate patients to these two groups according to the timing of LVH in each patient's course,

i.e. whether LVH was absent or present

(i) on admission (Groups 1A and 2A respectively),

(ii) at any stage of the course, including at the onset, during or at the end, and whether intermittently or continually (Groups 1C and 2C), or

(iii) at the end of the study period or at death, whether LVH was present before this or not, i.e. terminally (Groups 1T and 2T).

The patients were categorised at the end of the study period (31st December, 1976).

2.2 RESULTS

Figure 4.1 indicates the number of patients changing status and the resultant numbers in each group ; the complete list of all patients in each category appears in Table 4.2.

Of the 92 patients allocated to Group 1 according to the ECG on admission (Group 1A), 71 remained in category 1 (without LVH) throughout the duration of the study, i.e. 1A→1C→1T.

In like manner, 20 of the 31 patients in Group 2 on admission (Group 2A) remained in category 2 (with LVH on ECG) throughout the study period, i.e. 2A→2C→2T.

The remaining 32 patients (21+11) changed status after admission, as follows:

15 patients started without LVH on admission (1A), developed LVH subsequently (2C), but lost the LVH prior to the end of the study

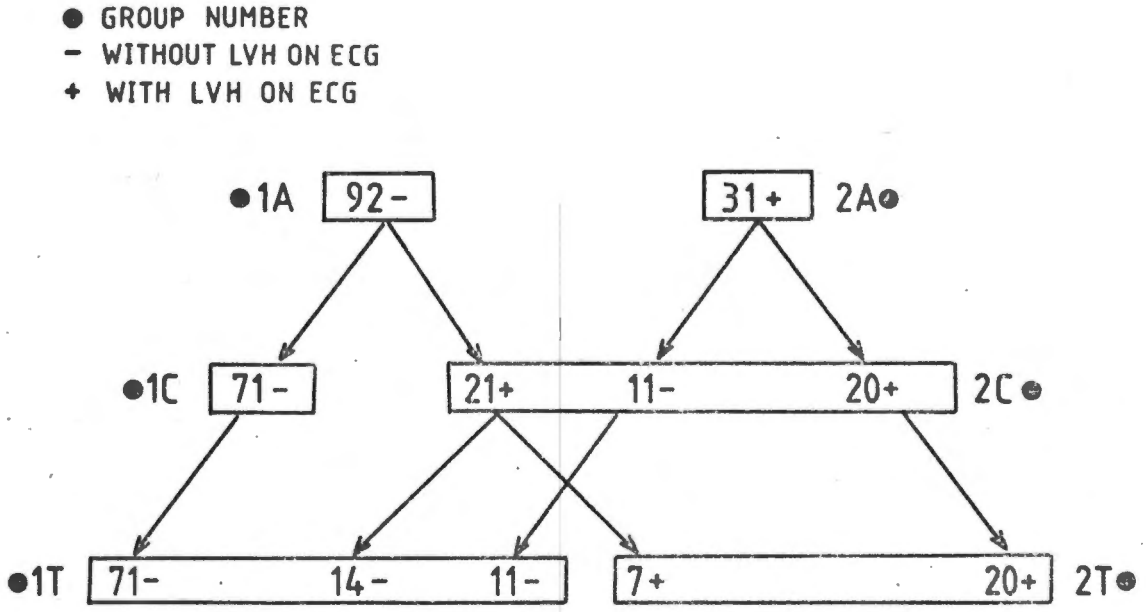


FIG. 4.1 Patient grouping - Clinical series. Number of patients in each group according to absence (Group 1) or presence (Group 2) of LVH on ECG on admission (1A and 2A), at any time during the course (1C and 2C), and at the end of the study or death, i.e. terminally (1T and 2T).

TABLE 4.2 CLASSIFICATION - CLINICAL SERIES.

Index numbers of patients allocated to Group 1 or Group 2 according to the absence or presence of LVH on ECG at different stages of the illness, i.e.

Groups 1A and 2A - on admission,
1C and 2C - at any stage during the patient's course,
1T and 2T - at the end of the study, or death (terminally).

INDEX NUMBERS OF PATIENTS IN EACH GROUP					
1A (92)	2A (31)	1C (71)	2C (52)	1T (96)	2T (27)
1 32 63	93	1 32 63	93	1 32 63 93	
2 33 64	94	2 64	33 94	2 33 64	94
3 34 65	95	3 34 65	95	3 34 65 95	
4 35 66	96	35 66	4 96	35 66	4 96
5 36 67	97		5 36 67 97	5 36 67	97
6 37 68	98	6 37 68	98	6 37 68 98	
7 38 69	99	7 38 69	99	7 38 69	99
8 39 70	100	8 39 70	100	8 39 70 100	
9 40 71	101	40 71	9 101	9 40 71	101
10 41 72	102	10 41 72	102	10 41 72	102
11 42 73	103	11 42 73	103	11 42 73	103
12 43 74	104	43 74	12 104	12 43 74	104
13 44 75	105	13 44 75	105	13 44 75 105	
14 45 76	106	14 76	45 106	14 45 76 106	
15 46 77	107	15 77	46 107	15 46 77	107
16 47 78	108	16 78	47 108	16 78	47
17 48 79	109	17 48 79	109	17 48 79	109
18 49 80	110	80	18 49 110	80	18 49 110
19 50 81	111	19 50 81	111	19 50 81	111
20 51 82	112	20 51 82	112	20 51 82	112
21 52 83	113	21 52 83	113	21 52 83 113	
22 53 84	114	53 84	22 114	22 53 84 114	
23 54 85	115		23 54 85 115	23 85 115	54
24 55 86	116	24 55 86	116	24 55 86	116
25 56 87	117	25 56	87 117	25 56 87	117
26 57 88	118	26 57 88	118	26 57 88	118
27 58 89	119	27 89	58 119	27 89	58 119
28 59 90	120	28 59 90	120	28 59 90 120	
29 60 91	121	29 60	91 121	29 60 91	121
30 61 92	122	30 92	61 122	30 61 92 122	
31 62	123	31	62 123	31	62 123

Total number of patients in each group appears in parentheses.

period or death (1T),

i.e. 1A→2C→1T (Patient no's 5, 9, 12, 22, 23, 33, 36, 45, 46, 58, 61, 67, 85, 87, 91).

6 patients started without LVH at presentation (1A), developed LVH during the course (2C), which persisted till the end of the study period or death (2T),

i.e. 1A→2C→1T (Patient no's 4, 18, 47, 49, 54, 62).

11 patients started with LVH (2A and 2C) which resolved prior to the end of the study period (1T),

i.e. 2A→2C→1T (Patient no's 93, 95, 98, 100, 105, 106, 113, 114, 115, 120, 122).

Comment

Since the fluctuation of LVH has not previously been taken into account in differentiating EFE from AM, all three methods of classifying LVH negative and LVH positive patients were used whenever appropriate to compare suspected AM and EFE.

3. RACE DISTRIBUTION.

There was a consistent and marked predominance of Cape coloured patients over black and over white patients in Groups 1, 2 and 3 (Table 4.3), with ratios of 102:27 and 102:11 respectively, for the total series. The difference was even more striking when comparing the combined Cape coloured and black group with whites (129:11).

There was no statistically significant difference in race distribution between LVH negative and LVH positive patients in all 3 modes of classification

TABLE 4.3 Race distribution in the Clinical (Groups 1 and 2) and Autopsy (Groups 3 and 4) series.

GROUP	RACE			TOTAL
	C	B	W	
1A	71	14	7	92
2A	20	9	2	31
1C	56	9	6	71
2C	35	14	3	52
1T	74	14	8	96
2T	17	9	1	27
CLINICAL SERIES	91	23	9	123
3	10	2	1	13
4	1	2	1	4
AUTOPSY SERIES	11	4	2	17
TOTAL SERIES	102	27	11	140

C = Cape coloureds; B = blacks; W = whites

TABLE 4.4 Distribution of sexes in the Clinical (Groups 1 and 2) and Autopsy (Groups 3 and 4) series.

GROUP	MALE	FEMALE	TOTAL
1A	46	46	92
2A	18	13	31
1C	37	34	71
2C	27	25	52
1T	51	45	96
2T	13	14	27
CLINICAL SERIES	64	59	123
3	4	9	13
4	3	1	4
AUTOPSY SERIES	7	10	17
TOTAL SERIES	71	69	140

(X^2 = 0.034, 1.528 and 1.511 ; $p>0.80$, 0.20 and 0.20, respectively), or between the clinical and autopsy series (X^2 = 0.266, $p>0.60$).

Comment

It is known that the admission rate in relation to population totals is higher in blacks and Cape coloured than whites, who tend to be treated privately in institutions other than those of the Department of Paediatrics and Child Health. A questionnaire was therefore sent to the nine private paediatricians in Cape Town (all responded), which revealed that since 1970 only one had encountered 2 white patients with AM or EFE fulfilling the strict clinical criteria of this study. Several paediatricians intimated that patients as severely affected as this would have been referred to the Department anyway for intensive care.

Furthermore, the percentage distribution of Cape coloured/black to white patients with AM and EFE in this series was 92:8, whereas the percentage racial distribution for all admissions to the paediatric wards during the same time-period was 80:20. Hence, the frequency of AM and EFE was significantly greater in the black groups than in white patients (X^2 = 5.025, $p<0.025$).

These findings support the conclusion that acute EMD is particularly prevalent in Cape coloured and black children.

There is little information in the literature regarding racial distribution in acute EMD. Miller et al[362] reported no racial predominance in EFE. Mitchell et al[367] detected EFE in 5 coloured and 2 white infants in a large perinatal study, but this ratio was within expected limits. However, Hutchins and Vie[255] reported an 82% incidence of post-mortem AM and EFE in blacks relative to whites, compared with a 30% incidence of blacks in all autopsies, and McLoughlin et al[352] found that 75% of patients with clinical EFE were

negroes compared with an overall admission rate in negroes of only 25%.

The latter concluded that "hereditary, environmental and socio-economic factors may play an aetiological or a modifying role in the expression" of EFE, and the former that there was "a propensity for fatal myocarditis and fibroelastosis in the socio-economically depressed". Since the vast majority of black/coloured patients in the present study belong to the socio-economically deprived segment of society, these views are supported.

The evidence suggests, firstly, that impoverished children are more prone to contracting acute viral myocarditis, as suggested by Whitehead [562] in relation to enteroviruses, and found experimentally with coxsackieviruses in undernourished mice. [574] Secondly, because EFE occurs in patients with the same socio-economic background, a possible relationship between AM and EFE is strengthened, in compliance with the stated hypothesis.

4. DISTRIBUTION OF SEXES.

The male:female ratio was approximately equal in LVH negative and LVH positive patients (Groups 1 and 2), however classified, and in the autopsy series. (Table 4.4)

Comment

An equal male:female ratio in EFE has been recorded by others, [195, 255, 352] but a female predominance ranging from slight [476] to 1:6:1 [84, 274] and 2:1 [368] has also been reported. An equal sex distribution has been reported in autopsy-confirmed cases of AM as well. [255]

5. AGE DISTRIBUTION.

Statistical comparison of the mean ages in Groups 1, 2 and 3 showed that patients in Group 1A were significantly older than those in Group 2A. (Table 4.5)

Although this conclusion may be invalid for the t-test, since the degree of variance of the standard deviations suggests that the samples were drawn from two unequal populations [378] ($F = 2.725$, $p < 0.01$), a valid difference between the 2 samples (both greater than 30) was indicated by the fact that the observed difference (9.9 months) was greater than twice the standard error of the difference of the means (3.69).

There were no statistically significant differences in mean age between the clinical Groups 1C and 2C, or 1T and 2T ; nor between Group 1A or 2A (without and with LVH on admission) and Group 3 (deaths soon after admission).

The age difference may also be demonstrated by the fact that the number of patients in the younger age groups was significantly greater in LVH positive than LVH negative patients, i.e. Group 2A > Group 1A ($p < 0.05$ for patients under 6 and 18 months, $p < 0.005$ under 12 months) ; Group 2C > Group 1C ($p < 0.05$ for patients under 6, 12 and 24 months) ; and Group 2T > Group 1T ($p < 0.05$ under 24 months). (Table 4.6)

Furthermore, in the graphic display of the number of patients (Figures 4.2, 4.3 and 4.4) in different age brackets in each group, it is apparent that LVH positive patients by any method of classification had earlier peak ages than LVH negative patients. The peak age for Group 1 was 12 to 14 months, and for Group 2 approximately 6 months. Group 3 appeared to have

TABLE 4.5 Age at presentation (mean ±SEM) in patients without (Group 1) and with (Group 2) LVH on ECG, on admission (Type A), at any stage (Type C) and terminally (Type T), and in the autopsy series (Group 3).

TYPE OF CLASSIFICATION	AGE (months) GROUP 1	GROUP 2	GROUP 3	t 1 cf 2	t 1 cf 3	t 2 cf 3
A	±21.7 −2.57	±11.8 −2.65	±12.5 −2.70	2.095*	1.273	-0.144
C	±21.5 −2.67	±16.1 −3.23	-	1.289	-	-
T	±21.1 −2.49	±12.6 −2.85	-	1.742		

t = statistical evaluation by Student's t-test for unpaired samples.
* = difference significant at $p<0.05$.

TABLE 4.6 Age at presentation. Number of patients in different age-ranges at presentation according to absence (Group 1) or presence (Group 2) of LVH on ECG on admission (A), at any stage of the course (C), and at the end of the study or death, i.e. terminally (T).

AGE (months)	NUMBER OF PATIENTS GROUP 1A (92)	GROUP 2A (31)	X^2	GROUP 1C (71)	GROUP 2C (52)	X^2	GROUP 1T (96)	GROUP 2T (27)	X^2
0 to <6	12	10	4.594*	8	14	3.999*	15	7	0.902
6 to <12	18	11	2.437	15	14	0.248	20	9	1.200
12 to <18	27	5	1.474	20	12	0.183	26	6	0.068
18 to <24	14	3	0.223	10	7	0.027	13	4	0.021
24 to <36	6	0	≠	6	0	≠	6	0	≠
36 to <48	6	1	≠	6	1	≠	7	0	≠
48 to <60	2	0	≠	1	1	≠	2	0	≠
60 to <72	4	0	≠	3	1	≠	4	0	≠
72 to <108	1	1	≠	1	1	≠	1	1	≠
108 to 152	2	0	≠	1	1	≠	2	0	≠
UNDER 12	30	21	10.389⊕	23	28	4.842*	35	16	3.623
UNDER 18	57	26	4.125*	43	40	2.953	61	22	2.327
UNDER 24	71	29	3.083	53	47	3.909*	74	26	3.931*

Total number of patients in each group appears in parentheses.
X^2 Statistical evaluation by Chi-square analysis.
* Significant difference at $p< 0.05$
⊕ " " " $p< 0.005$
≠ numbers too small for statistical analysis.

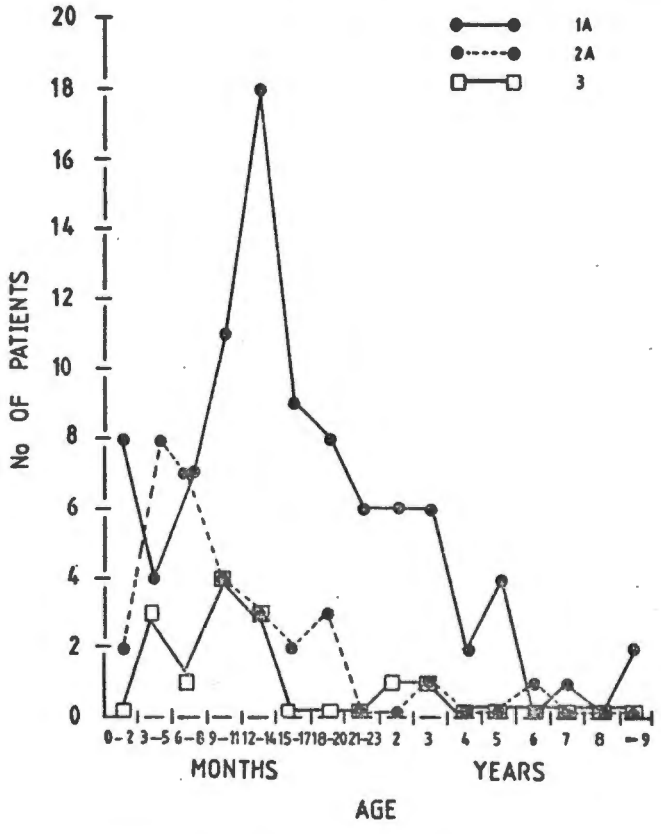


FIG. 4.2 Number of patients of different ages at presentation among those without (Group 1A) and with (Group 2A) LVH on ECG on admission, and in autopsy series (Group 3).

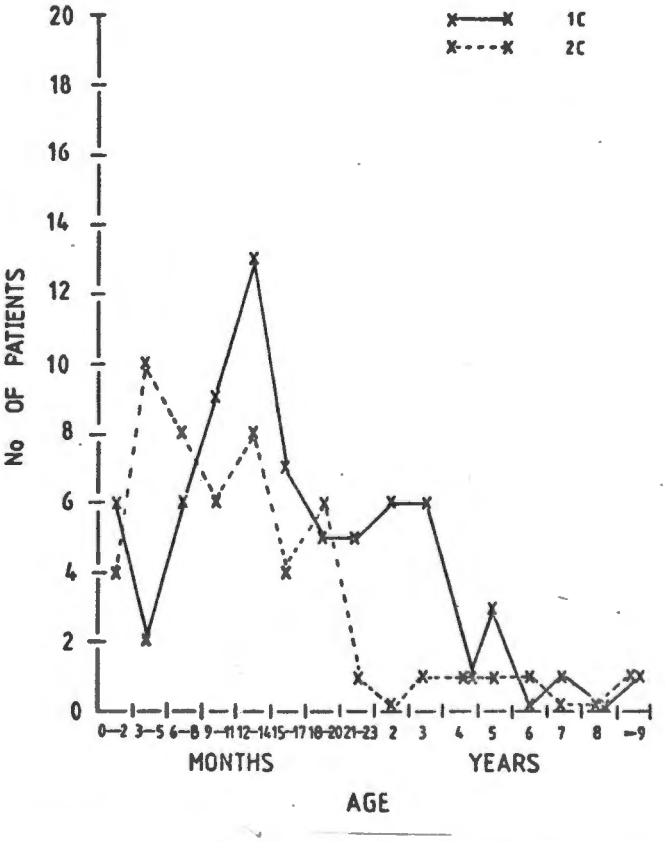


FIG. 4.3 Number of patients of patients of different ages at presentation among those without (Group 1C) and with (Group 2C) LVH at any stage.

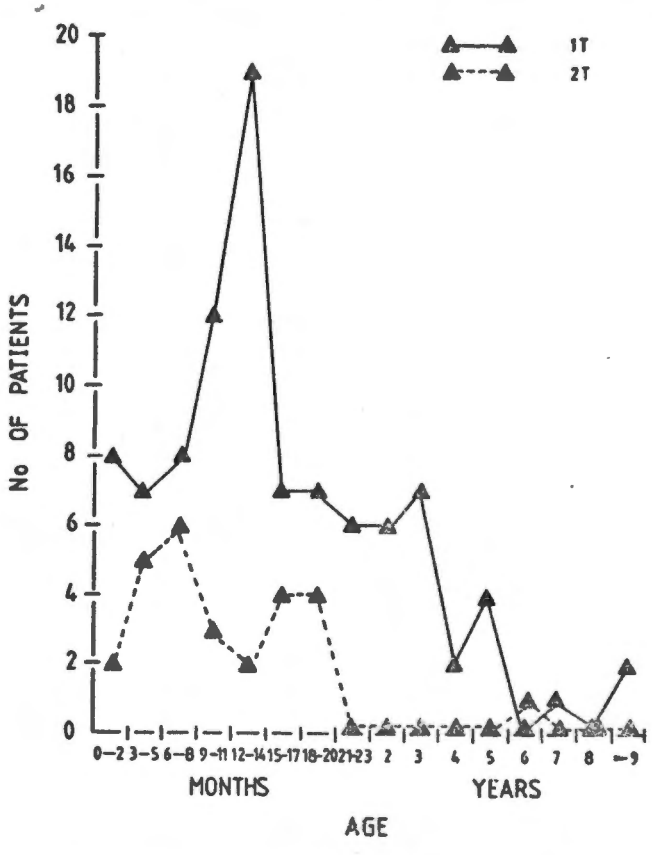


FIG 4.4 Number of patients of <u>different ages</u> at presentation among those <u>without</u> (Group 1T) and <u>with</u> (Group 2T)$_{LVH}$ at the end of the study.

peaks at both these ages, in keeping with a mixed group. (Figure 4.2)

It is concluded that patients with LVH on admission, at any stage of the illness, or terminally, present at a younger age than those without LVH. This is statistically significant in the type A and C classifications when comparing the relative frequency of younger patients, and in the type A classification in respect of mean age.

Comment

This result coincides with previous findings that EFE occurs mainly in early infancy, [47, 195, 226, 342, 476] while acute myocarditis, other than the epidemic neonatal form is reported to occur sporadically at any age. [476, 564, 573, 288, 353] The peak prevalence of 12 to 14 months for sporadic AM noted in this study has not been reported previously.

If EFE coincides with the presence of LVH on ECG and is a response to AM, as claimed, then an explanation must be sought to account for its seemingly paradoxical prevalence in younger patients. The possibility of a special predilection for EFE in the first few months of life is considered in Chapter 14.

It is noteworthy in the figures that, of the three groups with LVH, only Group 2C had a second peak age which coincided with the peak age seen in all three groups without LVH (Groups 1A, 1C and 1T). (Figure 4.3) This is in keeping with the suggestion that a certain number of patients in Group 2C were primarily cases of AM on admission who developed LVH at a later stage which then tended to resolve. In the patients who have LVH from the time of presentation it is postulated that an earlier bout of AM occurred that was mild and unrecognised, or sub-clinical, but sufficient to initiate the de-

velopment of EFE. (see page 179)

CHAPTER 5.

EPIDEMIOLOGY.

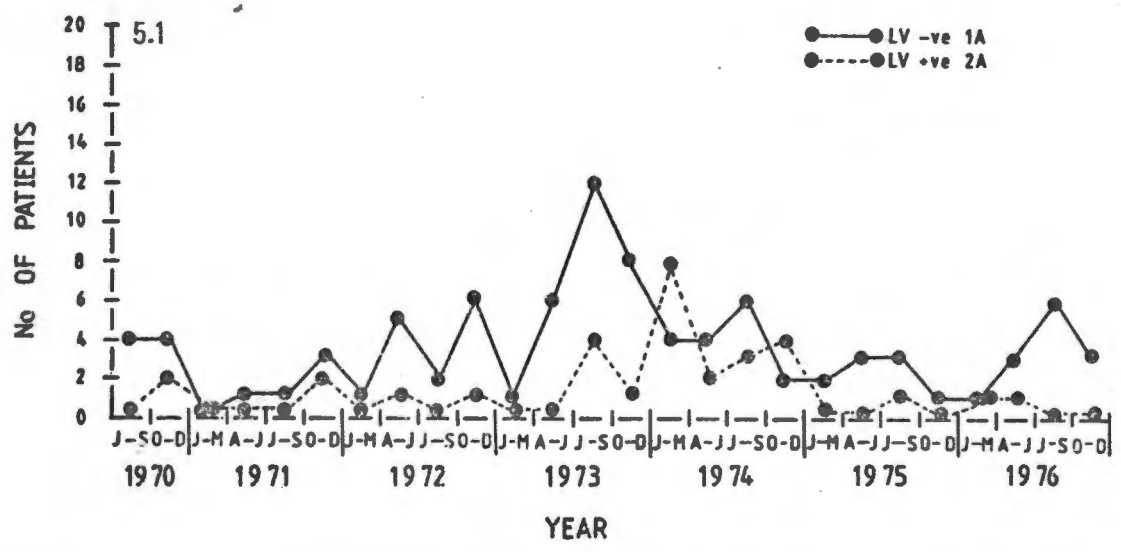
If AM is due to a viral infection and EFE is an independent non-viral condition, the former would be expected to show seasonal variations in incidence with fluctuations from year to year, while the latter should have a consistent pattern over the long-term.

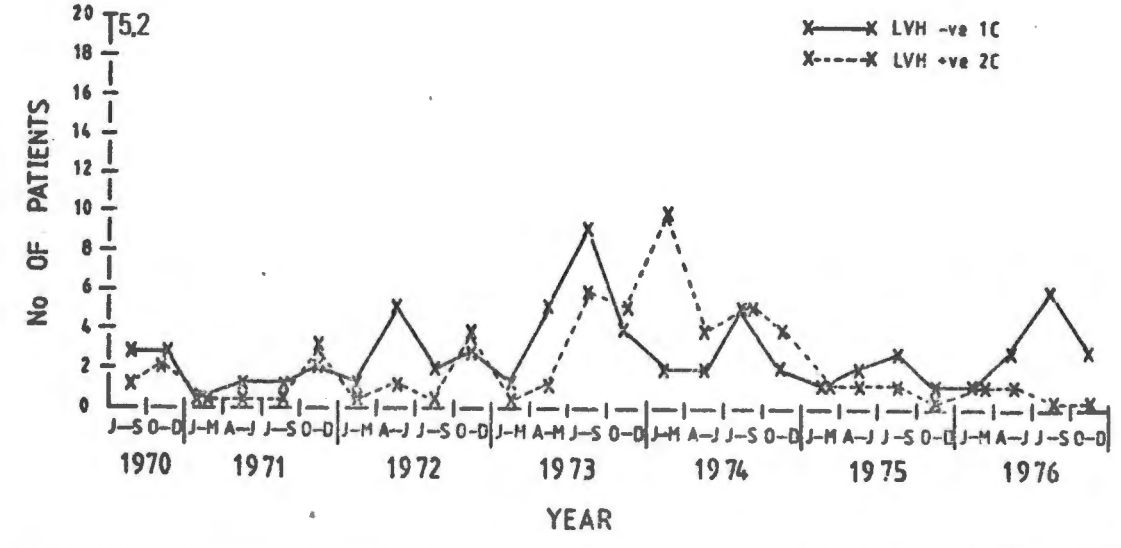
On the other hand, if AM and EFE are related and viral-induced, these variations in incidence should be discerned in both conditions.

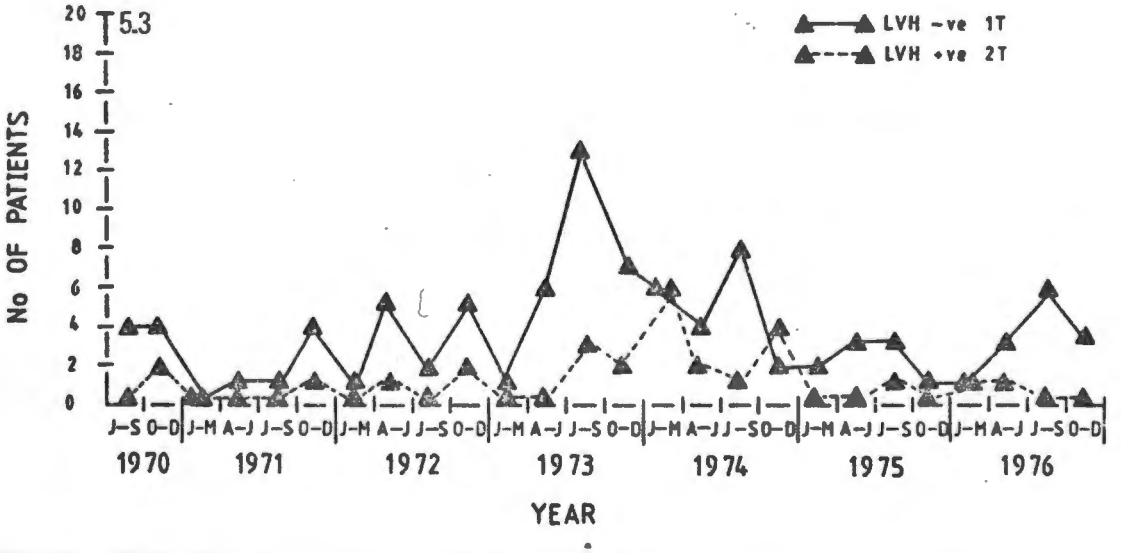
1. METHODS.

To this end, patient admissions were plotted chronologically on an annual and 3-monthly time-scale encompassing the 6½ year duration of the study period. (Figures 5.1 to 5.7) Total admissions for each calendar month throughout this period are depicted graphically in Figure 5.8.

Patients were divided into LVH negative and LVH positive groups (Chapter 4) as based on the initial ECG's (Groups 1A and 2A), on tracings from throughout the study (Groups 1C and 2C), or on ECG's assessed at the end of the study or







FIGS. 5.1-3 THREE MONTHLY DISTRIBUTION.
Number of patients presenting per 3 month period according to absence (Group 1) or presence (Group 2) of LVH:
Fig. 5.1 - on admission (Groups 1A and 2A)
Fig. 5.2 - at any stage (Groups 1C and 2C)
Fig. 5.3 - at end of study or terminally (Groups 1T and 2T).

just prior to death (Groups 1T and 2T), to examine which classification would facilitate differentiation between AM and EFE.

2. RESULTS.

2.1 THREE MONTHLY DISTRIBUTION.

In the 3-monthly distribution of patient admissions for Groups 1A and 2A (Figure 5.1), both groups had concurrent peaks from 1970 to 1973. The maximal peak for Group 1A in July to September, 1973 and a subsequent peak in July to September, 1974 were followed, respectively,by the maximal Group 2A peak in January to March, 1974 and a second peak in 1974, in October to December. Thereafter, the two curves did not coincide with each other. Group 1A peaks all occurred in the second half of each year except for 1972 when this group had two peaks (April to June and October to November).

In the graph for Groups 1C and 2C (Figure 5.2), a similar pattern is evident with peaks for the two groups coinciding prior to, but not after, 1973 and with the maximum group 2C peak in January to March 1974 occurring approximately 6 months after the maximum peak for Group 1C in June to September, 1973.

A similar pattern is also seen in the Group 1T and 2T graph (Figure 5.3), with the two dominant peaks in Group 2T (January to March and October to December 1974) occurring approximately 6 and 3 months, respectively, after the two dominant peaks of Group 1T (July to September, 1973 and 1974).

2.2 ANNUAL DISTRIBUTION.

The annual distribution of patients (Figures 5.4 to 5.6)revealed that the number of LVH negative patients, however classified, reached minor epidemic

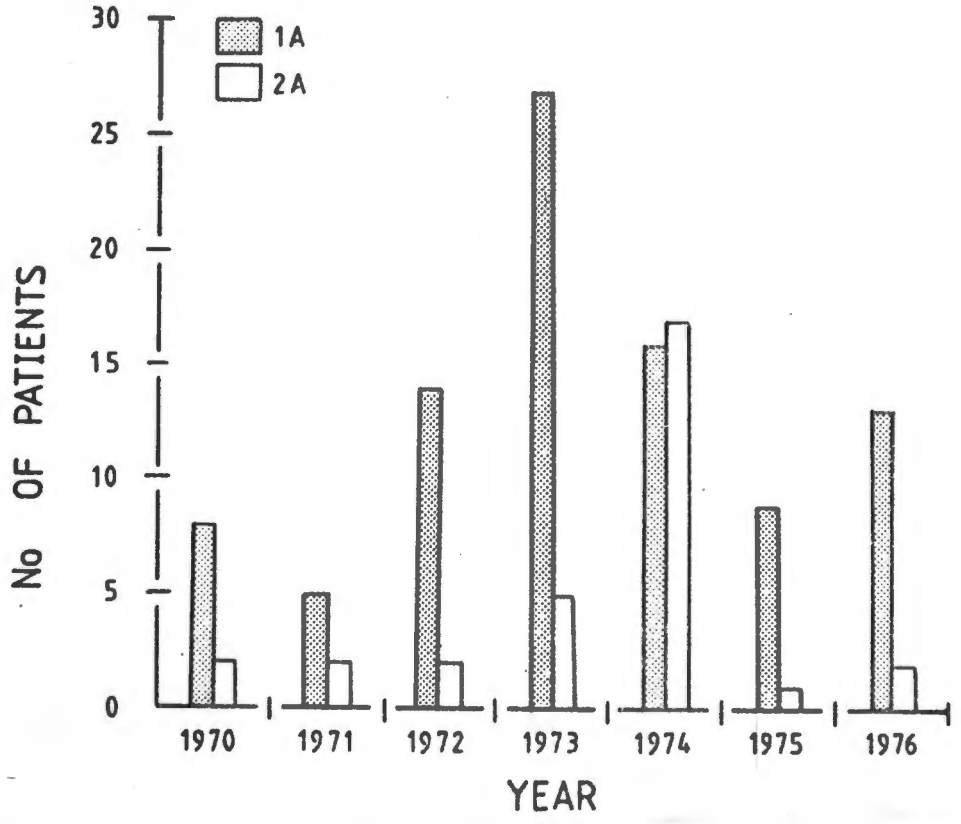


FIG. 5.4 ANNUAL DISTRIBUTION. Number of patients presenting per annum among those without (Group 1A) and with (Group 2) LVH on admission.

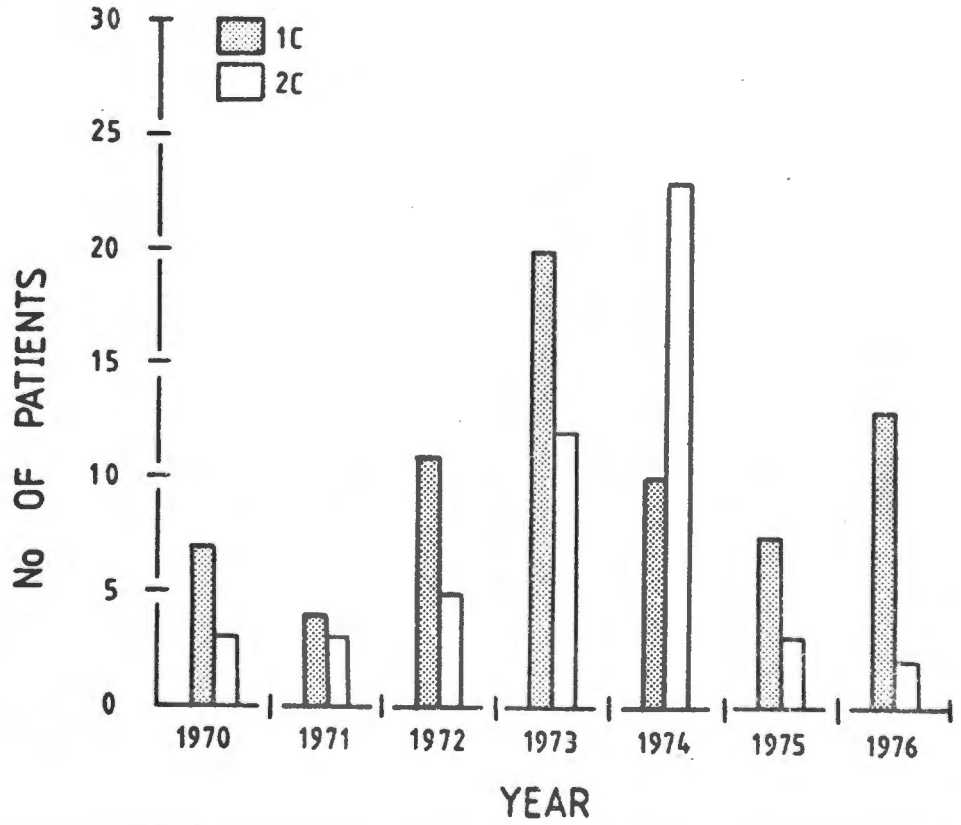


FIG. 5.5 ANNUAL DISTRIBUTION. Number of patients presenting per annum among those without (Group 1C) and with (Group 2C) LVH at any stage.

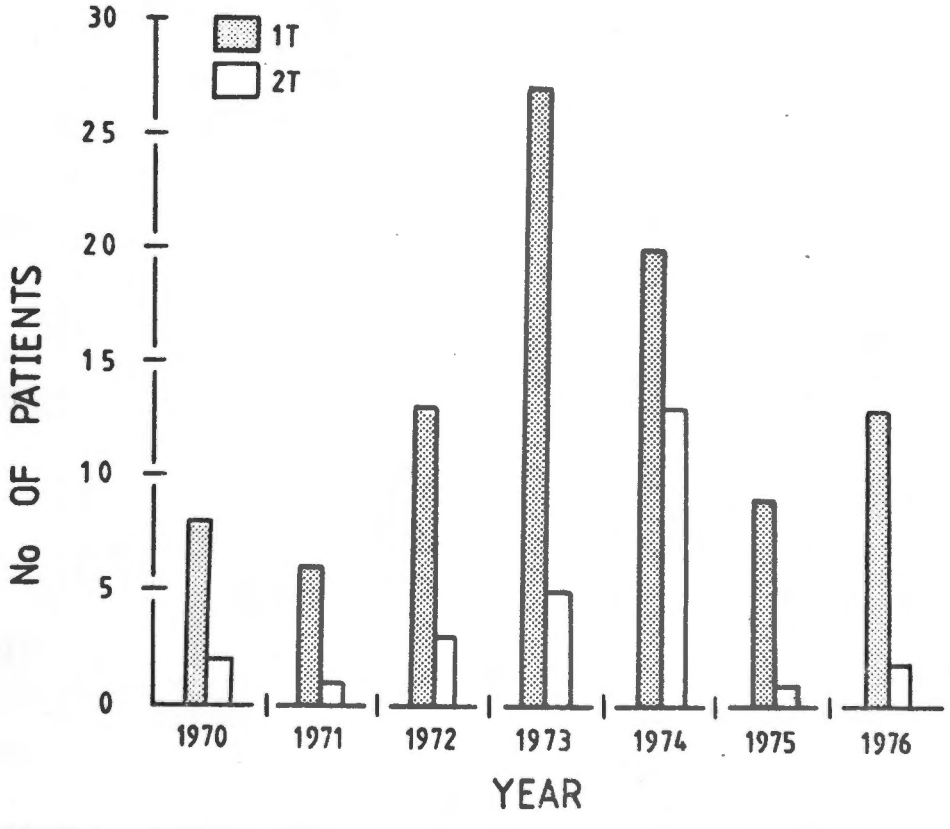


FIG. 5.6 ANNUAL DISTRIBUTION. Number of patients presenting per annum among those without (Group 1T) and with (Group 2T) LVH at end of study or death.

proportions in 1973, with the maximal annual incidence of LVH positive cases occurring in the following year (1974) in each case. This effect is most clearly demonstrated when comparing Groups 1C and 2C where the two sets of patients were equal in numbers (Figure 5.5).

2.3 PERCENTAGE ANNUAL DISTRIBUTION.

The number of patient admissions per annum as a percentage of the total admissions for each group is depicted in Figure 5.7. The percentage distribution of patients in each year was similar for Groups 1A, 1C and 1T, and also for Groups 2A, 2C and 2T. The percentage of Group 1 cases, by any classification, was similar to or greater than the percentage of Group 2 cases in each year except for 1974, when the Group 2 percentage was higher. The peak incidence of Group 2 cases (1974) followed the peak incidence of Group 1 cases (1973), as previously noted.

2.4 CUMULATIVE MONTHLY DISTRIBUTION.

The cumulative number of patients for each month of the year throughout the study period is diagrammatically represented in Figure 5.8. The distribution shows that the majority of patients presented between the months of July and October (58 patients), compared with either of the other 4-month periods (34 patients in November to February and 31 patients from March to June). This occurred with LVH negative and LVH positive patients, but was more striking in the former.

Despite their relative paucity, LVH positive cases (Groups 2A, 2C and 2T) equalled or exceeded the number of LVH negative cases in January and February and to a lesser extent in December and March. Further analysis revealed that the increase in LVH positive cases during the early months of the year occurred

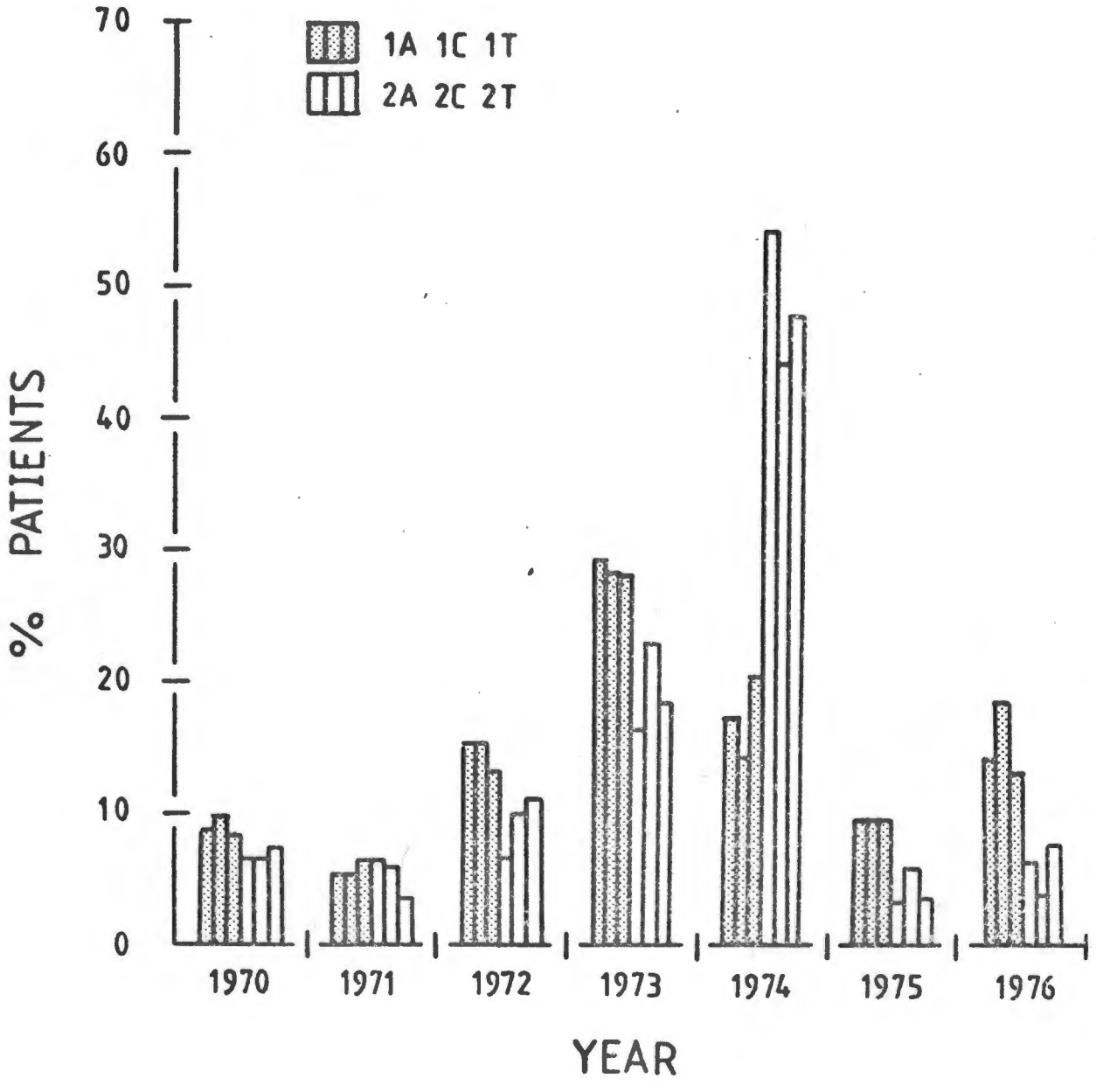
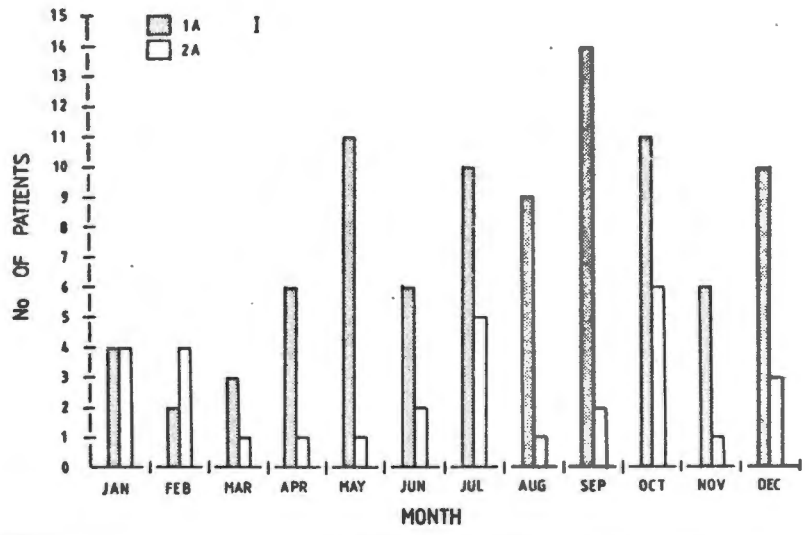
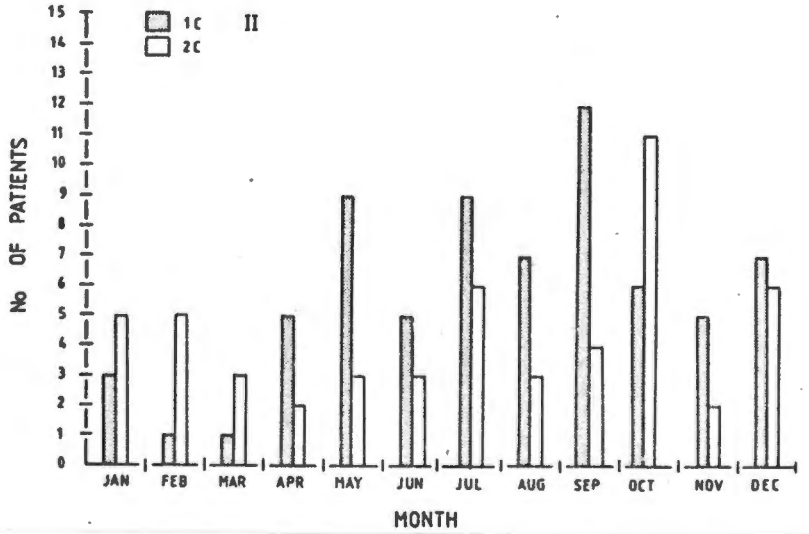


FIG. 5.7 Percentage of patients presenting per annum without (Group 1) and with (Group 2) LVH on ECG, on admission (Groups 1A and 2A), at any stage of the course (Groups 1C and 2C), and at the end of the study or death, i.e. terminally (Groups 1T and 2T).





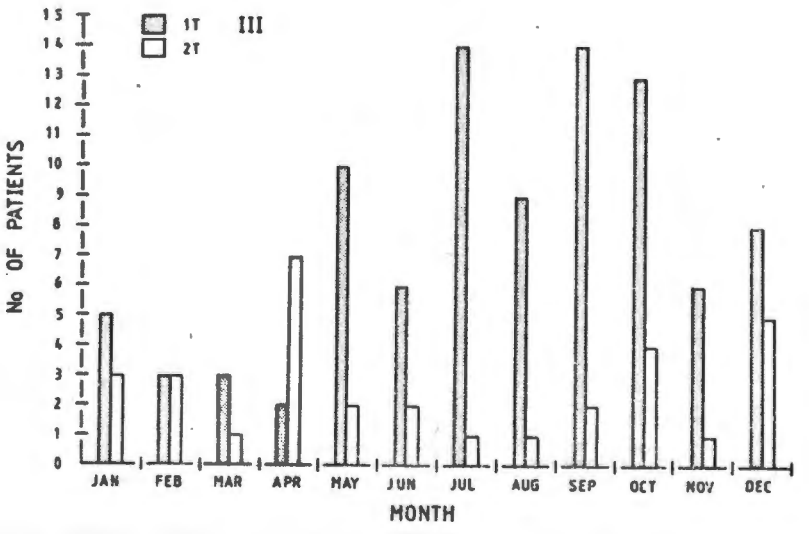


FIG. 5.8 CUMULATIVE MONTHLY DISTRIBUTION of patients without (Group 1) and with (Group 2) LVH

I. on admission (Groups 1A and 2A),
II. at any stage of the course (Groups 1C and 2C) and
III. at the end of the study or death (Groups 1T and 2T).

mainly in 1974, after the maximal frequency of LVH negative patients in the second half of 1973.

DISCUSSION.

The type C classification (with or without LVH at any stage) appeared to differentiate the incidence trends between AM and EFE most clearly, but similar conclusions could be drawn from all 3 classifications.

Assuming that LVH negativity correlates with AM and LVH positivity with the presence of EFE, the factors that support an infective aetiology for AM include

(i) the seasonal variation (peak incidence in late winter and early spring), and

(ii) the annual fluctuations in incidence, with a sudden rise to minor epidemic proportions in 1973.

The association of EFE with infection is less convincing. Although there was a rapid increase in incidence of EFE in 1974, the incidence from year to year and throughout each year was more uniform than in AM.

However, a relationship between AM and EFE is supported by

(i) the concurrence of peaks of incidence of both conditions before 1973,

(ii) the higher ratio of EFE to AM in the summer months following AM peaks in the preceding winter and spring,

(iii) the particularly marked increase in incidence of EFE (with LVH at presentation) in 1974 approximately 6 months after the minor epidemic of AM in 1973, and

(iv) the increased frequency of conversions from LVH negative to LVH positive status (Group 1A to 2C) pari passuwith the increased incidence of AM (1973).

Hence, it may be concluded that AM is of infective origin and that EFE is related to, and probably a consequence of, prior outbreaks of overt AM in the community.

The absence of a previous history of AM in patients presenting with EFE (LVH positive) ab initio, suggests that these cases follow sub-clinical episodes of myocarditis.

There is little evidence in the literature either for[80] or against[84] a seasonal variation in EFE, but an increased frequency of deaths due to EFE has been noted following epidemics of viral disease.[367,501,500] The decreasing incidence of EFE in Western countries over the years,[84,195] probably due to better socio-economic conditions,[226] may be indirect evidence of an infective (viral) aetiology for EFE.

Chen et al[84] found an increased incidence of EFE in later births and a greatly increased incidence of EFE (3.8%), but not of other congenital anomalies, in siblings. The latter favoured a post-natal acquired condition. These factors were not evaluated in this study.

CHAPTER 6.

EVALUATION OF DIAGNOSTIC CRITERIA.

The diagnostic criteria are compared in Groups 1 and 2 in all three modes of classification to identify which, if any, permits differentiation between AM and EFE.

1. DURATION OF HISTORY.

The mean duration of history for patients in Group 2A was significantly longer than for Group 1A patients ($p < 0.05$). (Table 6.1)

The Variance-Ratio test (Snedecor's F test)[378] makes this statistic untenable ($F = 4.28$, $p < 0.01$), despite the fact that by definition histories were under 1 month in both populations. Furthermore, in contrast to the position regarding age, (page 37) the observed difference between the means (2.3 days) is less than twice the standard error of the difference of means (1.55), so that the conclusion that Group 1A patients have more acute illnesses is probably not valid.

There was no significant difference between Groups 1C and 2C, or Groups 1T and 2T (Student's t-test valid : $F = 1.398$, $p > 0.05$; and $F = 1.203$, $p > 0.05$, respectively).

TABLE 6.1 Duration of History, Cardiothoracic Ratio, and Heart Rate. Comparison of mean values ±SEM for patients without (Group 1) and with (Group 2) LVH on ECG on admission (A), at any stage during the course (C), and at the end of the study or at death, i.e. terminally (T).

PATIENT DATA	GROUP 1A (92)	GROUP 2A (31)	t	GROUP 1C (71)	GROUP 2C (52)	t	GROUP 1T (96)	GROUP 2T (27)	t
DURATION OF HISTORY (days)	5.9 ±0.42	8.2 ±1.50	-2.007*	7.0 ±0.74	7.5 ±1.01	-0.398	6.7 ±0.62	5.9 ±1.27	0.594
HEART RATE (beats per minute)	164.5 ±3.41	162.5 ±5.15	0.311	167.9 ±3.04	163.1 ±3.95	0.980	164.9 ±2.79	169.4 ±4.90	-0.763
CARDIOTHORACIC RATIO (%)	64.4 ±0.58	67.5 ±1.02	-2.617°	63.9 ±0.68	67.0 ±0.75	-3.016⊕	64.6 ±0.57	66.9 ±1.12	-1.854

Total number of patients in each group appears in parentheses.
t Statistical evaluation by Student's t-test for unpaired samples.
* Statistically significant at $p < 0.05$
° " " " $p < 0.02$
⊕ " " " $p < 0.005$

2. CLINICAL CRITERIA.

2.1 HEART RATE

There was no significant difference in the mean heart rate between Groups 1 and 2 patients, whatever the method of classification. (Table 6.1) (Student's t-test valid in each case ; $F = 1.274$, 1.245 and 1.123, respectively ; $p > 0.05$ in all). However, there was a significantly larger number of patients with a heart rate above the 95th percentile for age among those LVH negative at any stage ($1C > 2C$, $p < 0.05$). (Table 6.2)

Comment

The latter coincides with the concept that AM represents a more acute condition than EFE.

2.2 CARDIOMEGALY

The frequency of cardiomegaly detected on clinical examination was not significantly different in Groups 1 and 2 patients, by any mode of classification. (Table 6.2)

2.3 SYSTEMIC VENOUS CONGESTION

a) Hepatomegaly

There was no significant difference in the frequency of hepatomegaly (> 2 cms below the costal margin) between Groups 1 and 2 patients, by any method of classification. (Table 6.2) The overall incidence of hepatomegaly in the series was 80.5%.

b) Elevated JVP

Venous pressure elevation was significantly more prevalent in Group 1A than 2A ($p < 0.01$) and in Group 1C than 2C ($p < 0.05$), but there was no significant

TABLE 6.2 Clinical Diagnostic Criteria. Comparison of frequency in patients without (Group 1) and with (Group 2) LVH on ECG on admission (A), at any stage during the course (C), and at the end of the study or death, i.e. terminally (T).

CLINICAL SIGN	NUMBER OF PATIENTS								
	GROUP		X^2	GROUP		X^2	GROUP		X^2
	1A (92)	2A (31)		1C (71)	2C (52)		1T (96)	2T (27)	
ELEVATED HEART RATE+	58	13	3.413	47	24	4.157*	55	16	0.001
CARDIOMEGALY	61	18	0.401	47	32	0.117	63	16	0.146
SYSTEMIC VENOUS CONGESTION									
Hepatomegaly^{o}	72	27	0.654	55	44	0.575	65	24	3.726
Elevated JVP	38	4	7.102†	30	12	4.093*	37	5	2.920
Oedema	30	6	1.379	27	9	5.264**	32	4	2.654
No abnormality	13	4	0.017	10	7	0.027**	14	3	0.021
1 abnormality	31	19	6.219**	22	28	5.589**	35	15	2.443
2 abnormalities	35	6	2.852	27	14	1.204	32	9	0
3 abnormalities	13	2	0.660	12	3	2.512	15	0	3.456
$\geq$1 present	79	27	0.017**	61	45	0.027**	82	24	0.021
$\geq$2 present	48	8	5.481**	39	17	5.122**	47	9	1.492
PULMONARY VENOUS CONGESTION	47	18	0.216	36	29	0.139	48	17	0.948
GALLOP RHYTHM	74	24	0.011	57	41	0.001	74	24	1.158
SHOCK	18	1	3.571	17	2	7.808†	18	1	2.592
APICAL SM	6	2	0.189	5	3	0.0001	6	2	0.051

Total number of patients in each group appears in parentheses.

SM Systolic murmur

\+ Heart rate >95th percentile for age.

o_2 Hepar >2 cms. below costal margin

X^2 Statistical evaluation by Chi-square analysis.

* Significant difference at $p<0.05$.

** " " " $p<0.025$.

† " " " $p<0.01$

difference between Groups 1T and 2T. (Table 6.2) This sign was detected in 34.2% of the series.

c) Oedema was significantly more frequent in Group 1C than 2C ($p<0.025$) but there was no statistically significant difference in the two other methods of classification. (Table 6.2) The overall incidence in the series was 29.3%.

A single abnormality indicating systemic venous congestion was significantly more common in patients positive for LVH on admission (Group 2A > 1A, $p<0.025$), and at any stage (Group 2C > 1C, $p<0.025$), but not terminally. On the other hand, two or more abnormalities were significantly more prevalent in patients negative for LVH on admission (Group 1A > 2A, $p<0.025$), and at any stage (1C > 2C, $p<0.025$), but not terminally.

Comment

These apparently contradictory results may indicate that features of more acute or severe right heart failure, especially elevated JVP, oedema and two or more signs in combination, occur in patients with AM, whereas the predominance of any single isolated abnormality in patients with EFE reflects a low-grade, chronic cardiac involvement.

As in this series, hepatomegaly is reported to be common in EFE, with oedema occurring in one fifth of patients.[226]

2.4 PULMONARY VENOUS CONGESTION

Clinical evidence of pulmonary venous congestion was similar in frequency in LVH negative and LVH positive patients in all 3 forms of classification. (Table 6.2)

Comment

The incidence of 53% in this series is greater than the 36% quoted for radiological pulmonary venous congestion in primary myocardial disease (PMD) in children.[195] The high incidence in EFE in this study also differs from other low estimates.[164]

2.5 GALLOP RHYTHM

Gallop rhythm was very common (over 77% in the series) but there was no significant difference in incidence between Groups 1 and 2 patients. (Table 6.2)

Comment

The reported incidence of gallop rhythm varies between 39.8% in PMD[195] and almost universal in EFE.[226]

2.6 SHOCK

Shock was rare in Groups 2A (1/31) and 2T (1/27), but was not significantly different in frequency from Groups 1A ($p > 0.10$), and 1T(> 0.05), respectively (Table 6.2). However, a highly significant predominance of shock occurred in patients LVH negative at any stage (1C > 2C, $p < 0.01$).

Comment

This result supports the proposal that patients without LVH (AM) have a more acute onset than those with LVH (EFE).

A state of shock has been well described in the neonatal epidemic form of AM,[506,527,534] but is not mentioned as a feature in sporadic cases.[64,195,395] In this series shock occurred in 19.6% of patients without LVH on admission (AM), and affected the outcome adversely.

2.7 APICAL SYSTOLIC MURMUR

A murmur compatible with mitral regurgitation was heard in only 8 patients in the entire clinical series. Only one was graded 3/6 in intensity, while two were graded 2/6 and three were just audible (1/6). There was no significant difference in the frequency of mitral murmurs between patients with and those without LVH, defined in any manner.

Comment

The reported incidence of mitral murmurs varies widely from 6% in PMD[195] to 40% in EFE[226] and 66% in AM,[43] but these murmurs were soft and often transient. Grade 3/6 or louder apical systolic murmurs were heard in EFE by McLoughlin et al in 5 of 24 cases,[352] by Moller et al in 16 of 23 patients,[368] and by others.[476] Moller et al noted that the presence of mitral murmurs was age-dependent. A relationship to duration of pathology seems more appropriate.

In this series, the paucity of mitral murmurs suggests that the cardiac involvement was indeed acute or of short duration in the vast majority of cases, i.e. before chronic dilatation in AM or fibroelastotic encroachment in EFE resulted in established mitral incompetence.

3. ECG CRITERIA

No statistically significant differences were demonstrated between Group 1 and 2 patients, by any mode of classification, in respect of ST segment or T wave abnormalities, independently or together. (Table 6.3)

4. RADIOLOGICAL CARDIOMEGALY

All but 3 of the 123 patients in the clinical series had a cardio-thoracic ratio (CTR%) of greater than 55% on admission (Appendix 1). Two patients were regarded as being positive for cardiomegaly since the CTR fell into the

TABLE 6.3 ECG Diagnostic Criteria. Number of patients with ECG abnormalities in those without (Group 1) and with (Group 2) LVH on admission (A), at any stage during the course (C), and at the end of the study or death, i.e. terminally (T).

ECG ABNORMALITY	NUMBER OF PATIENTS								
	GROUP		X^2	GROUP		X^2	GROUP		X^2
	1A (92)	2A (31)		1C (71)	2C (52)		1T (96)	2T (27)	
LVH	0	31		0	52		0	27	
T-WAVE ALONE	66	20	0.283	51	35	0.117	70	16	1.276
ST SEGMENT ALONE	5	0	≠	4	1	≠	5	0	≠
T-WAVE + ST SEGMENT	20	9	0.340	15	14	0.284	20	9	1.120
NEITHER	0	2	≠	0	2	≠	0	2	≠
ARRYTHMIA	1	0	≠	0	1	≠	1	0	≠
TOTAL T-WAVE	86	29	0.166	66	49	0.008	90	25	0.051
TOTAL ST SEGMENT	25	9	0.001	19	15	0.003	25	9	0.255

Total number of patients in each group appears in parentheses.
X^2 Statistical evaluation by Chi-square analysis. No significant differences demonstrated.
≠ numbers too small for analysis.

abnormal range later during the first admission, i.e. increasing from 54.3% on admission to 63.3% after 10 days in patient no. 6, and from 51.5% on admission to 56.8% after 17 days in patient no. 57. (No chest x-ray was available in patient no. 39 but he was included in the clinical series for reasons given on page 27).

On statistical analysis, the presenting CTR% was significantly greater in LVH positive than LVH negative patients as classified on admission (Group 2A>1A, $p<0.02$), and at any stage (Group 2C>1C, $p<0.005$), but not terminally(Table 6.1). However, the wide overlapping range of 51.5% to 84.7% in Groups 1A and 1C, and 55.1% to 79.3% in Groups 2A and 2C, limited the value of this finding in the individual case.

Comment

The more marked cardiomegaly in LVH positive patients at presentation is in keeping with more prolonged cardiac involvement in EFE than AM despite their younger age.

The reported incidence of cardiomegaly in EFE is 30% for a CTR between 0.55 and 0.65, 50% between 0.65 and 0.75 and 20% for a CTR over 0.75.[226] In the present series as a whole the comparable incidences for the same CTR ranges were 50%, 45% and 5%, respectively. The lower incidence of marked cardiomegaly probably reflects the inclusion of more acute cases (AM) in this material. There appear to be no detailed reports in the literature of heart size in AM.

5. AUTOPSY FINDINGS

Pathological features are discussed in Chapter 13.

The clinical diagnosis of acute EMD (AM or EFE) was confirmed in all 23 patients from Groups 1 and 2 who came to autopsy ($X^2 = 42.087$, $p<0.0005$).

Limited clinical data was available in 10 of the 13 patients in Group 3. It is noteworthy that the incidence of shock in Group 3 (9/10) was very significantly greater than in Group 1A (18/92, $p < 0.005$) and Group 2A (1/31, $p < 0.0005$).

Comment

This finding was not unexpected, since these patients were put into Group 3 because of insufficient data, which was mainly due to their fulminant course and early demise within hours of admission.

6. CONCLUSIONS

From the clinical and radiological findings it may be concluded that AM is a more acute illness than EFE. In particular, the state of shock in these sporadic cases of AM, well recognised in the epidemic form, emphasize the immediacy of the pathological insult. In contrast, the less dramatic onset of EFE supports the belief that the fibroelastotic thickening of the endocardium is not an immediate response but a more insidious and protracted process.

Clinical differences between AM and EFE were demonstrated equally with the type A and C, but not at all with the type T, classifications.

The strict clinical diagnostic criteria used in this study proved highly accurate in diagnosing acute EMD.

CHAPTER 7.

CLINICAL PRESENTATION.

The initial presentation of patients in the clinical series is reviewed in terms of

(i) pre-admission symptomatology,

(ii) clinical features, other than diagnostic criteria,

(iii) routine investigations, excluding radiological (Chapters 6 and 12), electrocardiographic (Chapters 6 and 9), serum enzyme (Chapter 10), and virological (Chapter 11) examinations,

(iv) treatment, and

(v) duration and outcome of first admission.

The appropriate information for each case is tabulated in Appendix B.

These findings are again compared in patients with and without LVH on ECG, classified as in Chapter 4, so as to evaluate which classification, if any, permits differentiation between these 2 groups.

1. PRE-ADMISSION SYMPTOMATOLOGY

The duration of history has already been analysed (page 52).

1.1 RELATIVE FREQUENCY OF SYMPTOMS

In the clinical series as a whole, respiratory symptoms were most common with 82.9% (102/123) being affected, fever occurred in 42.3% (52/123), oedema in 18.7% (23/123), general malaise in 13.0% (16/123), gastrointestinal symptoms in 11.4% (14/123), a history of measles in 5.7% (7/123) and convulsions in 4.9% (6/123).

Comment

The predominance of respiratory symptoms is in agreement with reported findings in patients with AM,[43] EFE[352] and primary myocardial disease.[195] Oedema is reported to be prominent in EFE[352] and fever in AM.[43]

1.2 COMPARISON OF LVH NEGATIVE AND LVH POSITIVE PATIENTS

The frequency of symptoms in each group appears in Table 7.1.

There was no significant difference in the frequency of any symptom between Group 1 and Group 2 patients, however classified, except that a history of pneumonic or grunting respiration was significantly more frequent in LVH positive patients on admission (Group 2A > 1A, $p < 0.05$).

1.3 RESPIRATORY SYMPTOMS

The respiratory symptoms could be divided into mild, i.e. features of upper respiratory tract infections, such as coughing and coryza ; and severe, i.e. dyspnoea (including shortness of breath, tight chest, wheezing, and respiratory distress), pneumonic or grunting respiration, and apnoea or cyanosis (one case each).

The milder symptoms were relatively more frequent in Group 1 patients, but the differences were not statistically significant. Severe symptoms occurred

TABLE 7.1 Symptoms prior to admission. Comparison of number of patients without (Group 1) and with (Group 2) LVH on ECG, on admission (A), at any stage during the course (C), and at the end of the study or death, i.e. terminally (T).

SYMPTOM	NUMBER OF PATIENTS								
	GROUP		X^2	GROUP		X^2	GROUP		X^2
	1A (92)	2A (31)		1C (71)	2C (52)		1T (96)	2T (27)	
RESPIRATORY	79	23	1.484	61	41	0.619	82	20	1.198
- MILD	44	8	3.749	35	17	2.573	43	9	0.713
- SEVERE	35	15	0.644	26	24	0.770	39	11	0.045
Dyspnoea	28	7	0.370	20	15	0.014	29	6	0.326
Pneumonic	6	7	4.741*	5	8	1.416	9	4	0.210
Apnoeic	1	0	≠	1	0	≠	1	0	≠
Cyanosis	0	1	≠	0	1	≠	0	1	≠
FEVER	30	7	0.683	23	14	0.207	31	6	0.594
OEDEMA	18	5	0.025	16	7	1.084	20	3	0.749
MALAISE	15	1	2.437	10	6	0.021	14	2	0.430
GASTRO-INTESTINAL	13	1	1.759	10	4	0.665	12	2	0.155
CONVULSIONS	6	0	≠	4	2	≠	6	0	≠
MEASLES	6	1	≠	5	2	≠	5	2	≠
MISCELLANEOUS	5	1	≠	5	1	≠	6	0	≠

Total number of patients in each group indicated in parentheses.
X^2 Statistical evaluation by Chi-square analysis.
* Difference significant at $p<0.05$ level. All other differences not significant.
≠ numbers too small for statistical analysis.

equally in all groups, except for features suggesting pneumonia, as mentioned above.

Comment

The significantly higher incidence of grunting respiration in Group 2A compared with 1A patients may indicate that concomitant pneumonia is more frequent in EFE, or may simply reflect the greater propensity for grunting in younger patients, whether due to pneumonia or pulmonary congestion. McLoughlin et al also noted a high incidence of severe respiratory symptoms in EFE (15 of 24 patients) compared with symptoms of upper respiratory tract infections (2 of 24).[352]

1.4 OEDEMA

Swelling of the feet, face or body, is usually only noticed by parents when advanced, so that a frequency of 18.7% is high. However, a diagnosis of cardiac oedema was questionable in several cases who had evidence of protein-calorie malnutrition or renal involvement.

1.5 FEVER, MALAISE AND GASTROINTESTINAL SYMPTOMS

These symptoms were all more common in Group 1 patients, but not significantly so.

1.6 CONVULSIONS

A history of convulsions was obtained in 6 patients, all of whom were LVH negative on admission (Group 1A) and terminally (Group 1T), though two developed LVH transiently (Group 2C). Numbers were too small for statistical evaluation.

Comment

Although a history of convulsions was relatively infrequent, its occurrence

is important since it points to cerebral involvement and is evidence of a generalised viraemic state (or of shock).

1.7 MEASLES

In 2 of the 7 patients (no's 57 and 88) a characteristic illness and rash was observed more than 14 days before presentation with EMD, while in the remaining 5 (no's 21, 58, 59, 70 and 97) measles was noted less than 4 days before.

Comment

This condition is so common among the Cape coloured and black populations attending Red Cross War Memorial Children's Hospital that a recent history of this condition may well be coincidental. However, in those patients who manifested full-blown measles and acute EMD concurrently, a real association was possible.

1.8 MISCELLANEOUS

Other symptoms were uncommon and included a non-specific rash (one case), pallor (2), weakness of limb (2), chest pain (1), arthralgia (1) and a history of recent general anaesthesia (1).

1.9 CONCLUSION

Most initial symptoms appeared to be related to infection, probably viral, followed days to weeks later by the cardiotropic effect, and a neurotropic effect in some cases. This is in keeping with a diphasic course described in AM.[171, 468, 527,534] Although mild respiratory symptoms, fever, malaise, gastrointestinal and cerebral symptoms were more frequent in LVH negative patients (AM) in concurrence with this concept, the difference from LVH positive patients (EFE) was not conclusive in any classification mode.

2. OTHER CLINICAL FINDINGS.

Apart from the clinical diagnostic criteria,features which were observed at the time of presentation or developed as complications during the initial admission, are tabulated in Table 7.2 with their frequency in each group.

2.1 ELEVATED TEMPERATURE

A temperature above normal was measured in 26% (32/123) of all patients, and the frequency was similar in each group. Elevated temperature as evidence of infection is discussed later (page 83).

2.2 PNEUMONIA

The incidence of radiological pneumonia was higher in LVH negative than LVH positive patients, but the difference was not statistically significant.

Comment

Although pulmonary adventitious sounds were common, a diagnosis of pneumonia on clinical examination often proved difficult because of the co-existence of pulmonary venous congestion in many cases. Hence, only unequivocal features of consolidation on chest x-ray were accepted in this category.

2.3 CENTRAL NERVOUS SYSTEM (CNS) ABNORMALITIES

Included in this category were 5 patients with neurological deficit (signs of mid brain and pontine lesion in case no. 30 , who also had convulsions; hemiparesis in case no's 64 and 71 ; bulbar palsy in case no's 76 and 78, with sixth cranial nerve and peripheral neuropathy in the latter): 5 patients with change in level of consciousness (coma in case no's 63 and 59 , both with abnormal cerebro-spinal fluid; depressed level of consciousness in case no's 44 and 81 , both with abnormal CSF ; and hyper-irritability in case no 46) : and 1 patient with convulsions only (case no 29).

TABLE 7.2 Other Clinical Findings. Comparison of number of patients with abnormal clinical features in patients without (Group 1) and with (Group 2) LVH on ECG on admission (A), at any stage of the course (C), and at the end of the study or death, i.e. terminally (T).

CLINICAL ABNORMALITY	NUMBER OF PATIENTS WITH ABNORMALITY								
	GROUP		X^2	GROUP		X^2	GROUP		X^2
	1A (92)	2A (31)		1C (71)	2C (52)		1T (96)	2T (27)	
ELEVATED TEMP.	24	8	0.042	18	14	0.0001	24	8	0.056
PNEUMONIA (radiological)	30	5	2.337	24	11	1.779	31	4	2.362
CNS ABNORMALITIES	11	0	2.735	10	1	4.061*	11	0	2.136
a) Neurological deficit	5	0	≠	5	0	≠	5	0	≠
b) LOC or hyper-irritability	5	0	≠	4	1	≠	5	0	≠
c) Convulsions	1	0	≠	1	0	≠	1	0	≠
VIRAL INFECTIONS	8	0		5	3		7	1	
a) Measles	3	0	≠	1	2	≠	2	1	≠
b) Herpes	2	0	≠	2	0	≠	2	0	≠
c) Varicella	3	0	≠	2	1	≠	3	0	≠
KWASHIORKOR	1	0	≠	1	0	≠	1	0	≠
NEPHRITIS	1	0	≠	1	0	≠	1	0	≠
RESPIRATORY ARREST	1	0	≠	1	0	≠	1	0	≠

Total number of patients in each group indicated in parentheses.
X^2 Statistical evaluation by Chi-square analysis.
CNS = central nervous system; LOC = loss of consciousness; TEMP = temperature.
* Difference is significant at $p < 0.05$.
≠ numbers too small for statistical analysis.

These CNS abnormalities occurred exclusively in LVH negative patients in all three classifications except for 1 patient who developed LVH transiently. The predominance in LVH negative patients was statistically significant in the C-classification (Group 2C>1C, $p<0.05$). (Table 7.2)

If one includes 4 of the 6 patients with a history of convulsions, i.e. case no's 17, 19, 61 and 77 (case no's 63 and 64 were already included above), then the number of patients with CNS involvement in each group is 15 in Group 1A and 0 in 2A ; 13 in 1C and 2 in 2C ; 15 in 1T and 0 in 2T.

The Chi-square statistic for the three comparisons are 4.334, 4.591 and 3.456, respectively. Hence, abnormal CNS features occurred significantly more frequently in patients LVH negative on admission and at any stage of the illness (Group 1A>2A and 1C>2C, $p<0.05$ in both cases).

Comment

In this situation, the most likely causes for CNS abnormalities are

(i) a direct inflammatory effect of a disseminated (probably viral) infection on the brain as well as the heart, or

(ii) severe cardiogenic shock with low cardiac output and secondary hypoxia of the brain.

Although these CNS events occurred relatively more commonly in shocked (6/19) than in non-shocked patients (9/104), a difference which is statistically significant ($X^2 = 5.889$, $p<0.025$), the fact that over half the patients with CNS conditions were not associated with shock strongly suggests that disseminated viraemia does play a role in some cases. The predominance of CNS abnormalities among LVH negative patients, therefore, emphasises the occurrence of viraemia as well as shock in AM as compared with EFE.

Aseptic meningitis is known to accompany AM in Coxsackievirus epidemics in the newborn[230,527,534] and has been reported in isolated cases in the neonate.[110,277] CNS abnormalities are rare in EFE[226] but occurred in 9% of patients with PMD.[195]

2.4 ASSOCIATED VIRAL INFECTIONS

In patient no 15 measles intervened 15 days after presentation, in patient no 72 chicken-pox developed 4 days after admission, and in patient no 45 chicken-pox and measles developed 20 and 36 days after presentation, respectively, so that these episodes are coincidental to the underlying AM.

On the other hand, florid clinical measles was a presenting feature in case no. 58 (who also had a positive serum complement fixation test for measles), as was varicella in case no. 88. Both patients with Herpes infections (case no. 52 with H. hominis and no. 81 with H. simplex) had typical skin lesions on admission.

Hence, 4 patients had convincing evidence of viral infection simultaneous with presentation of endomyocardial disease. All 4 were in Group 1A, and 3 in Groups 1C and 1T, but the numbers were too small for statistical analysis.

2.5 KWASHIORKOR

Only one patient presented with characteristic clinical features of kwashiorkor, but oedema was common in this study (page 56) and was probably due to incipient kwashiorkor in some cases.

2.6 NEPHRITIS

Clinical features of nephritis (systemic hypertension, an elevated blood urea

of 97 mgs/100 ml and hyaline and granular casts in the urine, as well as congestive cardiac failure)was noted in 1 patient (no 72). However, the incidence of urinary abnormalities and elevated blood urea was suprisingly high (see section 3).

2.7 RESPIRATORY ARREST

Respiratory arrest occurred after admission in only 1 patient (no 41) but was a more frequent sign at presentation (see page 79).

3. ROUTINE INVESTIGATIONS

All positive or abnormal results of investigations, apart from the electrocardiographic (Chapters 6 and 9), radiological (Chapters 6 and 12), serum enzyme (Chapter 10), and virological (Chapter 11) findings, are recorded in Table 7.3. There were no statistically significant differences in frequency of abnormalities between LVH negative (1A, 1C and 1T) and LVH positive groups (2A, 2C and 2T) for any of the routine investigations.

3.1 HAEMOGLOBIN

Because of the high incidence of iron-deficiency anaemia in the patient population attending this hospital, and the preponderance of young children in this series, a relatively low haemoglobin of 11 gms/100 ml was arbitrarily selected as the lower limit of normal for all ages.

Haemoglobin values were available in 110 of the 123 patients (89%) in the clinical series. Of these, 65% (72/110) with values below 11 gms/100 ml were regarded as having anaemia, including 18% (20/110) with values below 8 gms/100 ml, i.e. with severe anaemia.

The mean haemoglobin values $\pm$SEM (gms/100 ml) were as follows:

TABLE 7.3 Routine investigations. Comparison of number of patients with abnormal findings in those without (Group 1) and with (Group 2) LVH on ECG on admission (A), at any stage during the course (C), and at the end of the study or death, i.e. terminally (T).

INVESTIGATION	NUMBER OF PATIENTS WITH ABNORMAL RESULTS								
	GROUP		X^2	GROUP		X^2	GROUP		X^2
	1A (92)	2A (31)		1C (71)	2C (52)		1T (96)	2T (27)	
HAEMOGLOBIN	(82)	(28)		(63)	(47)		(84)	(26)	
< 11G/100ml	57	15	1.694	43	29	0.262	55	17	0.052
< 8G/100ml	17	3	0.815	14	6	1.045	15	5	0.018
WBC	(69)	(24)		(51)	(42)		(70)	(23)	
(>12000 cells/ml^3)	37	9	1.263	28	18	0.898	34	12	0.004
BLOOD UREA									
(>30mg/100ml)	30	8	0.234	25	13	1.027	29	9	0.006
URINE	12	3	0.032	9	6	0.008	13	2	0.279
a)rbc's,casts or protein	7	2	≠	6	3	≠	8	1	≠
b)culture	5	1	≠	3	3	≠	5	1	≠
URT CULTURE	10	4	0.0003	8	6	0.058	12	2	0.155
a) Throat swab	3	1	≠	2	2	≠	4	0	≠
b) Sputum	6	3	≠	5	4	≠	7	2	≠
c) Tracheal aspirate	1	0	≠	1	0	≠	1	0	≠
STOOL CULTURE	4	0	≠	4	0	≠	4	0	≠
EAR CULTURE	1	1	≠	1	1	≠	1	1	≠
ALL BACTERIAL CULTURES	20	6	0.001	16	10	0.048	22	4	0.415
CSF	3	0	≠	3	0	≠	3	0	≠
BRAIN SCAN	1	0	≠	0	1	≠	1	0	≠

Total number of patients in each group indicated in parentheses.
rbc's = red blood cells; CULTURE = Bacterial culture; URT = upper respiratory tract; CSF = cerebro-spinal fluid.
X^2 Statistical evaluation by Chi-square analysis. No significant differences detected.
≠ numbers too small for analysis.

Group 1A - 9.7 ± 0.25; Group 2A - 10.8 ± 0.41

1C - 9.6 ± 0.30; 2C - 10.4 ± 0.30

1T - 9.9 ± 0.25 2T - 10.1 ± 0.41

Statistical evaluation by Student's t-test for unpaired samples was carried out. The mean haemoglobin value for LVH negative patients was significantly lower than for LVH positive patients on admission ($1A > 2A$; $t = -2.310$, $p < 0.025$), but not at any stage or terminally ($t = -1.699$ and -0.318, respectively, $p > 0.05$ in both).

Comment

The prevalence of anaemia is further evidence of the sub-optimal nutritional status of the population sample in this study. The lower mean haemoglobin level in patients with AM is probably age-dependent (see page 37), since these patients present after longer periods of iron deficiency. Anaemia is reported to be common in EFE.[226]

3.2 ELEVATED WHITE BLOOD CELL COUNT (WBC)

White blood cell estimations were available in 93 of the 123 cases (76%). Of these, 49% (46/93) exceeded the generally accepted upper limit of normal of 12,000 white cells/ml^3, but there were no significant differences in frequency between Group 1 and Group 2 patients. An elevated WBC as an index of infection is discussed in section 4.

Statistical Comment

The total number of patients in each group who were subjected to the following investigations is not known, since only positive or abnormal results were recorded in the protocols of each patient (Appendix B). However, it is argued that the ratio of the number of Group 1 to Group 2 patients tested would

be approximately proportional to the ratio of the total number of Group 1 to Group 2 patients. Use of the Group totals as the denominators would therefore not invalidate the Chi-square analysis.

3.3 BLOOD UREA

Blood urea estimations were abnormally elevated (over 30 mgs/100 ml) in as many as 31% of patients (38/123). The increased values ranged from 34 to 116 mgs/100 ml with a mean $\pm$SEM of 57.4$\pm$3.21 mgs/100 ml. There was no significant differences in the frequency of abnormal results between Group 1 and Group 2 patients (Table 7.3).

The mean elevated blood urea values $\pm$SEM (in mg/100 ml) for each group were:

Group 1A - 59.0$\pm$3.89;	Group 2A - 51.3$\pm$4.22
1C - 59.2$\pm$4.58;	2C - 50.8$\pm$3.37
1T - 58.8$\pm$4.10;	2T - 48.3$\pm$2.89

Statistical analysis resulted in the following t-values for each comparison of Group 1 and 2 : 0.987, 1.239, and 1.383, respectively; $p>0.05$ in each case.

Comment

The high incidence of uraemia may be due to intrinsic nephropathy or to a pre-renal state secondary to cardiogenic shock. Further statistical analysis revealed that uraemia did occur significantly more frequently in patients with shock (10/19) than in those without shock (28/104) - $X^2 = 3.842$, $p<0.05$. However, in the group of uraemic patients without shock, it is likely that the virus causing myocarditis produced renal damage as well.

Mesangial hyperplasia of glomeruli was recently demonstrated in 2 patients

with EFE,[412] who had urinary manifestations simulating glomerulonephritis, and reports of glomerulonephritis associated with AM are also rare.[413]

3.4 URINARY ABNORMALITIES

Abnormal urinary findings were detected in 11.4% of the clinical series (14/123). Examination of the urine revealed red blood cells and granular casts in 2 patients (no's 6 and 122), red cells and hyaline casts in 1 (no 40), red cells alone in 1 (no 28), hyaline and granular casts in 1 (no 72), granular casts and proteinuria++ in 1 (no 69) and 2+ proteinuria alone in 3 (no's 39, 85 and 116).

Evidence of a probable bacterial infection of the genito-urinary-tract (positive urine culture) was detected in 6 patients; Klebsiella aerogenes in 3 (no's 10, 49 and 93), Escherichia coli in 2 (no's 20 and 85), and E. coli + Candida albicans in 1 (no 14).

Comment

Although a mild proteinuria can occur in severe congestive heart failure, the presence of formed elements, especially red blood cells and casts, strongly supports an inflammatory process of the renal cortex. Only one of these patients (no 85) was associated with a positive urinary bacterial culture, so that nephritis was probably due to disseminated virus infection in the remaining 8 patients, though an association with EFE has been reported.[412] Four of these patients had an increased blood urea (without shock).

Considering all evidence of renal involvement (sections 3.3 and 3.4), a total of 32 patients had either uraemia (24) or changes in the urine (4) or both (4), not attributable t shock or bacterial urinary tract infection, and thus probably due to a disseminated virus which is nephrotropic as well as cardiotropic.

It is of interest that there was no overlap between this group of 32 patients and the 10 patients with CNS abnormalities (without shock). This suggests infection by two groups of viruses, one essentially cardio- and nephrotropic, the other mainly cardio- and neurotropic.

3.5 UPPER RESPIRATORY TRACT (URT) INFECTION

Bacterial organisms were grown from URT specimens in 14 patients. Throat swabs were positive in 4 patients (all with beta-haemolytic streptococci) ; sputa in 9 (Klebsiella aerogenes, Haemophilus influenza, and Escherichia coli in 2 patients each ; Enterobacter aerogenes and Pseudomonas aeriginosa in 1 patient each ; and Enterobacter, Pseudomonas aeriginosa and Klebsiella aerogenes together in 1 patient) ; and tracheal aspirate in 1 patient (Pseudomonas aeriginosa).

3.6 OTHER CULTURES

Stool cultures were positive for bacteria in 4 patients (Salmonella B in 2, Salmonella C1 in 1 and Salmonella C of unknown type in 1). Ear culture in 2 patients with otitis media grew Proteus mirabilis in 1 and Staphylococcus and Diplococcus pneumoniae in the other.

Because the numbers of cultures from each site were too small for statistical evaluation, all positive bacterial cultures were summed for each group (Table 7.3). No significant difference between Group 1 and 2 patients, by any method of classification, was demonstrated.

3.7 CEREBROSPINAL FLUID (CSF) AND BRAIN SCAN

A lumbar puncture was performed on 25 occasions in 21 patients. Abnormal findings were detected in 3 patients. The CSF contained 7 polymorphs and 1 lymphocyte in case no 44, and 5 lymphocytes in case no 81. Patient no 59,

with clinical measles two days earlier and loss of consciousness, had an elevated CSF protein (50 mgs/100 ml), positive globulin test, slightly reduced sugar, and 1 lymphocyte in the first CSF specimen, 12 polymorphs in the second CSF specimen 18 hours later, and a normal CSF 3 days later.

A brain scan showed infarction of the left middle cerebral artery region in patient no 46.

Comment

The large number of lumbar punctures performed reflects the high index of suspicion of cerebral involvement such as meningitis or encephalitis in the study population. However, positive confirmation of cerebral pathology was found in only 4 cases.

4. TREATMENT

No statistically significant differences were demonstrated between Groups 1 and 2 patients, however classified, in respect of the number of patients undergoing various forms of treatment. (Table 7.4)

4.1 DIGOXIN

Digoxin was administered routinely in all but 2 cases. Patient no 39 presented in extremis with severe shock and the diagnosis of AM was not immediately recognised. The major clinical problem in patient no 59 was neurological (see above) and digoxin treatment was inadvertently omitted.

4.2 DIURETICS

A diuretic was administered if heart failure was clinically obvious. Furosemide (Lasix) was used exclusively in this study as the diuretic of first choice, though Spironolactone or Moduretic was added in isolated cases.

TABLE 7.4 Major forms of treatment. Comparison of number of patients without (Group 1) and with (Group 2) LVH on ECG on admission (A), at any stage in the course (C), and at the end of the study or death, i.e. terminally (T).

TREATMENT	NUMBER OF PATIENTS TREATED								
	GROUP		X^2	GROUP		X^2	GROUP		X^2
	1A (92)	2A (31)		1C (71)	2C (52)		1T (96)	2T (27)	
DIGOXIN	90	31		69	52	0.249	94	27	0.011
FUROSEMIDE	69	23	0.022	54	38	0.028	72	20	0.023
ANTIBIOTICS	58	22	0.333	47	33	0.015	60	20	0.785
IPPV	10	1	0.857	9	2	1.892	9	2	0.004
BLOOD TRANSFUSION	4	1	≠	3	2	≠	3	2	≠
STEROIDS	2	0	≠	2	0	≠	2	0	≠

Total number of patients in each group indicated in parentheses.
IPPV = intermittent positive pressure ventilation.
X^2 Statistical evaluation by Chi-square analysis. No significant differences detected.
≠ numbers too small for evaluation.

The fact that 75% of patients (92/123) were treated with Furosemide testifies to the severity of heart failure in the majority of patients.

4.3 ANTIBIOTICS

Various antibiotics were administered either singly or in combination, and by the intravenous, intramuscular or oral route, depending on the assessment of severity of the accompanying infection. The antibiotics selected was the responsibility of the medical officer in charge of the patient's overall management and is noted for each patient in Appendix B. A large proportion of patients (65% - 80/123) received antibiotics though the majority of infections were probably viral in origin.

4.4 INTERMITTENT POSITIVE PRESSURE VENTILATION (IPPV)

Assisted ventilation was required in 7.4% of patients (11/123), either for neurological apnoea (case no's 76 and 78), respiratory failure (no's 11, 14 and 29), cardiogenic shock (no 63), or acute cardio-respiratory arrest on admission (no's 19, 37, 39 and 96) or terminally (no 62). Only 4 patients survived (case no's 11, 29, 76 and 78). Those requiring IPPV for cardio-respiratory arrest all succumbed.

IPPV was more frequently required in Group 1 than Group 2 patients, but the numbers were too small to reveal statistically significant differences.

Comment

These cases emphasize the acute onset and fulminant course in some patients with AM.

4.5 BLOOD TRANSFUSION

A blood transfusion was given to 5 patients ; for severe anaemia in 2

(case no's 47 and 79) and for moderate anaemia and presumed infection in 3 (no's 11, 14 and 97).

4.6 STEROIDS

Hydrocortisone was administered to patient no's 59 (see section 4.1) and 30, both for suspected cerebral oedema.

Comment

The use of steroids in AM remains highly controversial[8,9,2,195,211,346,473] because of the demonstration in animals of fatal viral dissemination and extensive myocardial necrosis,[281,282] though some authors have reported beneficial effects in humans.[112,244,224,466] Steroids were not employed for AM per se in this study.

5. DURATION AND OUTCOME OF FIRST ADMISSION

A total of 121 patients was admitted to the wards for treatment. Two patients (no's 23 and 67) were managed as outpatients and are therefore excluded from further analysis in this section.

5.1 MORTALITY RATE

There were no statistically significant differences in the mortality rates between Groups 1 and 2 patients, however classified (Table 7.5). The overall mortality rate during the initial admission was 19% (23/121). All deaths in the clinical series (Groups 1 and 2), including those occurring after the first admission, are discussed in Chapter 12 and, together with the autopsy series (Groups 3 and 4), in Chapter 13.

5.2 DURATION

The duration of first admission ranged between 2 and 142 days in survivors,

TABLE 7.5 First admission. Mortality rate and duration in patients without (Group 1) and with (Group 2) LVH on ECG on admission (A), during the course (C), and terminally (T).

	NUMBER OF PATIENTS								
	GROUP		X^2	GROUP		X^2	GROUP		X^2
	1A (90) *	2A (31)		1C (71)	2C (50)		1T (94)	2T (27)	
SURVIVORS	71	7		56	42		78	20	
DEATHS	19	4	0.546	15	8	0.223	16	7	0.579
	DURATION (DAYS) - MEAN $\pm$SEM								
	1A	2A	t	1C	2C	t	1T	2T	t
SURVIVORS	$\pm$32.1 $\pm$4.08	$\pm$22.6 $\pm$3.45	1.391	$\pm$32.8 $\pm$4.96	$\pm$25.1 $\pm$3.01	1.224	$\pm$30.4 $\pm$3.78	$\pm$23.9 $\pm$3.95	0.852
DEATHS	$\pm$12.4 $\pm$5.07	$\pm$3.7 $\pm$2.67	0.667	$\pm$3.8 $\pm$1.69	$\pm$27.0 $\pm$11.81	-2.820 +	$\pm$8.1 $\pm$4.55	$\pm$19.5 $\pm$10.73	-1.162
TOTAL	$\pm$28.0 $\pm$3.49	$\pm$20.7 $\pm$3.28	1.152	$\pm$26.6 $\pm$4.17	$\pm$25.4 $\pm$3.02	0.228	$\pm$25.6 $\pm$3.26	$\pm$22.9 $\pm$3.80	0.424

Total number of patients in each group appears in parentheses.
* 2 patients treated as outpatients are excluded ; both survived.

X^2 Statistical evaluation by Chi-square analysis.
t Statistical evaluation by Student's t-test for unpaired samples.
+ Significant difference at $p < 0.01$. All other differences are not significant.

and 1 and 72 days in patients dying. There were no statistically significant differences in the mean duration in hospital between Groups 1 and 2 patients in survivors and in the total group. Among patients dying, however, duration in hospital was significantly shorter in patients LVH negative at any stage than in LVH positive patients ($1C < 2C$, $p < 0.01$).

Comment

The significantly earlier deaths in LVH negative patients reflect the more acute illness and rapid progression in AM than EFE.

CHAPTER 8.

EVIDENCE OF INFECTION

If the assumption is correct that AM has a viral aetiology and that EFE is either non-viral or a late consequence of earlier viral infection, patients with AM would be expected at presentation to have signs of infection more frequently than EFE patients. Several features likely to be due to an infective process were assessed in LVH negative and LVH positive patients to test this observation.

The selected parameters and their absence or presence in each patient are tabulated in Appendix C. An attempt was made to limit positive results to viral rather than bacterial infections where possible.

1. CRITERIA FOR INFECTION

1.1 PYREXIA

A history of fever was accepted as an index of infection, as well as an elevated temperature ($>37^{\circ}C$) on admission, since it was recognised that the pyrexia of infection may have subsided by the time the patient was brought to hospital with the more alarming features of heart failure or shock. A bacterial aetiology could not be excluded, however.

1.2 ELEVATED WHITE BLOOD COUNT (WBC)

A WBC of over 12,000 cells/ml^3 was regarded as significant, although it is known that a leucopenia is not unusual with viral infections. Unfortunately, a differential count was not regularly performed so that the polymorph:lymphocyte ratio was not available to assist in differentiating viral from bacterial infections. However, an elevated WBC on its own has been used as evidence of viral infection in previous reports.[171,230,506]

1.3 PNEUMONIA

Because of the difficulty in differentiating pneumonia from pulmonary venous congestion clinically, only clear-cut radiological lobar consolidation or bronchopneumonia were accepted as positive. A bacterial aetiology could not be differentiated from a viral, however.

1.4 CNS ABNORMALITY

As previously noted (page 69), convulsions or neurological disorders were highly suggestive of an associated neurotropic effect of the virus causing the cardiopathy, if shock could be excluded.

1.5 URAEMIA

Similarly, uraemia occurred commonly in the absence of shock, and could be ascribed to a nephrotropic effect of the virus (see page 74).

1.6 URINARY ABNORMALITY

The presence of protein, red blood cells and/or casts in the urine was accepted as indicating an inflammatory process in the upper renal tract, i.e. due to concomitant nephritis. If bacterial organisms were identified in the urine (with or without the above features) a diagnosis of viral-induced nephritis was rejected.

1.7 POSITIVE VIROLOGY

Although viral identification did not establish a cause and effect relationship, its detection was regarded as a valid index of infection for comparison of LVH negative and LVH positive patients. (see Chapter 11).

Evidence of bacterial infection, such as a positive culture in the sputum or stool, was excluded from this assessment.

2. RESULTS.

The number of patients with positive results for the above criteria in LVH negative and LVH positive groups, as defined in the three ways previously described, appears in Table 8.1.

2.1 INCIDENCE

The overall incidence of one or more of these criteria in the entire series was 83.7% (103/123). A history of fever was encountered in 32.5% (40/123) of patients ; an elevated temperature in 28.5% (33/123) ; an elevated WBC in 35.8% (44/123) ; pneumonia in 28.5% (35/123) ; CNS abnormalities in 12.2% (15/123), 9.6% (10/104) in patients without shock ; uraemia in 30.1% (37/123), 26.9% (28/104) in patients without shock ; urinary abnormalities in 7.3% (9/123) ; and positive virology in 18.7% (23/123), or 30.7% (23/75) of patients actually tested.

2.2 COMPARISON OF LVH NEGATIVE AND LVH POSITIVE PATIENTS

Since patients with clinical shock have a high incidence of CNS abnormalities and uraemia, which may not be due to infection, they have been excluded from the total number of positives for statistical analysis (see Appendix C).

TABLE 8.1 Evidence of Infection. Comparison of number of affected patients without (Group 1) and with (Group 2) LVH on ECG on admission (A), at any stage of the course (C), or at the end of the study or death, i.e. terminally (T).

EVIDENCE OF INFECTION	NUMBER OF PATIENTS								
	GROUP			GROUP			GROUP		
	1A (92)	2A (31)	X^2	1C (71)	2C (52)	X^2	1T (96)	2T (27)	X^2
ISOLATED									
HIST. OF FEVER	3	1	≠	2	2	≠	4	0	≠
TEMP. ELEVATION	4	2	≠	2	4	≠	4	2	≠
WBC ELEVATION	5	0	≠	4	1	≠	4	1	≠
PNEUMONIA	2	1	≠	2	1	≠	2	1	≠
CNS ABNORMALITY	2	0	≠	2	0	≠	2	0	≠
URAEMIA	3	1	≠	2	2	≠	3	1	≠
URIN. ABNORMALITY	0	0	≠	0	0	≠	0	0	≠
POS. VIROLOGY	2	2	≠	2	2	≠	2	2	≠
TOTAL WITH									
FEVER	32	8	0.491	24	16	0.026	34	6	1.125
TEMP. ELEVATION	25	8	0.007	19	14	0.035	25	8	0.016
WBC ELEVATION	35	9	0.474	26	18	0.002	32	12	0.700
PNEUMONIA	30	5	2.337	24	11	1.779	31	4	2.362
CNS ABNORMALITY	10	0	2.357	9	1	3.319	10	0	1.826
URAEMIA	20	8	0.048	15	13	0.083	19	9	1.495
URIN. ABNORMALITY	7	2	0.034	6	3	0.046	8	1	0.158
VIROLOGY	16	7	0.140	11	12	0.692	14	9	3.718
0 ABNORMALITY	11	9	3.790	8	12	2.268	15	5	0.004
ANY 1 ABNORMALITY	21	7	0.048	16	12	0.083	21	7	0.034
" 2 "	29	8	0.140	23	14	0.207	30	7	0.087
" 3 "	20	5	0.171	16	9	0.235	19	6	0
" 4 "	9	1	0.601	7	3	0.236	10	0	1.826
" 5 "	2	1	≠	1	2	≠	1	2	≠

Total number of patients in each group appears in parentheses.
HIST. - history; TEMP. - temperature; WBC - white blood cell count; CNS - central nervous system; URIN. - urinary; POS. - positive

X^2 - statistical evaluation by Chi-square analysis
≠ - numbers too small for statistical analysis
No significant differences demonstrated.

There were no statistically significant differences, between LVH negative and LVH positive patients, by any classification, in the frequency of a history of fever, elevated temperature, elevated WBC, pneumonia, CNS abnormalities, uraemia, urinary abnormalities or positive virology.

Nor were there any statistically significant differences between Group 1 and 2, by any classification, for any single abnormality, or any combination of two, three, or four abnormalities. The frequency of one or more signs of infection was greater in LVH negative than LVH positive patients on admission - 88.0% (81/92) compared with 71.0% (22/31) - but this difference was also not statistically significant (Group 1A > 2A, $X^2 = 3.790$, $p < 0.10 > 0.05$).

The only two indices of infection which were predominant in LVH negative patients in each classification, but not at statistically significant levels, were pneumonia and CNS abnormalities. In contrast, there was a preponderance of positive virology in LVH positive patients terminally, but the difference is short of statistical significance (Group 2T > 1T, $p < 0.10 > 0.05$).

3. DISCUSSION.

A high incidence (83.7%) of infection was demonstrated in the study sample as a whole, but there was no statistically significant difference between LVH negative and LVH positive patients, however classified. Assuming that the absence or presence of LVH effectively differentiates AM and EFE, both conditions manifested features of infection to a similar degree, contrary to the expectation stated at the beginning of this chapter.

One possible explanation is that AM is associated with a viral infection, and EFE with a bacterial infection. This is unlikely since the selection of parameters favoured a viral infection, even though the data did not permit a

clear separation of viral and bacterial origins. Furthermore, identification of a virus was actually more frequent in LVH positive patients, which tends to contradict this possibility.

A more cogent explanation is that both AM and EFE are associated with viral infections. It would be appropriate to regard the viral infection as the causative agent in AM, but difficult to ascribe the fully developed fibro-elastotic endocardium seen at autopsy soon after admission in some cases of EFE (see Chapter 13) to an acute infection lasting only days or weeks. It seems more likely that the viral infection acts as the initiating factor in AM, and a precipitating factor in EFE.

The latter would comply with the overall hypothesis that EFE is initiated at an earlier stage by a sub-clinical or mild viral illness, which then progresses slowly with the development of the typical pathological changes in the endocardium, and which becomes clinically manifest through a second viral infection acting as a booster or precipitating agent.

Although an antecedent viral infection has been gaining popularity as a cause for EFE (see page 10) there are few reports on the frequency of signs of infection concurrent with the clinical presentation of EFE. Greenwood et al[195] reported the presence of fever in 76.9% of patients with AM but also in 27.8% with EFE, and emphasised that fever was common (33%) in patients without AM at autopsy. Hastreiter and Fisher[226] found that EFE was precipitated by an infection in approximately half their cases, in whom fever and an elevated WBC were common. In no other series was the evidence of infection as common as in the present one, probably because particular attention was not directed to this aspect.

CHAPTER 9

ELECTROCARDIOGRAPHY.

The ECG is of major importance in the diagnosis of AM[341,438] and EFE.[476] ST/T wave changes occur in both conditions, whereas LVH is the most valuable sign for differentiating EFE from AM and is used as such in this study. However, the fact that LVH fluctuated during the course necessitated 3 alternative modes of classification to separate AM and EFE clinically (Chapter 4).

In this chapter, the variability of LVH is examined more fully, and other ECG abnormalities are evaluated and compared in LVH negative and LVH positive patients. The C-type classification was selected for this purpose since ECG abnormalities were themselves observed at various stages during the course.

METHODS

An attempt was made to obtain ECG's in all patients on admission, daily for 3 days, on alternate days for 1 week, biweekly thereafter till discharge, and 3 to 6 monthly during the remainder of the study period which ended in December 1976 ; a final ECG was obtained in long-term survivors during the patient's last visit up to March 1979 (observation period). Additional tracings were obtained as determined by the clinical condition of the patient. The complete protocol could not be achieved during the first admission in 33 patients

who died early (under 2 months), in 20 patients who had to be admitted to the paediatric wards at Groote Schuur Hospital or New Somerset Hospital because of the lack of beds at Red Cross Children's Hospital, in 32 long-term survivors who failed to attend regularly or were transferred to home centres far from Cape Town, and through complete non-compliance in 5 patients.

Despite these difficulties a total of 1,050 ECG's were available and suitable for detailed analysis, i.e. an average of 8.5 tracings/patient. (This included 176 ECG's from 40 patients who died - 4.4 tracings/patient ; and 874 ECG's from the 83 survivors - 10.5/patient).

The timing of ECG's following presentation and the abnormalities detected in each tracing for each patient, are tabulated in Appendix D. The criteria used for these selected ECG abnormalities are indicated in the key to Appendix D.

RESULTS

The 10 ECG abnormalities evaluated appear in rank order of frequency in Table 9.1. The frequency of each ECG sign in LVH negative and LVH positive patients (Groups 1C and 2C), and in survivors and deaths, is depicted in Tables 9.2 to 9.5. These ECG features will be discussed under the following headings:

i) Heart rate
ii) Arrhythmias
iii) Conduction abnormalities
iv) QRS vector
v) P wave
vi) Left ventricular hypertrophy
vii) Q wave
viii) ST segment
ix) T wave

TABLE 9.1 ECG Abnormalities. Frequency and Rank order in the clinical series during the entire study.

RANK	ECG ABNORMALITY	NUMBER OF PATIENTS (123)	%
1	T WAVE	119	96.8
2	P WAVE	85	69.1
3	SINUS TACHYCARDIA	62	50.4
4	ST SEGMENT	59	48.0
5	MEAN QRS AXIS	58	47.2
6	R/S RATIO (V1)	56	45.5
7	LVH BY VOLTAGE	52	42.3
8	1ST DEGREE HEART BLOCK	23	18.7
9	Q WAVE	20	16.3
10	ARRHYTHMIAS	14	11.4

1. HEART RATE

Sinus tachycardia (ST) on ECG (>95th percentile for age) occurred in 62 of 123 patients. Tachycardia appeared within 3 days in 47 of the 62 patients, and was usually of short duration, i.e. 1 day only in 37 of the 62 patients and 2 days to 3.5 months in 22 patients. (ST lasted 8 months in 1, 18 months in 1 and intermittently for 65 months in 1 patient).

In survivors persistence of ST was no more frequent in those with late-onset (after 3 days - 5/11) than in those with early-onset ST (under 3 days - 5/11).

There was no statistically significant difference in frequency of ST between Group 1C and 2C patients, or between survivors and deaths (Table 9.2).

Comment

Although regarded as a very reliable clinical sign of myocardial involvement, ST was observed in only half the series. The value of ST as an index of acute-onset EMD was further reduced by its late onset and short duration in many patients.

2. ARRHYTHMIAS

Arrhythmias were detected in 11.4% of cases (14/123) and were least frequent of all the ECG abnormalities (Table 9.1). A break-down of the different arrhythmias appears in Table 9.2.

Atrial extrasystoles were observed in 6 patients, i.e. no's 44 (atrial bigeminy), 82, 94 and 122 (all day 1 to 3), 115 (day 11 and 13), and 48 (day 21 with ventricular extrasystoles at 4 months). Patient no 47 had ventricular

TABLE 9.2 ECG Abnormalities : Rhythm and Conduction Disturbances. Comparison of frequency in patients without and with LVH at any stage of the course (Groups 1C and 2C, respectively), and in survivors and deaths.

ECG ABNORMALITY	NUMBER OF PATIENTS					
	GROUP		X^2	GROUP		X^2
	1C (71)	2C (52)		ALIVE (83)	DEAD (40)	
SINUS TACHYCARDIA	34	28	0.135	40	22	0.265
ATRIAL EXTRASYSTOLES	2+	4	≠	5+	1	≠
SUPRAVENTRICULAR TACHYCARDIA	1	0	≠	1	0	≠
WANDERING PACEMAKER	2	0	≠	1	1	≠
JUNCTIONAL TACHYCARDIA WITH A-V DISSOCIATION	0	3	≠	1	2	≠
WPW SYNDROME	0	1	≠	1	0	≠
VENTRICULAR EXTRA-SYSTOLES	1+	1	≠	1+	1	≠
TOTAL ARRHYTHMIAS	5	9	2.201	9	5	0.001
1ST DEGREE HEART BLOCK	12	11	0.132	18	5	0.999

Total number of patients in each group indicated in parentheses.

+1 patient (No. 48) had both atrial and ventricular extrasystoles.

X^2 - statistical evaluation by Chi-square analysis.

≠ - numbers too small for statistical analysis.
No statistically significant differences demonstrated.

extrasystoles on day 9 and 16, and no 11 had a wandering pacemaker with intermittent junctional extrasystoles between admission and day 5, but not thereafter. Patient no 17 developed the same arrhythmia with aberration preterminally, at 9 months. Supraventricular tachycardia (SVT) was noted in patient no 59 from admission to day 30. The Wolff-Parkinson-White (WPW) syndrome was seen in 1 patient.

Episodes of junctional tachycardia with ventricular aberration alternating with atrio-ventricular (AV) dissociation were observed in 3 patients ; for a period of 28 months in patient no 5, who is alive and well after 43 months ; for 39 days in patient no 9 and for 35 days in patient no 49, both of whom succumbed.

Assessing these patients as a group, there was no statistically significant difference in frequency between survivors or deaths, or between Group 1C and 2C patients (Table 9.2).

Comment

Arrhythmias were relatively uncommon and mild. However, the pattern of junctional tachycardia and aberration alternating with AV dissociation was long lasting and had a poor prognosis.

A similar incidence of arrhythmias has been reported in both AM (SVT[85,258,528] supraventricular[43,373,517] and ventricular[147,355] arrhythmias) and EFE (SVT,[195,226,368] WPW syndrome,[195,226,306] AV dissociation,[226,368] supraventricular[252,368] and ventricular[195,368,537] arrhythmias). Greenwood et al[195] found arrhythmias in 16% of cases which were no more frequent in AM than in other categories of primary myocardial disease. Pathological changes in the conduction

system have been demonstrated in EFE[6] (and infantile COCM[269]).

3. CONDUCTION ABNORMALITIES

Apart from the patients with junctional rhythm and AV dissociation mentioned above, the only conduction disturbance noted was first degree heart block in 18.7% (23/123) of patients. The prolonged PR interval for age endured for under 1 month in 17 patients (observed once only in 9 patients and twice in 6), and for periods of 5-38 months in 6 patients.

There was no statistically significant difference in frequency between Groups 1C and 2C, or between survivors and deaths (Table 9.2).

It is likely that first degree heart block was due to digitalis treatment in most cases,[226] since it was detected on day 1 and 2 in only 2 patients and after 8 days of treatment in the other 21 patients.

Comment

Conduction disturbances have been reported in AM[280] (including second degree[24,43] and complete[264,43,428,320] heart block) and in EFE[195] (including first degree,[368] second degree[226] and complete[166,226,217,415] heart block).

4. QRS VECTOR

Although vectorcardiograms were not performed, the mean frontal plane QRS axis could readily be derived from the standard leads of the ECG's. The mean vector deviated from the normal range (see key to Appendix D) in 47.2% (58/123) of patients ; 26 % (32/123) having right axis deviation (RAD) alone, 13 % (16/123) left axis deviation (LAD) alone, and 8 % (10/123) RAD at one time and LAD at another (RAD initially in 7, and LAD initially in 3).

There was no statistically significant difference between Group 1C and 2C patients in frequency of RAD alone, LAD alone, or RAD + LAD, or in the total number of patients with RAD, with LAD, or with either vector deviation (Table 9.3).

However, the frequency of axis deviation was greater among survivors than deaths, the difference being almost significant in respect of the total number of patients with LAD ($p<0.10 >0.05$), significant for the total number of patients with RAD ($p<0.05$), and highly significant for the total number of patients with either vector shift ($p<0.01$).

Comment

An explanation for the latter finding is not readily apparent. One might expect patients with LAD or RAD to have more severe right or left heart failure and, hence, to have a higher MR, but this is contradicted by the above results.

Mean QRS axis deviation was suprisingly common in this series and occupied 5th position in order of frequency of ECG abnormalities (Table 9.1). RAD occurred in 34 % (42/123) and LAD in 21 % (26/123) which are similar to the figures of 38.6% and 10.7%, respectively, quoted by Greenwood et al[195] in primary myocardial disease. LAD is thought to be uncommon in EFE,[476] but Hastreiter and Fisher[226] noted that the mean QRS axis in EFE shifted towards the left with treatment and towards the right with time. Only 1 report mentions a high incidence of RAD in AM.[164] In the present study RAD and LAD were equally common in both AM and EFE.

5. P WAVE

P wave abnormalities occurred in 69.1% (85/123) of the series, second only to T wave changes in order of frequency (Table 9.1).

TABLE 9.3 ECG Abnormalities : Mean frontal plane QRS Axis Deviations. Comparison of frequency in patients without and with LVH at any stage of the course (Groups 1C and 2C, respectively), and in survivors and deaths.

ECG ABNORMALITY	NUMBER OF PATIENTS					
	GROUP		X^2	GROUP		X^2
	1C (71)	2C (52)		ALIVE (83)	DEAD (40)	
LAD ALONE	7	9	0.887	13	3	0.950
RAD ALONE	20	12	0.183	25	7	1.626
LAD + RAD^{o}	6	4	0.033	9	1	1.523
TOTAL LAD	13	13	0.455	22	4	3.477
TOTAL RAD	26	16	0.234	34	8	4.384*
TOTAL AXIS DEVIATION	33	25	0.0001	47	11	8.058$^{\Phi}$

Total number of patients in each group indicated in parentheses.
LAD - left axis deviation of mean frontal plane QRS vector
RAD - right axis deviation of mean frontal plane QRS vector
o - at different times
X^2 - statistical evaluation by Chi-square analysis
* - significant difference at $p < 0.05$
Φ - " " " $p < 0.005$

5.1 CRITERIA FOR ATRIAL ENLARGEMENT

Criteria for right atrial hypertrophy or enlargement (Pra) in children are well established, i.e. a tall peaked P wave of greater than 2.5 mm (or 3 mm[293]) in lead II[319] or in any lead.[13] Criteria for this study are noted in the key to Appendix D.

Identification of left atrial enlargement depends more on descriptive criteria such as ,

"flat-topped P waves of normal height in leads I and II with prolonged duration (normal being 0.06 ± 0.02 mm in standard leads[29]) and with two notches at least 0.05 seconds apart[383]" ;

"broad, notched or prolonged P waves in leads I, II, V5 and V6, or bi-phasic P waves in V3R or V1 with negative portion slurred and of greater duration than preceding positive portion[293]" ; or

"prolonged terminal vector to the left and posterior, the latter usually being the larger".[319]

In this study, negative, bifid or notched P waves were frequently seen, either alone or in combination. Although these patterns did not comply with recommended quantitative indices for left atrial enlargement, such as the MaCruz index or those mentioned above, the characteristic shapes favoured a left atrial origin. The regularity with which these features appeared in the early phase and disappeared on treatment after a variable time, strongly suggested that they were caused by an acute but reversible event. The term "left atrial stress" (Pla) is therefore used, in preference to left atrial hypertrophy.

It has been claimed that a distinct notch can always be seen in the normal

P wave, coincident with the change from a predominantly anterior to a posterior orientation,[319,192] but this pre-supposes recording the ECG at double speed and double standardisation.[193,319] The presence of such notching is distinctly unusual in standard ECG's of normal children.

5.2 FREQUENCY OF ATRIAL ABNORMALITIES

Of the total of 85 affected patients, only 7 had evidence of Pra alone, whereas 63 had features of Pla alone and 15 had both, either in the same ECG (in different leads) or in separate ECG's at different times (Table 9.4). Hence, the overall incidence of Pla in the series was 63.4% (78/123) and of Pra, 17.9% (22/123).

There were no statistically significant differences in frequency of atrial abnormalities between Group 1C and 2C patients or between survivors and patients dying (Table 9.4).

5.3 MORPHOLOGY OF ATRIAL ABNORMALITIES

A bifid P wave was the commonest sign of left atrial stress, occurring in 71 patients, while a notched P wave was noted in 33 patients and a negative P wave in 17. The bifid P as an isolated feature was seen in 28 patients, and an isolated negative or notched P in 7. The remaining patients had a combination of 2 (19 cases) or 3 (9 cases) abnormalities. A peaked P wave of right atrial enlargement was found in 22 patients.

5.4 EXTENT OF P WAVE ABNORMALITIES

The features of Pla were observed in lead V1 in every affected patient, with extension to lead V2 in 10, to V3 in 13 and to V4, V5 or V6 in 9 cases. Involvement of the standard leads was unusual (7 patients), with lead II affected in each case. Evidence of Pra was characteristically observed in

TABLE 9.4 ECG Abnormalities : Atrial and Ventricular Enlargement. Comparison of frequency in patients without and with LVH at any stage of the course (Groups 1C and 2C, respectively), and in survivors and deaths.

ECG ABNORMALITY	NUMBER OF PATIENTS					
	GROUP			GROUP		
	1C (71)	2C (52)	X^2	ALIVE (83)	DEAD (40)	X^2
P1a ALONE	35	28	0.100	44	19	0.145
Pra ALONE	4	3	≠	4	3	≠
P1a + Pra	6	9	1.450	10	5	0.030
TOTAL P1a	41	37	1.784	54	24	0.120
TOTAL Pra	10	12	1.097	14	8	0.030
TOTAL ATRIAL ABNORMALITIES	45	40	1.983	58	27	0.004
SV1 ALONE	0	22	-	15	7	0.030
RV6 ALONE	0	8	-	5	3	0.006
SV1 + RV6	0	22	-	13	9	0.457
TOTAL SV1	0	44	-	28	16	0.229
TOTAL RV6	0	30	-	18	12	0.611
TOTAL LVH	0	52	-	33	19	0.384
R/S V1	29	27	1.072	40	16	0.438

Total number of patients in each group indicated in parentheses.
P1a = P wave features of left atrial stress
Pra = P wave features of right atrial enlargement
SV1 = LVH by S wave voltage in lead V1
RV6 = LVH by R wave voltage in lead V6
R/SV1 = R to S wave ratio in lead V1
X^2 = statistical evaluation by Chi-square analysis
≠ = numbers too small for statistical analysis
No significant differences demonstrated.
- patient distribution by definition.

lead II in 95.0% of cases, with involvement of the right chest leads in only 2 patients.

5.5 TIME OF ONSET AND DURATION

The majority of P wave abnormalities was present within the first 48 hours (53/85), or developed during the first week (75/85). In no patient did these features commence after 3 months.

The abnormalities persisted for under 48 hours in 19 patients, 2 to 7 days in 16, 8 to 31 days in 17, 1 to 3 months in 15, and over 4 months in 18 patients.

Comment

The reported incidence of left atrial overwork in EFE varies between 40%,[368] 50%[226] and 58%[352] ; of right atrial overwork between 25%[368] and 33%[226] ; and of biatrial enlargement, up to 45%.[368] There is no equivalent data in AM, but Greenwood et al[195] report a 55.7% incidence of left, right or biatrial enlargement in primary myocardial disease in children.

Strict quantitative criteria are not necessary to identify transient and reversible left atrial stress. Having excluded artefact, even a slightly notched or small bifid or negative P wave appears to represent an acute, dynamic event different from persistent left atrial hypertrophy, e.g. p-mitrale of mitral stenosis.

In this series, P wave abnormalities occurred with equal frequency in patients with AM and EFE, and neither the morphology, extent, duration nor time of onset influenced the mortality rate. The high incidence of P abnormalities makes this a valuable diagnostic sign.

6. LEFT VENTRICULAR HYPERTROPHY

6.1 CRITERIA FOR LVH

Several indices of LVH were ruled out for the following reasons. The pattern of deep Q waves with tall R and T waves in the inferior and left chest leads[74] is excluded by virtue of the tall T waves. LAD of the mean frontal QRS vector is a poor sign of LVH in children,[319] and is usually due to a conduction defect.[318] The wide variation in QRS width in normal children negated its use as a dependable index of LVH.[319] The fact that T wave flattening or depression was interpreted as an index of myocardial involvement in this study, precluded its use as a sign of LV strain[161,231] or of LVH by virtue of a widened QRS-T angle.[43,438]

According to Liebman and Plonsey,[319] increased voltage of the R wave in lead AVF, reflecting increased magnitude of the inferior vector, is common in normal children. Increased magnitude of the leftward vector is regarded as more dependable, and of the posterior vector as probably the best single criterion for LVH. Although these are best measured on the standard ECG by the R voltage in V5 and the S voltage in V2, respectively, the R voltage in V6 and S voltage in V1 approximate these vectors closely.[319] Age-related SV1 and RV6 voltages were therefore used as the sole criteria of LVH in this study (see key to Appendix D).

Because a larger posterior vector will reduce the relative contribution of the anterior vector, the R to S ratio in V1 (R/SV1) would be expected to decrease significantly. This feature was evaluated but not adopted as an index of LVH because of lack of consistent norms (see key to Appendix D).

6.2 FREQUENCY OF LVH

LVH was identified in 25.2% (31/123) of patients at presentation ; in 42.3% (52/123) at some stage of the illness, i.e. initially, intercurrently, or terminally ; and in 22.0% (27/123) at the end of the study period (December 1976). (see Chapter 4)

A break-down of the indices of LVH appears in Table 9.4. An increase in posterior forces (SV1) was the dominant finding, occurring in 84.6% (44/52), compared with an increase in leftward forces (RV6) in 57.7% (30/52).

There was no statistically significant difference in frequency of LVH between survivors and deaths.

6.3 TIME OF ONSET

LVH was present on admission in 31 patients. In the remaining 21 patients, LVH began early in the course in most, i.e. during the first week in 9, between 1 and 4 weeks in 6, and between 1 and 6 months in 5. In only 1 patient did transient LVH develop later, i.e. at 26 months in patient number 67.

The MR was similar whether LVH was present on admission (11/31) or developed subsequently (8/21).

6.4 DURATION

The duration of LVH and mortality are illustrated in Figure 9.1.

Of the 32 survivors, LVH resolved in 29 and possibly resolved in 2 (LVH present on last ECG after 20 days in patient no 97 and after 1 month in patient no 108, both of whom were completely well clinically at 47 and 32 months, respectively). Hence, only 1 patient (no 123) was known to have persistent LVH

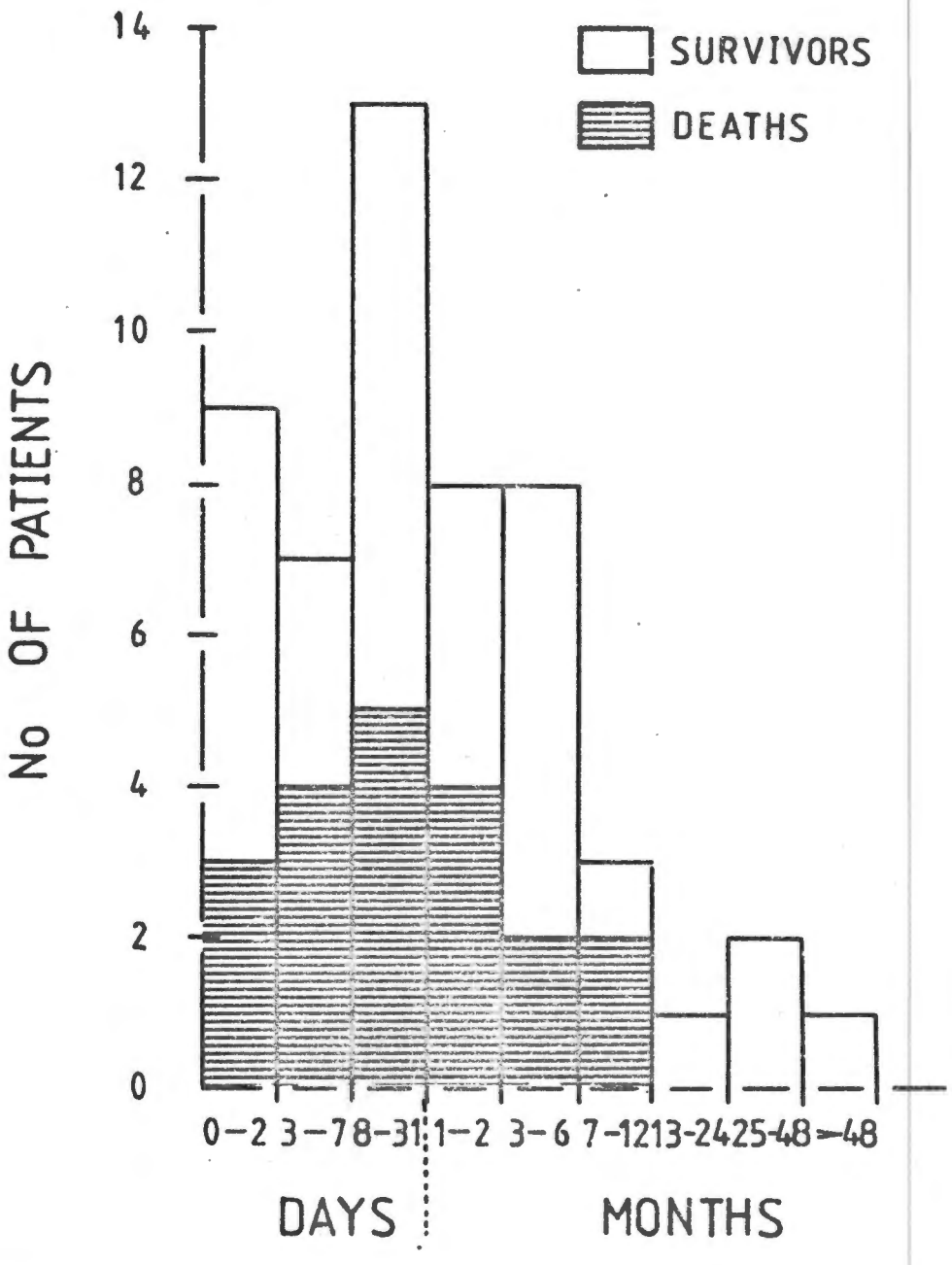


FIG. 9.1 DURATION OF LVH ON ECG in the 52 patients with LVH at any stage of the course (Group 2C).

after 55 months duration. (This patient was 81 months old at presentation and may have had undetected long-standing myocardial disease at the time).

Resolution of LVH occurred within 6 months in 26 survivors, but was still possible after 18, 34 and 38 months (patient no's 116, 121 and 114, respectively).

All but 2 of the 20 patients who died still had LVH at the time of death. Patient no's 9 and 91 died 6 days and 1 month after losing their LVH.

The MR appeared to be uninfluenced by the duration of LVH, except that there were no deaths in patients with LVH for more than 1 year.

6.5 R/S RATIO IN LEAD V1 (R/SV1)

A small R/SV1 ratio for age was observed in 45.5% (56/123) of patients. (Table 9.4) This sign was associated with an increased SV1 and/or RV6 in 27 cases, but was independent of other evidence of LVH in 29. Hence, if a diminished R/SV1 was accepted as a criterion for LVH, the overall number of patients with left ventricular overload would be 65.9% (81/123).

There was no statistically significant difference in the number of patients with a diminished R/SV1 between Group 1C and 2C, or between survivors and patients dying. (Table 9.4)

Time of onset

As with LVH, the decreased R/S ratio was present on admission in over half the cases (30/56), and developed before 3 months in 21 of the remaining 26. The MR was not significantly different whether the decreased R/SV1 commenced before (15/41) or after (1/15) one week ($X^2 = 3.462$, $p<0.10 >0.05$).

Duration

Decreased R/S ratios tended to be more protracted than other indices of LVH, persisting for over a year in 12 of the 56 patients compared with only 4 of the 52 patients with definitive LVH. However, the decreased R/S ratio also resolved with time, persisting in only 3 of the 40 survivors at the end of the follow-up period (page 153) ; intermittently for 54 months in patient no 77, for 47 months in no 98, and 72 months in no 58.

Comment

In EFE, Sellers et al[476] found the percentage frequency of SV1 and RV6 alone to be 66% and 17% respectively in their autopsy group, and 26% and 41% in their clinical group, while SV1 + RV6 together occurred in 10% in both groups. In the present series (autopsy plus clinical cases), the percentage frequency of SV1 and RV6 alone was 43% and 15%, but the incidence of SV1 + RV6 was considerably higher (42%).

Although the authors[476] stated that LVH is reliable in differentiating AM from EFE, their finding of a 17% incidence of RV6 or SV1 + RV6 in 23 cases of autopsy-proved AM emphasizes the overlap that exists between these 2 conditions.

The reported 83% incidence of a prominent posterior vector (diminished R/SV1) in AM, relative to 17% in clinical EFE and 7% in autopsy EFE,[476] implies that this sign is more selective of AM. In the present study, however, a decreased R/SV1 was of similar frequency in clinical AM (29/71) and clinical EFE (27/52).

The similarity of frequency, duration, mode of onset and resolution in this study between a diminished R/SV1 and SV1 and/or RV6 suggested that the former could be a useful additional sign of LVH in EMD.

In terms of the objective of this study, the late onset of LVH in 40.4% (21/52) of positive cases and its resolution within 1 year in virtually all survivors, supports the concept that EFE is a phasic event in acute EMD. Hence, individual cases of AM could manifest LVH at any stage depending on the development and timing of the EFE process.

7. Q WAVE

Pathological Q waves (criteria in key to Appendix D) occurred in 16.3% (20/123) of patients (Table 9.1). There was no significant difference in frequency between Group 1C and 2C patients, or between survivors and deaths (Table 9.5).

Associated ST segment changes occurred in 16 of the 20 cases. Twelve had ST segment elevation and depression in different leads (infarct pattern), and 3 had ST segment depression alone (subendocardial ischaemia). Only one patient had ST segment elevation alone, possibly due to pericarditis.

Pathological Q waves were present within 48 hours in 13 and within 1 week in 16 patients. Q waves persisted for under 48 hours in 8 patients and for periods of 4 days to 6 months in 11. In the remaining patient (no 121) this sign was continuously present from 2 months to 21 months. The MR was not significantly different whether pathological Q waves were present ab initio (6/13) or later (2/7), or whether they were short-lived (4/8) or persisted (4/12).

Comment

An infarct pattern is well-recognised in AM in both adults[178,353] and children,[64,119,195,202,402,527] in about 10% of cases,[476] but is rare in EFE.[101,324,368,356,476] In this study pathological Q waves and infarct

TABLE 9.5 ECG Abnormalities : Q wave, ST segment and T wave abnormalities. Comparison of frequency in patients without and with LVH at any stage of the course (Groups 1C and 2C, respectively), and in survivors and deaths.

ECG ABNORMALITY	NUMBER OF PATIENTS					
	GROUP			GROUP		
	1C (71)	2C (52)	X^2	ALIVE (83)	DEAD (40)	X^2
PATHOLOGICAL Q WAVES	10	10	0.267	11	9	1.084
ST SEGMENT						
ST + ALONE	19	8	1.652	18	9	0.017
ST - ALONE	4	4	0.008	5	3	0.006
ST+ AND ST-	9	15	4.021*	12	12	3.221
TOTAL ST+	28	23	0.121	30	21	2.189
TOTAL ST-	13	19	4.278*	17	15	3.225
TOTAL ST ABNORMALITIES	32	27	0.324	35	24	2.761
T WAVES						
NORMAL	2	2	≠	1	3	≠
FLAT/SHALLOW	66	42	3.104	76	32	2.379
DEEP	3	8	3.322	6	5	0.387

Total number of patients in each group indicated in parentheses.
ST+ = ST segment elevation
ST- = ST segment depression
FLAT = upright T wave <1 mm in V5 and V6
SHALLOW = inverted T wave ≤ 2 mm in V5 and V6
DEEP = inverted T wave >2 mm in V5 and V6
X^2 = statistical evaluation by Chi-square analysis
* Difference significant at $p < 0.05$
All other differences not significant
≠ numbers too small for analysis

patterns were more common (16%) and occurred with equal frequency in both AM and EFE. The higher MR reported in EFE patients with an infarct pattern[101] was not confirmed in this series.

8. ST SEGMENT

ST segment abnormalities were common, 48.0% (59/123) of patients being affected (Table 9.1). ST segment elevation (51 cases) was more prevalent than ST depression (32 cases), occurring on its own in 27 patients and together with ST segment depression in different leads in 24. ST depression alone was observed in 8 patients (Table 9.5).

The total number of patients with ST segment depression, or ST depression plus elevation, was significantly greater in LVH positive than LVH negative patients. (Group 2C $>$ 1C, $p < 0.05$ in both cases). (Table 9.5)

There was no statistically significant difference between survivors and deaths in respect of incidence of ST segment elevation or depression, or both together.

Comment

The predominance of ST depression in suspected EFE is explicable on the basis of subendocardial ischaemia due to severe LVH, as seen in hypertrophic cardiomyopathy or severe aortic stenosis. This pattern is reported to occur in two thirds of patients with EFE.[226] ST segment elevation is more likely to occur in AM, due to an acute current of injury from myocardial cell necrosis, or to acute pericarditis from extension of the inflammatory process.

9. T WAVES

T wave flattening or inversion in the left chest leads (V5 and V6) is the

"sine quanon" of diagnosis in both AM and EFE.[22,116,476,538] This abnormality was observed in 96.8% (119/123) of patients and was first in order of frequency of ECG abnormalities (Table 9.1). (The remaining 4 patients had ST segment abnormalities without T wave changes).

9.1 T WAVE MORPHOLOGY IN RELATION TO LVH (Table 9.5)

Of the 4 patients with normal T waves 1 had LVH at presentation, 1 developed LVH later, and 2 did not have LVH at any stage. Three patients died and 1 (no 12) resolved completely.

Flat (<1 mm), mildly inverted (<2 mm) or bifid T waves were observed in 108 patients. Associated LVH was not seen at any stage in 66 patients : 18 succumbed, 2 were lost to follow-up (case no's 29 and 38), 2 had residual T wave abnormalities when last examined (case no's 48 and 52), and 44 resolved completely.

LVH was present in 42 patients, from presentation in 27 and later in 15. Fourteen patients died, 4 were lost to follow-up immediately after admission (case no's 93, 97, 107, 118), 5 had persistent abnormalities when last seen - 3 with residual T wave flattening (case no's 85, 95 and 122), 1 with residual LVH (case no 123), and 1 with both (case no 108)-and 19 resolved completely.

Deep T wave inversion (>2 mm) was uncommon in this study, occurring in only 11 patients, 3 without LVH at any stage (all resolved) and 8 with LVH (3 from the onset and 5 later). Of the latter, 5 patients died and 3 resolved completely.

Thus, of the 119 patients with T wave abnormalities, 37 succumbed, 6 were

lost to follow-up after admission, 69 resolved completely (1 had residual LVH), and only 6 had residual T wave flattening 22.6±9,2 months (mean ±SEM) after presentation.

There was a tendency for deep T wave inversion to occur in patients with LVH, and normal or flat T waves in those without LVH, but the differences were not statistically significant ($p<0.10, >0.05$ in both cases). (Table 9.5).

Comment

Complete resolution of T wave abnormalities was the rule in survivors, whether LVH coexisted or not. Deep T wave inversion tended to be associated with LVH.

9.2 T WAVE MORPHOLOGY IN RELATION TO EFE

Despite the paucity of autopsy-proved EFE in the clinical series (see Chapter 13), this pathology was significantly more frequent in patients with deep T inversion than in those with normal, flat or shallow T waves, whether related to the number of postmortems ($p<0.05$), deaths ($p<0.025$) or patients ($p<0.005$) in each group (Table 9.6). This finding was not significantly influenced by the relative MR (5/11 and 35/112, respectively - $X^2 = 0.387$, $p>0.50$), or number of PM's performed (3/11 and 17/112, respectively - $X^2 = 0.371$, $p>0.50$) which were similar in both groups.

Comment

Deep T wave inversion was a reliable index of underlying EFE, but occurred infrequently. The finding of deep T inversion in 3 patients in Group 1C implies that EFE may be present in the absence of LVH.

TABLE 9.6 Pathological endocardial fibroelastosis (EFE) in relation to number of postmortems, deaths and clinical cases in patients with different T wave morphologies.

	NUMBER OF PATIENTS		X^2
	NORMAL/FLAT/ SHALLOW T WAVES	DEEP T WAVES	
EFE	3	3	-
RELATIVE TO:			
POSTMORTEMS	17	3	4.781 *
DEATHS	35	5	5.490 **
TOTAL	112	11	8.295 ϕ

Explanatory notes and abbreviations as in Table 9.5
* Difference statistically significant at $p < 0.05$
** " " " " $p < 0.025$
ϕ " " " " $p < 0.005$

CHAPTER 10

SERUM ENZYME ANALYSIS

1. INTRODUCTION

Serum enzymes are widely used for the diagnosis of acute myocardial infarction[7,432] but little attention has been directed to enzyme levels in acute myocarditis (AM),[402] endocardial fibroelastosis (EFE), or in their differentiation. Theoretically, myocardial cellular destruction which accompanies the acute inflammatory process in AM (see Chapter 13) should result in excessive release into the serum of enzymes active in cardiac muscle, such as creatine kinase (CPK) and lactate dehydrogenase (LDH). If EFE is non-infective or a pathological response to inflammation initiated at an earlier stage, serum enzymes should not be elevated at the time of presentation.

ST segment abnormalities on ECG accompany AM in about 10% of cases[476] and EFE rarely,[368,476] but it is not known if these changes are pericardial or ischaemic in origin. Higher serum enzyme values in association with ST changes may indicate myocardial damage. Furthermore, if mortality in patients with acute-onset endomyocardial disease (EMD) is related to the extent of myocardial damage, serum enzyme analysis may be prognostically valuable.

1.1 AIMS

Serum enzymes were therefore measured to investigate

(i) their behaviour pattern in acute-onset EMD,

(ii) their value in differentiating EFE from AM,

(iii) their response in patients with and without ST segment changes on ECG, and

(iv) their prognostic value in survivors and in patients dying.

1.2 SELECTION OF ENZYMES

When this study commenced in 1970, CPK, LDH and especially alpha-hydroxybutyrate dehydrogenase (HBDH), which reflects LDH_1 isoenzyme activity mainly, were regarded as the most reliable enzymes for detecting myocardial cellular damage, and were therefore selected for evaluation. Estimation of the MB isoenzyme of CPK has become the more definitive test for myocardial infarction in recent years.[433,530,546]

1.3 TIMING OF ENZYME ESTIMATIONS

Because the onset of cardiac involvement could not be accurately timed (unlike acute myocardial infarction), and a history of variable duration (up to one month) was accepted for entry of the patient into the study, frequent enzyme estimations in the first days after admission were not performed. Serum for LDH, HBDH and CPK estimations was obtained, subject to the constraints of the clinical situation, during the first 48 hours after admission, and again during the remainder of the first week, during the second and third weeks, and after 21 days if the patient was still in hospital. These five intervals were considered sufficient to indicate trends in enzyme behaviour and patterns of response, and to permit comparisons.

1.4 METHOD

The serum LDH estimation was based on the conversion of pyruvate to lactate with the conversion of $NADH_2$ to NAD^+, according to Henry.[232] Serum HBDH activity was measured by the method of Ellis and Goldberg,[133] and CPK by the "Calbiochem" method, using the Super-Stat-pac^{tm} (Catalogue No. 869214).

1.5 NORMAL VALUES

Enzyme values in normal infants and children are known to be high and variable and reach the adult range during the first 3 years.[484,531] In this study, the normal ranges for children were established in the Biochemistry laboratory of the Department of Pathology in the Institute of Child Health, UCT. The upper limit of normal for LDH was set at 320 u/l ; for HBDH 250 u/l before August 1975 and 225 u/l after this date ; and for CPK, 50 u/l before August 1975 and the same for females, but 80 u/l for males, after this date. (The higher values were selected to demonstrate the upper limit of normal in the Figures).

2. RESULTS

The detailed results for each enzyme in the five time-periods are tabulated in Appendix E. When more than one estimate of an enzyme was obtained in any single time-period (on fifteen occasions in 14 patients), the highest value was accepted for analysis.

At least one enzyme was measured in 100 of the 123 patients in the clinical series. LDH values were obtained in 96 patients ; once only in 49 patients, twice in 26, three times in 16, four times in 3 and five times in 2 patients. HBDH levels were measured in 87 patients ; once in 39, twice in 29, three times in 15, four times in 3 and five times in 1 patient. CPK values were obtained in 78 patients ; once in 36, twice in 27, three times in 10, four times in 3 and five times in 2 patients.

2.1 FREQUENCY OF ABNORMAL RESULTS

In the first 48 hours, LDH values were above normal in 92.6% (75/81) of patients, HBDH in 88.2% (60/73), and CPK in 40.3% (25/62). LDH was abnormally elevated at some stage of the illness in 91.7% (88/96) of patients, HBDH in 80.5% (70/87), and CPK in 44.9% (35/78).

The frequency of elevated LDH did not differ significantly from that of HBDH

initially or at any stage, but both were significantly greater than the frequency of elevated CPK initially (X^2 = 43.178 and 23.439, $p<0.005$ and <0.001, respectively) and at any stage (X^2 = 43.251 and 20.998, $p<0.005$ and <0.001, respectively).

2.2 OVERALL TRENDS

The mean values for the three enzymes in each of the five time-periods are tabulated in Table 10.1 and illustrated in Figure 10.1. The most striking elevations were noted soon after admission in respect of LDH (3.4 times normal) and HBDH (2.5 times normal), with a progressive fall during the ensuing weeks, but with higher than normal levels persisting after 3 weeks. The mean CPK level was almost twice normal in the first, second and fourth time-periods, but only because of very few grossly elevated results (case no's 11, 19, and 29).

There was no statistically significant difference in the mean values of any of the three enzymes between consecutive time-periods, or between the initial and subsequent time-periods (except for the difference between the first and final time-periods in respect of LDH).

Comment

Although not compared with a normal control group, LDH and HBDH values were so high in many cases that cellular damage could be confidently diagnosed. However, cells other than myocardial also release these enzymes.[465] In the face of concomitant viral pneumonitis and/or encephalitis, hepatic congestion from heart failure, and shock, the specificity for cardiac involvement could not be confirmed.

In shocked patients, CPK is released from non-cardiac sources,[131,286] such as underperfused skeletal muscle. CPK levels were markedly elevated in a few

TABLE 10.1 Comparison of mean serum enzyme levels (u/L) at different times after presentation.

TIME-PERIOD (DAYS)	ENZYME VALUES (MEAN ±SEM)				
	1-2	3-7	8-14	15-21	21
	(81)	(34)	(23)	(19)	(14)
LDH	1077.8 ±114.36	855.4 ±125.43	727.7 ±152.10	624.4 ±74.03	455.9 ±49.14
	(73)	(33)	(26)	(15)	(12)
HBDH	626.8 ±90.39	515.2 ±102.55	442.1 ±83.82	375.5 ±42.55	280.3 ±25.01
	(62)	(30)	(20)	(16)	(13)
CPK	126.7 ±34.18	134.7 ±62.54	37.6 ±6.51	120.5 ±83.90	43.6 ±6.00

	t - statistic				
CONSECUTIVE PERIODS					
LDH	1.143	0.647	0.572	1.751	
HBDH	0.597	0.531	0.576	1.807	
CPK	-0.122	1.261	-1.104	0.822	
INITIAL *cf* LATER PERIODS					
LDH	-	1.143	1.523	1.892	2.245*
HBDH	-	0.597	1.156	1.249	1.545
CPK	-	-0.122	1.472	0.079	1.107

Total number of patients in each group indicated in parentheses.
u/L = international units per litre; LDH = lactate dehydrogenase; HBDH = alpha hydroxybutyrate dehydrogenase; CPK = creatine kinase
cf = compared with
t = Statistical evaluation by Student's t-test for unpaired samples.
* = difference between 1-2 day and >21 day periods significant at $p < 0.05$
All other differences not significant.

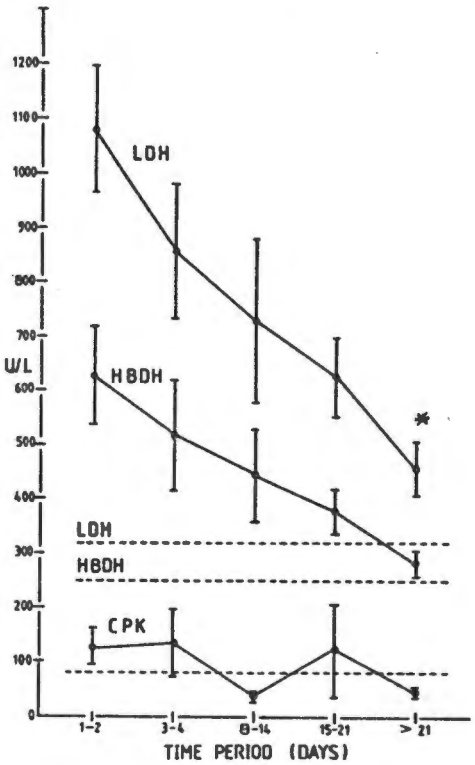


FIG 10.1 SERUM ENZYME VALUES (mean ±SEM) at different times after presentation.
(LDH = lactate dehydrogenase, HBDH = hydroxybutyrate dehydrogenase, CPK = creatine kinase.
Dashed lines indicate upper limits of normal.
* = significantly lower than initial LDH value at $p < 0.05$ level).

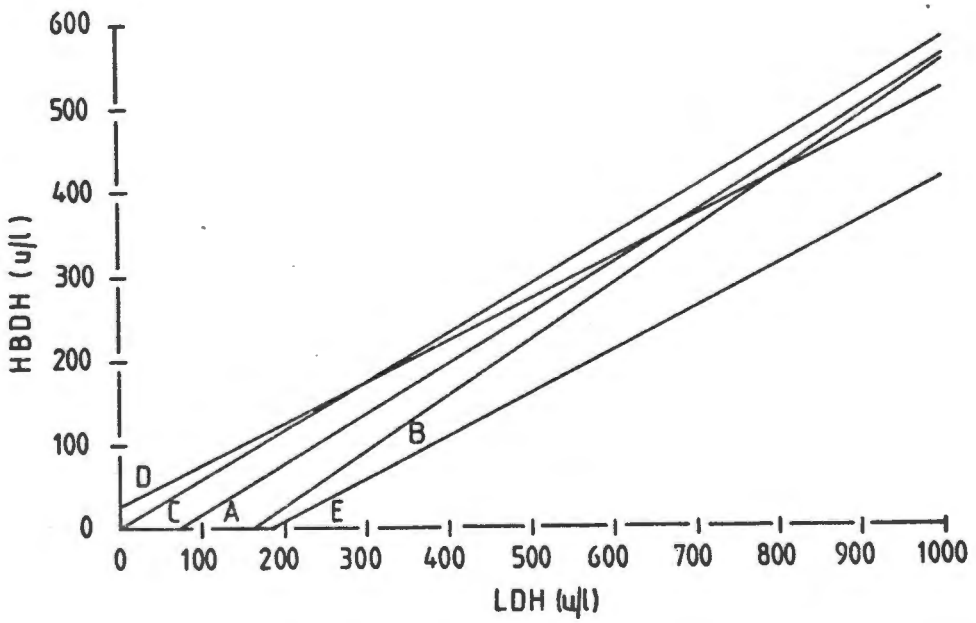


FIG. 10.2 Correlation of serum HBDH with LDH values at different times after presentation. (Linear regression and correlation coefficients;

A. 1-2 days (70) : y = 0.598 x - 42.6, r = 0.85
B. 3-7 " (32) : y = 0.683 x - 113.5, r = 0.92
C. 8-14 " (22) : y = 0.582 x + 1.1, r = 0.94
D. 15-21 " (15) : y = 0.404 x + 124.1, r = 0.76
E. > 21 " (11) : y = 0.266 x + 154.7, r = 0.56
Number of patients indicated in parentheses).

non-shocked patients but not consistently enough to be helpful diagnostically. The CPK enzyme has a shorter half life than either LDH or HBDH[465] and levels may already have decreased by the time the first samples were taken.

2.3 CORRELATION OF ENZYME RESULTS

Correlation between HBDH and LDH, HBDH and CPK, and LDH and CPK has been analysed statistically. The derived linear regression equations and graphs, and the correlation coefficients for each time-period, are demonstrated in Figures 10.2, 10.3 and 10.4 for each enzyme correlation.

A high degree of correlation ($r > 0.75$) was found between HBDH and LDH in each of the first four time-periods. Similar strong correlations were noted between HBDH and CPK in the second and fourth time-periods, and between LDH and CPK in the second time-period only. The similarity in position and slope of the lines of identity between HBDH and LDH for each time-period is strikingly apparent in Figure 10.2, as compared with the scattered positions of the linear regression lines in relation to HBDH and CPK (Figure 10.3) and LDH and CPK (Figure 10.4).

Comment

The strong correlation between LDH and HBDH is not unexpected, since the latter reflects the activity of LDH_1 isoenzyme mainly. However, it does suggest that the generally excessive LDH activity is due essentially to the more cardiac-specific enzyme moiety.

2.4 COMPARISON OF LVH NEGATIVE AND LVH POSITIVE PATIENTS

The comparison was made between patients without and with LVH on admission (Groups 1A and 2A), since this classification was most closely associated with

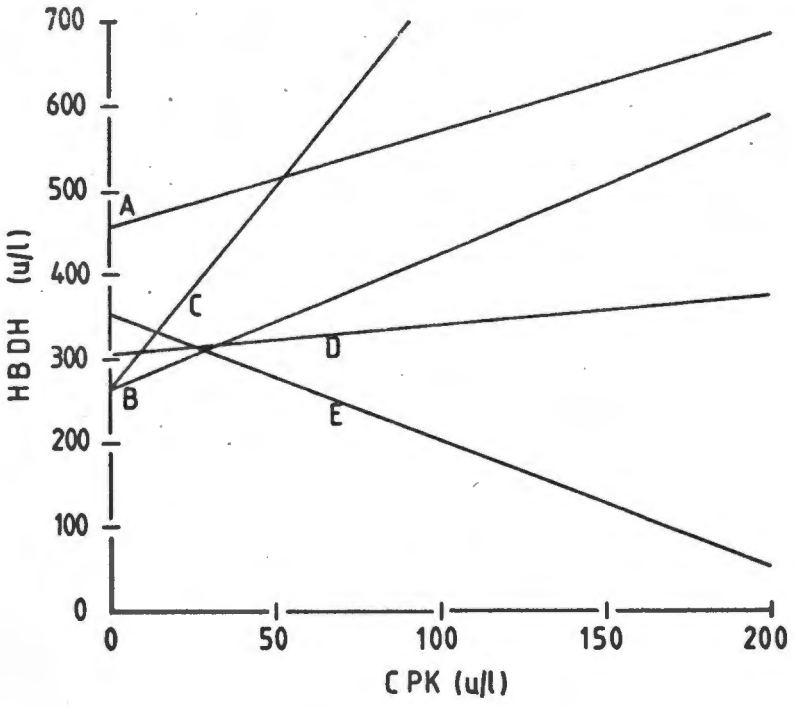


FIG. 10.3 Correlation of serum HBDH with CPK values at different times after presentation. (Linear regression and correlation coefficients;

A. 1-2 days (58) : y = 1.092 x + 464.2, r = 0.39
B. 3-7 " (26) : y = 1.590 x + 268.0, r = 0.95
C. 8-14 " (19) : y = 4.762 x + 268.5, r = 0.29
D. 15-21 " (12) : y = 0.356 x + 304.0, r = 0.82
E. 21 " (10) : y =-1.505 x + 351.7, r = 0.31
Number of patients indicated in parentheses).

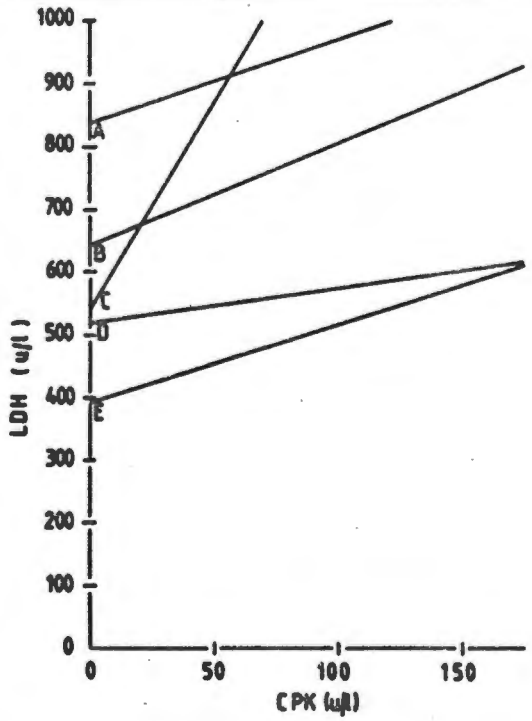


FIG. 10.4 Correlation of serum LDH with CPK values, at different times after presentation. (Linear regression and correlation coefficients;

A. 1-2 days (57) : y = 1.329 x + 836.1, r = 0.39
B. 3-7 " (28) : y = 1.678 x + 639.5, r = 0.77
C. 8-14 " (17) : y = 6.570 x + 540.9, r = 0.24
D. 15-21 " (16) : y = 0.544 x + 518.2, r = 0.55
E. 21 " (11) : y = 1.266 x + 391.7, r = 0.18
Number of patients indicated in parentheses).

the timing of enzyme analyses. The mean values in each time-period for LVH negative and LVH positive patients in respect of LDH, HBDH and CPK are tabulated in Tables 10.2, 10.3 and 10.4, respectively, and graphically demonstrated in Figures 10.5, 10.6 and 10.7, respectively.

Patients without LVH had higher mean values than those with LVH in all time-periods in respect of LDH ; in the first, second, third and fifth time-periods regarding HBDH ; and in the first four time-periods in respect of CPK. However, none of these differences was statistically significant.

The mean LDH and HBDH values were above the normal range in both LVH negative and LVH positive patients in all time-periods, except for a normal mean HBDH value in the LVH positive group in the last time-period. Mean CPK values were abnormally elevated in LVH negative patients in the first, second and fourth time-periods, but were normal in LVH positive patients in all time-periods.

Comment

The higher LDH and HBDH values in LVH negative compared with LVH positive patients, especially during the first week, is in keeping with the hypotheses that AM produces myocardial cellular damage more readily than EFE. However, the lack of statistically significant differences, and the fact that the values in LVH positive patients were also well above the normal range, precluded the use of these enzyme estimations as a differential test between AM and EFE. Although the difference in CPK values between LVH negative and LVH positive patients were also non-significant, the fact that abnormally raised levels were obtained only in the LVH negative group, albeit less frequently, suggested that this test might be more discriminating in differentiating AM from EFE.

TABLE 10.2 Serum LDH values (u/L) at different times after presentation: Comparison of patients without and with LVH on admission (Groups 1A and 2A, respectively).

TIME-PERIOD (DAYS)	LDH VALUES (MEAN ±SEM)				
	1-2	3-7	8-14	15-21	>21
GROUP 1A	(60) 1157.4 ±146.93	(24) 925.4 ±173.58	(18) 735.7 ±193.93	(15) 657.3 ±84.95	(11) 459.0 ±59.41
GROUP 2A	(21) 850.2 ±127.84	(10) 687.3 ±82.97	(5) 699.2 ±98.11	(4) 500.8 ±153.08	(3) 444.7 ±91.94
t 1A cf 2A	0.642	0.862	0.097	0.856	0.115

Total number of patients in each group indicated in parentheses.
u/L = international units per litre.
t = Statistical evaluation by Student's t-test for unpaired samples.
No significant differences demonstrated.

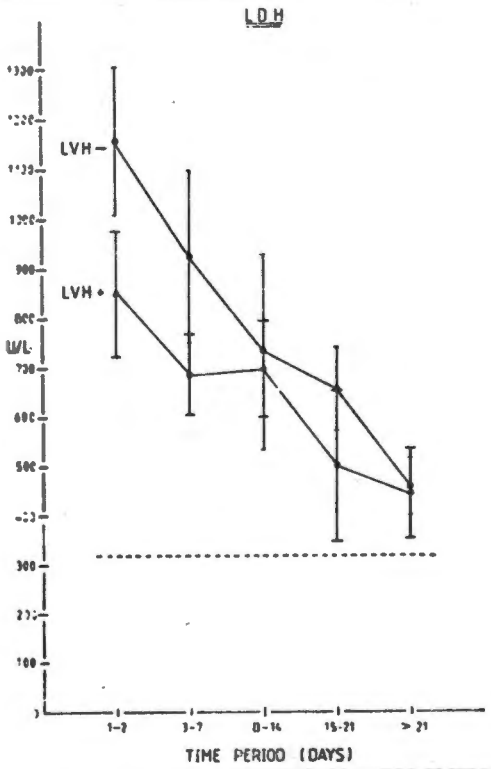


FIG 10.5 Serum LDH values (mean ±SEM) at different times after presentation, in patients with and without LVH on admission (Groups 2A and 1A, respectively). (LDH = lactate dehydrogenase. No statistically significant differences demonstrated. Dashed line indicates upper limit of normal).

TABLE 10.3 Serum HBDH values (u/L) at different times after presentation: Comparison of patients without and with LVH on admission (Groups 1A and 2A, respectively).

TIME-PERIOD (DAYS)	HBDH VALUES (MEAN ±SEM)				
	1-2	3-7	8-14	15-21	>21
GROUP 1A	(54) 677.7 ±113.58	(23) 594.9 ±144.27	(21) 455.9 ±99.76	(12) 364.1 ±48.08	(9) 295.6 ±31.17
GROUP 2A	(19) 499.2 ±128.03	(10) 331.7 ±31.91	(5) 383.4 ±135.33	(3) 421.3 ±105.79	(3) 234.7 ±26.67
t 1A cf 2A	0.835	1.187	0.335	-0.524	1.060

Total number of patients in each group indicated in parentheses.
u/L = international units per litre.
t = Statistical evaluation by Student's t-test for unpaired samples.
No significant differences demonstrated.

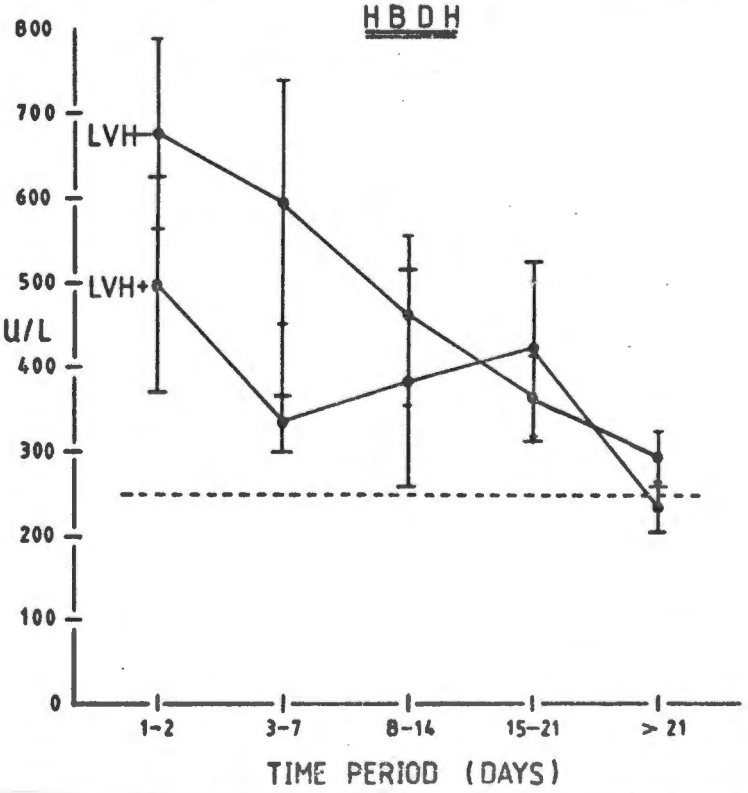


FIG. 10.6 Serum HBDH values (mean ±SEM) at different times after presentation, in patients with and without LVH on admission (Groups 2A and 1A, respectively). (HBDH = hydroxybutyrate dehydrogenase. No statistically significant differences demonstrated).

TABLE 10.4 Serum CPK values (u/L) at different times after presentation: Comparison in patients without and with LVH on admission (Groups 1A and 2A, respectively).

TIME-PERIOD (DAYS)	CPK VALUES (MEAN ±SEM)				
	1-2	3-7	8-14	15-21	>21
GROUP 1A	(43) 151.4 ±48.05	(19) 188.3 ±97.21	(16) 41.6 ±7.73	(14) 127.0 ±96.21	(10) 41.4 ±5.88
GROUP 2A	(19) 70.9 ±21.87	(11) 42.3 ±14.11	(4) 21.5 ±6.13	(2) 75.0 ±5.00	(3) 51.0 ±19.50
t 1A cf 2A	1.088	1.317	1.256	0.198	-0.659

Total number of patients in each group indicated in parentheses.
u/L = international units per litre.
t = Statistical evaluation by Student's t-test for unpaired samples.
No significant differences demonstrated.

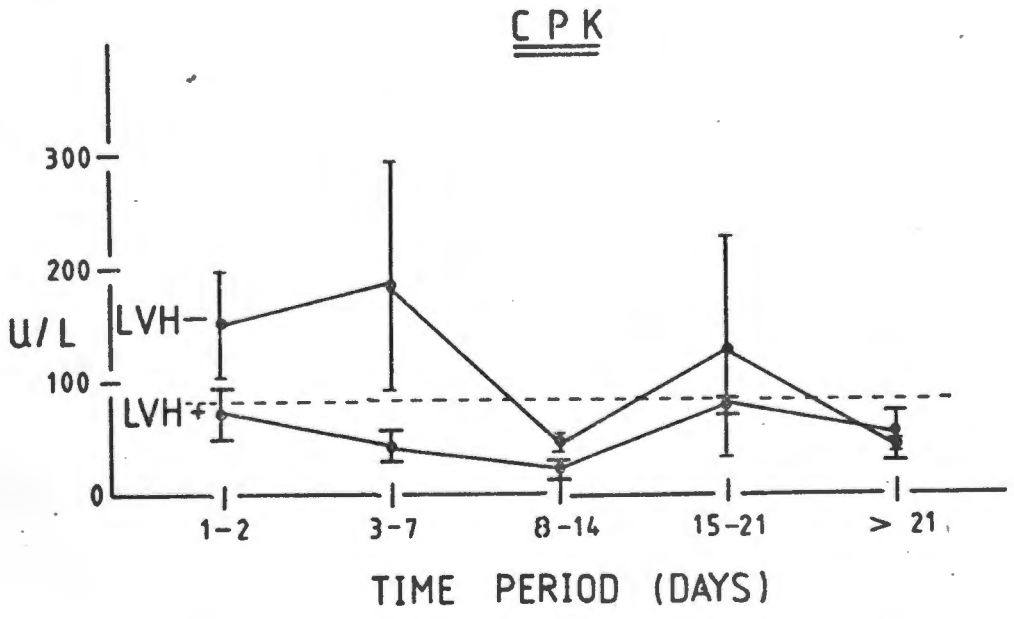


FIG. 10.7 Serum CPK values (mean ±SEM) at different times after presentation, in patients with and without LVH on admission (Groups 2A and 1A, respectively). (CPK = creatine kinase. No statistically significant differences demonstrated).

2.5 COMPARISON OF PATIENTS WITH AND WITHOUT ST SEGMENT ABNORMALITIES

Mean serum LDH, HBDH and CPK values in patients with and without ST segment abnormalities on ECG are denoted in Tables 10.5, 10.6 and 10.7, respectively.

Mean LDH and HBDH levels were higher in all time-periods in patients with ST segment changes on ECG than in those without, except for the first time-period in respect of HBDH. This predominance was statistically significant in the final time-period only for both LDH and HBDH. Mean CPK values were higher in patients with ST segment changes in the second, fourth and fifth time-periods, but none of the differences was statistically significant.

2.6 COMPARISON OF SURVIVORS AND PATIENTS DYING

Mean serum LDH, HBDH and CPK values in patients surviving or dying subsequently are noted in Tables 10.8, 10.9, and 10.10, respectively.

Mean LDH levels were higher in patients dying than in survivors in the second, fourth and fifth time-periods, but only the latter difference was statistically significant. Mean HBDH and CPK levels were higher in survivors than in patients dying during the first four time-periods, but there were no statistically significant differences.

DISCUSSION

The large number of patients with elevated serum enzyme values in this series and the high levels reached in many cases indicate gross cellular derangement in patients with acute endomyocardial disease (EMD). Although the selected enzyme tests lack specificity for myocardial involvement, their measurement appeared to be of value in several respects.

In acute myocardial infarction serum LDH and HBDH levels are reported to rise

TABLE 10.5 Serum LDH values (u/L) at different times after presentation: Comparison in patients with and without ST segment changes on ECG.

TIME-PERIOD (DAYS)	LDH VALUES (MEAN ±SEM)				
	1-2	3-7	8-14	15-21	>21
WITH ST ABNORMALITY	(41) 961.9 ±123.09	(17) 1010.6 ±232.31	(13) 808.0 ±264.15	(9) 661.6 ±127.25	(8) 548.9 ±41.48
WITHOUT ST ABNORMALITY	(40) 1196.5 ±194.13	(17) 700.3 ±109.63	(10) 623.4 ±83.54	(10) 590.9 ±87.22	(6) 332.0 ±77.85
t-statistic	-1.026	1.247	0.593	0.466	2.638**

Total number of patients in each group indicated in parentheses.
t = statistical comparison by Student's t-test for unpaired samples.
u/L = international units per litre.
** = difference statistically significant at $p < 0.025$.

TABLE 10.6 Serum HBDH values (u/L) at different times after presentation: Comparison in patients with and without ST segment changes on ECG.

TIME-PERIOD (DAYS)	HBDH VALUES (MEAN ±SEM)				
	1-2	3-7	8-14	15-21	>21
WITH ST ABNORMALITY	(42) 589.9 ±101.61	(18) 608.6 ±176.43	(14) 471.1 ±147.46	(6) 413.3 ±81.11	(8) 321.5 ±25.60
WITHOUT ST ABNORMALITY	(31) 676.7 ±164.05	(15) 403.1 ±76.71	(12) 407.9 ±66.54	(9) 350.3 ±48.37	(4) 198.0 ±20.83
t-STATISTIC	-0.472	0.998	0.369	0.713	3.115°

Total number of patients in each group indicated in parentheses.
u/L = international units per litre.
t = statistical comparison by Student's t-test for unpaired samples.
o = difference statistically significant at $p < 0.02$.

TABLE 10.7 Serum CPK values (u/L) at different times after presentation: Comparison in patients with and without ST segment changes on ECG.

TIME-PERIOD (DAYS)	CPK VALUES (MEAN ±SEM)				
	1-2	3-7	8-14	15-21	>21
WITH ST ABNORMALITY	(34) 121.2 ±47.79	(13) 170.1 ±126.09	(10) 35.0 ±7.04	(9) 184.8 ±148.98	(7) 50.3 ±8.85
WITHOUT ST ABNORMALITY	(28) 135.5 ±49.51	(17) 107.7 ±57.32	(10) 40.2 ±11.30	(7) 37.9 ±12.34	(6) 35.8 ±7.40
t-STATISTIC	-0.177	1.242	-0.391	0.861	1.227

Total number of patients in each group indicated in parentheses.
u/L = international units per litre.
t = statistical comparison by Student's t-test for unpaired samples.
No significant differences demonstrated.

TABLE 10.8 Serum LDH values (u/L) at different times after presentation: Comparison in survivors and deaths.

TIME-PERIOD (DAYS)	LDH VALUES (MEAN ±SEM)				
	1-2	3-7	8-14	15-21	>21
SURVIVORS	(55) 1175.4 ±154.92	(29) 841.6 ±143.99	(20) 730.9 ±173.12	(15) 615.4 ±84.36	(10) 386.3 ±50.83
DEATHS	(26) 871.3 ±134.96	(5) 936.0 ±197.32	(3) 706.7 ±229.30	(4) 658.0 ±176.38	(4) 630.0 ±55.68
t-STATISTIC	1.246	-0.263	0.052	-0.228	-2.747 o

Total number of patients in each group indicated in parentheses.
u/L = international units per litre.
t = statistical comparison by Student's t-test for unpaired samples.
o = difference significant at $p < 0.02$.

TABLE 10.9 Serum HBDH values (u/L) at different times after presentation: Comparison in survivors and deaths.

TIME-PERIOD (DAYS)	HBDH VALUES (MEAN ±SEM)				
	1-2	3-7	8-14	15-21	>21
SURVIVORS	(50) 723.8 ±128.62	(28) 547.0 ±119.75	(23) 453.4 ±94.34	(12) 379.8 ±52.94	(7) 266.3 ±42.30
DEATHS	(23) 416.0 ±42.57	(5) 336.8 ±62.18	(3) 354.3 ±79.53	(3) 358.7 ±38.92	(5) 300.0 ±14.33
t-STATISTIC	1.599	0.730	0.371	0.191	-0.647

Total number of patients in each group indicated in parentheses.
u/L = international units per litre.
t = statistical comparison by Student's t-test for unpaired samples.
No significant differences demonstrated.

TABLE 10.10 Serum CPK values (u/L) at different times after presentation: Comparison in survivors and deaths.

TIME-PERIOD (DAYS)	CPK VALUES (MEAN ±SEM)				
	1-2	3-7	8-14	15-21	>21
SURVIVORS	(42) 134.4 ±47.12	(25) 156.4 ±74.51	(17) 38.8 ±7.47	(12) 144.3 ±112.12	(10) 41.5 ±7.75
DEATHS	(20) 110.6 ±39.30	(5) 26.20 ±4.32	(3) 31.0 ±11.36	(4) 49.3 ±15.88	(3) 50.7 ±0.67
t-STATISTIC	0.324	0.771	0.417	0.478	-0.628

Total number of patients in each group indicated in parentheses.
u/L = international units per litre.
t = statistical comparison by Student's t-test for unpaired samples.
No significant differences demonstrated.

after 6 to 12 hours, reach a maximum of 3.3-3.5 times normal between 24 and 72 hours and return to normal after 7 to 20 days, the time course being slightly more rapid with LDH than HBDH.[465] In inflammatory cardiac disease, these enzymes are only slightly raised unless myocardial damage is severe, in which case enzyme elevation may be prolonged.[465]

In this series, mean LDH and HBDH levels were at their maximum of 2.5-3.4 times normal when first measured during the initial 48 hours and decreased slowly thereafter, but mean LDH values had not returned to normal even after 21 days. Hence, the enzyme response simulates that of acute myocardial infarction and the duration of abnormality indicates that myocardial damage in acute EMD may be extensive.

The results for both LDH and HBDH were very similar and there appears to be no advantage in using the HBDH test, despite its theoretically greater specificity for heart muscle and reported reliability in monitoring progress.[465]

Although higher LDH and HBDH levels were reached in LVH negative than LVH positive patients, the differences were not sufficiently large to allow discrimination between AM and EFE. In fact, the degree of abnormality found in LVH positive patients encouraged the belief that EFE was also associated with an "active" disease process. However, these enzymes are known to be elevated with acute liver congestion (not with chronic liver congestion or acute left ventricular failure),[465] and this could have provoked the immediate enzyme response in both AM and EFE.

Though less common, CPK elevation appeared to be more reliable in differentiating AM from EFE since mean values remained normal in LVH positive patients.

However, this enzyme may also be raised by skeletal muscle disease (associated viral myositis, possibly) and transiently by shock,[465] which is common in AM (see page 57).

The higher early serum enzyme values in patients with ST segment abnormalities than in those without, suggested a greater degree of myocardial cell damage in the former patients, but the results were not conclusive. However, the significantly higher levels of LDH and HBDH after 3 weeks in patients with ST abnormalities indicated that ST changes may herald long-standing myocardial cell damage.

Serum enzyme estimations in the first three weeks after admission were of little value as a prognostic indicator of survival or death. However, significantly higher levels of LDH after 3 weeks in patients dying later suggested that late enzyme analysis may be prognostically more helpful. This differs from the close correlation between serial changes in total CPK activity and early acute mortality in myocardial infarction.[51,487]

The overall impression was that these serum enzyme estimations provided a useful adjunct to the ECG in diagnosing acute EMD. Further studies with more cardio-specific enzymes are required to validate the findings of this study. It is of interest that measurement of the CPK_2 isoenzyme, i.e. the MB fraction, was recently shown to be an effective means of detecting papillary muscle necrosis in neonates with transient tricuspid insufficiency.[388]

CHAPTER 11

VIROLOGICAL INVESTIGATION

1. AIM

Although confirmation of a viral aetiology for either AM or EFE was not a primary objective in this study, an attempt was made to identify viruses by direct culture or by serological means in as many patients as possible, to establish if there was any difference in the yield of viruses between LVH negative and LVH positive patients.

2. METHODS

Throat swab, urine, stool and blood specimens were collected within 48 hours of admission whenever possible, and refrigerated in previously prepared media until conveyed to the laboratory of the Department of Bacteriology, Medical School, University of Cape Town. Direct culture was performed on all specimens, and complement fixing and neutralising antibody titres were measured in sera by standard techniques. Antibody titres were repeated in specimens obtained after 2 weeks whenever possible.

3. MATERIAL

A detailed list of the specimens submitted for investigation in each patient, and the positive and negative results obtained, are tabulated in Appendix F.

The number of patients (and samples) tested in the clinical series (Groups 1 and 2) for each specimen submitted for viral culture and/or serology, and the number of positives obtained in each instance, appear in Table 11.1.

Including the 3 post-mortem patients (no's 126, 131 and 133), viral culture and/or serology was performed in 78 of the 136 cases (57%) in Groups 1, 2 and 3. Investigations were not performed in many patients who died within hours of admission and in most Group 3 patients.

4. RESULTS - NUMBER OF POSITIVES

4.1 TOTAL SERIES

A virus was isolated by direct culture in 22 patients (from a single source in 19, and two different specimens in 3). Positive serology was obtained in 6 patients, in 3 of whom the same virus was detected by direct culture, and in one (no 97) an adenovirus was grown from sputum culture and a serum antibody titre to measles of 1:1024 was detected. Hence, 25 viruses were detected in 24 of the 78 patients tested (30.8%).

Comment

This yield compares favourably with reported results among similar patients, such as the 32.1% positive yield of virus in black children with respiratory disease in the Johannesburg area between 1966 and 1972.[265]

In epidemic AM, where the yield is expected to be higher, the number of viruses isolated relative to patients studied has varied from 9 of 9 cases[386] to 2 of 3[372] and 1 of 3 cases.[262] In sporadic AM, Berkovich et al reported positive virus isolation in 8 of 12 selected cases. Hutchins and Vie[255] obtained negative results in 5 patients with AM or EFE studied post-mortem, and only 1 positive in a pre-mortem study.[357]

TABLE 11.1 Investigations for viruses. The number of patients and samples tested by culture or serology, and the number of positive results in those without (Group 1) and with (Group 2) LVH on ECG, on admission (A), at any stage during the course (C), and at the end of the study or death, i.e. terminally (T).△

SPECIMEN	NUMBER OF PATIENTS (SAMPLES)															
	GROUP				X^2	GROUP				X^2	GROUP				X^2
	1A "92"		2A "31"			1C "71"		2C "52"			1T "96"		2T "27"		
URT	38	(49)	15	(15)	0.279	26	(36)	27	(28)	2.277	38	(49)	15	(15)	1.589
POSITIVE	5	(7)	3	(3)	0.040	5	(7)	3	(3)	0.195	6	(8)	2	(2)	0.040
URINE	20	(20)	9	(10)	0.340	16	(16)	13	(14)	0.011	22	(23)	7	(7)	0.005
POSITIVE	0	(0)	2	(2)	≠	0	(0)	2	(2)	≠	0	(0)	2	(2)	≠
STOOL	37	(49)	13	(15)	0.002	25	(34)	25	(30)	1.561	37	(47)	13	(17)	0.457
POSITIVE	8	(10)	3	(4)	0.079	6	(8)	5	(6)	0	7	(9)	4	(5)	0.249
BLOOD	37	(48)	19	(20)	3.346	24	(31)	32	(37)	8.226⊕	38	(49)	18	(19)	5.189**
POSITIVE CULTURE	2	(2)	0	(0)	0.0003	1	(1)	1	(1)	0.003	2	(2)	0	(0)	0.003
POSITIVE SEROLOGY	3	(3)	3	(4)		2	(2)	4	(5)		3	(4)	3	(3)	
PM ORGANS	3		2		≠	2		3		≠	2		3		≠
ALL SPECIMENS	135	(169)	58	(62)	-	93	(119)	100	(112)	-	137	(170)	56	(61)	-
POSITIVE +	19	(22)	11	(13)	0.414	14	(18)	16	(17)	0.0003	18	(23)	12	(12)	1.497
PATIENTS TESTED△	52		23		2.346	36		39		6.253 **	54		21		3.249
POSITIVE +	16		7		0.059	11		12		0.053	14		9		1.320

Total number of patients in each group denoted by inverted commas.
Number of samples taken from each tissue specimen appears in parentheses.
URT - upper respiratory tract; including throat swabs in 47 patients (57 samples), sputa in 5 (6 samples), and tracheal aspirate in 1 (1).
PM - post-mortem
X^2 - statistical evaluation of patient numbers by Chi-square analysis
≠ - numbers too small for statistical analysis
** - difference statistically significant at $p<0.025$
⊕ - " " " at $p<0.005$

△ - excluding 3 from autopsy series (Group 3)
+ - positive results in 2 different specimens in 7 patients; excludes 1 positive from Group 3.

4.2 COMPARISON OF LVH NEGATIVE AND LVH POSITIVE PATIENTS

There were no statistically significant differences between Group 1 and 2 patients by any classification, either in the total number of patients with positive results, or in the number of positives for any particular specimen tested or for all the tests together. (Table 11.1)

Similar numbers of patients were tested in Groups 1A and 2A for each of the specimens sent for investigation. However, when patients were re-allocated to form different groupings (see Chapter 4), there was a significantly larger number tested by blood culture and serology in patients LVH positive at any stage (Group 2C>1C, $p<0.005$), and at the end of the study (Group 2T>1T, $p<0.025$). This resulted in a preponderance of the total number of LVH positive patients tested (Group 2C>1C, $p<0.025$).

This distribution might be expected to result in the number of positive results being over-represented in these groups but this was not so, partly because of the small numbers of positive results obtained from blood culture or serology (8 out of 56 patients, and 9 out of 68 specimens tested).

Comment

Virus isolation in EFE is most unusual,[255,274,357] so that the relatively high yield in LVH positive patients in this study is suprising. According to Lerner and co-workers,[310,311] the evidence is insufficient for a cause-and-effect relationship, but Waterson[548] points out that a high order association is rarely achieved. It is possible that these viruses caused intercurrent infections which precipitated the clinical presentation of underlying EFE.

5. RESULTS - VIRUSES IDENTIFIED

All viruses identified, in relation to the date of presentation and number of patients investigated, are noted in Table 11.2.

A wide variety of viruses (9 in all) was detected.

TABLE 11.2 Viruses identified in the total series (Groups 1, 2 and 3). in relation to date of presentation and number of patients investigated.

YEAR	NO OF PATIENTS	NO INVESTIGATED	MONTH	VIRUS ISOLATED	CASE NO
1970	10	5	SEPTEMBER	ECHOVIRUS (? TYPE)	66
			OCTOBER	ECHOVIRUS TYPE 9	51
			DECEMBER	MEASLES *	58
1971	7	4		NIL	
1972	16	15	APRIL	HERPES HOMINIS	52
			MAY	HERPES HOMINIS	117
			OCTOBER	CYTOMEGALOVIRUS**	2
			"	ECHOVIRUS	4
			"	COXSACKIE VIRUS A	36
			NOVEMBER	COXSACKIE VIRUS B	28
			DECEMBER	ENTEROVIRUS (? TYPE)	54 +
1973	33	17	APRIL	POLIOVIRUS TYPE 2	32
			JULY	HERPES HOMINIS **	120
			"	ADENOVIRUS	71
			SEPTEMBER	ADENOVIRUS	94
			OCTOBER	ADENOVIRUS	45
			"	RUBELLA *	6
1974	37	26	FEBRUARY	CYTOMEGALOVIRUS**	103
			MAY	PARA INFLUENZA TYPE 3	14
			SEPTEMBER	HERPES SIMPLEX	81
			NOVEMBER	ADENOVIRUS ; MEASLES*	97
			DECEMBER	ADENOVIRUS	108
1975	13	7	JULY	COXSACKIE VIRUS B	104
			JULY	PARA INFLUENZA TYPE 3 or 4	133+
1976	20	4	SEPTEMBER	ENTEROVIRUS (? TYPE)	27

* Virus detection by serology.
** Virus detection by culture and serology.
All other viruses were identified by direct culture.
\+ Virus detected post-mortem.

Enteroviruses comprised 36% (9/25) of all viruses identified.

The majority of viruses was detected in the second half of the year (20/25) which coincided with the maximum seasonal incidence of case presentations (see Chapter 5). Furthermore, despite the paucity of numbers of each type, certain viruses appeared to cluster together in time. For instance, echovirus was isolated in 2 cases in September-October 1970, Herpes hominis virus in 2 cases in April-May 1971, Coxsackievirus and an unidentified enterovirus in 3 cases in October-November 1972 (though the Coxsackieviruses appeared to be of two distinct types), adenovirus in 3 cases, coincident with a major outbreak of AM in July-October 1973, and adenovirus again in 2 cases in November-December 1974.

5.2 COMPARISON OF LVH NEGATIVE AND LVH POSITIVE PATIENTS

Frequency of isolation of specific viruses was assessed in LVH negative and positive patients on admission, since this classification coincided with the timing of virus investigations. (Table 11.3)

Of the 9 enteroviruses, 8 occurred in LVH negative patients (Group 1A) and only 1 in LVH positive patients (Group 2A). Other viruses were equally distributed between Group 1A and 2A patients.

Comment

The enteroviruses (especially Coxsackievirus,[69,134,155,171,196,186,230,246,262,258,280,277,309,372,468,386,528,534,171] and less commonly echovirus[36,280,337] and poliovirus[237,267,391,520]) are well-recognised causes of AM,[562] and their relative preponderance in suspected AM cases compared with suspected EFE patients in this study comp[illegible]ies with this experience.

TABLE 11.3 Viruses isolated in patients without (Group 1) and with (Group 2) LVH on ECG on admission (A).

VIRUS	NUMBER ISOLATED		
	GROUP 1A (16)	GROUP 2A (9)	TOTAL
ENTEROVIRUSES	8	1	9
COXSACKIE	2	1	3
ECHO	3	0	3
POLIO	1	0	1
UNIDENTIFIED	2	0	2
OTHER VIRUSES	8	8	16
ADENO	2	3	5
HERPES	2	2	4
MEASLES	1	1	2
CYTOMEGALO	1	1	2
PARA INFLUENZA	1	1	2
RUBELLA	1	0	1

Many of the other viruses identified in this study have been reported to cause AM in isolated cases, such as adenovirus,[233] measles,[416] rubella,[10,11] Herpes simplex[576,558] and cytomegalovirus,[73,569] the latter having been implicated in EFE as well.[529] There have been no previous reports of Herpes homininis or parainfluenzavirus being associated with either AM or EFE.

CONCLUSION

The association of virus infection with the clinical condition in this study is of a low-order, as defined by the stringent criteria of Lerner and Wilson.[310] However, the concurrence of positive results with the maximum incidence of case presentations, the tendency for the same viruses to cluster together during these time-periods, and the correlation of enteroviruses with suspected AM, encourages the belief that these organisms were aetiologically significant, either as causative (AM) or precipitating (EFE) agents.

In terms of the objective of this study, it is apparent that there was no significant difference in the overall yield of virus between patients with and those without LVH on ECG.

Assuming that LVH positivity on ECG correlates with EFE, it may be concluded

(i) that viruses play an aetiological role at the time of presentation in both AM and EFE,

(ii) that enteroviruses are particularly associated with sporadic AM, and

(iii) that a wide variety of other viruses may be causal in AM and precipitant in EFE.

CHAPTER 12

NATURAL HISTORY

The 123 patients in the clinical series were initially followed from the time of their admission after the onset of the study in June 1970 till December 1976 (a study period of 6 years 7 months), at which point patients were classified into LVH positive or negative groups for comparative purposes (see Chapter 4). No new cases were admitted to the study thereafter, but observation was maintained for a further 2 years 3 months (observation period), so that the total follow-up period was 8 years 10 months.

The long-term progress of these patients is discussed under the following headings:

(i) Review of classification,

(ii) Duration of follow-up,

(iii) Interim course and mortality,

(iv) Final status.

1. REVIEW OF CLASSIFICATION

Patient allocations to each group as at the end of the study period (December 1976) were reviewed at the end of the follow-up period (March 1979). There was

no change of group allocation in the A-type classification (LVH negative or positive on admission). Similarly, because no patient developed LVH for the first time after December 1976, the number of patients in Groups 1C and 2C (LVH negative or positive at any stage of the course) remained constant.

However, the T-type classification required alteration because resolution of LVH after December 1976 occurred in 5 of the 27 LVH positive patients (no's 58, 102, 103, 116, 121), resulting in their conversion from Group 2T (now 22 patients) to Group 1T (now 101 patients). Since 18 of the Group 2T patients died and 3 have been transferred or lost to follow-up after 19 to 48 months (no's 97, 108 and 118) there is only 1 patient (no 123) still being observed with persistent LVH (after 55 months). This form of classification was therefore not used for comparing LVH negative and positive patients in this chapter.

2. DURATION OF FOLLOW-UP

The duration of observation till death or final clinical, radiological, and ECG examination for each patient is tabulated in Appendix G. The mean duration of follow-up in each group is noted in Table 12.1. The C-type classification was used to compare LVH negative with LVH positive patients since this included patients who developed LVH at any stage.

2.1 CLINICAL

During the total follow-up period, 32.5% (40/123) of patients died within 1 day to 386 days after presentation. The 83 survivors were followed for 19 days to 104 months. Of these, 2 were lost to follow-up early, 23 days and 19 days after admission (case no's 38 and 93, respectively) ; and 5 patients (no's 33, 73, 76, 79 and 118) were transferred to their referral centres for continuation of management, 34 days to 19 months (mean of 6.4 ± 3.27 months) after admission.

TABLE 12.1 Duration (mean ± standard error of mean) of Clinical, Radiological and Electrocardiographic Follow-up of survivors and deaths in patients without (Group 1) and with (Group 2) LVH at any stage (C).

PATIENT STATUS	DURATION OF FOLLOW-UP			
	GROUP		t	TOTAL SERIES (123)
	1C (71)	2C (52)		
SURVIVORS (months)	(51)	(32)		(83)
CLINICAL	41.7 ± 3.95	50.3 ± 4.29	-1.426	45.0 ± 2.96
RADIOLOGICAL	31.5 ± 3.53	37.7 ± 4.42	-1.092	33.9 ± 2.76
ECG	34.7 ± 4.05	41.4 ± 4.46	-1.083	37.3 ± 3.03
DEATHS (days)	(20)	(20)		(40)
CLINICAL	31.5 ± 15.07	81.3 ± 21.06	-1.923	56.4 ± 13.39
RADIOLOGICAL	19.6 ± 9.33	67.5 ± 18.65	-2.300*	43.5 ± 10.98
ECG	19.6 ± 13.32	65.4 ± 18.97	-1.976	42.5 ± 12.02

Total number of patients in each group and sub-group indicated in parentheses.
t = statistical evaluation by student's t-test for unpaired samples
* = difference is statistically significant at $p < 0.05$
All other differences are not significant.

The remaining 76 patients (91.6%) were followed for 3 to 104 months with a mean of 48.7±5.59 months.

There was no significant difference in mean duration of follow-up between LVH negative and LVH positive patients among survivors and deaths. (Table 12.1)

Comment

There are few reported studies on the natural history of either AM[300] or EFE.[87,533] Sellers et al[476] followed 33 patients with clinical EFE for 2 to 8 years, but the author has been unable to find a single detailed report on the natural history of AM in children, and very few in adults.[39,40,453]

Greenwood et al[195] retrospectively reviewed a 20 year experience of 161 patients with primary myocardial disease (including chronic non-obstructive cardiomyopathy, AM and EFE). Although the mean duration of follow-up was 55 months in the 104 survivors compared with 45 months in 80 survivors in the present series, the percentage observed for over 2 years was 40.4% (65/161) compared with 49.6% (61/123) in this study. Recently, Ribierre et al [430] reported their experience of "apparently primary acute heart failure" (including AM, EFE and COCM) in 61 infant survivors followed for a 5 to 20 year period.

2.2 RADIOLOGICAL

The duration from admission until the final chest x-ray was performed varied from 4 days to 95 months in survivors and from 1 day to 330 days in patients dying. The mean duration of observation among the latter patients was significantly longer in LVH positive than in LVH negative patients (Table 12.1).

Comment

This result confirms the more protracted course in patients with EFE.

2.3 ELECTROCARDIOGRAPHIC

The duration from admission until the last ECG was performed varied from 2 days to 96 months in survivors and from 1 day to 330 days in patients dying. There was no significant difference in mean duration of follow-up between LVH negative and LVH positive patients among survivors and deaths (Table 12.1).

3. INTERIM COURSE AND MORTALITY

3.1 CLINICAL

(a) READMISSIONS

In general, patients continued to improve after initial hospitalisation, but 22 patients required readmission on 25 occasions 8 to 345 days (mean $\pm$SEM of 81.6 ± 17.0 days) after discharge. Readmission was precipitated by cardiac decompensation (17 instances) - mainly due to failure to take medication (10) or pneumonia (3) - or by pneumonia itself (8).

There was no significant difference between Group 1 and 2 patients in either type A or C classifications, in respect of the delay between admissions or the duration of admissions themselves (Table 12.2). However, the incidence of readmission was significantly greater statistically in LVH positive than in LVH negative patients on admission (Group $2A > 1A$, $p < 0.05$).

Comment

This finding suggests that patients presenting with established EFE are more resistant to treatment and run a more protracted course than those with AM or those developing EFE (LVH) later.

TABLE 12.2 Readmissions. Number of patients readmitted, and duration of readmissions and between admissions, in patients without (Group 1) and with (Group 2) LVH on admission (A) and at any stage of the course (C).

	NUMBER OF PATIENTS					
	GROUP		X^2	GROUP		X^2
	1A (92)	2A (31)		1C (71)	2C (52)	
READMISSIONS	14	11+	4.696 *	11	14+	1.882
DEATHS	1	3	≠	1	3	≠
	DURATION (DAYS) - MEAN ±SEM					
	1A (14)	2A (11)	t	1C (11)	2C (14)	t
BETWEEN ADMISSIONS	84.7 ±25.53	77.6 ±22.08	0.203	57.2 ±15.92	100.8 ±27.03	-1.294
READMISSIONS	37.4 ±13.05	29.1 ±11.20	0.469	26.9 ±7.35	24.9 ±9.00	0.164

Total number of patients in each group appears in parentheses.
+ Including 3 patients readmitted twice.
X^2 statistical evaluation by Chi-square analysis
* Significant difference at $p < 0.05$
≠ too small for statistical analysis
t Statistical evaluation by Student's t-test for unpaired samples
No significant differences are demonstrated.

(b) MORTALITY

In addition to the 23 patients dying during the first admission (Appendix B and Table 7.5), and the 4 during readmission (Table 12.2), 13 died at home or were brought to hospital in a terminal condition.

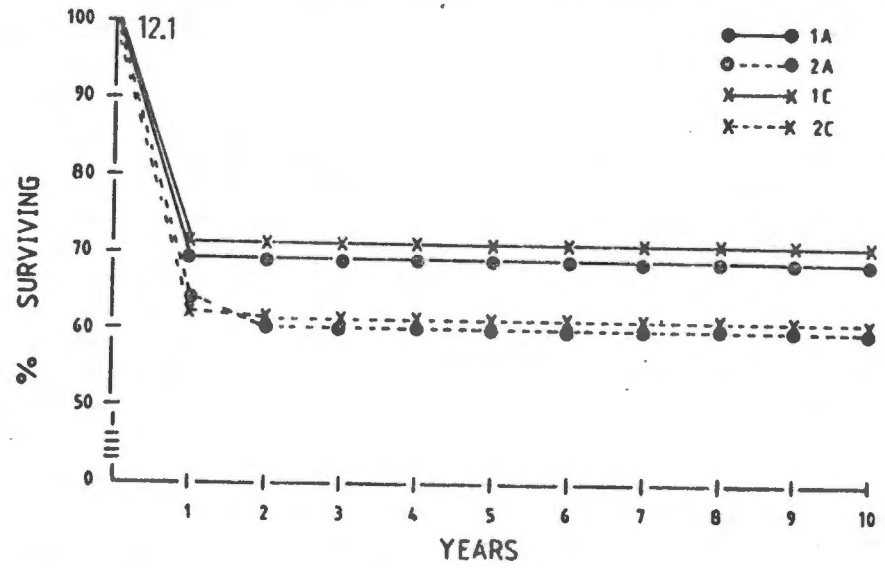
Actuarial survival curves[17,97,204,358] for LVH positive and LVH negative patients in the type A and C classifications are depicted in Figures 12.1 and 12.3. The percentage follow-up of survivors (number of patient-months observed divided by the total possible, including patients lost or removed[358]) up to the end of the follow-up period was 69.3%.

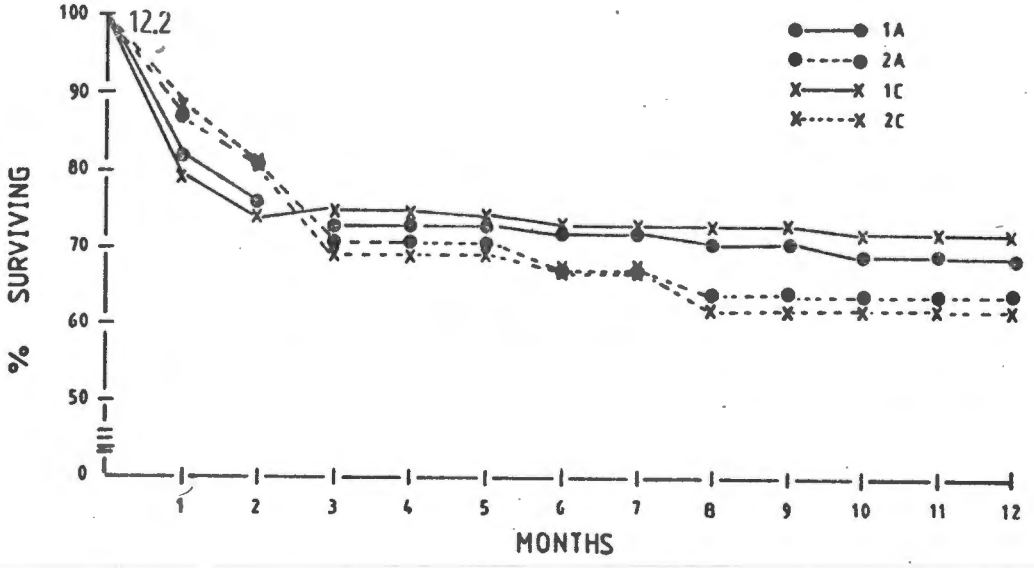
It is apparent from Figure 12.1 that almost the entire fall in survival occurred during the first year after presentation. Only 1 patient (no 112) died after this period (at 13 months). The survival curves of the LVH positive groups (2A and 2C) were approximately 10% lower than the LVH negative groups (1A and 1C) from 2 years onwards.

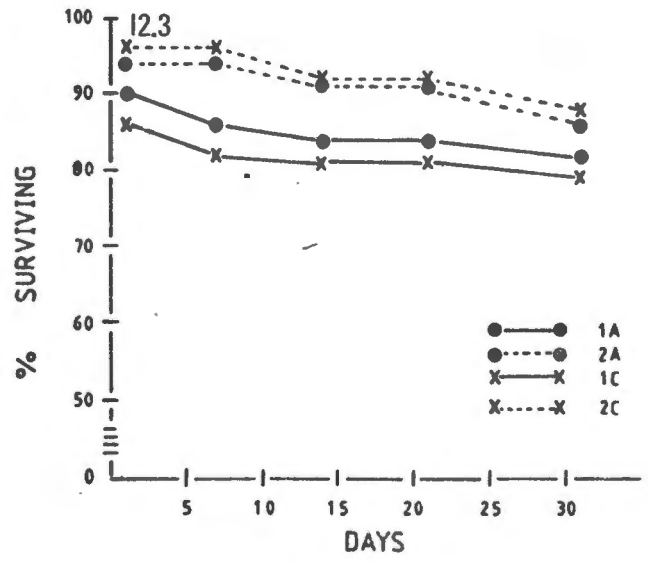
More detailed survival curves for the first year are depicted in Figure 12.2. Group 1 curves fell more acutely than Group 2 curves during the first month but showed little change after the second month. Group 2 curves dropped at a slightly slower rate but for a period of 3 months, to reach a lower level than Group 1 patients.

Figure 12.3 details the survival curves during the first month and highlights the fact that Group 1 curves fell more rapidly than Group 2 curves, particularly during the first 48 hours.

There was no statistically significant difference between Group 1 and 2 patients in respect of the overall or early (<1 day) mortality rates in the







FIGS. 12.1-3 ACTUARIAL SURVIVAL CURVES in patients without (Group 1) and with (Group 2) LVH on admission (Groups 1A and 2A) and at any stage (Groups 1C and 2C) during the total period of follow-up (Fig. 12.1), the first year (Fig. 12.2), and the first month (Fig. 12.3).

total series. (Table 12.3). However, early deaths in relation to total mortality were significantly less frequent in patients who developed LVH at any stage than in LVH negative patients (Group 2C>1C, $p<0.01$).

Comment

It may be concluded that long-term survival was slightly better in patients with AM than in those with EFE. However, AM patients ran a more fulminant course in the first months, and particularly in the first 48 hours, while mortality in EFE patients occurred mainly between 1 and 3 months. This is exemplified by the mean survival rates at 48 hours, 1 month, 3 months and 1 year, respectively, of 86%, 79%, 75% and 71% in LVH negative patients (Group 1C) and 96%, 89%, 69% and 63% in LVH positive patients (Group 2C). The mean survival rates at these times for the series as a whole were 90%, 83%, 72% and 68%, respectively.

High mortality rates early in the course have been recorded in AM epidemics,[163, 171, 262, 283] and in one report 12 of 13 proven cases of sporadic AM succumbed within 1 month.[195] The majority of deaths in EFE have been reported to occur within 2 years,[84] 18 months[226] or 1 year (17 of 20 proven cases),[195] but may be sudden and unexpected.[573]

3.2 RADIOLOGICAL

The cardio-thoracic ratio (CTR) on admission and terminally, the maximum and minimum CTR during the course, and their timing after presentation, are presented in Appendix H. The mean admission, maximum, minimum and final CTR's are summarised in Table 12.4.

(a) COMPARISON BETWEEN SURVIVORS AND PATIENTS DYING

There was no significant difference between survivors and deaths in admission

TABLE 12.3 Overall and early mortality rates in patients without (Group 1) and with (Group 2) LVH on admission (A) and at any stage of the course (C).

MORTALITY RATE	NUMBER OF PATIENTS					
	GROUP		X^2	GROUP		X^2
	1A	2A		1C	2C	
TOTAL SERIES	(92)	(31)		(71)	(52)	
OVERALL	28	12	0.396	20	20	1.018
EARLY*	10	2	0.135	10	2	2.506
TOTAL DEATHS	(28)	(12)		(20)	(20)	
EARLY*	10	2	0.686	10	2	6.944+

Total number of patients in each group indicated in parentheses.
*≪1 day
X^2 statistical evaluation by Chi-square analysis
+ difference significant at $p < 0.01$

TABLE 12.4 Radiological Cardiomegaly. Comparison of admission, maximum, minimum and final cardiothoracic ratios in survivors and deaths.

	CTR %				t-statistic		
	ADM	MAX	MIN	FIN	ADM *cf* MAX	MIN *cf* FIN	ADM *cf* FIN
SURVIVORS (83)	64.9 ±0.62	66.3 ±0.54	53.8 ±0.45	55.3 ±0.43	-1.794	-2.308 **	12.145 ⊕
DEATHS (39)o	65.9 ±0.94	68.4 ±0.96	62.8 ±0.77	65.6 ±0.97	-1.841	-2.208 *	0.260
t-statistic							
SURVIVORS *cf* DEATHS	-0.944	-1.977	-10.613 ⊕	-11.228 ⊕			

Number of patients in each group indicated in parentheses.
o No x-rays available in patient No. 39
CTR% - percentage cardio-thoracic ratio
ADM - on admission
MAX - maximum at any stage of the course
MIN - minimum " " " " " "
FIN - final x-ray performed at end of follow-up or prior to death
cf - compared with
t - statistical evaluation by t-test for unpaired samples
* - difference significant at $p < 0.05$
** - " " " $p < 0.025$
⊕ - " " " $p < 0.001$

or in maximal heart size (though in the latter case the CTR was greater in patients who died, $p < 0.10, > 0.05$). However, both the minimal and final CTR's were very significantly greater in patients dying than in survivors ($p < 0.001$ in each case).

Comment

It is to be expected that the CTR in patients dying would remain large, and this finding is unlikely to reflect an intrinsic difference between these two patient categories. Heart size on admission is reported to be of no prognostic value in determining outcome,[225,339,506] except for one series.[476]

(b) COMPARISON BETWEEN LVH NEGATIVE AND LVH POSITIVE PATIENTS

Statistical analysis revealed no significant differences between LVH negative (Group 1C) and LVH positive (Group 2C) patients in respect of mean admission, maximum, minimum and final CTR's.

(c) COMPARISON BETWEEN ADMISSION AND MAXIMUM CTR's

The mean maximum CTR was greater than the mean admission CTR among survivors and patients dying, but the differences were not statistically significant.

(d) COMPARISON BETWEEN MINIMUM AND FINAL CTR's

The mean minimum CTR was significantly smaller than the mean final CTR among both survivors and patients dying ($p < 0.025$ and < 0.05, respectively), though both mean values in survivors were within the normal range.

Comment

It was expected that patients dying would have larger hearts terminally but this finding in survivors was not anticipated and reflects the considerable variability of CTR in individual cases during the course, the final CTR being

larger than the minimum CTR in as many as 53 patients.

(e) COMPARISON BETWEEN ADMISSION AND FINAL CTR's

There was a highly significant decrease in mean CTR from admission to the final films in survivors ($p<0.001$), but no significant difference in patients dying.

Comment

The persistence of marked cardiomegaly (indicative of heart failure) despite adequate therapy is a poor prognostic sign, as pointed out by others.[22,195,225,339,364]

3.3 ELECTROCARDIOGRAPHIC

The ECG features throughout each patient's course is tabulated in Appendix D and discussed in detail in Chapter 9.

4. FINAL STATUS

Each patient's status at the last clinical, radiological, or ECG examination at the end of the observation period, or before death, is tabulated in Appendix G. The number of patients allocated to normal, probable normal and abnormal categories is indicated in Table 12.5.

4.1 CLINICAL

Of the 83 survivors, 74 were clinically normal ; 5 patients were probably normal in that the LV apex was either slightly displaced but not prominent, as frequently seen in normal young children with distended abdomens, or slightly prominent in the normal position, as often seen in anxious patients. There were only 4 patients (4.8%) with definite LVH on palpation.

TABLE 12.5 Final clinical, radiological and electrocardiographic status among survivors and deaths.

CONCLUDING STATUS	NUMBER OF PATIENTS					
	SURVIVORS (83)			DEATHS (40)		
	N	PROB N	AbN	N	PROB N	AbN
CLINICAL	74	5	4	-	-	-
X-RAY	55	19	9	3	1	36
ECG	55	14	14	1	1	38

Total number of patients in each group appears in parentheses.
N = normal
PROB N = probable normal, as defined in sections 4.1, 4.2 and 4.3
AbN = abnormal

TABLE 12.6 Cardiothoracic ratio (CTR) in control patients during inspiration and expiration.

NAME	AGE (years)	CTR %	
		INSPIRATION	EXPIRATION
LA	8.0	44.6	50.5
GL	11.0	49.3	53.2
NA	9.5	46.7	50.5
LH	7.0	42.9	41.1
VN	7.0	50.0	55.7
CA	6.5	47.8	54.4
AB	9.0	43.7	44.6
LB	8.0	46.0	54.9
MEAN ±SEM	8.25 ±0.53	46.4 ±0.91	50.6 ±1.85

4.2 RADIOLOGICAL

In the final x-rays a normal CTR (less than 55%) was demonstrated in 42 of the 83 survivors. Hence, as many as 49.4% (41/83) of patients were in the abnormal range as defined (page 23).

Comment

The interpretation of the CTR at any time was complicated by two factors. Firstly, the CTR varied considerably depending on the phase of respiration during exposure, the degree of abdominal distention present and the state of sedation or otherwise of the patient at the time. In a control series of 8 normal older children aged between 6½ and 11 years (in whom these factors are even less likely to operate) the difference in CTR between inspiration and expiration was a mean $\pm$SEM of 4.7$\pm$0.93% (Table 12.6), so that incorrect classification was highly likely. For this reason patients with a CTR% between 55 and 60% in the final films were regarded as probably normal.

Secondly, wide fluctuations in CTR were observed in many cases so that, despite the marked decrease in mean CTR between admission and final films in survivors (Table 12.4), mean maximum CTR during the course was greater than mean admission CTR and mean minimum CTR was significantly smaller than final CTR - see sections 3.2 (b) and 3.2 (c). For this reason patients with a final CTR% between 55 and 60% who had CTR's of under 55% in earlier films were regarded as normal.

Revised status

Of the 32 survivors with a final CTR of between 55 and 60%, 13 had a previous CTR of under 55%. Hence, of the 83 survivors, 55 were classified normal, 19 probably normal and 9 abnormal.

Among the 40 patients who died, 1 was similarly reclassified normal and 1 probably normal, giving final figures of 3 normal, 1 probably normal and 36 abnormal (Table 12.5).

4.3 ELECTROCARDIOGRAPHIC

Details of the final ECG's are discussed in Chapter 9. Patients with minor ECG changes, including left or right axis deviation of the mean frontal QRS vector, prolonged PR interval, or decreased R/SV1 ratio, were regarded as probably normal ; those with major changes such as atrial abnormality, LVH, ST-T wave changes or arrhythmias, were regarded as abnormal. On this basis, 55 of the 83 survivors were normal, 14 probably normal and 14 abnormal. Of the 40 deaths, 1 was normal, 1 probably normal and 38 abnormal (Table 12.5).

4.4 COMPARISON OF LVH NEGATIVE AND LVH POSITIVE PATIENTS

Because of the varying LVH status during the course (see page 29), only the C-type classification (with or without LVH at any stage) was evaluated in comparing the final outcome. Probable normal patients were incorporated into the normal groups for this purpose (Table 12.7).

There were no statistically significant differences in frequency of abnormal status, clinically, radiologically or on ECG between LVH negative and LVH positive patients, among survivors or patients dying.

4.5 COMPOSITE RESULTS

The combined final results are summarised in Figure 12.4.

Of the 83 survivors, 61 were normal in all respects.

Ten patients had ECG abnormalities only. In 3 of these (case no's 29, 59 and 97) final ECG's were performed within 1 month of admission, but the patients were well 9 to 49 months later ; 2 patients (no's 52 and 93) were lost to follow-up 6 months and 19 days after admission ; and in 5 (case no's 48, 85, 95, 122 and 123) ECG abnormalities persisted for between 12 and 65 months.

Six patients had radiological cardiomegaly only; 3 (case no's 11, 79 and 102)

TABLE 12.7 Clinical, radiological and electrocardiographic status at end of study. Number of patients with residual abnormalities in Groups 1C and 2C among survivors and deaths.

CONCLUDING STATUS	NUMBER OF PATIENTS					
	SURVIVORS			DEATHS		
	GROUP		X^2	GROUP		X^2
	1C (51)	2C (32)		1C (20)	2C (20)	
CLINICAL - LVH	2	2	0.002	-	-	
X-RAY - C	5	4	0.001	16	20	2.500
ECG - AbN	5	9	3.491	18	20	0.526

Total number of patients in each group indicated in parentheses.
C = cardiomegaly; AbN = abnormal
X^2 = statistical evaluation by Chi-square analysis.
No significant differences demonstrated.

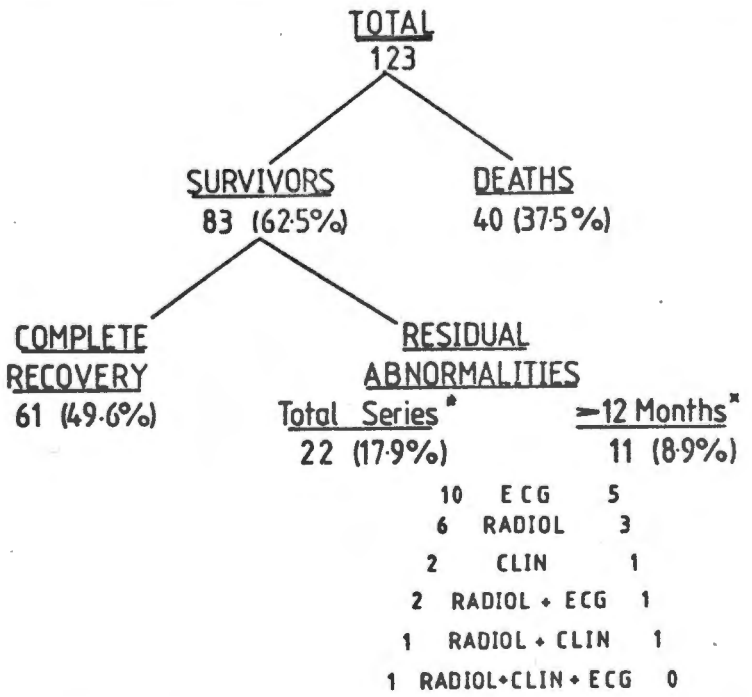


FIG. 12.4 FINAL OUTCOME. Number of patients in each category.
including patients lost to follow-up or transferred.
+ follow-up of all parameters for at least 12 months.
ECG = electrocardiographic abnormalities, RADIOL = radiological cardiomegaly, CLIN = clinical cardiomegaly (LVH).

between 1 and 8 months and 3 (case no's 21, 55 and 72) between 23 and 30 months post-admission.

Clinical cardiomegaly alone was noted in two patients (no's 32 and 106) 26 and 8 months after presentation.

Patient no 38 had clinical cardiomegaly and T wave flattening on ECG but was lost to follow-up after 23 days ; and 2 patients had radiological and ECG abnormalities at 31 and 28 months (case no 5) and 11 months and 7 days (case no 118). (The latter patient was clinically normal at 19 months but later ECG's were not available).

Only 1 patient (no 108) had clinical and radiological cardiomegaly (after 32 months) as well as ECG abnormalities (at 2 months - later ECG's not available).

None of these 22 patients was symptomatic.

Hence, where follow-up data was available in each parameter for at least 12 months, only 11 (13.3%) patients had residual abnormalities - 5 on ECG only, 3 on x-ray only, 1 clinically only, 1 clinically and radiologically, and 1 radiologically and on ECG (Figure 12.4).

Of the 40 deaths, 35 patients had abnormalities of x-ray and ECG, 3 (case no's 17, 34 and 75) had ECG abnormalities alone, and 1 (case no 6) radiological cardiomegaly alone. Patient no 2 was the only one to die with an apparently normal ECG and x-ray.

In summary, therefore, of the original 123 patients presenting with severe and acute endomyocardial disease (EMD), 32.5% died, 49.6% recovered completely, and 17.9% have residual abnormalities (8.9% after follow-up of all parameters for over 1 year).

5. DISCUSSION

5.1 ENDOCARDIAL FIBROELASTOSIS (EFE)

EFE was considered to be almost uniformly fatal[16,113,203,274] until reports in the 1960's indicated that survival was possible,[322,339] and that asymptomatic cases with residual radiological and ECG abnormalities occurred.[353,532] Recently, Hastreiter and Fisher[226] claimed that only 14% of patients with EFE survived beyond 18 months of age, while Chen et al[84] quoted a mortality rate (MR) of 44% in 132 cases diagnosed clinically and pathologically. Sellers et al[476] asserted that one-third of patients died, one-third had residual abnormalities and one-third resolved completely.

The overall MR of patients with EFE in this study - 38.7% (12/31) in those with LVH on ECG on admission and 38.5% (20/52) in those with LVH at any stage of the course - coincides with the latter estimates, but the frequency of residual abnormalities after follow-up of all parameters for at least 12 months was very low - 12.9% (4/31) in patients with LVH on admission and 11.5% (6/52) in those with LVH at any stage.

5.2 ACUTE MYOCARDITIS (AM)

Although the MR in epidemic AM is known to be high,[163,171,262,283] there is no report in the English literature of a large series of patients presenting with sporadic AM (albeit on clinical grounds) comparable to the present one.[525] The MR was 30.4% (28/92) in patients without LVH (ECG) on admission and 28.2% (20/71) in those without LVH at any stage.

There is also very little information on the long-term outcome of survivors of clinically diagnosed AM in adults[39,40,199,453] and even less in children.[43] According to Gear and Measroch,[171] survivors of epidemic neonatal AM recover completely, but Berkovich et al[43] found abnormal cardiac signs 1 to 5 years

after presentation in 5 of 12 patients diagnosed as sporadic AM on the basis of clinical and ECG evidence and positive virology.

In the present study, the frequency of residual abnormalities after follow-up of clinical, radiological and ECG parameters for at least 12 months was only 7.7% (7/91) in patients without LVH (ECG) on admission and 7.0% (5/71) in those without LVH at any stage.

5.3 ACUTE ENDOMYOCARDIAL DISEASE (EMD)

If one accepts that AM and EFE are 2 phases of one condition, i.e. acute EMD of infants and young children, then the overall frequency of abnormalities after follow-up of all parameters for at least a year was 8.9% (Figure 12.4).

This figure differs considerably from the 37.9% (61/161) incidence of residua in primary myocardial disease (PMD) in children quoted by Greenwood et al[195] (58.7% of all survivors), of whom 51 patients had ST-T wave changes, 37 had radiological cardiomegaly and 21 clinical heart failure. Ribierre et al[430] reported a slightly more favourable outcome for 61 survivors with "apparently primary acute heart failure" in infants under 30 months (including AM, EFE and COCM), followed for 5 to 20 years. Residua were found in 28 (45.9%) of whom 22 had ECG and radiological abnormalities, 3 had persistent heart failure, and 3 died subsequently.

The lower incidence of residua in the present series is probably due to the rigorous exclusion of patients with COCM wherever possible, and to the constant surveillance of patients who are being followed prospectively. This favourable outlook following a high early MR is in line with the opinion of Ribierre et al.[430]

5.4 CONCLUSION

It is therefore concluded that, despite the high early MR, the vast majority of patients with acute EMD (AM and EFE) surviving more than 1 year, and receiving adequate observation and treatment, will recover in time.

This finding, and the fact that even those patients with residua are progressively improving, makes it very unlikely that either clinical AM or EFE is a significant aetiological factor in the development of idiopathic, chronic congestive cardiomyopathy (in children), contrary to the claims of some authors.[199,457] However, the possibility that sub-clinical viral infection may be pathogenetically important through some other mechanism cannot be discounted.

CHAPTER 13

PATHOLOGY

Autopsy results were available in a total of 37 patients, including 20 from the clinical series (Group 1 and 2), 13 from the autopsy series with a short history (Group 3), and therefore comparable with the former patients, and 4 from the autopsy group with a long history (Group 4). (Appendix A).

Of the 40 deaths in the clinical series, autopsy was not possible on religious grounds in 6 instances, Moslem in 5 and Apostolic in 1 (case no's 3, 4, 13, 17, 24 and 94), and because of death at home in 4 (case no's 6, 8, 47 and 111). Permission for autopsy was refused in the remaining 10 patients (case no's 2, 16, 18, 49, 75, 91, 104, 107, 110 and 112). The clinical diagnosis of acute EMD was confirmed in all 20 patients who came to autopsy. The autopsy rate for all deaths was 65% (37/57).

The cardiac and major non-cardiac findings in the 37 patients are listed in Appendix I and summarised in Tables 13.1 to 13.4. Patients have been separated into groups according to the presence of

(i) the characteristic viral-type, mononuclear inflammatory cell infiltration, intercellularly in the myocardium, either diffusely or focally in the peri-vascular areas[482] (indicated by the letter M),

(ii) the typical features of EFE, i.e. a thickened, white or pale, opaque endocardial membrane with excessive collagen and elastic tissue on histology [497,515] (indicated by the letter F), or

(iii) features of both (indicated as M+F).

1. CARDIAC FINDINGS

1.1 MORPHOLOGY

All 15 patients with EFE were identified on macroscopic examination. The fibroelastotic endocardium was thick and obvious in the 7 patients classified F (grade 3+ in 2, and 2+ in 5) and in 6 of the 8 patients with M+F (graded 3+ in 1, and 2+ in 5). The features were less impressive in patient no 64, and in patient no 117 the endocardium was opacified but thin - histology confirmed the presence of considerable collagen and elastic tissue (Appendix I).

Generalised cardiac enlargement was noted in all groups, most commonly in patients with M+F. (Table 13.1) The appearance of a pale, flabby heart, with small pericardial effusions (5 to 20 ml), congestion, and petechiae, was typical of patients with M and uncommon in those with F or M+F, though the difference in frequency between these groups was not statistically significant (Table 13.1). Mottling tended to occur in M+F patients as well as those with M alone.

The single patient with pericarditis (case no 135) and the 2 with antemortem thromboses in the left ventricle (case no's 62 and 129) all had M alone. Both patients with intrinsic mitral valve fibrosis and distortion (case no's 138 and 140) had F alone and histories of long-standing.

Left ventricular hypertrophy (LVH) and left atrial enlargement (LAH) were more frequent in the patients with F and M+F than in those with M, the diffe-

TABLE 13.1 Pathology. Frequency of macroscopic cardiac features in patients with pathological myocarditis (M), fibroelastosis (F), and both (M+F).

MACROSCOPIC FEATURES	NUMBER OF PATIENTS				X^2
	M (22)	M+F (8)	F (7)	TOTAL F (15)	M *cf* TOTAL F
ENLARGED	13	8	2	10	0.015
PALE	7	1	1	2	0.804
FLABBY	7	1	0	1	2.011
PERIC. EFFUSION	8	1	2	3	0.494
CONGESTED	8	0	1	1	2.812
MOTTLED	12	3	1	4	1.803
PETECHIAE	5	0	1	1	0.718

Total number of patients in each group indicated in parentheses.
cf = compared with
PERIC. = pericardial
X^2 = statistical evaluation by Chi-square analysis.
No significant differences demonstrated.

TABLE 13.2 Pathology. Frequency of cardiac chamber enlargement in patients with pathological myocarditis (M), fibroelastosis (F), and both (M+F).

CHAMBER HYPERTROPHY	NUMBER OF PATIENTS				X^2
	M (22)	M+F (8)	F (7)	TOTAL F (15)	M *cf* TOTAL F
LVH	10	7	6	13	4.807 *
RVH	6	3	5	8	1.254
LAH	1	1	4	5	3.391
RAH	2	1	1	1	≠

Total number of patients in each group indicated in parentheses.
cf = compared with
LVH = left ventricular hypertrophy; RVH = right ventricular hypertrophy;
LAH = left atrial enlargement; RAH = right atrial enlargement.
X^2 = statistical evaluation by Chi-square analysis.
* = Difference significant at $p < 0.05$.

rence being statistically significant for LVH ($p<0.05$). (Table 13.2).

Comment

Macroscopic features in hearts of the M+F group tended to be similar to those in the F group and showed a similar propensity for left-sided cardiac chamber enlargement.

1.2 HISTOLOGY

Microscopically, evidence of myofibre degeneration (loss of striations, vacuolization, and pyknotic nuclei), fragmentation (disruption of cell membranes) and necrosis (destruction of recognisable myocardial cell shape with presence of cell debris, hyalinization, and collagen deposition in the myocardium), was significantly more frequent in patients with M than in those with F and M+F ($p<0.01$). (Table 13.3). Furthermore, the severe degree of myocellular destruction (necrosis) was common in patients with M (11/22) but did not occur in patients with M+F (0/8). By contrast, hypertrophy was more common in patients with F.

Inflammatory cell infiltration with mononuclear cells, mainly lymphocytes (Table 13.3), varied in intensity from diffuse and severe (3+) to patchy and moderately intense (2+), in 21/22 patients with M and 5/8 with M+F. Focal and mild (1+) inflammation was observed in 1/22 patients with M and 3/8 with M+F. Evidence of cellular infiltration was, therefore, somewhat less marked in the M+F group.

Correlation of the degree of myocardial destruction with the degree of inflammatory cell infiltration (Figure 13.1) demonstrates the tendency for patients with M to have ++ or +++ cellular infiltration associated with severe destruction (necrosis), while patients with M+F tended to have + or ++ cellular infiltration with milder or no evidence of myocardial destruction. Occasional

TABLE 13.3 Pathology. Microscopic cardiac features in patients with pathological myocarditis (M), fibroelastosis (F), and both (M+F).

MICROSCOPIC FEATURES	NUMBER OF PATIENTS				X^2
	M (22)	M+F (8)	F (7)	TOTAL F (15)	M *cf* TOTAL F
MYOFIBRES:					
DEGENERATION	8	2	2	4	
FRAGMENTATION	5	2	0	2	
NECROSIS	11	0	0	0	
⩾1 ABNORMALITY	17	2	2	4	7.359+
HYPERTROPHY	1	1	4	5	3.391
INTERSTITIUM:					
LYMPHOCYTES	15	1	-		
MONOCYTES	1	0	-		
PLASMA CELLS	4	1	-		
HISTIOCYTES	1	1	-		
MONONUCLEARS	5	7	-		
⩾1 ABNORMALITY	22	8	-		
CONGESTION	8	2	2	4	0.068

Total number of patients in each group indicated in parentheses.
cf = compared with
X^2 = statistical evaluation by Chi-square analysis.
\+ = Difference significant at $p < 0.01$.

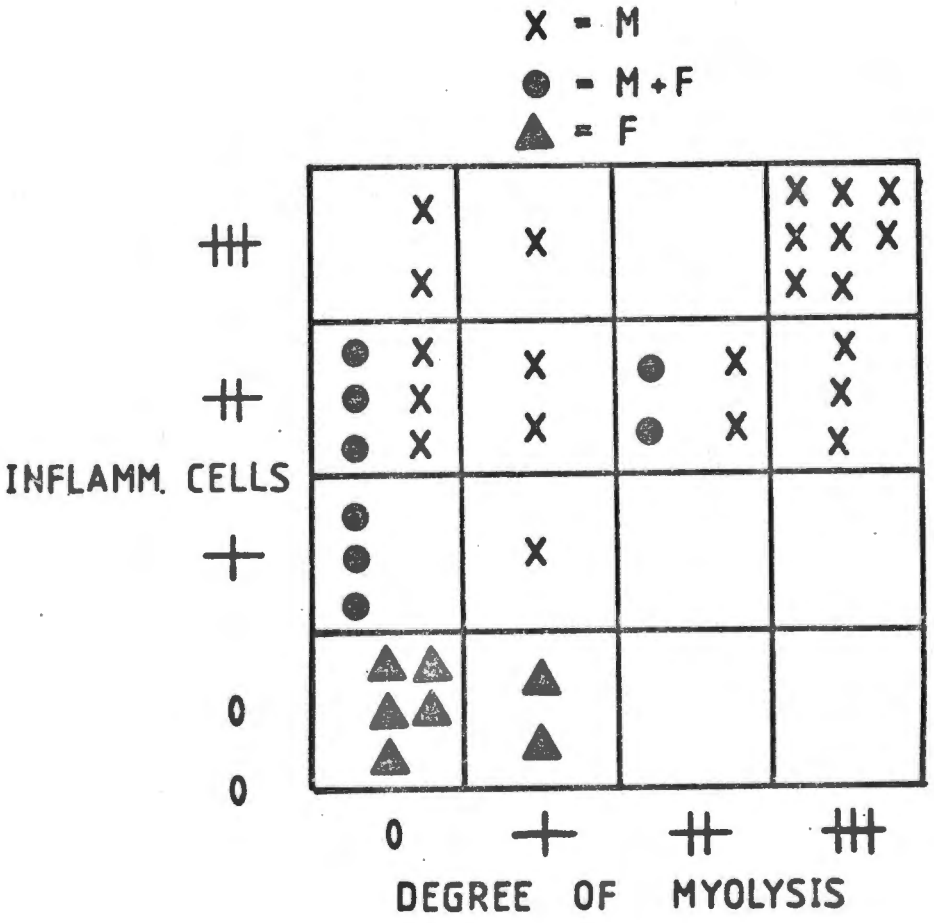


FIG. 13.1 PATHOLOGY. Correlation of degree of myocardial cell destruction (+ = degeneration; ++ = fragmentation; +++ = necrosis) with inflammatory cell infiltration (+ = mild and focal; ++ = moderate and patchy; +++ = severe and diffuse).

patients with F had degenerative changes but no inflammatory cells (by definition).

Comment

The coexistence of features of both AM and EFE in 21.6% (8/37) of patients is highly suggestive of a common aetiological factor. The fact that this group (M+F) manifests varying grades of pathology intermediate between AM with acute inflammation and myocardial necrosis at one end of the spectrum, and EFE with chronic endocardial fibroelastotic "reaction" and myocardial hypertrophy at the other, supports the contention that EFE may evolve from AM over a period of time.[255,467]

Further evidence in favour of this conclusion includes the high incidence of interstitial myocarditis in patients with EFE reported by Frühling et al,[166] Schryer and Karnauchow[467] and others[43,126,255,512,466] (see page 9 for further details). Several of these authors[166,255] also described necrosis (as in this study), fibrosis and even calcification in the interstitium, which refutes the findings of Weinberg and Himmelfarb[555] and others[415,426] that myocardial scars are absent in EFE. The disappearance of these features may be time-dependent as suggested by Hutchins and Vie,[255] who found trivial or no myocarditis if EFE persisted for more than 4 months. These authors also emphasized the gradation of pathological features, as found in the present series.

2. NON-CARDIAC FINDINGS

A summary of the major non-cardiac pathology appears in Table 13.4.

Pathological features of viral pneumonitis and/or bronchiolitis occurred in 78.4% (29/37) of the autopsy cases, and were equally common in patients with M,

TABLE 13.4 Pathology. Non-cardiac findings in patients with pathological myocarditis (M), fibroelastosis (F) and both (M+F).

PATHOLOGY	NUMBER OF PATIENTS				X^2
	M (22)	M+F (8)	F (7)	TOTAL F (15)	M *cf* TOTAL F
VIRAL PNEUMONITIS	17	7	4	11	0.014
" BRONCHIOLITIS	8	3	2	5	0.026
⩾1 ABNORMALITY	18	7	4	11	0.044
BACTERIAL PNEUMONIA	4	0	3	3	0.083
- PRIMARY	2	0	2	2	≠
- SECONDARY	2	0	1	1	≠
LYMPHOID HYPERPLASIA	18	6	4	10	0.442
PULMONARY CONGESTION	10	5	4	9	0.283
HEPATIC CONGESTION	16	0	4	4	5.877
- FATTY CHANGE	12	4	4	8	0.111
- CIRRHOSIS	0	1	0	1	≠
⩾1 ABNORMALITY	16	5	7	12	0.014
RENAL CONGESTION	5	1	1	2	0.083
- INFARCTS	2	0	0	0	≠
- ACUTE TUBULAR NECROSIS	1	1	0	1	≠
- ACUTE GLOMERULO-NEPHRITIS	1	0	1	1	≠
⩾1 ABNORMALITY	9	2	2	4	0.292
CEREBRAL OEDEMA	7	2	0	2	0.804
- INFARCT	1	0	0	0	≠
- MENINGITIS	1	2	0	2	≠
- ANOXIA	4	2	2	4	≠
⩾1 ABNORMALITY	13	6	2	8	0.0001
SPLENIC CONGESTION	4	1	2	3	≠
- INFARCT	2	0	0	0	≠
⩾1 ABNORMALITY	6	1	2	3	0.014

Total number of patients in each group indicated in parentheses.

X^2 = statistical evaluation by Chi-square analysis.

No significant differences demonstrated.

cf = compared with

F or M+F. Bacterial pneumonia was an occasional complication.

Reactive lymphoid tissue (in lymph nodes, intestine or spleen) typical of viral infection was also common, occurring in 75.7% (28/37) of all cases, and was equally distributed in the three groups.

Pulmonary, renal and splenic congestion due to heart failure occurred with similar frequency in the three pathological groups, though hepatic congestion was almost significantly more common in M than in groups with F ($p<0.10, >0.05$).

Renal (2), splenic (2) and cerebral (1) infarction was limited to patients with M alone.

Evidence of shock, i.e. acute tubular necrosis and cerebral oedema and anoxia, was observed in all groups.

There were no statistically significant differences in frequency between the three groups for any of the pathological conditions noted in Table 13.4.

Comment

Although the pathological involvement of organs other than the heart is well-known in AM,[155,230,171,279,262,361] this aspect has received little, if any, attention in EFE. The striking feature in this study is the equal prevalence of viral-induced pathology (mainly pulmonary and lymphatic) in patients with AM (19/22), EFE (5/7) or both (7/8). It is tempting to conclude that this evidence "proves" a common viral aetiology in both conditions. In patients with AM, it is reasonable to assume that the current viral infection is aetiological. But it is difficult in patients dying soon after presentation with AM plus EFE, and especially with EFE alone, to equate the acute inflammation in non-cardiac organs with the more chronic fibroelastotic process in their hearts. It is more probable that patients with (sub-clinical) AM develop EFE in the course of time, and that an intercurrent infection precipitates its clinical expression.

3. CORRELATION WITH CLINICAL FINDINGS

Detailed clinical data was available in 20 autopsy patients.

3.1 ECG

LVH on ECG, defined according to RV1 and SV6 voltages (see page 24), was present in 2 of 14 patients with M, 2 of 4 with M+F and 1 of 2 with F. If the R/SV1 ratio is included as a criterion for LVH, the proportion of patients with LVH increases to 4/14, 3/4 and 2/2, respectively. Although these numbers are too small for accurate evaluation, the greater frequency of LVH in the M+F and F groups compared with the M group was just short of statistical significance ($X^2 = 3.117$, $p < 0.10 > 0.05$).

Other ECG abnormalities were equally distributed in the 3 groups, except that pathological Q waves (3 patients) occurred in the M group only.

The incidence of autopsy-proved fibroelastosis in LVH negative and positive patients, classified as in Chapter 4, was also assessed (Table 13.5). The T-type classification (LVH status at the end of the study period or preterminally) was included, since this represented the ECG findings closest in time to the autopsy data.

The incidence of F, relative to the total number of patients in each group, was almost significantly greater in Group 2A than 1A ($p < 0.10 > 0.05$), and significantly greater in Group 2T than 1T ($p < 0.005$). Similarly, relative to the total PM's performed, F was almost significantly more frequent in Group 2A than 1A and in Group 2C than 1C ($p < 0.10 > 0.05$), and significantly more frequent in Group 2T than 1T ($p < 0.05$).

TABLE 13.5 Frequency of autopsy-proved EFE in patients without (Group 1) and with (Group 2) LVH on ECG on admission (A), at any stage (C) or terminally (T).

CATEGORY	NUMBER OF PATIENTS								
	GROUP^{o}		X^2	GROUP^{o}		X^2	GROUP^{o}		X^2
	1A	2A		1C	2C		1T	2T	
TOTAL F	2	4		1	5		1	5	
RELATIVE TO:									
TOTAL PATIENTS	92	31	3.673	71	52	2.768	96	27	10.361$^{\Phi}$
TOTAL DEATHS	28	12	2.698	20	20	1.765	22	18	2.567
TOTAL PM's	14	6	3.277	11	9	3.117	12	8	4.375*

o = Clinical groups defined as in Chapter
F = pathological endocardial fibroelastosis alone (2) or with myocarditis (4)
X^2 = statistical evaluation by Chi-square analysis
* = difference significant at $p < 0.05$
Φ = " " " $p < 0.005$

Comment

The correlation of EFE with LVH on ECG supports the conclusion of several authors[226,302,364,476] that this is the most helpful diagnostic sign for EFE. In autopsy-proved cases, LVH has been found in 10 of 14,[195] 17 of 21,[368] 19 of 21,[352] 20 of 23,[476] and 19 of 20[466] cases.

The fact that this correlation is strongest when LVH is present pre-terminally, rather than on admission or transiently during the course

(i) indicates that EFE is closely related to concurrent LVH, and

(ii) suggests that EFE itself may be mild and reversible, contemporaneously with resolving LVH.

Mild or sub-clinical EFE is supported by the demonstration of EFE at autopsy in 3.4% of infants with overtly normal hearts.[548] Serial endomyocardial biopsies would be required to prove the resolution of clinical EFE.

3.2 PNEUMONIA

Although pneumonia was confirmed in all 6 cases diagnosed radiologically during life, there were 10 additional cases from the clinical series not previously diagnosed.

Comment

This finding emphasises the high frequency of clinically undetected viral disease in the lungs in all groups.

3.3 SHOCK

Clinical shock was previously diagnosed in 8 of 14 patients with M, and 2 of 6 with F (both with M+F).

Comment

The prevalence of shock in patients with pathological myocarditis coincides with the high frequency in those with clinical myocarditis (see page 57).

3.4 OTHER FINDINGS

Elevated blood urea and/or urinary abnormalities were detected pre-mortem in 5 of 13 patients with M, and 2 of 6 with F. Cerebral abnormalities were observed clinically in 2 patients with M and 1 with M+F.

CHAPTER 14.

CONCLUSIONS.

The relationship, if any, between AM and EFE has perplexed paediatricians, cardiologists and pathologists for generations. It appears that no previous study has evaluated their possible relationship by a comprehensive clinical, natural history and pathological study of these two conditions, prospectively and simultaneously, over the long-term.

A project of this nature was undertaken in Cape Town over a period of almost 9 years and the findings are reviewed in the preceding chapters. The results, which are coordinated in this chapter, lead to support of hypothesis A "that AM and EFE represent different phases of the same disease process," and rejection of hypothesis B, "that either AM or EFE evolves into idiopathic chronic congestive cardiomyopathy in children."

VALIDITY OF LVH ON ECG AS AN INDEX OF CLINICAL EFE

Without histological evidence from endomyocardial biopsy, differentiation of clinical EFE from AM depends on the presence of LVH on ECG. The reliability of this sign has been emphasised by many authors,[144,195,349,352,368,466,476] and

was confirmed in this study in the limited number of patients with both pathological EFE at autopsy and pre-terminal ECG data (page 167).

HYPOTHESIS A.

1. EVIDENCE OF A RELATIONSHIP BETWEEN AM AND EFE.

Evidence that AM and EFE represent stages of a common disease process is derived from the following information:

1.1 EPIDEMIOLOGY

A preponderance of Cape coloured patients was found in both AM and EFE (Chapter 4). Both conditions were thus prevalent in the socio-economically deprived section of the community.

The relative increase in the number of patients with clinical EFE in the summer months, following the predominance of AM in late winter and spring, and the marked increase of EFE within 3 to 12 months of a major outbreak of AM, provided strong evidence of a link between these two conditions. The pattern favoured a common viral etiology with the evolution of EFE in time in a proportion of patients who survived the initial insult, but failed to resolve completely.

1.2 SIMILARITIES BETWEEN CLINICAL AM AND EFE

Those features which showed no significant differences between AM and EFE on statistical analysis, are noted in Table 14.1.

(a) SYMPTOMATOLOGY: Symptoms prior to presentation were remarkably similar in patients with either AM or EFE, and favoured a preceding viral infection (Chapter 7).

(b) CLINICAL SIGNS: Various clinical signs occurred with similar frequency, notably pyrexia, pneumonia, hepatomegaly, pulmonary venous congestion, gallop rhythm and apical systolic murmurs (Chapters 6 and 7).

TABLE 14.1 Conditions statistically analysed - no significant differences between clinical AM and EFE.

URT = upper respiratory tract; JVP = jugular venous pressure; CNS = central nervous system; LDH = lactate dehydrogenase; HBDH = hydroxybutyrate dehydrogenase; CPK = creatine kinase.
*omitting conditions with insufficient numbers of affected patients for statistical analysis.

(c) ROUTINE INVESTIGATIONS: Elevated white blood counts and elevated blood urea levels occurred with similar frequency in AM and EFE (Chapter 7).

(d) EVIDENCE OF INFECTION: Various clinical and laboratory parameters suggesting viral infection were equally prevalent in AM and EFE (Chapter 8).

(e) ECG: There was a similar incidence in both conditions of arrhythmias, conduction abnormalities, frontal plane QRS axis deviations, atrial abnormalities, pathological Q waves, ST segment elevation and T wave flattening, on admission and throughout the follow-up period (Chapter 9).

(f) SERUM ENZYMES: The frequency of abnormally elevated serum LDH, HBDH and CPK enzymes, the mean values reached, and their pattern of behaviour during the 3 week period after admission, were all similar in AM and EFE (Chapter 10).

(g) VIROLOGY: The overall yield of viruses by direct culture and serology was similar in both conditions (Chapter 11).

(h) MORTALITY: Overall mortality and survival curves during the entire study were similar in both conditions (Chapter 12). All deaths occurred within the first 13 months.

(i) NATURAL HISTORY: Resolution of clinical, radiological and electrocardiographic abnormalities in survivors was the rule in both AM and, contrary to previous reports, in EFE (Chapter 12).

1.3 COEXISTENCE OF PATHOLOGIES

Autopsy evidence in this study revealed that pathological features of both AM and EFE coexisted in 21.6% of cases (Chapter 13).

Non-cardiac pathology reflected heart failure and shock, but evidence of viral infection (mainly pulmonary and lymphoid) was particularly common and equally prevalent in AM and EFE.

2. EVIDENCE OF THE BIMODAL PRESENTATION OF A COMMON ENTITY

Evidence that AM and EFE represent two phases of a single disease process is

derived from the following:

2.1 EPIDEMIOLOGY

The uniform, non-seasonal, pattern of presentation of EFE, as compared with AM, implies a different mode of presentation (Chapter 5).

2.2 DIFFERENCES BETWEEN CLINICAL AM AND EFE

Statistically significant differences, which favour a bimodal presentation, are noted in Table 14.2.

(a) CLINICAL FEATURES: The greater frequency on admission of sinus tachycardia, elevated jugular venous pressure, oedema or a combination of signs of heart failure in patients with AM reflect a more acute presentation than occurs in patients with EFE (Chapter 6). This is emphasised by the fact that almost all patients (18/19) presenting with acute shock had clinical AM. The greater incidence of central nervous system abnormalities in AM is probably due to acute hypotension in some cases, and to a virus which is neurotropic as well as cardiotropic in others (Chapter 7).
Conversely, the greater degree of radiological cardiomegaly on admission in patients with EFE, coincides with their less precipitous mode of presentation and slower evolution of cardiomegaly before presentation (Chapter 6).

(b) ECG: Apart from LVH, which separates clinical EFE from AM (by definition), ST segment depression and deep T wave inversion also occur significantly more frequently in patients with EFE, and provide further evidence of severe and probably long-standing left ventricular strain (Chapter 9).

(c) VIROLOGY: Although the yield and range of viruses was similar in both AM and EFE, those viruses known to be causative agents

TABLE 14.2 Conditions statistically analysed - significant differences between clinical AM and EFE, favouring a bimodal presentation.

CONDITION*	SIGNIFICANT DIFFERENCE+	PAGE
SIGNS:		
HEART RATE (> 95th percentile)	AM > EFE	54
OEDEMA	AM > EFE	56
ELEVATED JVP	AM > EFE	54
MULTIPLE SIGNS OF HEART FAILURE	AM > EFE	56
SHOCK	AM > EFE	57
CNS ABNORMALITIES	AM > EFE	67
INVESTIGATIONS:		
RADIOLOGICAL CARDIOMEGALY (mean CTR)o	EFE > AM	60
ECG:		
LVH	EFE only	102
ST SEGMENT DEPRESSION	EFE > AM	109
DEEP T WAVE INVERSION	EFE > AM ⊕	110
NATURAL HISTORY:		
DURATION OF FIRST ADMISSION (mean) - DEATHS	AM < EFE	82
READMISSIONS	EFE > AM	143

JVP = jugular venous pressure; CNS = central nervous system.

* omitting conditions with insufficient numbers of affected patients for statistical analysis.

\+ in incidence unless otherwise stated.

o on admission.

⊕ autopsy-proved cases.

in myocarditis (enteroviruses)[69,36,155,196,171,230,262,280,309,391,520,528] were isolated only in patients with clinical AM. The viruses detected in patients with EFE are unlikely to be causative, but appear to be associated with intercurrent infections which provoke the clinical expression of underlying EFE (Chapter 11).

(d) MORTALITY AND NATURAL HISTORY: The shorter duration in hospital before death in patients with AM (Chapter 7), and the more frequent readmission rate in patients with EFE (Chapter 12), emphasize the acute mode of presentation in the former, and the more protracted course in the latter patients.

2.3 LVH VARIABILITY

Although accurate and reliable as a means of detecting concurrent EFE (see above), this study revealed that LVH on ECG may fluctuate considerably at different times (see Classification - Chapters 4 and 12). LVH commenced after presentation in as many as 40% (21/52) of all patients with LVH, and resolved in almost all survivors after a variable period of up to 48 months (Figure 9.1). Hence, the underlying EFE may itself be transient and reversible.

2.4 PATHOLOGY

In those patients who had histological evidence of both AM and EFE at autopsy (section A.3), there was a tendency for the fibroelastosis to increase as inflammatory cell infiltration and myocardial cell necrosis decreased, in keeping with a progression from AM to EFE[255,467] (Chapter 13). These patients comprised an intermediate spectrum between isolated AM at one end and pure EFE at the other, thus favouring different modes of presentation of the same disease process, depending on the stage of pathology reached.

Comment

Although resolution of the extensive fibroelastosis described at post-mortem

by many authors[226] seems inconceivable, the observed fluctuations of LVH, the interim grades of EFE found in this and other series,[166,255,512,467] and the reported presence of EFE in apparently normal infant hearts,[565] indicate that lesser degrees of EFE do exist and may well be reversible. The relatively good long-term outlook for patients with EFE, and the occurrence of mixed pathology in this series, suggest that these patients present in an earlier phase of EFE than most previously reported cases.

In order to confirm the dynamic nature of EFE, and the correlation of EFE, with LVH on ECG, serial endomyocardial biopsies would be required, but this procedure was considered ethically unjustifiable when this study commenced in 1970. Although experience with this technique in children is growing,[107,290, 162,167,331,418,284,451,377,406] its usefulness remains controversial.[146,330,407]

3. OTHER SIGNIFICANT DIFFERENCES BETWEEN AM AND EFE

Statistically significant differences between AM and EFE, which are not attributable to different modes of presentation, are noted in Table 14.3.

3.1 AGE-RELATED DIFFERENCES

(a) CLINICAL: The increased frequency of grunting respiration in EFE in response to respiratory infection or pulmonary venous congestion (Chapter 7) is thought to be age-related, since this phenomenon is peculiarly prevalent in young infants.

(b) ROUTINE INVESTIGATIONS: The more severe anaemia in AM (Chapter 7) is probably a function of time, since these patients present at an older age and may have been iron-deficient for longer.

3.2 AGE AT PRESENTATION

The seemingly paradoxical finding that patients with EFE are younger at presentation than those with AM, despite the fact that EFE is considered to be

TABLE 14.3 Conditions statistically analysed - other significant differences between clinical AM and EFE.

CONDITION *	SIGNIFICANT DIFFERENCE +	PAGE
AGE (mean)	EFE < AM	37
SIGNS:		
GRUNTING RESPIRATION	EFE > AM	63
INVESTIGATIONS:		
HAEMOGLOBIN (mean)	AM < EFE	71

* omitting conditions with insufficient numbers of affected patients for statistical analysis.

TABLE 14.4 Age in months (mean $\pm$SEM) according to

(i) Pathology at autopsy and
(ii) LVH on ECG.

	EFE (4) +	EFE + AM (7) +	AM (22)
AUTOPSY	$\pm^{4.3}_{7.13}$	$\pm^{11.1}_{4.21}$	$\pm^{15.8}_{3.36}$
	LVH FROM ONSET (31)	LVH AFTER PRESENTATION (20) *	NO LVH (71)
ECG	$\pm^{11.8}_{2.65}$	$\pm^{16.3}_{3.32}$	$\pm^{21.5}_{2.67}$

Total number of patients in each group indicated in parentheses.
+ 4 patients with long histories (group 4) omitted.
* patient no 123 aged 144 months at presentation is omitted.

a consequence of myocarditis, requires further consideration. In order to explain this phenomenon, it is postulated that the tendency to develop EFE is itself age-related, the younger infant being specially predisposed to this condition.

This view gains credence from 3 findings:

(i) Patients with autopsy-proved EFE + AM are older than those with EFE alone, and younger than patients with AM alone (Table 14.4), suggesting that the potential for conversion of AM to EFE diminishes with increasing age.

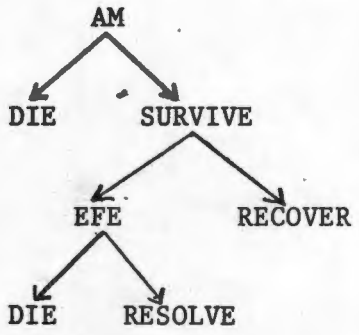
(ii) Patients who develop LVH on ECG after presentation are older than those with LVH ab initio, and younger than patients who remain LVH negative (Table 14.4), suggesting that the rate of pathological evolution of EFE decreases with increasing age.

(iii) Since the peak incidence of EFE is in early infancy it is likely that the precursor condition (AM) occurs in-utero in some cases, and this is borne out by case reports of EFE (without other cardiac anomalies) at birth.[113,159,222,223,270,347,381]

The younger age of patients with EFE, presenting months after an outbreak of AM, may be explained as follows. At the time of the seasonal outbreak of AM, the increased prevalence of cardiotropic viruses in the community results in an increased incidence of mild or inapparent viral infections in, inter alia, mothers in late pregnancy and neonates and young infants. Such sub-clinical infections have been described in the perinatal period in relation to Coxsackie B viruses.[69,247,213,311,562] If associated myocarditis remains sub-clinical, EFE may be initiated pre- or post-natally at this stage and become clinically manifest in ensuing months.

4. PATHOGENESIS OF EFE

From the above evidence, the pathogenetic course of EFE in relation to AM can be represented diagramatically as follows:



5. SUMMARY

In summary, therefore, patients with AM and EFE simulate each other in terms of racial and socio-economic background, symptomatology, clinical presentation, evidence of infection, ECG abnormalities, enzyme responses, overall yield of viruses, mortality rate, and natural history, while pathological features of both coexist in over 20% of cases. Significant differences point to a bi-modal presentation, with a more acute onset in AM, severe LVH and strain (ECG) in EFE, and a particular predisposition of the young infant to EFE. The transition between AM and EFE may be observed pathologically, and is reflected electrocardiographically.

Although largely circumstantial, this evidence favours the hypothesis that AM and EFE are different phases of a common clinical entity, i.e. acute EMD.

HYPOTHESIS B.

This hypothesis is rejected on the basis of the natural history data. Recovery was the rule for patients with either AM or EFE who survived beyond 1 year. Even in the 9% of patients with residual abnormalities after follow-up of all parameters for at least 1 year, the tendency was towards progressive improvement. Not a single patient displayed the myocardial deterioration with

time characteristic of congestive cardiomyopathy (COCM). Further follow-up of the recovered patients is required to exclude late-onset COCM, but AM and EFE are unlikely to be significant factors in the aetiology of this condition in children.

This evidence contradicts the claim that COCM in children is part of a spectrum of primary myocardial disease (including AM and EFE) resulting from injury to cardiac muscle.[195] It is argued that COCM should be regarded as a separate entity from acute onset EMD wherever possible, and not as a different mode of presentation of a single condition[430] in the same way as AM and EFE, until further investigation establishes its aetiology.

SPECULATION.

The main purpose of this study was to establish whether a relationship existed between AM and EFE, and not to investigate the specific aetiology of either condition. However, from the above conclusions it is possible to derive a comprehensive theory for the pathogenesis of EFE, which incorporates several of the factors discussed in the introductory review.

It is recognised that EFE may occur in infants with diverse conditions other than viral. Common to most is the possibility of (acute) cardiac dilatation pre- or post-natally. Probably because the atrial and ventricular walls are still relatively thin, especially on the left side, the myocardium of the foetus and young infant appears to be specially predisposed to (acute) dilatation. In consequence, the individual responds to the (sudden) increase of myocardial and especially endocardial tension[72,254] by the deposition of elastin[65] and fibrous tissue,[65,249] in an attempt to limit the dilatation and decrease the energy expenditure which is required to maintain cardiac function. In this way, the normal cardiac output is usually maintained in the early stages.[353]

When the precipitating stimulus is removed, the endomyocardial pathology may progress to cause the death of the patient or, if less extensive, may resolve in time.

Hence, EFE is essentially a non-specific pathological reaction[96,48,394,255,254] to severe cardiac dilatation, rather than to myocardial degeneration[467] or to a product of viral metabolism.[313,477] Such endomyocardial distention may be caused by multiple aetiologies.[48,255,446] Although particularly prone to develop in the foetus and young infant,[1,109] in whom AM is a common precursor, EFE does occur in adolescents[25,483,526,460] and adults[254,207,289] subjected to similar haemodynamic stress, but is pathologically less extensive.[153]

Ultrastructural studies of EFE in endomyocardial biopsy specimens,[167,327,328] reported recently be Neustein et al,[389] encourage the belief that EFE is a reactive phenomenon following stimulation of smooth muscle cells. These cells undergo proliferation,[153,475] and then transformation into fibroblasts[444] via intermediate leiomyoid cells, and produce increased elastin[445] and collagen. A difference in elastic fibres between congenital and acquired EFE[153] could not be evaluated.

It is possible that a similar response to dilatory stress in early gestation may lead to the development of EFE, with interruption of further growth and maturation resulting in the so-called contracted variety of EFE, usually with associated left-sided cardiac anomalies.

These concepts are purely derivative and require further investigation, but it is believed that an approach which is mutually inclusive, rather than exclusive, of the wide array of conditions associated with EFE is more likely to solve the aetiological and pathogenetic mysteries of acute EMD in infants and children.

'While from the bounded level of our mind,
Short views we take, nor see the lengths behind,
But more advanced, behold with strange surprise
New, distant scenes of endless science rise!

An Essay on Criticism.

Alexander Pope.

REFERENCES

1 Abelmann WH. Myocarditis.
New Eng. J. Med. 275 : 832, 1966.

2 Aber LP, and Jones WW. Corticotropin and corticosteroids in the management of acute and chronic heart block.
Brit. Heart J. 27 : 916, 1965.

3 Adams CW. Postviral myopericarditis associated with the influenza virus : report of eight cases.
Amer. J. Cardiol. 4 : 56, 1959.

4 Adams FH, and Katz BL. Endocardial fibroelastosis.
J. Pediatr. 41 : 141, 1952.

5 Afanas'eva VM, Ivanovskaya TF, and Zhukova EK. Concerning question of myocarditis in predominantly younger children (Russian).
Pediatrics. 3 : 46, 1961.

6 Afanasiev IuV. Morphological changes in the heart conduction system in congenital endocardial fibroelastosis with disorders of cardiac rhythm and conductivity.
Pediatriia. 9 : 55, 1975.

7 Ahumada G, Roberts R, and Sobel BE. Evaluation of myocardial infarction with enzymatic indices.
Prog. Cardiovasc. Dis. 18 : 405, 1976.

8 Ainger LE, Somersill B, Fitch CW, Lane NK and Harper WH. Corticosteroid therapy of acute nonrheumatic myocarditis.
Amer. J. Dis. Child. 100 : 737. 1960.

9 Ainger LE. Acute aseptic myocarditis : corticosteroid therapy.
J. Pediatr. 64 : 716, 1964.

10 Ainger LE, Lawyer NG, and Fitch CW. Neonatal rubella myocarditis.
Brit. Heart J. 28 : 691, 1966.

11 Ainger LE. Heart disease in congenital rubella syndrome.
Cardiol. Dig. 2 : 21, 1967.

12 Ainger LE. Mitral and aortic valve incompetence in endocardial fibroelastosis.
Amer. J. Cardiol. 28 : 309, 1971.

13 Alimurung MM, Joseph LG, Nadas AS, and Massell BF. The unipolar precordial and extremity electrocardiogram in normal infants and children.
Circulation. 4 : 420, 1956.

14 Altman H, and Stein H. Idiopathic hypertrophy of the heart in African children. A report of four cases.
Brit. Med. J. 1 : 1207, 1956.

15 Amplatz K. Endocardial fibroelastosis.
Seminars Roentgen. 4 : 360, 1969.

16 Anderson DH, and Kelly J. Endocardial fibroelastosis. I. Endocardial fibroelastosis associated with congenital malformations of the heart.
Pediatrics. 18 : 513, 1956.

17 Anderson RP, Bonchek LI, Grunkemeier GL, Lambert LE, and Starr A. The analysis and presentation of surgical results by actuarial methods. J. Surg. Res. 16 : 224, 1974.

18 Andrade ZA, Guimaraes AC. Endomyocardial fibrosis in Bahia, Brazil. Brit. Heart J. 26 : 813, 1964.

19 Antia AU, Talbert JL, and Paplanus SH. Etiology of endomyocardial fibrosis. Johns Hopkins Med. J. 122 : 87, 1968.

20 Antia AU, Cockshott WP, and Thorpe GJ. Idiopathic cardiomegaly in Nigerian children. Brit. Heart J. 31 : 178, 1969.

21 Antia AU. Idiopathic cardiomegaly in African children. Further experience with cases seen in Nigeria. Pathol. Microbiol. (Basel) 35 : 44, 1970.

22 Apley J. Primary myocardial disease in infancy : clinical aspects. Arch. Dis. Childh. 36 : 366, 1961.

23 Arena G, Constantini G, and Rastelli G. Study of Fiedler's primary interstitial myocarditis (report of 2 cases). Pediatriia. 50 : 84, 1971.

24 Armanta J, Tovaruella A. Pneumonic myocarditis with disorders of intraventricular conduction and electric alternation. Rev. Esp. Cardiol. 24 : 631, 1971.

25 Auld WHR and Watson H. Fibroelastosis of heart in adolescence. Brit. Heart J. 18-19 : 186, 1956-57.

26 Averill JH, Randall RV, Joffe E and White PD. Heart disease of unknown cause in siblings. Ann. Intern Med. 47 : 49, 1957.

27 Azcuna JI, Cabrera A, Chouza M, Bilbao F, Pastor E, and O'nate Landa A. Radiological and angiocardiographical aspects of primary endocardial fibroelastosis in children. An. Esp. Pediatr. 9 : 364, 1976.

28 Bahn RC, Edwards JE and DuShane JW. Coarctation of aorta as a cause of death in early infancy. Pediatrics. 8 : 192, 1951.

29 Bailey CP. The surgical treatment of mitral stenosis (mitral commisurotomy). Dis. of Chest. 15 : 377, 1949.

30 Barritt DW and Al-Shamma'a M. Heart failure from unexplained cardiomyopathy. Brit. Heart J. 28 : 674, 1966.

31 Beck W. Cardiomyopathies in South Africa - a brief survey of the problem and current therapeutic approaches. Postgrad. Med. J. 54 : 469, 1978.

32 Becker BJP. Idiopathic mural endocardial disease in South Africa. Med. Proc. 9 : 124, 1963.

33 Becker BJP. Studies on the human mural endocardium.
J. Pathol. and Bact. 88 : 541, 1964.

34 Becker K. Problem of the endocardial fibrosis of the young infant.
Kahrb. Kinderheilk. 134 : 64, 1931.

35 Bell EJ, and Grist NR. Further studies of enterovirus infections in cardiac disease and pleurodynia.
Scand. J. Infect. Dis. 2 : 1, 1970.

36 Bell EJ, and Grist NR. Echoviruses, carditis, and acute pleurodynia.
Lancet 1 : 326, 1970.

37 Bellet S, and Gouley BA. Congenital heart disease with multiple cardiac anomalies.
Amer. J. Med. Sci. 183 : 458, 1932.

38 Bengtsson E, and Orndahl G. Complications of mumps with special reference to the incidence of myocarditis.
Acta. Med. Scand. 149 : 381, 1954.

39 Bengtsson E, and Lamberger B. Five-year follow-up study of cases suggestive of acute myocarditis.
Amer. Heart J. 72 : 751, 1966.

40 Bengtsson E. Acute myocarditis and its consequences in Sweden.
Postgrad. Med. J. 48 : 754, 1972.

41 Benjamin B, and Simon MA. So-called congenital idiopathic hypertrophy of heart.
Amer. J. Dis. Child. 59 : 842, 1940.

42 Benyesh-Melnick M, Rosenberg HS, and Watson B. Viruses in cell cultures of kidneys of children with congenital heart malformations and other diseases.
Proc. Soc. Exper. Biol.

43 Berkovich S, Rodrigues-Torres,R and Lin JS. Virologic studies in children with acute myocarditis.
Amer. J. Dis. Child. 115 : 207, 1968.

44 Bertolim R. über patologische-histologische Befunde bei fünf Fallen von frühkindlicher Endokard-fibroelastose.
Zblt. Allg. Pathol. Anat. 97 : 430, 1958.

45 Bertoye P, Mounet P, Bret J and Touraine. Cardiopathic congenitale chez des jumeaux dizygotes par embryopathic.
J. Med. Lyon. 33 : 391, 1952.

46 Beveridge J. Endocardial fibroelastosis.
Aust. Ann. Med. 6 : 155, 1957.

47 Bieńkowski M, Przybyszewska E, and Bieńkowska A. Endocardial fibroelastosis in infants observed at the children's ward of the County Hospital in Wloclawek.
Probl. Med. Wieku Rozwoj. 5 : 277, 1975.

48 Black-Schaffer B. Infantile endocardial fibroelastosis : A suggested etiology.
Arch. Pathol. 63 : 281, 1957.

49 Black-Schaffer B, and Turner ME. Hyperplastic infantile cardiomegaly : A form of "idiopathic hypertrophy" with or without endocardial fibroelastosis, and a comment on cardiac "atrophy".
Amer. J. Pathol. 34 : 745, 1958.

50 Blanshard TP. Isolated diffuse myocarditis.
Brit. Heart J. 15 : 453, 1953.

51 Bleifeld W, Mathey D, Hanrath P
Infarct size estimated from serial serum creatine phosphokinase in relation to left ventricular haemodynamics.
Circulation. 55 : 303, 1977.

52 Blumberg RW, and Lyon RA. Endocardial sclerosis.
Amer. J. Dis. Child. 84 : 291, 1952.

53 Boger A. Uber die Endocardsklerosen.
Beitr. Pathol. Anat. 81 : 441, 1929.

54 Boikan WS. Myocarditis perniciosa.
Virchows Arch. Pathol. Anat. 282 : 46, 1931.

55 Bolshakova AM, Buiko VP, Gromova LP, and Rangald AA. Peculiarities of the clinical picture and therapy of infectious-allergic (nonspecific) myocarditis in children.
Indian Pediatr. 5 : 107, 1968.

56 Bolte HD, and Schultheiss P. Immunological results in myocardial diseases.
Postgrad. Med. J. 54 : 500, 1978.

57 Bradlow BA, Zion MM, and Fleishman SJ. Heart disease in Africa with particular reference to Southern Africa.
Amer. J. Cardiol. 13 : 650, 1964.

58 Brainbridge MV, Darracott S, Chayen J, Bitensky L, and Poulter LW. Possibility of a new infective agent in congestive cardiomyopathy.
Lancet. 1 : 71, 1967.

59 Brigden W. Uncommon myocardial diseases. The non-coronary cardiomyopathies.
Lancet 2 : 1179, 1957 and
" 2 : 1243, 1957.

60 Brightman VJ, McNair Scott TF, Westphal M, and Boggs TR. An outbreak of Coxsackie B5 virus infection in a newborn nursery.
J. Pediatr. 69 : 179, 1966.

61 Brooksby AB, Swanton RH and Jenkins BS. Long sheath technique for introduction of catheter tip manometer or endomyocardial bioptome into left or right heart.
Brit. Heart J. 36 : 908, 1974.

62 Brown GC, and Evans TN. Serologic evidence of coxsackie virus etiology of congenital heart disease.
J. Amer. Med. Assoc. 199 : 151, 1967.

63 Bryan CS, Oppenheimer EH. Ventricular endocardial fibroelastosis. Basis for its presence or absence in cases of pulmonic and aortic atresia.
Arch. Pathol. 87 : 82, 1969.

64 Bukowska W, Bako W, and Ejsmont L. Viral myocarditis with infarct-like ECG findings in a 19 month old boy.
Pediatr. Pol. 53 : 89, 1978.

65 Bunting CH. New formation of elastic tissue in adhesions between serous membranes and in myocardial scars.
Arch. Pathol. 28 : 306, 1939.

66 Burch GE, and De Pasquale NP. Viral myocarditis, in Ciba Foundation Symposium on Cardiomyopathies.
Summit, NJ, 1964, Ciba Pharmaceutical Products, Inc., p 376.

67 Burch GE, De Pasquale NP, Sun SC, Hale AR, and Mogabgab WJ. Experimental Coxsackievirus endocarditis.
J. Amer. Med. Assoc. 196 : 349, 1966.

68 Burch GE, Sun SC, Colcolough HL, Sohal RS and De Pasquale NP. Coxsackie B viral myocarditis and valvulitis identified in routine autopsy specimens by immunofluorescent techniques.
Amer. Heart J. 74 : 13, 1967.

69 Burch GE, Sun SC, Chu KC, Sohal RS, and Colcolough HL. Interstitial and Coxsackie B myocarditis in infants and children.
J. Amer. Med. Ass. 203 : 1, 1968.

70 Burch GE, and Giles TD. The role of viruses in the production of heart disease.
Amer. J. Cardiol. 29 : 231, 1972.

71 Burch GE. Ultrastructural myocardial changes produced by viruses.
Recent Adv. Stud. Cardiac Struct. Metab. 6 : 501, 1975.

72 Burton AC. Physiology and Biophysics of the Circulation.
Chicago, Year Book Medical Publishers, Inc, 1965.

73 Buttrick DD, and Roberts L. Generalized cytomegalic inclusion disease.
Amer. J. Dis. Child. 110 : 319, 1965.

74 Cabrera E, and Monroy JR. Systolic and diastolic overloading of the heart.
Amer. Heart J. 43 : 661, 1952.

75 Cadell JL, Warley A, Connor DH, D'Arbella PG, and Billinghurst JR. Acquired heart disease in Ugandan children.
Brit. Heart J. 28 : 759, 1966.

76 Calodney MM, and Carson MJ. Coarctation of aorta in eady infancy.
J. Pediatr. 37 : 46, 1950.

77 Camp TF, Hess EV, Conway G, and Fowler NO. Immunologic findings in idiopathic cardiomyopathy.
Amer. Heart J. 77 : 610, 1969.

78 Campesi G. Fibroelastosi endocardica biatriale in un caso di atresia congenita della tricuspide.
Giornal Ital. Patol. Scienze affini. 4 : 317, 1957.

79 Carstens PHB. Postnatal mumps virus infection associated with endocardial fibroelastosis.
Arch. Pathol. 88 : 399, 1969.

80 Case QC. Primary endocardial fibroelastosis (with observations on seasonal incidences).
United States Armed Forces Med. J. 11 : 1408, 1960.

81 Cassels DE. Aspects of the electrocardiogram in left ventricular hypertrophy.In Electrocardiography in Infants and children, Editors Cassels DE, and Ziegler RF, New York, 1966, Grune and Stratton, p 216-244.

82 Ceelen W. Uber Herzvergrösserung im frühen kindesalter.
Berl. Klin. Wochenschr. 57 : 197, 1920.

83 Cheetham HD, Hart J, Coghill NF, and Fox B. Rabies with myocarditis : two cases in England.
Lancet. 1 : 921, 1970.

84 Chen S, Thompson MW, and Rose V. Endocardial fibroelastosis : family studies with special reference to counseling.
J. Pediatr. 79 : 385, 1971.

85 Cherry JD, Jahn CL, and Meyer TC. Paroxysmal atrial tachycardia associated with ECHO 9 virus infection.
Amer. Heart J. 73 : 681, 1967.

86 Chopra P. Pathology of cardiomyopathy. An autopsy analysis of twenty-five cases.
Acta. Cardiol. (Brux.) 32 : 1, 1977.

87 Christiaens L,Dupuis C, Nuyts JP, Delomez M, and Itsweire A. The prognosis of fibroelastosis (apropos of 12 cases).
Arch. Mal. Coeur. 58 : 1616, 1965.

88 Coltman CA. Influenza myocarditis.
JAMA. 180 : 204, 1962.

89 Conlin GJ, and Mantz FA. Isolated myocarditis in infants.
J. Pediat. 42 : 414, 1953.

90 Connor DH, Somers K, Hutt MSR, Manion WC, and D'Arbela PG. Endomyocardial fibrosis in Uganda (Davies' disease).
Part 1. Amer. Heart J. 74 : 687, 1967.
Part 2. Amer. Heart J. 75 : 107, 1968.

91 Correa P, Restrepo C, Garcia C, Quiroz AC. Pathology of heart diseases of undetermined etiology which occur in Cali, Colombia.
Amer. Heart J. 66 : 584, 1963.

92 Corvisant JN. Essai sur les maladies et les lesions organiques du coeur et des gros vaisseaux.
Nicolle, Paris, 1811.

93 Cosgrove GE Jr, and Kaump DH. Endocardial sclerosis in infants children.
Amer. J. Clin. Pathol. 16 : 322, 1946.

94 Covey GW. Acute isolated myocarditis (Fiedler's myocarditis).
Amer. J. Clin. Pathol. 12 : 160, 1942.

95 Craig JM. Congenital endocardial sclerosis.
Bull. Intern Assoc. Med. Museums. 30 : 15, 1949.

96 Crome L. Epiloia and endocardial fibroelastosis.
Arch. Dis. Child. 29 : 136, 1954.

97 Cutler SJ, and Ederer F. Maximum utilization of the life table method in analyzing survival.
J. Chronic Dis. 8 : 699, 1958.

98 Czeizel A. Coxsackievirus and congenital malformation.
J. Amer. Med. Assoc. 201 : 142, 1967.

99 Dammin GJ, and Moore RA. Cardiac muscle in idiopathic hypertrophy of the heart in infancy and in normal growth.
Arch. Pathol. 27 : 122, 1939.

100 Dander B, Rossi R, and Buonanno C. Idiopathic cardiomyopathies in children : a description of two rare cases.
G. Ital. Cardiol. 7 : 77, 1977.

101 Danilowicz DA. Prognostic value of the electrocardiogram in endocardial fibroelastosis.
Brit. Heart J. 38 : 516, 1976.

102 Das SK, Callen JP, Dodson VN, and Cassidy JT. Immunologic binding in cardiomyopathic hearts.
Circulation. 44 : 612, 1971.

103 Datta BN, Babu SK, Khattri HN, Bidwai PS, and Wahi PL. Endomyocardial fibrosis in Chandigarb area, India. A study of nine autopsies.
Trop. Geogr. Med. 29 : 346, 1977.

104 Davies JPN. Endomyocardial fibrosis in Africans.
E. Afr. Med. J. 25 : 10, 1948.

105 Davies JPN, and Ball JD. The pathology of endomyocardial fibrosis in Uganda.
Brit. Heart J. 17 : 337, 1955.

106 Debrunner F, Rutishauser M. Primary myocardial disease and infectious myocarditis.
Z. Kreislaufforsch. 58 : 1246, 1969.

107 Dècourt LV, Garcia DP, Montenegro MR, and Tsuzuki S. Biopsia do Coracao Humano.
Editora da Universidade de Sao Paulo, S. Paulo, 1965.

108 Dehn H, Feil H, and Rinderkrecht RE. Electrocardiographic changes in cases of infectious hepatitis : study of eleven cases occurring in an epidemic.
Amer. Heart J. 31 : 183, 1946.

109 De La Chapelle CE, and Kossmann CE. Myocarditis.
Circulation. 10 : 747, 1954.

110 Delaney TB, and Fukunaga FH. Myocarditis in a newborn infant with encephalomeningitis due to Coxsackievirus Group B type 5.
New Engl. J. Med. 259 : 234, 1958.

111 Dèlèze J. Calcium ions and the healing over of heart fibres.
In Electrophysiology of the Heart, edited by B. Taccardi.

112 DeMedeiros Neto GA, de Almeida DB, and Facchini FP. Myocarditis associated with chicken-pox. Presentation of a case treated by corticosteroids.
Rev. Hosp. Clin. Fac. Med. S. Paulo. 16 : 427, 1961.

113 Dennis JL, Hansen AE, and Corpening TN. Endocardial fibroelastosis.
Pediatrics. 12 : 130, 1953.

114 Dewitski WL. Uber Endokardialflecken.
Frankf. Zschr. Pathol. 9 : 82, 1912.

115 Didier F, Hoeffel JC, Worms AM, Henry M, Lerbier N, and Pernot C. An anatomo-radiological study of the syndrome of hypoplasia of the left heart. With reference to 72 cases.
Ann. Radiol. 19 : 673, 1976.

116 Dimond EG, Allen F, and Moriarity LR. The clinical picture of endocardial fibroelastosis.
Amer. Heart J. 50 : 651, 1955.

117 Dincsoy MY, Dincsoy HP, Kessler AD, Jackson MA, and Sidbury JB Jr. Generalised glycogenosis and associated fibroelastosis : report of three cases with biochemical studies.
J. Pediatr. 67 : 728, 1965.

118 Dissman E. Ein Fall von Kongenitaler Aortenstenose und Endokardhyperplasie bei einem Neugeborenen.
Frankf. Zschr. Pathol. 43 : 476, 1932.

119 Dominguez P, Landrum BL, and Pick A. False "coronary patterns" in the infant electrocardiogram.
Circulation. 19 : 409, 1959.

120 Donat R. Zur Frage der Föetalen Endokarditis.
Frankf. Zschr. Pathol. 53 : 120, 1939.

121 Dordick GR. Diffuse endocardial fibroelastosis and cardiac hypertrophy in infancy : Report of 2 cases in consecutive siblings.
Amer. J. Clin. Pathol. 21 : 743, 1951.

122 Doshi R, and Lodge K. Idiopathic cardiomyopathy in children.
Arch. Dis. Child. 48 : 431, 1973.

123 Drennan JM. Acute isolated myocarditis in newborn infants.
Arch. Dis. Childh. 28 : 288, 1953.

124 DuShane JW, and Edwards JE. Congenital aortic stenosis in association with endocardial sclerosis of the left ventricle.
Mayo Clinic Proc. 29 : 102, 1954.

125 Dymnicka SM. Epidemiology of primary myocardial disease in children in the northern part of Poland.
Proc. Ass. Europ. Pediat. Cardiol. 5 : 28, 1969.

126 Easterly JR, and Oppenheimer EH. Some aspects of cardiac pathology in infancy and childhood.
Pediatrics. 39 : 896, 1967.

127 Edington GM, and Jackson JG. The pathology of heart muscle disease and endomyocardial fibrosis in Nigeria.
J. Pathol. Bact. 65 : 13, 1963.

128 Edmonds HW, and Seelye WB. Endocardial sclerosis.
Pediatrics. 7 : 651, 1951.

129 Edwards JE, and DuShane JW. Thoracic vascular anomalies.
Arch. Pathol. 49 : 517, 1950.

130 Edwards JE, and Burchell HB. Endocardial and initial lesions (jet impact) as possible sites of origin of murmurs.
Circulation. 18 : 946, 1958.

131 Ehsani A, Ewy GA, and Sobel BE. Effects of electrical countershock on serum creatine phosphokinase (CPK) isoenzyme activity.
Amer. J. Cardiol. 37 : 12, 1976.

132 Elliot GB, and Elliot JDA. Myocardial component in fibroelastosis scar.
Arch. Pathol. 95 : 321, 1973.

133 Ellis G, and Goldberg DM. Serum alpha Hydroxybutyrate Dehydrogenase Activity.
Amer. J. Clin. Pathol. 56 : 627, 1971.

134 Enders JF. Coxsackie viruses (discussion).
Ann. N.Y. Acad. Sci. 67 : 241, 1957.

135 Engels E. Fötale Endokarditis und Endokardfibrose.
Zblt. Pathol. 84 : 290, 1948.

136 Erecinski K, and Malecka-Dymnicka S. Epidemiologic aspects of endocardial fibroelastosis and interstitial myocarditis of the Gdansk region.
Cesk. Pediatr. 22 : 496, 1967.

137 Essed CE, Klein HW, Krediet P, and Vorst EJ. Coronary and endocardial fibroelastosis of the ventricles in the hypoplastic left and right heart syndromes.
Virchows Arch. Pathol. Anat. 368 : 87, 1975.

138 Evans B. Obscure cardiopathy.
Brit. Heart J. 19 : 164, 1957.

139 Eyler WR, Eigler RF, Shea JJ, and Kuabe GW. Endocardial fibroelastosis.
Radiology. 64 : 797, 1955.

140 Factor SM. Endocardial fibroelastosis : myocardial and vascular alterations associated with viral-like nuclear particles.
Amer. Heart J. 96 : 791, 1978.

141 Fagundes LA. Endomyocardial fibrosis : report of three cases in southern Brazil.
Rev. Instit. Med. Trop. Sao Paulo. 5 : 198, 1963.

142 Falk W, and Elken A. An outbreak of primary myocarditis in infants ; an epidemiological study.
Israel Med. J. 18 : 103, 1959.

143 Farber S, and Hubbard J. Fetal endomyocarditis. Intrauterine infection as the cause of congenital cardiac anomalies.
Amer. J. Med. Sci. 186 : 705, 1933.

144 Faruque AA. Adult endomyocardial fibrosis in Britain.
Lancet. 2 : 331, 1963.

145 Feldioreanu T, Ciofu C, Ciofu E, and Esanu M. Association of leucinosis and fibroelastosis. Findings on a clinical case.
Pediatria (Bucur) 22 : 461, 1973.

146 Ferrans VJ, and Roberts WC. Myocardial biopsy : a useful diagnostic procedure or only a research tool.
Amer. J. Cardiol. 41 : 965, 1978.

147 Fiddler GI, Campbell RWF, Pottage A, and Godman MJ. Varicella myocarditis presenting with unusual ventricular arrhythmias.
Brit. Heart J. 39 : 1150, 1977.

148 Fiedler A. Uber akute interstitielle myokarditis. Festschrift zur Feier des funfzigjährigen Bestehens des Stadtkrankenhauses zu Dresden - Friedrichstadt. Part 2. Edited by Rathe zu Dresden. Dresden, Wilhelm Baensch, 1899, pp 3-24.

149 Fine I, Brainerd H, and Sokolow M. Myocarditis in acute infectious diseases.
Circulation. 20 : 859, 1959.

150 Finland M, Parker F, Jr., Barnes MW, and Joliffe LS. Acute myocarditis in influenza A infections : two cases of non-bacterial myocarditis with isolation of virus from lungs.
Amer. J. Med. Sci. 209 : 455, 1945.

151 Fischer B. Uber Fötale Infectionskrankheiten und Fötale Endokarditis.
Frankf. Zschr. Pathol. 7 : 83, 1911.

152 Fish M, and Barton HR. Heart involvement in infectious mononucleosis.
Arch. Intern. Med. 101 : 636, 1958.

153 Fishbein MC, Ferrans VJ, and Roberts WC. Histologic and ultrastructural features of primary and secondary endocardial fibroelastosis.
Arch. Pathol. Lab. Med. 101 : 49, 1977.

154 Fisher JH. Primary endocardial fibroelastosis : a review of fifteen cases.
Canad. Med. Assoc. J. 87 : 105, 1962.

155 Fletcher E, and Brennan CF. Cardiac complications of Coxsackievirus infection.
Lancet. 1 : 913, 1957.

156 Fletcher GF, and Wenger NK. Autoimmune studies in patients with primary myocardial disease.
Circulation. 37 : 1032, 1968.

157 Folger GM Jr. Endocardial fibroelastosis. A continuing and unsolved dilemma.
Clin. Pediatr. (Phila). 10 : 246, 1971.

158 Fontana RS, and Edwards JE. Congenital cardiac disease : a review of 357 cases studied pathologically.
WB Saunders Company, Philadelphia, 1962, pp 141-146.

159 Forfar JO, Miller RA, Bain AD, and McCleod W. Endocardial fibroelastosis.
Brit. Med. J. 2 : 7, 1964.

160 Forrester RM, Lees VT, and Watson GH. Rubella syndrome. Escape of a twin.
Brit. Med. J. 1 : 1403, 1966.

161 Fowler RS, and Khouoy GH. Spatial QRS-T angle in ventricular pressure and volume loading in children.
Circulation (Suppl. 3). 34 : 103, 1966.

162 Frantseu VI, Kalikshte in DB, Odinokava VA and Koskin IuA. Clinical importance of intra-cavital biopsy of the myocardium.
Ter. Arkh. 48 : 80, 1976.

163 Freundlich E, Berkowitz M, Elkon A, and Wilder A. Primary interstitial myocarditis. Report of an epidemic outbreak.
Amer. Dis. Child. 96 : 43, 1958.

164 Freundlich E, Munk J, Griffel B, and Steinlanf J. Primary myocardial disease in infancy.
Amer. J. Cardiol. 13 : 721, 1964.

165 Frühling L, and Adam CH. Etude anatomopathologique de la myo-endocardite chronique fibroelastique du nourrisson.
Ann. Anat. Pathol. 1 : 59, 1956.

166 Frühling L, Korn R, Lavillaureix J, Surgus A, and Foussereaux S. La myo-endocardite chronique fibro-elastique du nouveau-né et du nourrisson (fibro-elastose).
Ann. Anat. Pathol. 7 : 227, 1962.

167 Fugita M, Neustein HB and Lurie PR. Transvascular endomyocardial biopsy in infants and small children.
Human Pathol. 10 : 15, 1979.

168 Gamba D, Doliro G, and Bozic C. Cases of viral myocarditis in newborn infants.
Rev. Med. Suisse Romande. 86 : 206, 1966.

169 Garello L, and Ribaldone D. Diagnostic criteria of myocardiopathies in childhood.
Cardiol. Pract. 22 : 413, 1971.

170 Gautier M, and Casasoprana A. Acute myocarditis in the newborn infant. Its relations with fibroelastosis. Its treatment.
Sem. Hop. Paris. 44 : 2878, 1968.

171 Gear JHS, and Measroch V. Coxsackievirus infections of the newborn.
Progr. Med. Virol. 15 : 42, 1973.

172 Gersony WM, Katz SL, and Nadas AS. Endocardial fibroelastosis and mumps virus.
Pediatrics. 37 : 430, 1966.

173 Giersten J. Chronic endocardial fibroelastosis.
Nord. Med. 58 : 1733, 1957.

174 Giersten J, and Pande M. Chronic endocardial fibroelastosis in identical twins.
Acta. Pathol. Microbiol. 45 : 250, 1959.

175 Giles TD, and Gohd RS. Respiratory syncitial virus and heart disease : A report of two cases.
J. Amer. Med. Ass. 236 : 1128, 1976.

176 Gillanders AD. Nutritional heart disease.
Brit. Heart J. 13 : 177, 1951.

177 Glynn LE, and Reinhold JDL. The relationship of idiopathic cardiac hypertrophy to foetal endocarditis.
Arch. Dis. Childh. 25 : 170, 1950.

178 Goldman AM. Acute myocarditis simulating myocardial infarction.
Dis. Chest. 41 : 61, 1962.

179 Golper MN. Endocardial fibroelastosis.
Radiology. 61 : 865, 1953.

180 Good RA, Condie RM, and Bridges RA. Development of Immune Response of Man and Animals : Mechanisms of Antibody Formation.
New York : Academic Press, Inc., 1960.

181 Goodwin JF, Gordon H, Hollman A, and Bishop MB. Clinical aspects of cardiomyopathy.
Brit. Med. J. 1 : 69, 1961.

182 Goodwin JF. Cardiac function in primary myocardial disorders, Part I.
Brit. Med. J. 1 : 1527, 1964.

183 Goodwin JF. Cardiac function in primary myocardial disorders. Part II.
Brit. Med. J. 1 : 1595, 1964.

184 Goodwin JF. Congestive and hypertrophic cardiomyopathies : a decade of study.
Lancet. 1 : 731, 1970.

185 Goodwin JF. Clarification of the cardiomyopathies.
Mod. Concepts Cardiovasc. Dis. 41 : 41, 1972.

186 Gordon RB, Lernette EH, and Sandrock RS. The varied clinical manifestations of Coxsackie virus infections.
Arch. Intern. Med. 103 : 63, 1959.

187 Gore I, and Saphir O. Myocarditis : a classification of 1402 cases.
Amer. Heart J. 34 : 827, 1947.

188 Gowing NFC. Congenital fibro-elastosis of the endocardium.
J. Pathol. and Bact. 65 : 13, 1953.

189 Goyer RA, and Bowden DH. Endocardial fibroelastosis associated with glycogen tumors of the heart and tuberose sclerosis.
Amer. Heart J. 64 : 539, 1962.

190 Graham TP Jr., Jarmakani MW, Canent RV, Capp MP, and Spach MS. Characterization of left heart volumes and mass in normal children and in infants with intrinsic myocardial disease.
Circulation. 38 : 826, 1969.

191 Greaves JL, Wilkins PSW, and Pearson S. Endocardial fibroelastosis in identical twins.
Arch. Dis. Child. 29 :447, 1954.

192 Green EW. The normal P wave. In Electrocardiography in Infants and Children, Editors, Cassels DE and Ziegler RF. New York, 1966, Grune and Stratton, p 109-115.

193 Green EW. Electrocardiographic pattern of atrial enlargement and abnormal impulse formation and conduction. p 65-78.

194 Greenebaum JV, Felson W, and Zelig SM. Acute interstitial myocarditis in an infant.
J. Pediatr. 18 : 799, 1941.

195 Greenwood RD, Nadas AS, and Fyler DC. The clinical course of primary myocardial disease in infants and children.
Amer. Heart J. 92 : 549, 1976.

196 Grist NR, and Bell EJ. Coxsackie viruses and the heart.
Amer. Heart J. 77 : 295, 1969.

197 Grist NR. Viruses and myocarditis.
Postgrad. Med. J. 48 : 750, 1972.

198 Grist NR, and Bell EJ. A six year study of Coxsackievirus B infections in heart disease.
J. Hyg., Camb. 73 : 165, 1974.

199 Grist NR. Viral cardiomyopathy. In : Symposium ; Disorders of the Heart and Circulation.
Royal College of Physicians, Edinburgh, p 117, 1966.

200 Grodums EI, and Dempster G. Myocarditis in experimental Coxsackievirus B3 infection.
Can. J. Microbiol. 5 : 605, 1959.

201 Gronvall H, and Selander P. Some virus diseases during pregnancy and their effect on the fetus.
Nord. Med. 37 : 409, 1948.

202 Gross H, Rubin JL, and Dardik I. Abnormal Q waves in a child with myocarditis.
N.Y. State J. Med. 67 : 283, 1967.

203 Gross P. A concept of fetal endocarditis : a general review with report of an illustrative case.
Arch. Pathol. 31 : 163, 1941.

204 Grunkemeier GL, and Starr A. Actuarial analysis of surgical results : rationale and method.
Annals Thor. Surg. 24 : 404, 1977.

205 Guimaraes AC, Filho AS, Esteves JP, Vinhaes LSA, and Abreu WN. Haemodynamics in endomyocardial fibrosis.
Amer. Heart J. 88 : 294, 1974.

206 Gunteroth WG. Pediatric Electrocardiography. Philadelphia, 1965, WB Saunders, p 79.

207 Guraieb SR, and Rigdon RH. Fibroelastosis in adults.
Amer. Heart J. 52 : 138, 1956.

208 Gurtler-Krawczy'nska E, Krawczy'nski K. Occurrence of anti-cardiac antibodies in idiopathic cardiomyopathy.
Kardiol. Pol. 15 : 427, 1972.

209 Habel K. The nature of viruses and viral diseases.
Med. Clin. North Amer. 43 : 1275, 1959.

210 Hackel DB. Myocarditis in association with varicella.
Amer. J. Pathol. 29 : 369, 1953.

211 Haggerty RV, and Eley RC. Varicella and cortisone.
Pediatrics. 18 : 160, 1956.

212 Hajek M. Fibroelastosis with atypical origin of the left coronary artery.
Cesk. Pediatr. 27 : 76, 1972.

213 Hall CB, and Miller DG. The detection of a silent Coxsackie B5 virus perinatal infection.
J. Pediatr. 75 : 124, 1969.

214 Halliday WR. Endomyocardial fibroelastosis : study of 30 cases.
Dis. Chest. 26 : 27, 1954.

215 Hamby RI, and Raia F. Electrocardiographic aspects of primary myocardial disease in 60 patients.
Amer. Heart J. 76 : 316, 1968.

216 Hamby RI. Primary myocardial disease.
Medicine. 49 : 55, 1970.

217 Handzel TZ, Aygen MM, Levy MJ, and Elian E. A case of primary endocardial fibroelastosis with complete heart block treated with artificial pacing.
Isr. J. Med. Sci. 5 : 1249, 1969.

218 Hansmann GH, and Schenken JR. Acute isolated myocarditis.
Amer. Heart J. 15 : 749, 1938.

219 Hanson LA, Lundgren S, Lycke E, Strannegard O, and Winberg J. Clinical and serological observations in cases of coxsackie B3 infections in early infancy.
Acta. Paediat. Scand. 55 : 577, 1966.

220 Hariga M. Fibroelastose sous-endocardique. Ralation de trois cas.
Acta. Pediatr. Belg. 16 : 263, 1962.

221 Harris LC, Rodin AE, and Nghiem QX. Idiopathic non-obstructive cardiomyopathy in children.
Amer. J. Cardiol. 21 : 153, 1968.

222 Harris LC, and Nghiem QX. Cardiomyopathies in infants and children.
Prog. Cardiovasc. Dis. 15 : 191, 1972.

223 Harris LC, Powell G, and Brown OW, III. Primary myocardial disease.
Paed. Clin. North Amer. 25 : 847, 1978.

224 Hartl O, and Clodi PH. Viral myocarditis.
Wien. Med. Wochenschr. 126 : 400, 1976.

225 Hastreiter AR, and Miller RA. Management of primary endomyocardial disease : The myocarditis-endocardial fibroelastosis syndrome.
Pediatr. Clin. North Amer. 11 : 401, 1964.

226 Hastreiter AR, and Fisher EA. "Endocardial Fibroelastosis" in Heart Disease in Infants, Children and Adolescents, Editors : Moss AJ, Adams FH, and Emmanouilides GC. Williams and Williams, Baltimore. 2nd Ed. 1977, p 496-505.

227 Heath HD, Shear HH, Inagawa DT, Jones MH, and Adams JM. Teratogenic effects of herpes simplex, vaccinia, influenza A (NWS), and distemper virus infections on early chick embryos. Proc. Soc. Exp. Biol. Med. 92 : 675, 1956.

228 Hedinger E. Primare abgeborene Herzhypertrophie. Virchows Arch. Pathol. Anat. 173 : 264, 1904.

229 Heichman J, and Bassan H. Electrocardiographic findings in acute interstitial myocarditis. Lancet. 2 : 263, 1959.

230 Helin M, Savola J, and Lapinleimu K. Cardiac manifestations during a Coxsackie B5 epidemic. Brit. Med. J. 3 : 97, 1968.

231 Helm RA, and Fowler NO Jr. A simplified method for determining the angle between two spatial vectors. Amer. Heart J. 45 : 835, 1953.

232 Henry RJ. Clinical Chemistry. Harper and Row, New York, 1966, p 505.

233 Henson D, and Mufson MA. Myocarditis and pneumonitis with type 21 adenovirus infection. Amer. J. Dis. Child. 121 : 334, 1971.

234 Hernandez A, Jr, Marchesi V, Goldring D, Kissane L, Jr, and Hargmann AF, Jr. Cardiac glycogenosis, haemodynamic, angiocardiographic, and electron microscopic findings - report of a case. J. Pediatr. 68 : 400, 1966.

235 Hertzog AJ, and Heyford WD. Acute isolated myocarditis (Fiedler's myocarditis). Minn. Med. 30 : 54, 1947.

236 Hibbs RG, Ferrans VJ, Black WC, Walsh JJ, and Burch GE. Virus-like particles in the heart of a patient with cardiomyopathy. Amer. Heart J. 69 : 327, 1965.

237 Hildes JA, Schaberg A, and Alcock AJW. Cardiovascular collapse in acute poliomyelitis. Circulation. 12 : 986, 1955.

238 Hill WT and Reilly WA. Endocardial fibroelastosis. Amer. J. Dis. Child. 82 : 579, 1951.

239 Hlavco J, and Horansky V. Fibroelastosis endocardii bei zwei Geschwister. Kinderartz Praxis. 10 : 433, 1963.

240 Hoagland RJ. Cardiac involvement in infectious mononucleosis. Amer. J. Med. Sci. 232 : 252, 1956.

241 Hoenicke M. Fibroelastosis Endocardica und Klumpfuss als Missbildungen bei je einem Partner von Eineigen Zwillingen.
Zblt. Allg. Pathol. 105 : 142, 1963.

242 Hollander MH, Berrey BH, and Palmer PW. Endocardial sclerosis : report of a case.
Arch. Pediatr. 69 : 457, 1952.

243 Holwach J, Thurston DL, and Becker B. Congenital defects in infants following mumps during pregnancy.
J. Pediatr. 50 : 689, 1957.

244 Horansky V, Merka J, and Hlavco J. The third sibling with endocardial fibroelastosis successfully treated with prednisone.
Cesk. Pediatr. 22 : 999, 1967.

245 Horley JF. Foetal fibroelastosis.
Brit. Med. J. 1 : 765, 1955.

246 Hosier DM, and Newton WA. Serious Coxsackie infection in infants and children.
Amer. J. Dis. Child. 96 : 251, 1958.

247 Horstmann DM. Viral infections in pregnancy.
Yale J. Biol. Med. 42 : 99, 1969.

248 House RK. Diffuse interstitial myocarditis in children.
Amer. J. Pathol. 24 : 1235, 1948.

249 Hubschmann P, as cited in Davies JNP. Some considerations regarding obscure diseases affecting the mural endocardium.
Amer. Heart J. 59 : 600, 1960.

250 Hudson RE. Pathology of cardiomyopathy.
Cardiovasc. Clin. 4 : 3, 1972.

251 Hull D, Binns BAO, and Joyce D. Congenital heartblock and widespread fibrosis due to maternal lupus erythematosus.
Arch. Dis. Child. 41 : 688, 1966.

252 Hung W, and Walsh BJ. Congenital auricular fibrillation in a newborn infant with endocardial fibroelastosis.
J. Pediatr. 61 : 65, 1962.

253 Hunter AS, and Keay AJ. Primary endocardial fibroelastosis. An inherited condition.
Arch. Dis. Child. 48 : 66, 1973.

254 Hutchins GM, and Bannayan GA. Development of EFE following myocardial infarction.
Arch. Pathol. 91 : 113, 1971.

255 Hutchins GM, and Vie SA. The progression of interstitial myocarditis to idiopathic endocardial fibroelastosis.
Amer. J. Pathol. 66 : 483, 1972.

256 Imai M, Takeishi M, Hirayama A, Toyoda C, and Koyama K. Idiopathic cardiomyopathy.
Acta. Pathol. Jap. 20 : 153, 1970.

257 Ino T, and Takeshita I. Natural history of the idiopathic cardiomyopathy.
Circ. J. Jap. 36 : 838, 1972.

258 Jack I, and Townley RRW. Acute aseptic myocarditis or newborn infants, due to Coxsackie viruses.
Med. J. Australia. 48 : 265, 1961.

259 Jacobs WF. Congenital endocardial and myocardial fibrosis with calcification.
Arch. Pathol. 14 :129, 1932.

260 Jain KK, and Grueber HL. Infantile myocarditis and endocardial fibroelastosis : report of a case.
Indian Pediatr. 3 : 373, 1966.

261 Jannach JR. Myocarditis in infants with inclusions characteristic of psittacosis.
Amer. J. Dis. Child. 95 : 734, 1958.

262 Javett SN, Heymann S, Mundel B, Pepler WJ, Lurie HI, Gear J, Measroch V, and Kirsch Z. Myocarditis in newborn infant. Study of an outbreak associated with Coxsackie Group B virus. Infection in a maternity home in Johannesburg.
J. Pediatr. 48 : 1, 1956.

263 Johnson FR. Anoxia as cause of endocardial fibroelastosis in infancy.
Arch. Pathol. 54 : 237, 1952.

264 Johnson JL, and Lee LP. Complete atrio-ventricular heart block secondary to acute myocarditis requiring intracardiac pacing.
J. Pediatr. 78 : 312, 1971.

265 Joosting ACC, Harwin RM, Orchard M, Martin E, and Gear JHS. Respiratory viruses in hospital patients on the Witwatersrand.
S. Afr. Med. J. 55 : 403, 1979.

266 Jones HE, and Marshall AG. Isolated (Fiedler's) myocarditis.
Bull. Johns Hopk. Hosp. 64 : 45, 1948.

267 Jungeblut CW. Newer knowledge on the pathogenesis of poliomyelitis.
J. Pediatr. 37 : 109, 1950.

268 Katz BE, and Adams FH. Endocardial fibroelastosis.
Amer. J. Dis. Child. 86 : 186, 1953.

269 Kauffman SL, Chandra N, Peress N, and Rodriguez-Torres R. Idiopathic infantile cardiomyopathy with involvement of the conduction system.
Amer. J. Cardiol. 30 : 648, 1972.

270 Kaufman OYA, and Neymark GI. A case of congenital fibroelastosis in a 1½ day old infant.
Voprosy Okhrary Materin. Detstva. 7 : 91, 1962.

271 Kawai C. Idiopathic cardiomyopathy. A study on the infectious-immune theory as a cause of the disease.
Jap. Circ. J. 35 : 765, 1971.

272 Keith JD, Rowe RD, and Vlad P. Endocardial fibroelastosis. In Heart Disease in Infancy and Childhood, 2nd edition, McMillan, New York, 1966. p 858

273 Keith JD, Rowe RD, and Vlad P. Electrocardiography. In Heart Disease in Infancy and Childhood, 2nd edition, McMillan, New York, 1967. p 43.

274 Kelly J, and Andersen DH. Congenital endocardial fibroelastosis. II. A clinical and pathologic investigation of those cases without associated cardiac malformations including a report of two familial instances. Pediatrics. 18 : 539, 1956.

275 Kempton JJ. Endocardial fibroelastosis in one of three-year-old twins. Proc. Roy Soc. Med. 57 : 271, 1953.

276 Kenny FE, and Sanes S. Dilatation of the heart in infancy due to parenchymatous myocarditis. J. Pediatr. 3 : 321, 1933.

277 Kibrick S, and Bernirschke K. Acute aseptic myocarditis and meningo-encephalitis in the newborn child infected with Coxsackie virus Group B, type 3. New Engl. J. Med. 255 : 883, 1956.

278 Kibrick S. Virus infections of fetus and newborn. In Perspectives in Virology. Edited by M. Pollard, Burgess Publishing Co., Minneapolis, 1961, p 140.

279 Kibrick S. Viral infections of the fetus and newborn. Prog. Med. Virol. 2 : 140, 1961.

280 Kibrick S. Current status of Coxsackie and ECHO viruses in human disease. Prog. Med. Virol. 6 : 27, 1964.

281 Kilbourne ED, and Hurstall FL. Lethal infection with Coxsackie virus of adult mice given cortisone. Proc. Soc. Exp. Biol. Med. 77 : 135, 1951.

282 Kilbourne ED, Wilson CB, and Perrier D. The induction of gross myocardial lesions by a Coxsackie (pleurodynia) virus and cortisone. J. Clin. Invest. 35 : 362, 1956.

283 Kipps A, Naude W du T., Dou P, Cooper ED. Coxsackie virus myocarditis of the newborn. Epidemiological features. Med. Proc. 4 : 401, 1958.

284 Kisliak NS, Petrosian IuS, Rapoport IaI, Belokon NA, and Garibian VA. Clinical course and diagnosis of endocardial fibroelastosis in children including endomyocardial biopsy of the left ventricle. Pediatrii. 9 : 45, 1975.

285 Kleiger RE, Seia K, Vitale JJ, and Lown B. Effects of chronic depletion of potassium and magnesium upon the action of acetylstrophanthidin on the heart. Amer. J. Cardiol. 17 : 520, 1966.

286 Klein MS, Shell WE, and Sobel BE. Serum creatine phosphokinase (CPK) isoenzymes after intramuscular injections, surgery and myocardial infarction. Experimental and clinical studies.
Cardiovasc. Res. 7 : 412, 1973.

287 Kline IK, and Saphir O. Chronic pernicious myocarditis.
Amer. Heart J. 59 : 681, 1960.

288 Kline IK, Miller AJ, Pick R, and Katz LN. The relationship between human endocardial fibroelastosis and obstruction of the cardiac lymphatics.
Circulation. 30 : 728, 1964.

289 Knight A. Endocardial fibroelastosis in an adult.
Canad. Med. Assoc. J. 79 : 994, 1958.

290 Konno S, Sekiguchi M, and Sakakibara S. Catheter biopsy of the heart.
Radiol. Clin. North Amer. 9 : 491, 1971.

291 Korones SB, Todaro J, Roane JA, and Sever JL. Maternal virus infection after the first trimester of pregnancy and status of offspring to 4 years of age in a predominantly Negro population.
J. Pediatr. 77 : 245, 1970.

292 Kreysig FL. Die Kraukheiten des Herzens, Maurer, Pt II, 1816, p 822.

293 Krovetz LJ, Gessner IH, and Schiebler GL. Handbook of Paediatric Cardiology, Harper and Row, New York, 1969, p 263.

294 Krovetz LJ, Maron BJ, Morse A, Brown H, and Goldbloom SD. Prognostic implications of left ventricular function in endomyocardial disease in infants and children.
J. Pediatr. 87 : 389, 1975.

295 Krstulovic E. Zur Frage der idiopathischen Herz hypertrophie.
Monatsschr. Kinderheilkd. 33 : 113, 1926.

296 Kugel MA, and Stoloff EG. Dilatation and hypertrophy of the heart in infants and in young children.
Amer. J. Dis. Child. 45 : 828, 1933.

297 Kugel MA. Enlargement of the hearts of infants and young children.
Amer. Heart J. 17 : 602, 1939.

298 Kurobane T, and Nagai K. On chronic idiopathic interstitial myocarditis.
Tohoku J. Exp. Med. 86 : 238, 1965.

299 La Brooy EB. Endomyocardial fibrosis.
Proc. Alumni A. Malaya. 10 : 303, 1957.

300 Laida NM. Long-term observations of children with idiopathic myocarditis.
Vopr. Okhr. Materin Det. 14 : 36, 1969.

301 Lambert EC, Shumway CN, and Terplan K. Clinical diagnosis of endocardial fibroelastosis.
Pediatrics. 11 : 255, 1953.

302 Lambert EC, and Vlad P. Primary endomyocardial disease.
Pediatr. Clin. North Amer. 5 : 1057, 1958.

303 Lansdown ABG. Coxsackievirus B3 infection in pregnancy and its influence on foetal heart development.
Brit. J. Exp. Pathol. 58 : 378, 1977.

304 Larbre F, Thivolet J, Hermier M, Cotton JB, Gandin G, and Richoux. Fatal acute myocarditis after smallpox vaccination.
Pediatrie. 21 : 345, 1966.

305 Laufer A et al. Experimental myocarditis : an autoimmune disease.
Recent Adv. Stud. Cardiac Struct. Metab. 1 : 386, 1972.

306 Lee MH, Liebman J, Steinberg AG, Perrin EV, and Whitman V. Familial occurrence of endocardial fibroelastosis in three siblings, including identical twins.
Pediatrics. 52 : 402, 1973.

307 Legiewski A, and Pliskowski E. Elastic fibrosis of the endocardium in twins.
Patol. Pol. 23 : 493, 1972.

308 Legler JF. Endocardial fibroelastosis : A review of the theories of etiology.
J. Kansas Med. Soc. 61 : 76, 1960.

309 Lerner AM. Coxsackie virus myocardiopathy.
J. Infect. Dis. 120 : 496, 1969.

310 Lerner AM, and Wilson FM. Virus myocardiopathy.
Progr. Med. Virol. 15 : 63, 1973.

311 Lerner AM, Wilson FM, and Reyes MP. Enteroviruses and the heart (with special emphasis on the probable role of coxsackieviruses, group B, types 1-5).
Mod. Conc. Cardiovasc. Dis. 44 : 7, 1975.

312 Letteer CR. Endocardial fibroelastosis.
Ann. Int. Med. 38 : 573, 1953.

313 Levinas IO. Endocardial fibroelastosis in children.
Pediatrics. 40 : 61, 1962.

314 Levine HA. Cardiac hypertrophy in infancy - associated with thickened endocardium and coarctation of aorta.
Amer. J. Dis. Child. 48 : 1072, 1934.

315 Levy RL. Idiopathic cardiomegaly.
J. Chron. Dis. 1 : 292, 1969.

316 Lewes D, and Rainford DJ. Echoviruses and carditis.
Lancet. i : 520, 1970.

317 Lewis KC. Cardiac enlargement of unknown etiology in infancy and childhood.
J. Pediatr. 39 : 698, 1951.

318 Liebman J, and Nadas AS. An abnormally superior vector. (formerly called marked left axis deviation). Editorial.
Amer. J. Cardiol. 27 : 577, 1971.

319 Liebman J, and Plonsey R. Electrocardiography. In Heart Disease in Infants, Children and Adolescents, Editors, Moss AJ, Adams FH, and Emmanouiledes GC, 2nd edition, Williams and Wilkins, Baltimore, 1977, p 18-61.

320 Lim CH, Toh CC, Chia BL, and Low LP. Stokes-Adams attacks due to acute non-specific myocarditis.
Amer. Heart J. 90 : 172, 1975.

321 Linde LM, Adams FH, and O'Loughlin BJ. Endocardial fibroelastosis. Angiocardiographic studies.
Circulation. 17 : 40, 1958.

322 Linde LM, and Adams FH. Prognosis in endocardial fibroelastosis.
Amer. J. Dis. Child. 105 : 329, 1963.

323 Lindenbaum RH, Andrews PS, and Kahn ASSI. Two cases of endocardial fibroelastosis - possible X-linked determination.
Brit. Heart J. 35 : 38, 1973.

324 Lintermans JP, Kaplan EL, Morgan BC, Baum D, and Gunteroth WG. Infarction patterns in endocardial fibroelastosis.
Circulation. 33 : 202, 1966.

325 Loew S, Lowenthal M, and Keusch J. Endocardial fibroelastosis.
Acta. Med. Orient. 12 : 95, 1953.

326 Loh H. Studies on the diffuse endocardial thickening in infants.
Beitr. Pathol. Anat. 101 : 253, 1938.

327 Lurie PR, Fugita M, and Neustein HB. Myocardial biopsy : a miniaturised technic for infants and small children - development, testing in animals and clinical application.
Circulation. 54 (Suppl. II) : 89, 1976.

328 Lurie PR, Fugita M, and Neustein HB. Transvascular endomyocardial biopsy in infants and small children : description of a new technic.
Amer. J. Cardiol. 42 : 453, 1978.

329 Lynfield J, Gasul BM, Luan LL, and Dillon RF. Right and left heart catheterization and angiocardiographic findings in idiopathic cardiac hypertrophy with endocardial fibroelastosis.
Circulation. 21 : 286, 1960.

330 Mackay EH, Littler WA, and Sleight P. Critical assessment of diagnostic value of endomyocardial biopsy.
Brit. Heart J. 40 : 69, 1978.

331 Mackay EH, Pickering D, and Littler WA. Cardiac biopsy in childhood.
Arch. Dis. Child. 52 : 785, 1977.

332 MacMahon HE. Hyperplasia and regeneration of the myocardium in infants and in children.
Amer. J. Pathol. 13 : 845, 1937.

333 Magida MD, and Roberts KE. Electrocardiographic alterations produced by an increase in plasma pH, bicarbonate and sodium as compared with those seen with a decrease in potassium.
Circ. Res. 1 : 214, 1953.

334 Magner D. A case of sub-acute fatal myocarditis of unknown etiology.
Amer. J. Med. Sc. 198 : 246, 1939.

335 Mahon GS. Idiopathic hypertrophy of the heart with endocardial fibrosis.
Amer. Heart J. 21 : 608, 1936.

336 Malecka-Dymnicka S. Elastic fibrosis of the endocardium and interstitial myocarditis in the Gdansk province.
Przeg. Epidemiol. 25 : 129, 1971.

337 Maller HM, Powars DF, Horowitz RE, and Portnoy B. Fatal myocarditis associated with apparent immunological deficiency.
J. Pediatr. 71 : 204, 1967.

338 Manion WC. Myocarditis - a frequent complication of systemic disease.
Am. Med. Assoc. Arch. Pathol. 61 : 329, 1956.

339 Manning JA, Sellers FJ, Bynum RS, and Keith JD. The medical management of clinical endocardial fibroelastosis.
Circulation. 29 : 60, 1964.

340 Manning JA, and Keith JD. Fibroelastosis in children.
Progr. Cardiovasc. Dis. 7 : 172, 1964.

341 Maranhao MF de, Germiniani H, Cat I, Marinoni LP, and Pacheco CN. Electrocardiographic study of viral myocarditis.
Arq. Bras. Cardiol. 19 : 55, 1966.

342 Marek Z, and Popczy'nska-Markowa M. Clinical and morphological observations on endocardial fibroelastosis.
Folia. Med. Cracov. 20 : 139, 1978.

343 Martuzzi M, Vianello A, and Zuchini C. Atresia valvolare aortica.
Arch. Ital. Anat. Istol. Patol. 35 : 259, 1961.

344 Mason JW. Techniques for right and left ventricular endomyocardial biopsy.
Amer. J. Cardiol. 41 : 887, 1978.

345 Maslow HL, and Lederer M. Interstitial myocarditis in a child 19 months of age.
Amer. J. Dis. Child. 45 : 807, 1933.

346 Mattingly JW. The clinical concept of primary myocardial disease.
Circulation. 32 : 845, 1965.

347 Mazur H, and Gajda B. Endocardial fibroelastosis.
Pol. Tyg. Lek. 30 : 2065, 1975.

348 McCormick WF. Endocardial fibroelastosis : a summary of the literature and a review of 24 new cases.
South Afr. Med. J. 51 : 1233, 1958.

349 McCue CM. Three cases of myocarditis in children less than one year of age.
Pediatrics. 21 : 710, 1958.

350 McGregor RR, and McKendry R. Fetal endocarditis.
Can. Med. Assoc. J. 50 : 433, 1944.

351 McKusick VA. A genetical view of cardio-vascular disease.
Circulation. 30 : 326, 1964.

352 McLoughlin TG, Schiebler GL, and Krovetz LJ. Endocardial fibroelastosis in American Negro children : a distinct entity?
Amer. Heart J. 71 : 748, 1966.

353 McLoughlin TG, Schiebler GL, and Krovetz LJ. Haemodynamic findings in children with endocardial fibroelastosis.
Amer. Heart J. 75 : 162, 1968.

354 McMillan JB, and Lev M. The aging heart. I. Endocardium.
J. Gerontology. 14 : 268, 1959.

355 Meehan WF, and Bertrand CA. Ventricular tachycardia associated with echovirus infection.
J. Amer. Med. Assoc. 212 :1701, 1970.

356 Mehrizi A, Rosenstein BJ, Pusch A, Askin JA, and Taussig HB. Myocardial infarction and endocardial fibroelastosis in children with polycystic kidneys.
Bull. Johns Hopkins Hosp. 115 : 92, 1964.

357 Mehrizi A, Hutchins GM, Medearis DN, and Rowe RD. Enterovirus infection and endocardial fibroelastosis.
Circulation. 32 : 150, 1965, abstr.

358 Merrel M, and Schulman LE. Determination of prognosis in chronic disease, illustrated by systemic lupus erythematosis.
J. Chron. Dis. 1 : 12, 1955.

359 Michaud L. Congenital idiopathic cardiac hypertrophy.
Korrespondenzbl. Schweiz. Artze. 36 : 779, 1906.

360 Midulla M, Marzetti G, Borra G, and Sabatino G. Myocarditis associated with Echo type 7 infection in a leukemic child.
Acta. Paediatr. Scand. 65 : 649, 1976.

361 Mihalca E, Balint T, Schuster T, and Margineanu O. Contribution to the study of myocardial damage in viral pneumopathies in infants.
Microbiol. Parazitol. Epidemiol. (Bucur). 14 : 71, 1969.

362 Miller AJ, Pick R, and Katz LN. Ventricular endocardial changes after impairment of cardiac lymph flow in dogs.
Brit. Heart J. 25 : 182, 1963.

363 Miller GAH, Rahimtoola SH, Ongley PA, and Swan HJC. Left ventricular volume and volume change in endocardial fibroelastosis.
Amer. J. Cardiol. 15 : 631, 1965.

364 Miller RA, and Hastreiter AR. Myocarditis. The acute and chronic acquired primary myocardial disease of infants and children.
Amer. J. Dis. Child. 100 : 736, 1960.

365 Mirculescu M, Onofrei T, Pirvulescu M, and Godja G. Myocarditic component of some acute diseases in children.
Pediatria. (Bucur). 19 : 409, 1970.

366 Mirimova TD and Ternova TI. Quantitative evaluation of the changes in the heart in children with infections, allergic myocarditis and other conditions.
Vopr. Okhr. Materin Det. 23 : 15, 1978.

367 Mitchell SC, Froehlich LA, Banas JS, and Gilkerson MR. An epidemiologic assessment of primary endocardial fibroelastosis.
Amer. J. Cardiol. 18 : 859, 1966.

368 Moller JH, Lucas RV Jr, Adams P Jr, Anderson RC, Jorgens J, and Edwards JE. Endocardial fibroelastosis : a clinical and anatomic study of 47 patients with emphasis on its relationship to mitral insufficiency.
Circulation. 30 : 759, 1964.

369 Moller JH, Fisch RO, From AH, and Edwards JE. Endocardial fibroelastosis occurring in a mother and son.
Pediatrics. 38 : 918, 1966.

370 Moller JH. Left ventricular failure in infancy.
Cardiovasc. Clin. 4 : 219, 1972.

371 Monif GRG, Lee C, and Hsuing GD. Isolated myocarditis with recovery of ECHO type 9 virus from the myocardium.
New Engl. J. Med. 227 : 1353, 1967.

372 Montgomery J, Gear J, Prinsloo FR, Kahn M, and Kirsch ZG. Myocarditis of the newborn.
So. Afr. Med. J. 29 : 608, 1955.

373 Moore CM, Henry J, Benzing G III, and Kaplan S. Varicella myocarditis.
Amer. J. Dis. Child. 118 : 899, 1969.

374 Morales AR, Adelman S, and Fine G. Varicella myocarditis : a case of sudden death.
Arch. Pathol. 91 : 29, 1971.

375 Morgagni JB. De sedibus et cansis morborum per anatomen inagatis libri quinque, 2nd ed, Padua, 1765.

376 Morison JE. Congenital malformations in one of monozygotic twins.
Arch. Dis. Child. 24 : 214, 1949.

377 Moron Diaz D, Espino Vela J, and Contreras R. Endocardial fibroelastosis.
Arch. Instit. Cardiol. Mex. 39 : 597, 1969.

378 Moroney MJ. Facts from Figures, 2nd edition, Penguin Books, Middlesex, 1953, p 233.

379 Moss AJ, Adams FH, and Emmanouilides GC (editors). Heart Disease in Infants, Children and Adolescents. Williams and Wilkins. 2nd ed., Baltimore, 1977.

380 Mumps and cardiac embryopathy (editorial).
Brit. Med. J. 516 : 372, 1967.

381 Muraki H, Iwama M, and Mori M et al. Fetal cardiac failure resulting from endocardial fibroelastosis.
Jap. Heart J. 15 : 623, 1974.

382 Muzykantova VS. Abramov-Fiedler myocarditis, the most severe variant of infectious allergic myocarditis in infants.
Arkh. Patol. 41 : 22, 1979.

383 Nadas AS. In Paediatric Cardiology, 2nd edition, WB Saunders, Philadelphia, 1963 , p 67.

384 Nagaratnam N, and Dissanayake RVP. Endomyocardial fibrosis in the Ceylonese.
Brit. Heart J. 21 : 167, 1959.

385 Namiu EP, and Miller RA. Normal electrocardiogram and vectorcardiogram in infants and children. Editors, Cassels DE, and Ziegler RF, Grune and Stratton, New York, 1966, p 99-108.

386 Naude W du T, Selzer G, and Kipps A. Coxsackie virus myocarditis of the newborn. Virus studies.
Med. Proc. 4 : 397, 1958.

387 Negri M, and Mosca L. Cuore calloso della prima infanzia.
Pediatria. 6 : 564, 1953.

388 Nelson RM, Bucciarelli RL, Eitzman DV, Egan EA II, and Gressner IH. Serum creatine phosphokinase MB fraction in newborns with transient tricuspid insufficiency.
New Engl. J. Med. 298 : 146, 1978.

389 Neustein HB, Lurie PR, and Fugita M. Endocardial fibroelastosis found on transvascular endomyocardial biopsy in children.
Arch. Pathol. Lab. Med. 103 : 214, 1979.

390 Nielsen JS. Primary endocardial fibroelastosis in three siblings.
Acta. Med. Scand. 177 : 145, 1965.

391 Nordenstam H. Pathoanatomical findings in twenty-six fatal cases of poliomyelitis.
Acta. Med. Scand. Suppl. 316 : 114, 1956.

392 Noren GR, Adams P Jr, and Anderson RC. Positive skin reactivity of mumps virus antigen in endocardial fibroelastosis.
J. Pediat. 62 : 604, 1963.

393 Noren GR, Raghib G, Moller JH, Amplatz K, Adams P Jr, and Edwards JE. Anomalous origin of the left coronary artery from the pulmonary trunk, with special reference to the occurrence of mitral insufficiency.
Circulation. 30 : 171, 1964.

394 Noren GR, Jankus EF, Staley NA, and Stevenson JE. Myocarditis in round heart disease of turkeys : a light and electron microscopic study.
Virchows Arch. Pathol. Anat. 352 : 285, 1971.

395 Noren GR, Kaplan EL, and Staley NA. "Nonrheumatic inflammatory cardiovascular diseases" in Heart Disease in Infants, Children and Adolescents, edited by Moss AJ, Adams FH, and Emmanouiledes GC. Williams and Wilkins, 2nd ed., Baltimore, 1977.

396 Novikov IuI, Stulova MA. Viral heart diseases.
Klin. Med. (Mosk). 52 : 23, 1974.

397 Oakley CM. Clinical definitions and classification of cardiomyopathies.
Postgrad. Med. J. 48 : 703, 1972.

398 Obeyesekere I, and Hermon Y. Myocarditis and cardiomyopathy after arbor-virus infections (dengue and Chiklungunya fever).
Brit. Heart J. 34 : 821, 1972.

399 Obodowska-Zysk W. Clinical analysis of cases of influenza observed in Poland in the years 1969-1971.
Przegl Epidémiol. 28 : 165, 1974.

400 O'Brien W. Endocardial fibrosis in the Sudan.
Brit. Med. J. 2 : 899, 1954.

401 Okada R, and Nasu T. Idiopathic myocardiopathy and allied cardiac diseases in Japan.
Pathol. Microbiol. (Basel). 35 : 56, 1970.

402 Okuni M, and Takaniya Y. Primary myocardial disease in children, with special references to idiopathic myocarditis.
Jap. Circ. J. 35 : 771, 1971.

403 Okuni M, Yamada T, Mochizuki S, and Sakurai I. Studies on myocarditis in childhood, with special reference to the possible role of immunological process and the thymus in the chronicity of the disease.
Jap. Circ. J. 39 : 463, 1975.

404 Olsen EGJ. in discussion of Reference 197.
Postgrad. Med. J. 48 : 753, 1972.

405 Olsen EGJ. Diagnostic value of the endomyocardial bioptome.
Lancet. 1 : 658, 1974.

406 Olsen EGJ. Endomyocardial biopsy.
Brit. Heart J. 40 : 95, 1978.

407 Olsen EGJ. Special investigations of COCM : endomyocardial biopsies.
Postgrad. Med. J. 54 : 486, 1978.

408 Oppenheimer EH. The association of adult type coarctation of the aorta with endocardial fibroelastosis in infancy.
Bull Johns Hopkins Hosp. 93 : 309, 1967.

409 Oppenheimer EH, and Easterly JR. Cardiac lesions in hypertensive infants and children.
Arch. Pathol. 84 : 318, 1967.

410 Orshanskaya RE. Fibroelastosis of endocardium in association with cytomegaly (Russian).
Arch. Pathol. 24 : 66, 1967.

411 Oseasohn R, Adelson L, and Kaji M. Clinicopathologic study of thirty-three fatal cases of Asian influenza.
New Eng. J. Med. 260 : 509, 1959.

412 Pardo V, Castro-Aballi R, Goorman HM, and Strauss J. Glomerular lesions in congenital endocardial fibroelastosis : clinical manifestations and ultrastructural studies in two patients.
Arch. Pathol. Lab. Med. 102 : 410, 1978.

413 Paul FM, and Thye CH. Myocardial involvement in acute glomerulonephritis in Singapore children.
J. Singapore Paediatr. Soc. 11 : 38, 1969.

414 Pavesio D, and Crosato M. Is endocardial fibroelastosis a disease of viral etiology?
G. Mal. Infett. Parassit. 19 : 417, 1967.

415 Pavlowich MW. Congenital endocardial fibroelastosis and complete (third-degree) A-V block in two sisters : case report.
J. Amer. Osteopath. Ass. 61 : 540, 1962.

416 Peale AR, and Lucchesi PF. Report of a case of measles encephalitis complicated by so-called "fetal endocarditis" and gonorrhoeal pyosalpinx.
Amer. J. Clin. Pathol. 12 : 357, 1942.

417 P'erz D'iaz LB, L'opez Send'on JL, Guti'errez Ju'arez J, Moreno Granado F, and Quero Jimenez M. Endocardial fibroelastosis. Pathologic and clinical findings in 20 cases.
An. Esp. Pediatr. 10 : 1, 1977.

418 Petrosian IuS, Belokon NA, Golosovskaia MA, Akaeva FIu, and Krymski'i LD. Endomyocardial biopsy in the diagnosis of various forms of cardiomyopathy in children.
Kardiologiia. 15 : 17, 1975.

419 Pietras RJ, Meadows WR, Fort M, and Sharp JT. Haemodynamic alterations in idiopathic myocardiopathy including cineangiography from the left heart chambers.
Amer. J. Cardiol. 16 : 672, 1965.

420 Pollen RH. Myocarditis due to Coxsackie virus, Group B, Type 5.
Amer. J. Cardiol. 12 : 736, 1963.

421 Pomerance A. Classification of the secondary cardiomyopathies. The pathologist's view.
Postgrad. Med. J. 48 : 714, 1972.

422 Pototschnig G. Uber die Kongenitale diffuse endokardhyperplasie des Linken Ventrikels.
Zschr. Ges. Anat. 4 : 235, 1919.

423 Powers GF, and Lecompte. Remarks on a case of congenital idiopathic hypertrophy of the heart.
J. Pediatr. 13 : 760, 1938.

424 Prior JT, and Wyatt TC. Endocardial fibroelastosis : a study of 8 cases.
Amer. J. Pathol. 26 : 969, 1950.

425 Provvidenza G, Ciarla MV, and DiNardo V. On a case of acute myocarditis during measles.
G. Mal. Infett. Parassit. 23 : 35, 1971.

426 Rafinski T, Goleima A, Wogniewicz B, and Wlad S. Familial endocardial fibroelastosis.
J. Pediatr. 70 : 574, 1967.

427 Rauchfuss C. In Handbuch des Kinderkrankheiten, Gerhardt C. editor, H. Laupp, Tübingen, 1878, pp 119, 123.

428 Reitman MJ, Zirin HJ, and De Angelis CJ. Complete heart block in Epstein-Barr myocarditis.
Pediatrics. 62 : 847, 1978.

429 Remen'ar E, and Kor'anyi G. Fatal cardiomyopathy in early infancy in 2 siblings.
Orv. Hetil. 118 : 2087, 1977.

430 Ribierre M, Leborgne P, Almange E, Landau JF, and Scordia P. Apparently primary acute heart failure in infants. Long-term outcome.
Arch. Mal. Coeur. 71 : 421, 1978.

431 Roberts KE, and Magida MD. Electrocardiographic alterations produced by a decrease in plasma pH, bicarbonate and sodium as compared with those seen with an increase in potassium.
Circ. Res. 1 : 206, 1953.

432 Roberts R, and Sobel BE. Isoenzyme of creatine phosphokinase and diagnosis of myocardial infarction.
Ann. Intern. Med. 79 : 741, 1973.

433 Roberts R, Gowda KS, and Ladbrook PA. Specificity of elevated serum MB creatine phosphokinase activity in the diagnosis of acute myocardial infarction.
Amer. J. Cardiol. 36 : 433, 1975.

434 Roberts WC, and Fox SA III. Mumps of the heart. Clinical and pathologic features.
Circulation. 32 : 342, 1965.

435 Robino G, Perlman A, Togo Y, and Reback J. Fatal neonatal infection due to Coxsackie B2 virus.
J. Pediatr. 61 : 911, 1962.

436 Rodin AE, Harris LC, and Nghiem QX. Idiopathic non-obstructive cardiomyopathy. Electron microscopic, histochemical and autopsy observations.
Arch. Pathol. (Chicago). 91 : 62, 1971.

437 Rodin AE, Harris LC, and Nghiem QX. Pediatric cardiomyopathies.
J. Molec. Cell. Cardiol. 3 : 63, 1971.

438 Rodriguez-Torres R, Lin JS, and Berkovich S. A sensitive electrocardiographic sign in myocarditis associated with viral infection.
Pediatrics. 43 : 846, 1969.

439 Rosalin PD. Endocardial fibroelastosis : old and new concepts.
Bull. NY Acad. Med. 31 : 453, 1955.

440 Rosenbaum HD, Nadas AS, and Neuhauser EBD. Primary myocardial disease in infancy and childhood.
Amer. J. Dis. Child. 86 : 28, 1953.

441 Rosenberg HS, and McNamara DG. Acute myocarditis in infancy and childhood.
Progr. Cardiovasc. Dis. 7 : 179, 1964.

442 Ross E, and Armentrout SA. Myocarditis associated with rabies : report of a case.
New Eng. J. Med. 266 : 1087, 1962.

443 Ross LJ. Electrocardiographic findings in measles.
Amer. J. Dis. Child. 83 : 282, 1952.

444 Ross R, and Klebanoff SJ. The smooth muscle cell : I. In vivo synthesis of connective tissue protein.
J. Cell. Biol. 50 : 159, 1971.

445 Ross R. The smooth muscle cell : II. Growth of smooth muscle in culture and formation of elastic fibres.
J. Cell. Biol. 50 : 172, 1971.

446 Rossi E. Endocardial fibroelastosis and its differential diagnosis.
Paediatr. Paedol. 11 : 23, 1976.

447 Rossi E. Herzkrankheiten in Sanglingsalter. G. Thieme, Stuttgart, 1954, pp 42, 230, 235, 239.

448 Rowe RD, and Mehrizi A. Myocardial disorders (cardiomyopathies). In The neonate with Congenital Heart Disease. WB Saunders. Philadelphia, 1968.

449 Russel SJM, and Bell EJ. Echoviruses and carditis.
Lancet. i : 784, 1970.

450 Ruttenberg HD, Steidl RM, Carey LS, and Edwards JE. Glycogen-storage disease of the heart.
Amer. Heart J. 67 : 469, 1964.

451 Saad FA, Atra E, Guimaraes RF, Pupo RA Jr, and Carvalhal SS. Heart biopsy.
Arq. Bras. Cardiol. 28 : 489, 1975.

452 Sacerdoti Favini F, and Gamba R. On a case of spontaneously cured post vaccinal acute myocarditis.
Fracastoro. 60 : 38, 1967.

453 Sainani GS, Krompotic E, and Slodki S. Adult heart disease due to the Coxsackie virus B infection.
Medicine. 47 : 133, 1968.

454 Sainani GS, Dekate MP, and Rao CP. Heart disease caused by Coxsackie virus B. infection.
Brit. Heart J. 37 : 819, 1975.

455 Samuel I, and Anklesaria XJ. Endomyocardial fibrosis in South India.
Indian J. Pathol. Bact. 3 : 157, 1960.

456 Sander JF, and Peets RC. Anomalous left coronary artery and endocardial fibroelastosis.
J. Michigan State Med. Soc. 58 : 80, 1957.

457 Sanders V. Viral myocarditis.
Amer. Heart J. 66 : 707, 1963.

458 Sanders V, and Ritts RE Jr. Ventricular localization of bound gamma globulin in idiopathic disease of the myocardium.
J. Amer. Med. Assoc. 194 : 171, 1965.

459 Sano ME, and Anderson NA. Elastic tissue hyperplasia of the endocardium.
Arch. Pathol. 33 : 533, 1942.

460 Sanyal SK, Mahdavy M, Gabrielson MO, Vidone RA, and Browne MJ. Fatal myocarditis in an adolescent caused by Coxsackie virus, group B, type four.
Pediatrics. 35 : 36, 1965.

461 Saphir O. Isolated myocarditis.
Amer. Heart J. 24 : 167, 1942.

462 Saphir O, Amromin GD, and Yokoo H. Myocarditis in viral (epidemic) hepatitis.
Amer. J. Med. Sci. 231 : 168, 1956.

463 Saphir O, and Cohen NA. Myocarditis in infancy.
Arch. Pathol. 64 : 446, 1957.

464 Scholmerich P. Diagnosis and course of viral myocarditis.
Internist (Berlin). 16 : 508, 1975.

465 Schmidt E, and Schmidt FW. Brief guide to practical enzyme diagnosis.
Diagnostica Boehringer Mannheim series, Mannheim, 1976.

466 Schneegans E, Fruhling L, Heumann G, Korn R, Lavillaureix J, and Arnold P. Anatomicoclinical and etiologic study of 20 cases of chronic fibroelastic myoendocarditis in infants (fibroelastosis).
Arch. franc. pediat. 20 : 645, 1963.

467 Schryer MJP, and Karnauchow PN. Endocardial fibroelastosis. Etiologic and pathogenetic considerations in children.
Amer. Heart J. 88 : 557, 1974.

468 Schwarz E, and Meze G. Familial occurrence of endocardial fibrosis in 3 siblings.
Pediatr. Grenzgeb. 8 : 67, 1969.

469 Scott AJ, and Zeiler AH. Congenital cardiac hypertrophy.
Amer. J. Dis. Child. 31 : 31, 1926.

470 Scott LP 3rd, Gutelius MF, and Parrott RH. Children with acute respiratory tract infections. An electrocardiographic study.
Amer. J. Dis. Child. 119 : 111, 1970.

471 Scott RW, and Saphir O. Acute isolated myocarditis.
Amer. Heart J. 5 : 129, 1929.

472 Seftel H, Metz J, and Lakier JB. Aetiology of cardiomyopathy in Johannesburg Bantu.
S. Afr. Med. J. 47 : 273, 1973.

473 Segal JP, Harvey WP, and Gurel T. Diagnosis and treatment of primary myocardial disease.
Circulation. 32 : 837, 1965.

474 Sekiguchi M, and Konno S. Diagnosis and classification of primary myocardial disease with the aid of endomyocardial biopsy.
Jap. Circ. J. 35 : 737, 1971.

475 Sekiguchi M, and Hirosawa K. Ultrastructural assessment of endocardial fibroelastosis using the endocardial biopsy technique.
J. Clin. Elect. Micros. 6 : 3, 1973.

476 Sellers FJ, Keith JD, and Manning JA. The diagnosis of primary endocardial fibroelastosis.
Circulation. 29 : 49, 1964.

477 Selye H. Experimental production of endomyocardial fibrosis.
Lancet. 1 : 1351, 1958.

478 Sever J, and White LR. Intrauterine viral infections.
Ann. Rev. Med. 19 : 471, 1968.

479 Shaper AG, Hutt MSR, and Coles RM. Necropsy study of endomyocardial fibrosis and rheumatic heart disease in Uganda 1950-1965.
Brit. Heart J. 30 : 391, 1968.

480 Shirey EK, Hawk WA, Mukerji D, and Effler DB. Percutaneous myocardial biopsy of the left ventricle.
Circulation. 46 : 112, 1972.

481 Shone JD, Armas SM, Manning JA, and Keith JD. The mumps antigen skin test in endocardial fibroelastosis.
Pediatrics. 37 : 423, 1966.

482 Simenhoff ML, and Uys CJ. Coxsackie virus myocarditis of the newborn. A pathological survey of four cases.
Med. Proc. 4 : 389, 1958.

483 Singh A, Doyle EF, Danilowicz DA, and Finegold MJ. Familial nonobstructive cardiomyopathy with endocardial fibroelastosis beyond infancy.
Pediatrics. 61 : 410, 1978.

484 Sitzmann FC et al. Klin Pädiatrie 184 : 59, 1972 and 186 : 346, 1974 ; and Arch Kinderheilkunde 183 : 1, 1971 ; quoted in "Brief guide to practical enzyme diagnosis" by E and FW Schmidt, Diagnostica Boehringer Mannheim series, Mannheim, 1976.

485 Smith WG. Adult heart disease due to the Coxsackie virus Group B.
Brit. Med. J. 28 : 204, 1966.

486 Smith WG. Coxsackie B myopericarditis in adults.
Amer. Heart J. 80 : 34, 1970.

487 Sobel BE, Bresnahan GF, and Shell WE. Estimation of infarct size in man and its relation to prognosis.
Circulation. 46 : 640, 1972.

488 Somerville W. Post carditic myocardiopathy.
Postgrad. Med. J. 48 : 746, 1972.

489 Spodick DH, and Littman D. Idiopathic myocardial hypertrophy.
Amer. J. Cardiol. 1 :610, 1958.

490 Staley NA, Noren GR, and Jankus EF. Virus-like particles associated with myocarditis of turkeys.
Amer. J. Vet. Res. 33 : 859, 1972.

491 Stein H, Shnier MH, Waylurne S, and Isaacson C. Cardiomyopathy in African children.
Arch. Dis. Child. 29 : 610, 1964.

492 St. Jeme JW Jr, Noren GR, and Adams P Jr. Proposed embryopathic relation between mumps virus and primary endocardial fibroelastosis.
New Eng. J. Med. 275 : 339, 1966.

493 St. Jeme JW Jr. Noren GR, Aase JM, Peralta H, and Van Pelt L. Split immunologic recognition of intrauterine mumps virus infection in the human and subhuman primate.
J. Lab. Clin. Med. 72 : 1012, 1968.

494 St. Jeme JW Jr, Noren GR, Evans CM, and Ozwoeld L. On the nonautoimmune aspects of endocardial fibroelastosis with continued inquiry into the significance of delayed sensitivity to mumps virus.
Pediatrics. 46 : 134, 1970.

495 St. Jeme JW Jr, Davis CWC, Cooper MD, and Noren GR. An experimental model of mumps virus embryopathy in the chick.
Fed. Proc. 29 : 284, 1970.

496 St. Jeme JW Jr, Peralta H, Farias E, Davis CWC, and Noren GR. Experimental gestational mumps virus infection and endocardial fibroelastosis.
Pediatrics. 48 : 821, 1971.

497 St. Jeme JW Jr, Davis CWC, Peralta HJ, Farias NE, Yamanchi T, and Cooper MD. The biologic pertubations of persistent embryonic mumps virus infection.
Pediatr. Res. 7 : 541, 1973.

498 St. Jeme JW Jr, Davis CWC, and Noren GR. An overview of primary endocardial fibroelastosis and chronic viral cardiomyopathy.
Perspect. Biol. Med. 17 : 495, 1974.

499 Still WJS. Endocardial fibroelastosis.
Amer. Heart J. 61 : 579, 1961.

500 Stöber E. Uber das "Schwielenherz" des Säuglings.
Zschr. Kinderheilk. 65 : 114, 1948.

501 Stöber E. Weitere Untersuchungen über Epidemische Myokarditis (Schwielenherz) des Säuglings.
Zschr. Kinderheilk. 71 : 319, 1952.

502 Stoloff EG. So-called idiopathic enlargement of the heart in infancy and in childhood.
Amer. J. Dis. Child. 36 : 1204, 1928.

503 Strauss FA. Case of parietal endocardofibrosis of a newborn.
Zentralbl. Gynak. 54 : 1235, 1960.

504 Strohr G. Malformations of the heart of the new-born. Congenital lesions suggestive of an inflammatory origin.
Arch. Pathol. 17 : 311, 1934.

505 Sty JR, Babbitt DP, and Gallen WJ. Scintigraphy in endocardial fibroelastosis.
Clin. Nucl. Med. 3 : 476, 1978.

506 Suckling PV, and Vogelpoel L. Coxsackie myocarditis of the newborn.
Med. Proc. 4 : 372, 1958.

507 Sudhas-Na-Ayuthya P, Jayavasu J, and Pongpanich B. Coxsackie group B virus and primary myocardial disease in infants and children.
Amer. Heart J. 88 : 311, 1974.

508 Surawicz B, Braun HA, Gum WB, Kemp RL, Wagner S, and Bellet S. Quantitative analysis of the electrocardiographic pattern of hypopotassemia.
Circulation. 16 : 750, 1957.

509 Surawicz B, and Lepeschkin E. The electrocardiogram in hyperpotassemia.
Heart Bull. 10 : 66, 1961.

510 Surawicz B. Electrolytes and the electrocardiogram.
Mod. Concepts Cardiovasc. Dis. 33 : 875, 1964.

511 Surawicz B. Primary and secondary T wave changes.
Heart Bull. 15 : 31, 1966.

512 Szanto PB, Lacera D, and Novak G. Fibroelastosis. An anatomic study.
Quoted by Hastreiter AR, and Miller RA.
Paed. Clin. North Amer. 11 : 404, 1964.

513 Takatsu T. Idiopathic cardiomyopathy.
Nippon Naika Gakhai Zasshi. 66 : 1669, 1977.

514 Takatsu T, Movita H, Uehara H, Tanaka T, and Sonotani N. Acute myocarditis - various types of myocarditis and descriptions of viral, Fiedler and giant-cell myocarditis.
Jpn. J. Clin. Med. 35 : 1930, 1977.

515 Takeda M, Kirkaldy-Willis WH, and Read SE. Secondary endocardial fibroelastosis : an electron microscopic study.
Can. Med. Assoc. J. 99 : 110, 1968.

516 Takeshita I. Clinical and pathological study on the idiopathic cardiomyopathy.
Jpn. Circ. J. 40 : 1039, 1976.

517 Tatter D, Gerard PW, Silverman AH, Wang C, and Pearson HE. Fatal varicella pancarditis in a child.
Amer. J. Dis. Child. 108 : 88, 1964.

518 Tedeschi CG, and Damodaran VN. Endocardial fibroelastosis : with report of three cases.
Boston Med. Quart. 4 : 106, 1953.

519 Tedeschi CG, and Stevenson TD. Interstitial myocarditis in children.
New Engl. J. Med. 244 : 352, 1951.

520 Teloh HA. Myocarditis in poliomyelitis.
Arch. Pathol. 55 : 408, 1953.

521 Tingelstad JB, Shiel F O'M, and McCue CM. The electrocardiogram in the contracted type of primary endocardial fibroelastosis.
Amer. J. Cardiol. 27 : 304, 1971.

522 Turner PP, Manson-Bahr REC. Endomyocardial fibrosis in Kenya and Tanganyika Africans.
Brit. Heart J. 22 : 305, 1960.

523 Ullrich O. Angeborene Herzhypertrophie mit Endokardfibrose bei zevei eineügen Partnern von mannlichen Drillingen.
Z. Menschl. Vererb. Konstitutional. 21 : 585, 1938.

524 Unger H. Diffuse interstitial myocarditis in a case of epidemic encephalitis.
Amer. J. Clin. Pathol. 18 : 48, 1948.

525 Urban M, and Krasowska I. Clinical analysis of the course of viral myocarditis in children.
Pediatr. Pol. 53 : 1285, 1978.

526 Van Buchen FSP, Arends A, and Schroëder EA. Endocardial fibroelastosis in adolescents and young adults.
Brit. Heart J. 21 : 229, 1959.

527 Van Creveld S, and De Jager H. Myocarditis in newborn caused by Coxsackie virus. Clinical and pathological data.
Ann. Paediat. 187 : 100, 1956.

528 Van Creveld S. Virus myocarditis in infancy - acute phase and possible late sequels. In Rose HM, editor : Viral infections of infancy and childhood, Hoeber-Harper, New York, 1960, p 33.

529 Vapcor I, Solor K, Pironkova M, Mineve C, and Vassilev I. Sur l'association de la maladie des inclusions cytomegaliques, la pneumonie a pneumoncystis carinii, et la fibroelastose endomyocardique du nourisson (å propos d'un cas observé).
Folia Med. 7 : 63, 1965.

530 Varat MA, and Mercer DW. Cardiac specific creatine phosphokinase isoenzyme in the diagnosis of acute myocardial infarction.
Circulation. 51 : 855, 1975.

531 Veit ST et al. Klin. Pädiatrie 187 : 244, 1975 ; quoted by E and FW Schmidt in "Brief guide to practical enzyme diagnosis".
Diagnostica Boehringer Mannheim series, Mannheim, 1976.

532 Vestermark S. Primary endocardial fibroelastosis in siblings.
Acta. Paediat. Scand. 51 : 94, 1962.

533 Vestermark S. Primary endocardial fibroelastosis.
Cardiology. 48 : 520, 1966.

534 Verlinde JD, Van Tongeren HAE, and Kret A. Myocarditis in newborns due to group B Coxsackie virus. Virus studies.
Ann. Paediatr. 187 : 113, 1956.

535 Vijayaraghavan G, Cherian G, Krishnaswami S, and Sukumar IP. Left ventricular endomyocardial fibrosis in India.
Brit. Heart J. 39 : 563, 1977.

536 Vitek B, Srackova D, Rozprimova L, and Snopkova J. Glycogenosis and its diagnosis.
Cesk. Pediatr. 24 : 608, 1969.

537 Vitek B, Valenta J, Habanec B, and Cernoch K. Fatal ventricular fibrillation in an infant with Bland-White-Garland syndrome and endocardial fibroelastosis.
Z. Kreislaufforsch. 59 : 1111, 1970.

538 Vlad P, Rowe RD, and Keith JD. The electrocardiogram in primary endocardial fibroelastosis.
Brit. Heart J. 2 : 189, 1955.

539 Von Gronefeld V, Hanke H. Endocardial fibroelastosis : radiological and angiocardiographic signs.
Ann. Radiol. (Paris). 17 : 405, 1974.

540 Von Hauser. Ein Fall von Cor bovinum bei einem elfmonatlichen Kinde.
Deutsche Med. Wchenschr. 22 : 705, 1896.

541 Vosburgh JB, Diehl AM, Liu C, Lauer RM, and Fabiyi A. Relationship of mumps to endocardial fibroelastosis.
Amer. J. Dis. Child. 109 : 69, 1965.

542 Vosti GJ, and Roffwarg H. Myocarditis and encephalitis in a case of suspected psittacosis.
Ann. Intern. Med. 54 : 764, 1961.

543 Voussure G, and Drochmans P. La fibro-elastose endocardique (endocardial sclerosis).
Acta. Paed. Belg. 7 : 241, 1953.

544 Vulliamy DG. Idiopathic cardiac hypertrophy.
Brit. Heart J. 9 : 161, 1947.

545 Wagner G. Coronary diseases and myocardial infarct in infancy and childhood.
Dtsch. Gesundheitsw. 24 : 2039, 1969.

546 Wagner GS, Roe CR, and Limbird LE. The importance of identification of the myocardial-specific isoenzyme of creatine phosphokinase (MB form) in the diagnosis of acute myocardial infarction.
Circulation. 47 : 263, 1973.

547 Waksman BH. Auto-immunization and the lesions of auto-immunity.
Medicine. 41 : 93, 1962.

548 Waterson AP. Virological investigations in congestive cardiomyopathy.
Postgrad. Med. J. 54 : 505, 1978.

549 Watson H (Editor). Paediatric Cardiology. Lloyd-Luke 1968.

550 Weber JW, Saputo V, and Mosca L. Chronische Myokarditis, Endokardfibrose, und Infarkt bei einem Säugling.
Helv.Pediatr. Acta. 17 : 341, 1962.

551 Weber MW, Baldwin JS, and Hall JW. Acute isolated myocarditis : review of the literature and report of a case in a 10 year old child. Pediatrics. 3 : 829, 1949.

552 Webster BH. Cardiac complications of infectious mononucleosis. A review of the literature and report of five cases. Amer. J. Med. Sci. 234 : 62, 1957.

553 Wechsler HF, Rosenblum AH, and Sills CT. EKG in infectious mononucleosis. Ann. Intern. Med. 25 : 113, 1946.

554 Weinberg RS, Izukawa T, and Rowe RD. Capillary to myocardial fibre volume ratios in endocardial fibroelastosis. Johns Hopkins Med. J. 123 : 183, 1968.

555 Weinberg T, and Himmelfarb AJ. Endocardial fibroelastosis (so-called fetal endocarditis) : A report of two cases occurring in siblings. Bull. Johns Hopkins Hosp. 72 : 299, 1943.

556 Weinstein L. Cardiovascular manifestations in some of the common infectious diseases. Mod. Concepts Cardiovasc. Dis. 23 : 229, 1954.

557 Weisman S. Congenital idiopathic cardiac hypertrophy. Arch. Pathol. 33 : 365, 1942.

558 Wenger NK. Infectious myocarditis. In : Cardiomyopathy, Ed. GE Burch, Vol 4/1, Cardiovascular Clinics, Ed. AN Brest, FA Davis Co., Philadelphia, 1972, pp 167-185.

559 Westwood M, Hams R, Burn JL, and Barson AJ. Heredity in primary endocardial fibroelastosis. Brit. Heart J. 37 : 1077, 1975.

560 White LR, Rosa FW, and Sever JL. Viral infections in 30,000 pregnancies. Paper presented at the Second Scientific Session of the Collaborative Study on Cerebral Palsy, Mental Retardation and other Neurological and Sensory Disorders of Infancy and Childhood, March, 1966.

561 White LR. Virologic aspects of the Perinatal Research Study. In Viral Etiology of Congenital Malformations. U.S. Government Printing Office; p 8, 1968.

562 Whitehead JEM. Silent infections and the epidemiology of viral carditis. Amer. Heart J. 85 : 711, 1973.

563 Whitehead R. Isolated myocarditis. Brit. Heart J. 27 : 220, 1965.

564 Williams H, O'Reilly RN, and Williams A. Fourteen cases of idiopathic myocarditis in infants and children. Arch. Dis. Child. 28 : 271, 1953.

565 Williams RB, and Emery JL. Endocardial fibrosis in apparently normal infant hearts. Histopathology. 2 : 283, 1978.

566 Williamson AP, Simonseu L, and Blattner RJ. Specific organ defects in early chick embryos following inoculation with influenza A virus. Proc. Soc. Exp. Biol. Med. 92 : 334, 1956.

567 Wilson FM, Miranda QR, Chason JL, and Lerner AM. Residual pathologic changes following murine Coxsackie A and B myocarditis. Amer. J. Pathol. 55 : 253, 1969.

568 Wilson RA, and Clark N. Endocardial fibroelastosis associated with generalised glycogenosis. Pediatrics. 26 : 86, 1960.

569 Wilson RSE, Morris TH, and Rees JR. Cytomegalovirus myocarditis. Brit. Heart J. 34 : 865, 1972.

570 Windorfer A. Acute viral myocarditis in infants and children. Munch. Med. Wochenschr. 108 : 2213, 1966.

571 Winkler W. Endokarditis fötalis, ein Beitrag zur Pathologie des angeborenen Herzfehlers. Verhndl. Dsch. Pathol. Gesellsch. 15 : 247, 1904.

572 Winter ST, Moses WS, Cohen NJ, and Naftalin JM. Primary endocardial fibroelastosis in two sisters. Amer. J. Dis. Child. 99 : 529, 1960.

573 Wolska K. Attempt at an explanation of the cause of sudden death in cases of endocardial fibroelastosis. Pol. Med. J. 8 : 637, 1969.

574 Woodruff JF, and Kilbourne ED. The influence of quantitative post-weaning undernutrition on Coxsackievirus B3 infection of adult mice. I. Viral persistence and increased susceptibility of lesions. J. Infect. Dis. 121 : 131, 1970.

575 Wright HT Jr, Lauding BH, Lennett EH, and McAllister RM. Fatal infection in an infant associated with Coxsackie virus group A, type 16. New Eng. J. Med. 268 : 1041, 1963.

576 Wright HT Jr, and Miller A. Fatal infection in a newborn infant due to herpes simplex virus : Report of a case diagnosed before death. J. Pediatr. 67 : 130, 1965.

577 Ylinen C, and Jarvinen PA. Parotitis during pregnancy. Acta. Obst. et Gynec. Scand. 32 : 121, 1953.

578 Yoshida T, Nimura Y, Sakakebara H, Matsutani K, Nishizaki K, and Nakata T. A diffuse endocardial fibroelastosis with markedly dilated right atrium observed in an adult. Jap. Heart J. 5 : 85, 1964.

579 Yoshida Y, Sato T, Kano I, Fukuda M, Sasaki T, Hoshino H, Tanaka M, and Terasawa Y. Ultrasonic studies on endocardial fibroelastosis. Tohoku J. Exp. Med. 123 : 329, 1977.

580 Yu N, Schreiner BF, Cohen J, and Murphy W. Idiopathic cardiomyopathy. A study of left ventricular function and pulmonary circulation in 15 patients. Amer. Heart J. 71 : 330, 1966.

581 Zaborszky B, and Kamaras J. Anomalous left coronary artery or left ventricular endocardial fibroelastosis?
Acta. Paediatr. Acad. Sci. Hung. 14 : 243, 1973.

582 Zaidi ZH. Primary endocardial fibro-elastosis.
J. Indian Med. Assoc. 33 : 459, 1959.

583 Zanker T, and Fisher RS. Endocardial fibroelastosis in siblings.
Maryland Med. J. 9 : 60, 1960.

APPENDIX A

PATIENT DATA + DIAGNOSTIC CRITERIA

SECTION A - CLINICAL SERIES

GROUP 1 - WITHOUT LVH* ON ECG

CASE NO	DATE OF PRESEN-TATION	NAME	RACE AND SEX	AGE (m)	DURATION OF HISTORY (d)	ECG ABNORMALITY			C'MEG X-RAY	CLINICAL CRITERIA									
						T-WAVE	ST-SEG	LVH		HR per min	C'MEG CLIN.	CONGESTIVE FAILURE				GALLOP RHYTHM	SHOCK	SM
												HEPAR (cms)	JVP (cms)	OED	CREPI-TATIONS			
1	29.4.73	GB	WF	0.5	3	+	-	-	+	142	-	6	-	+	-	+	+	-
2	13.10.72	SH	CF	0.7	7	+	-	-	+	160	-	4	-	-	-	+	-	-
3	21.11.73	EH	CM	1.3	7	+	-	-	+	160	+	4	-	-	-	+	+	-
4	22.10.72	AL	CM	1.3	21	+	-	-	+	160	+	2	3	-	R	+	-	-
5	16.8.74	WB	CM	1.3	1	+	-	-	+	200	+	4	-	-	-	+	-	-
6	7.10.73	JW	WM	1.5	14	+	-	-	+	165	+	1	-	+	-	-	-	-
7	9.2.74	NM	WF	1.7	21	+	-	-	+	200	-	-	-	-	-	-	-	-
8	15.4.74	KH	CM	2	1	+	-	-	+	150	-	4	-	+	-	+	-	-
9	7.7.72	AQ	AM	3	4	-	-*	-	+	180	-	2	-	-	Bil	-	-	-
10	2.4.75	BB	AM	4	14	+	-	-	+	160	+	1	-	-	L	-	-	-
11	7.12.76	ZM	AM	4	2	+	+	-	+	200	+	2	-	-	Bil	-	-	-
12	27.3.75	CM	AM	5	1	-	+	-	+	160	+	3	-	-	Bil	-	-	-
13	23.11.70	MA	CF	6	7	-	+	-	+	160	+	5	-	+	(wheeze)	+	-	-
14	6.5.74	CN	AM	6	3	+	-	-	+	180	+	1	-	-	Bil	-	-	-
15	5.8.75	KJ	CM	6	21	+	-	-	+	160	+	5	-	+	-	-	-	-
16	7.12.70	FS	CM	7	2	+	-	-	+	154	+	2	-	-	-	+	-	-
17	21.9.73	EE	CM	7	1	+	+	-	+	200	+	4	3	-	-	+	+	-
18	6.12.73	AP	CF	7	4	+	-	-	+	168	-	2	-	-	-	+	-	-
19	18.7.76	NF	CF	8	14	+	-	-	+	160	-	3	-	-	-	-	+	-
20	26.8.72	AN	AF	9	1	+	-	-	+	160	+	1	-	-	-	+	-	-

* See final subscript for abbreviations.

CASE NO	DATE OF PRESEN-TATION	NAME	RACE AND SEX	AGE (m)	DURATION OF HISTORY (d)	ECG ABNORMALITY			C'MEG X-RAY	CLINICAL CRITERIA									
						T-WAVE	ST-SEG	LVH		HR per min	C'MEG CLIN.	CONGESTIVE FAILURE				GALLOP RHYTHM	SHOCK	SM
												HEPAR (cms)	JVP (cms)	OED	CREPI-TATIONS			
21	10.5.76	BM	CM	9	4	+	-	-	+	160	-	1	-	-	Bil	-	-	-
22	28.11.71	DN	AF	10	5	+	-	-	+	190	+	5	4	-	Bil	+	-	-
23	4.9.73	BS	CF	10	1	+	-	-	+	120	-	-	-	-	-	+	-	-
24	17.9.73	GI	CM	10	3	+	-	-	+	190	+	5	-	-	-	+	+	-
25	3.12.73	TP	CM	10	6	+	-	-	+	168	+	2	3	-	-	+	-	-
26	9.7.76	MvO	CF	10	5	+	+	-	+	172	+	5	3	-	-	+	-	-
27	21.9.76	RK	CF	10	5	+	-	-	+	156	+	7	-	+	-	+	+	-
28	6.11.72	AJ	CF	11	7	+	-	-	+	130	+	4	5	-	-	+	+	-
29	18.8.75	MvN	CF	11	4	+	-	-	+	195	+	3	-	-	Bil	-	-	-
30	4.9.76	SM	CF	11	3	+	-	-	+	180	+	5	4	-	-	+	+	-
31	5.5.72	EC	CM	12	7	+	-	-	+	200	-	3	-	-	Bil	+	-	-
32	9.4.73	RA	CF	12	3	+	+	-	+	200	+	4	-	-	-	+	-	-
33	11.6.75	MP	AF	12	14	+	+	-	+	172	+	5	-	+	Bil	-	-	-
34	28.5.76	TW	CF	12	3	+	+	-	+	200	+	5	-	-	-	+	+	-
35	29.5.72	EP	CF	13	1	+	+	-	+	200	-	3	3	+	-	+	+	-
36	17.10.72	AF	CF	13	7	+	-	-	+	140	+	4	+	+	Bil	+	-	2/6
37	13.7.73	GC	CM	13	1	+	+	-	+	196	-	2	-	-	-	+	-	-
38	7.7.74	JS	AM	13	2	+	-	-	+	160	-	-	-	-	R	+	-	-
39	13.7.75	JS	WM	13	1	+	-	-	o*	188	-	5	5	-	-	+	+	-
40	7.10.76	MJ	CF	13	1	+	-	-	+	200	+	6	-	-	-	+	+	-
41	8.9.71	HvN	CF	14	5	+	-	-	+	160	-	3	-	-	Bil	+	+	-
42	9.10.71	SS	CM	14	2	+	-	-	+	180	+	6	-	+	Bil	+	-	1/6
43	5.12.71	AS	CM	14	7	+	-	-	+	160	+	-	-	+	-	+	-	-
44	17.7.73	TvW	WF	14	14	+	-	-	+	166	+	5	-	-	-	+	-	-
45	4.10.73	EdV	CM	14	14	+	+	-	+	240	+	-	-	-	-	+	-	-
46	28.1.74	RP	CF	14	4	+	-	-	+	188	-	5	-	-	-	+	+	-

CASE NO	DATE OF PRESEN-TATION	NAME	RACE AND SEX	AGE (m)	DURATION OF HISTORY (d)	ECG ABNORMALITY			C'MEG X-RAY	CLINICAL CRITERIA								
						T-WAVE	ST-SEG	LVH		HR per min	C'MEG CLIN.	CONGESTIVE FAILURE				GALLOP RHYTHM	SHOCK	SM
												HEPAR (cms)	JVP (cms)	OED	CREPI-TATIONS			
47	27.5.74	EdB	WF	14	10	+	-	-	+	168	+	3	-	+	Bil	+	-	-
48	15.7.74	CD	CF	14	4	-	+	-	+	140	+	1	-	+	Bil	+	-	-
49	3.8.73	AM	CM	15	3	+	+	-	+	160	+	2	5	-	-	+	-	-
50	12.1.76	MR	CF	15	14	+	+	-	+	200	+	7	+	-	-	+	-	-
51	21.10.70	TM	CM	16	7	+	-	-	+	180	-	3	-	-	Bil	+	-	-
52	7.4.72	BF	CM	16	4	+	-	-	+	130	+	1	-	-	Bil	+	-	-
53	16.8.74	RB	CM	16	1	+	-	-	+	160	+	-	-	-	-	-	-	3/6
54	19.12.72	AW	AF	17	7	+	-	-	+	140	+	3	-	-	Bil	+	-	-
55	12.9.73	NS	CF	17	7	+	-	-	+	160	+	4	3	-	L	+	-	-
56	5.9.73	PB	CM	17	1	+	-	-	+	182	+	4	10	+	(wheeze)	+	-	-
57	8.1.75	WvW	CM	17	14	+	+	-	+	160	-	2	-	+	Bil	+	-	-
58	31.12.70	FO	CF	18	1	+	-	-	+	160	+	2	+	-	Bil	+	-	-
59	16.9.73	HR	CM	18	4	+	-	-	+	130	-	1	3	+	Bil	+	-	-
60	3.9.70	RL	CM	19	1	-	+	-	+	240	+	3	10	-	L	-	-	-
61	19.5.73	FH	CM	19	4	+	-	-	+	140	-	4	+	-	Bil	+	-	-
62	17.10.73	GA	CF	19	1	+	+	-	+	180	-	2	-	-	-	+	-	-
63	10.11.73	MD	AM	19	3	+	-	-	+	160	+	4	-	-	Bil	+	+	-
64	28.12.76	SA	CF	19	7	+	-	-	+	168	+	5	-	+	Bil	+	-	-
65	8.1.72	JM	CM	20	7	+	-	-	+	190	+	5	-	-	-	+	-	1/6
66	11.9.70	CG	WF	21	7	+	-	-	+	156	+	4	+	-	-	+	-	-
67	20.10.73	AS	CM	21	1	+	-	-	+	120	+	1	-	-	-	+	-	-
68	27.11.74	HG	CF	21	1	-	+	-	+	240	+	6	+	+	-	+	+	-
69	10.8.76	LD	AF	21	3	+	-	-	+	170	+	7	3	+	Bil	+	-	-
70	22.6.73	ZS	CF	23	3	+	-	-	+	150	-	-	-	-	Bil	+	-	-
71	6.7.73	RJ	CM	23	7	+	-	-	+	170	-	4	3	-	Bil	+	-	-
72	6.8.76	RA	CF	28	7	+	-	-	+	160	+	6	-	+	Bil	+	+	-
73	14.5.72	TdB	CM	29	1	+	+	-	+	180	-	8	+	+	Bil	+	-	-

CASE NO	DATE OF PRESEN-TATION	NAME	RACE AND SEX	AGE (m)	DURATION OF HISTORY (d)	ECG ABNORMALITY			C'MEG X-RAY	CLINICAL CRITERIA									
						T-WAVE	ST-SEG	LVH		HR per min	C'MEG CLIN.	CONGESTIVE FAILURE				GALLOP RHYTHM	SHOCK	SM
												HEPAR (cms)	JVP (cms)	OED	CREPI-TATIONS			
74	1.3.74	SS	CF	29	3	+	-	-	+	150	-	4	3	+	Bil	+	-	1/6
75	18.6.73	ES	CM	30	7	+	+	-	+	180	-	-	-	-	Bil	+	-	-
76	6.6.75	NV	CM	30	14	+	-	-	+	130	+	-	3	+	-	-	-	-
77	18.6.71	RE	CF	33	10	+	-	-	+	180	+	-	3	-	-	+	-	-
78	12.2.73	SN	CF	36	14	+	+	-	+	180	+	5	10	+	Bil	+	+	-
79	21.8.73	GF	CM	36	21	+	-	-	+	148	+	3	-	+	Bil	-	-	-
80	6.9.73	JR	CF	36	7	+	+	-	+	160	-	3	10	+	Bil	+	-	-
81	21.9.74	BR	CM	43	3	+	+	-	+	120	-	2	-	-	Bil	-	-	-
82	22.6.70	IH	CM	44	5	+	+	-	+	180	-	2	3	-	-	+	-	-
83	25.10.74	JS	CM	45	21	+	-	-	+	100	+	8	2	+	Bil	-	-	2/6
84	22.5.72	TD	CF	48	7	+	-	-	+	180	+	3	3	-	R	+	-	-
85	9.4.74	KT	CF	52	3	+	-	-	+	120	+	2	-	-	Bil	+	-	-
86	12.12.72	AvdW	CF	60	21	+	-	-	+	120	+	6	5	-	-	+	-	-
87	13.3.74	MA	CF	60	7	+	-	-	+	176	-	3	5	-	-	+	-	-
88	11.12.75	CH	CM	60	25	+	-	-	+	140	+	5	7	+	R	+	-	-
89	13.5.76	MS	CF	60	10	+	-	-	+	168	+	2	3	-	(wheeze)	+	-	-
90	28.7.74	AM	AF	94	4	+	-	-	+	152	+	6	+	+	L	+	-	-
91	7.9.70	EA	CM	144	10	+	+	-	+	160	+	-	5	-	-	+	-	-
92	10.5.73	SM	AM	147	21	+	-	-	+	132	-	4	4	+	-	+	-	-

GROUP 2 - WITH LVH ON ECG

93	4.7.74	JF	CF	1	1	+	-	+	+	180	+	5	-	-	-	+	-	-
94	8.9.73	QD	CF	2	5	+	-	+	+	165	-	4	-	-	-	-	-	-
95	20.8.73	GR	WM	3	7	+	-	+	+	140	-	2	-	-	-	-	-	-

CASE NO	DATE OF PRESEN-TATION	NAME	RACE AND SEX	AGE (m)	DURATION OF HISTORY (d)	ECG ABNORMALITY			C'MEG X-RAY	CLINICAL CRITERIA								
						T-WAVE	ST-SEG	LVH		HR per min	C'MEG CLIN.	CONGESTIVE FAILURE				GALLOP RHYTHM	SHOCK	SM
												HEPAR (cms)	JVP (cms)	OED	CREPI-TATIONS			
96	25.7.74	SM	CF	3	5	+	–	+	+	180	+	4	–	–	Bil	+	–	–
97	14.11.74	TM	AM	3	4	+	–	+	+	210	+	2	–	–	R	–	–	–
98	14.10.71	JE	WM	4	10	+	–	+	+	140	–	–	–	–	Bil	–	–	–
99	10.9.73	LD	AF	4	1	+	+	+	+	150	+	2	–	–	L	+	–	–
100	1.4.74	PG	CF	4	1	+	–	+	+	120	–	3	–	–	–	–	–	–
101	22.10.74	EZ	AM	5	14	+	–	+	+	128	–	–	–	–	–	+	–	2/6
102	5.1.76	JM	AM	5	31	+	–	+	+	180	–	3	–	–	Bil	+	–	2/6
103	18.2,74	MvB	CM	6	4	+	–	+	+	150	–	–	–	–	–	–	–	–
104	19.7.75	DA	CM	6	3	+	+	+	+	200	+	4	–	–	Bil	+	–	–
105	17.12.70	NP	CF	7	21	+	–	+	+	160	+	2	–	–	–	+	–	–
106	26.1.74	RB	CF	7	6	+	–	+	+	140	+	2	–	–	Bil	+	–	–
107	26.6.74	FA	CM	7	3	+	+	+	+	190	–	2	–	–	L	+	–	–
108	9.12.74	GM	AM	7	2	+	–	+	+	148	–	1	–	–	L	+	–	–
109	3.6.76	AH	CF	8	4	+	+	+	+	170	+	4	–	–	–	+	+	–
110	23.1.74	PF	CM	9	14	+	+	+	+	180	–	4	–	+	L	+	–	–
111	2.12.70	FS	CM	10	6	–	–	+	+	140	+	3	–	–	–	+	–	–
112	18.10.74	CM	AF	10	9	+	–	+	+	196	+	5	–	–	–	+	–	–
113	31.7.74	BW	CM	11	4	+	–	+	+	180	+	2	–	–	Bil	+	–	–
114	22.10.72	KT	AM	12	30	+	+	+	+	130	–	3	–	+	–	+	–	–
115	1.2.74	WK	CM	13	7	+	–	+	+	150	+	3	–	–	–	+	–	–
116	16.1.74	MS	CF	14	5	+	+	+	+	176	+	4	–	–	Bil	+	–	–
117	17.5.72	PK	AF	15	21	–	–	+	+	170	+	3	–	–	–	+	–	–
118	24.3.74	TM	AM	15	21	+	+	+	+	250	–	3	–	+	Bil	+	–	–
119	9.10.71	RF	CF	18	1	+	–	+	+	158	–	5	+	–	R	+	–	–
120	6.7.73	SMcK	CM	20	7	+	+	+	+	140	+	5	3	+	Bil	–	–	–
121	18.2.74	FW	CF	20	4	+	–	+	+	156	+	4	3	–	Bil	+	–	–
122	3.10.73	WJ	CM	37	1	+	–	+	+	120	+	6	+	+	Bil	+	–	–
123	10.2.74	RM	CM	81	2	+	–	+	+	140	+	6	–	+	Bil	+	–	–

SECTION B - AUTOPSY SERIES

GROUP 3 - WITH SHORT HISTORY

CASE NO	DATE OF PRESEN-TATION	NAME	RACE AND SEX	AGE (m)	DURATION OF HISTORY (d)	ECG ABNORMALITY			C'MEG X-RAY	CLINICAL CRITERIA									PM
						T-WAVE	ST-SEG	LVH		HR per min	C'MEG CLIN.	CONGESTIVE FAILURE				GALLOP RHYTHM	SHOCK	SM	
												HEPAR (cms)	JVP (cms)	OED	CREPI-TATIONS				
124	27.11.74	AS	CM	3	4				+	128	+	4	-	-	-	+	+	-	F
125	14.12.76	EC	CF	4	1				+	160	-	3	-	-	-	+	+	-	F(M)
126	18.11.75	DJ	CF	5	2					140		1		-	(wheeze)	+	-	-	F(M)
127	29.5.76	NA	CF	9	1														M
128	16.6.76	AW	CM	9	21				+	165	-	4	-	-	Bil	-	+	-	M
129	28.8.76	CM	AM	10	7				+	140	-	2	-	-	Bil	-	+	-	M
130	6.5.73	AG	WF	11	1														M
131	23.8.74	TM	CF	12	3				+	190	-	6	-	-	Bil	+	-	-	M
132	14.10.74	KW	CF	12	14				+	180	+	4	-	-	-	+	-	-	F(M)
133	30.7.75	GG	CF	14	7				+	140	-	4	-	-	-	-	+	-	M(F)
134	15.9.75	SO	CF	25	1				+	140	-	4	-	-	-	+	+	-	M
135	28.7.76	FM	AM	36	1					168	-	3	-	-	-	-	+	-	M
136	29.5.74	RM	CF	54	1					120	-	-	-	+	Bil	-	-	-	

GROUP 4 - WITH LONG HISTORY

137	14.11.72	AK	WM	6	2 m	+	+	+	+	100	+	+	-	-	-	+	-	-	F
138	29.7.73	BM	AM	18	>2 m	-	-	+	+	200	+	4	4	-	-	+	-	2/6 +MDM	F
139	23.1.76	GP	CM	30	>2 m	-	+	-	-	170	-	-	-	+	-	+	-	2/6	F
140	19.10.74	MD	AF	36	14 m	+	-	+	+	120	+	10	10	+	-	+	-	2/6 +TI	F(M)

Subscript/APPENDIX A

Abbreviations in headings: ST-SEG = ST segment; LVH = left ventricular hypertrophy; C'MEG X-RAY = radiological cardiomegaly; HR = heart rate; C'MEG CLIN = clinical cardiomegaly; JVP = jugular venous pressure; OED = oedema; SM = systolic murmur; m = months; d = days.

Abbreviations in text: W = white; C = Cape coloured; A = African (black); M = male; F = female; R = right side; L = left side; Bil = bilateral; F = autopsy-proved endocardial fibroelastosis; M = autopsy-proved myocarditis; MDM = mid-diastolic murmur; TI = tricuspid incompetence.

+ = present; - = absent
* = frequent supraventricular arrythmias on ECG, myocarditis proved at autopsy
o* = no x-ray; patient died soon after admission; gross cardiomegaly and myocarditis at autopsy
1/6, 2/6, 3/6 = grade of intensity of systolic murmur

APPENDIX B

OTHER CLINICAL FINDINGS

Key: * Duration of first or subsequent admissions, with period in convalescent home in brackets;
TEMP = temperature; Hb = haemoglobin (Grams per 100 ml); WBC = white blood count per ml^3;
DIG = digoxin; A'BIOTICS = antibiotics
(For other abbreviations, see subscript).

	HISTORY	ADMISSION	TEMP	COMPLICATIONS	INVESTIGATIONS			TREATMENT				OUTCOME
CASE NO	Symptom & duration (days)	Duration* (days)	(>37°C)		Hb	WBC	OTHER	DIG	LASIX	A'BIOTICS	OTHER	ALIVE or DEAD
1	Malaise, SOB -3	3	-	-	15.0	10 000	-	+	+	Pen, Kan	-	A
2	RT., GIT -7	11	-	-	14.4	18 500	LP - NAD Blood urea - 80	+	+	Pen, Genta	-	A
3	SOB -7	(i) 12 Delay 8 (ii) 24	-	- CCF	11.6	12 600	Stool - Salm B	+	+	Pen, Kan	-	A D
4	RT -21, fever	13	-	-	13.7	14 200	-	+	+	Pen, Amp, Genta	-	D
5	SOB -1	37	-	-	11.0	8 400	Blood urea - 73 Serum K - 6.8°	+	+	-	-	A
6	RT -14, Oedema - 4	76	-	-	8.1	9 800	LP - NAD Urine - rbc's, granular casts	+	-	Genta, Kef	-	A
7	SOB - 30	13	-	-	13.4	15 700	-	+	-	-	-	A
8	RT-1, fever-1 apnoeic attack	21	-	-	12.0	13 700	-	+	+	Pen, Kan	-	A

CASE NO	HISTORY	ADMISSION	TEMP	COMPLICATIONS	INVESTIGATIONS			TREATMENT				OUTCOME
	Symptom & duration (days)	Duration* (days)	(>37°C)		Hb	WBC	OTHER	DIG	LASIX	A'BIOTICS	OTHER	ALIVE or DEAD
9	RT -4, fever	6	-	Pneumonia	10.9	11 500	-	+	-	Pen	Ventolin Propranolol Isoptin	A
10	RT -14, fever	(i) 21 Delay 75 (ii) 14	-	- Br-pneum/PCM	12.0	14 500	Blood urea - 92 Urine-Klebsiella	+ +	+ +	Pen, Kan	-	A A
11	RT -2, GIT-2, fever	17	-	-	10.5	-	LP - NAD Sputum - E.coli Blood urea - 79	+	-	Pen, Genta, Clox	IPPV Blood T/F	A
12	RT -1, SOB-1, fever	14	-	-	11.5	6 500	-	+	+	Pen	Ipradol Solphyllin	A
13	SOB -1, RT-1, Malaise -7	26	-	Pneumonia	12.1	19 600	-	+	+	Kan	-	D
14	RT -3	8	-	-	9.6		Tracheal aspirate -PS. aeriginosa Blood urea - 41 Urine - E.coli & C. albicans	+	-	Pen, Chloro, Genta	PEEP IPPV Blood T/F	D
15	SOB -21, Oedema, fever	30	-	Measles Pneumonia	7.6	44 100	Blood urea - 38	+	-	Pen, Genta	-	A
16	Malaise, GIT -2, fever	2	-	-	-	-	-	+	-	-	-	D

CASE NO	HISTORY	ADMISSION	TEMP	COMPLICATIONS	INVESTIGATIONS			TREATMENT				OUTCOME
	Symptom & duration (days)	Duration* (days)	(>37°C)		Hb	WBC	OTHER	DIG	LASIX	A'BIOTICS	OTHER	ALIVE or DEAD
17	Convulsions -1	18	-	-	-	-	LP - NAD Blood urea -79	+	+	-	-	A
18	RT -4	(i) 20 Delay 189 (ii) 5	+	- Pneumonia	9.7 -	3 400 -	- -	+	-	-	-	A A
19	RT -14 convulsions -1	1	-	Pneumonia + cardio-pulm arrest	-	-	Blood urea -49	+	+	Pen,Genta	IPPV Isuprel	D
20	RT -1, GIT -1	(i) 28 Delay 41 (ii) 15(+38)	-	Pneumonia CCF(off dig)	11.3	9 700	Urine - E.coli	+ +	+ +	Pen,Septran	-	A A
21	RT -21,fever Measles -2	10	-	Pneumonia	11.9	3 500	-	+	-	Pen,Septran Clox, Amp	-	A
22	RT -5,fever	22	-	-	9.7	12 300	-	+	+	Pen	-	A
23	RT -1	OPD	-	-	10.2	10 500	-	+	-	-	-	A
24	RT -3, oedema -1, fever	1	-	-	9.5	-	-	+	+	-		D
25	RT -6	16	+	Pneumonia	10.8	28 000	-	+	-	Ilosone	-	A
26	Malaise -5 fever	15	-	-	11.0	4 900	LP - NAD Blood urea - 47	+	+	-	-	A

CASE NO	HISTORY	ADMISSION	TEMP	COMPLICATIONS	INVESTIGATIONS			TREATMENT				OUTCOME
	Symptom & duration (days)	* Duration (days)	(>37°C)		Hb	WBC	OTHER	DIG	LASIX	A'BIOTICS	OTHER	ALIVE or DEAD
27	Malaise -5, SOB -2	(i) 7 Delay 19 (ii) 10(+28)	+	- CCF (? off dig)	5.0	-	Blood urea - 43	+	+	Septran	Isuprel	A A
28	RT -7,GIT-7, SOB -1	1	-	-	10.0	19 100	Blood urea - 97 Urine - rbc's	+	+	-	-	D
29	RT -4,GIT-4, fever	10	+	Convulsions Pneumonia	9.7	22 100	LP - NAD	+	+	Pen,Kan	IPPV Ipradol Valium	A
30	RT -3,fever	4	-	Convulsions, mid-brain & pontine lesion	9.5	9 300	Blood urea - 53	+	+	-	Steroids	D
31	RT -7, fever SOB -1	15	+	Pneumonia	8.4	20 400	Sputum - Klebs Blood urea - 64	+	+	Pen,Kan	Adrenaline Ventolin	A
32	Malaise -3, SOB -3	39(+20)	-	-	8.6	9 000	-	+	+	Pen	-	A
33	SOB-14,fever	14	+	Pleural effu-sions	10.7	16 800	Blood urea - 39	+	+	-	-	A
34	RT -2	1	-	Pneumonia	8.0	-	-	+	+	-	-	D
35	Malaise -1	1	-	-	9.1	11 900	-	+	+	-	Isuprel	D
36	RT -21, Oedema -7, SOB -7	19	-	Pneumonia	6.5	15 200	-	+	+	Pen	-	A

CASE NO	HISTORY	ADMISSION	TEMP	COMPLICATIONS	INVESTIGATIONS			TREATMENT				OUTCOME
	Symptom & duration (days)	Duration* (days)	(>37°C)		Hb	WBC	OTHER	DIG	LASIX	A'BIOTICS	OTHER	ALIVE or DEAD
37	RT -1, SOB -1	1	+	Pneumonia, Cardio-pulmonary arrest	-	-	-	+	-	-	IPPV	D
38	Rash-14, RT-2 fever	15	-	Pneumonia	9.7	12 600	-	+	+	Pen	-	A
39	RT -1, SOB -1	1	+	Cardio-pulmonary arrest	5.5	-	LP - NAD Urine protein++ Blood urea - 68	-	-	-	IPPV	D
40	Malaise -1, Grunt -1	11	-	-	8.3	21 800	Urine - hyaline casts, rbc's Blood urea - 37 LP - NAD	+	+	-	-	A
41	Malaise -5, SOB -1, fever	7	-	Respiratory arrest Pneumonia	11.6	16 900	Blood urea - 52 LP - NAD	+	+	Pen	-	A
42	RT -2	(i) 11 Delay 42 (ii) 34(+54)	-	Otitis media CCF - off dig	-	-	Blood urea - 40 LP - NAD	+ +	+ +	Pen, Chloro	-	A A
43	RT -7, GIT -7, oedema -7	2	-	-	-	-	-	+	+	-	PAS, INH	A
44	RT-6, pallor, fever	(i) 4 Delay 192 (ii) 16	+	Otitis media Depressed LOC RT.I + CCF	11.2	8 900	LP - (7 polymorphs 1 lymphocyte)	+ +	+ +	+	-	A A

CASE NO	HISTORY	ADMISSION	TEMP	COMPLICATIONS	INVESTIGATIONS			TREATMENT				OUTCOME
	Symptom & duration (days)	Duration* (days)	(>37°C)		Hb	WBC	OTHER	DIG	LASIX	A'BIOTICS	OTHER	ALIVE or DEAD
45	RT-14, fever	20(+52)	-	Chicken-pox Measles	9.6	11 900	-	+	+	-	-	A
46	RT-4, Malaise-4, fever	19	-	Irritability Pneumonia	9.4	14 200	LP - NAD Brain scan - infarct L middle cerebral artery	+	+	Pen	-	A
47	Malaise-10, grunt-1	19	-	-	6.3	11 800	-	+	+	-	Blood T/F	A
48	RT-4, Oedema-4	(i) 6 Delay 10 (ii) 19	+	- CCF - off dig	8.9	40 100	Blood urea - 116	+ +	+ +	-	-	A A
49	GIT-3	27	-	-	11.4	18 000	Urine-Klebsiella LP - NAD	+	+	-	-	A
50	RT-14	(i) 11 Delay 94 (ii) 10	+	- CCF - off dig	9.9	10 700	Blood urea - 55	+ +	+ +	Pen	-	A A
51	RT-7, SOB-7	(i) 2 Delay 39 (ii) 7	-	Pneumonia CCF	6.5	-	-	+	+	Pen, Clox	Aminophylline	A A
52	GIT-4	33(+37)	-	Herpes	7.9	-	LP - NAD	+	-	Pen, Septran Genta	-	A
53	RT-1, SOB-1, fever	2	+	-	-	-	-	+	-	Pen	-	A

CASE NO	HISTORY	ADMISSION	TEMP	COMPLICATIONS	INVESTIGATIONS			TREATMENT				OUTCOME
	Symptom & duration (days)	Duration* (days)	(>37°C)		Hb	WBC	OTHER	DIG	LASIX	A'BIOTICS	OTHER	ALIVE or DEAD
54	RT-30	33(+38)	-	Pneumonia	7.6	7 000	-	+	+	Pen,Septran	-	D
55	RT-7,SOB-2	16	-	-	9.4	7 900	-	+	+	Pen	-	A
56	SOB-1, Oedema-1, fever	23	-	-	6.0	22 300	-	+	+	-	-	A
57	Measles-14	24	+	Pneumonia	-	-	Sputum-Enterobacter,Pseudomonas, Klebsiella	+	+	Pen,Kan	-	A
58	RT-1,SOB-1, Measles	(i) 34(+35) + 8	+	Measles Pneumonia	9.8	12 900	Blood urea - 53	+	-	Pen	-	A
59	RT-4,fever, Measles-2	9	-	PCM Pneumonia Encephalitis	9.6	18 600	LP-encephalitis x3	-	-	Pen,Kan	Steroids	A
60	RT-1	36(+42)	-	-	10.2	27 500	ESR - 74 LP - NAD	+	-		-	A
61	SOB-4, Oedema-4, Convulsions	(i) 17 Delay 23 (ii) 15	-	- CCF - off dig	11.5	12 600	-	+ +	+ +	Septran	-	A A
62	Malaise-1, SOB-1	22	+	Cardio-pulmonary arrest	8.9	13 100	Blood urea - 43 LP - NAD x2	+	-	Pen	IPPV	D

CASE NO	HISTORY	ADMISSION	TEMP	COMPLICATIONS	INVESTIGATIONS			TREATMENT				OUTCOME
	Symptom & duration (days)	Duration* (days)	(>37°C)		Hb	WBC	OTHER	DIG	LASIX	A'BIOTICS	OTHER	ALIVE or DEAD
63	RT-3, fever, Convulsions	1	-	Comatose Pneumonia	6.7	129 000	LP - NAD	+	+	Pen, Kan	IPPV	D
64	Grunt-7, Convulsions weak limb	1	-	Hemiparesis	7.0	-	LP - NAD	+	+	Amp, Genta	Isuprel	D
65	RT-7, SOB-7, fever	10(+97) +14(+21)	-	- Pneumonia	6.5	-	-	+	+	Amp	-	A
66	RT-7, SOB	21	-	Pneumonia	7.2		-	+	+	Pen	-	A
67	GIT-1	OPD	+	-	-	-	-	+	-	-	-	A
68	Malaise-2, SOB-1	1	-	Pneumonia	6.5	-	Urine-protein++, granular casts	+	+	-	-	D
69	RT-3, Oedema-1	11	-	-	10.7	9 100	Sputum-H.influenza Stool-Salmonella Cl	+	+	Pen	-	A
70	Measles-3	(i) 7 Delay 31 (ii) 14	+	Pneumonia Pneumonia	10.9	14 200	-	+ +	-	Pen, Strep	-	A A
71	RT-7, weak limb-1	24	+	Hemiparesis Otitis media	10.2	11 000	LP - NAD Ear-Pr.mirabilis	+	-		-	A

ASE NO	HISTORY	ADMISSION	TEMP	COMPLICATIONS	INVESTIGATIONS			TREATMENT				OUTCOME
	Symptom & duration (days)	Duration* (days)	(>37°C)		Hb	WBC	OTHER	DIG	LASIX	A'BIOTICS	OTHER	ALIVE or DEAD
2	RT-2, Oedema-2	17	-	Nephritis Chicken-pox	10.0	18 700	Urine-hyaline & granular casts Blood urea - 97 LP - NAD	+	+	-	-	A
3	RT-1,GIT-1	20	-	Pneumonia	10.2	14 500	Sputum - H. influenza Blood urea - 44	+	+	Pen, Kan, Septran	-	A
4	SOB-30,RT-3, fever	12(+14)	-	-	6.1	12 900	-	+	+	-	-	A
5	RT-7	7	-	Down's syndrome	10.8	32 000	Stool-Salmonella	+	+	Pen, Kef	-	D
6	Oedema-14	46(+86)	-	Bulbar palsy	11.4	8 800	LP - NAD x2	+	+	Pen	Trachy, IPPV	A
7	RT-10, Convulsions -4	26(+115)	-	-	11.3	8 700	Blood urea - 34 ESR - 33	+	+	-	-	A
8	GIT-14, Oedema-1, fever	75	-	Bulbar palsy, Peripheral neuropathy & 6th nerve palsy	11.2	10 700	Blood urea - 45 LP - NAD	+	+	-	Trachy, IPPV	A
9	Oedema-21	35	-	-	3.6	7 400	-	+	+	Pen	Blood T/F	A
0	RT-7, Oedema-7	12	+	-	11.0	18 300	-	+	+	-	-	A

CASE NO	HISTORY	ADMISSION	TEMP	COMPLICATIONS	INVESTIGATIONS			TREATMENT				OUTCOME
	Symptom & duration (days)	Duration* (days)	(>37°C)		Hb	WBC	OTHER	DIG	LASIX	A'BIOTICS	OTHER	ALIVE or DEAD
81	RT-3	9	-	Herpes Pneumonia Encephalitis	11.5	11 200	LP-5 lymphocytes	+	+	Pen, Kan	-	A
82	RT-5, Oedema-5	35(+30)	+	-	8.3	11 100	Blood urea - 49	+	+	Pen, Amp, Cloxacillin	-	A
83	SOB-21, Oedema-7	13	-	-	14.1	8 800	-	+	+	-	-	A
84	Oedema-14, RT-7, fever	21	-	Pneumonia	12.3	9 600	Blood urea - 37 T/S-B Haemolytic streptococcus	+	-	Pen	-	A
85	RT-3	(i) 22 Delay 345 (ii) 9	-	Pneumonia Pneumonia	8.3	8 600	Sputum-Enterobacter aerogenes Blood urea - 42 Urine-protein++ E.coli	+	+	Amp, Clox, Septran	-	A A
86	RT-21, Oedema-21	15(+87)	-	-	8.5	7 900	Blood urea - 45 ESR - 80	+	+	-	-	A
87	Malaise-7, SOB-7, fever	62	+	-	-	-	T/S-B Haemolytic Streptococcus	+	+	-	-	A
88	Measles-25, RT-14	43(+67)	+	Chicken-pox	8.1	-	T/S-B Haemolytic Streptococcus ESR - 90 Stool-Salmonella	+	+	Genta	-	A

CASE NO	HISTORY	ADMISSION	TEMP	COMPLICATIONS	INVESTIGATIONS			TREATMENT				OUTCOME
	Symptom & duration (days)	Duration* (days)	(>37°C)		Hb	WBC	OTHER	DIG	LASIX	A'BIOTICS	OTHER	ALIVE or DEAD
89	RT-10, fever	71(+40)	+	-	6.1	13 700	ESR - 65	+	+	Pen, Clox, Septran	Anti-TB	A
90	RT-4, fever	37	+	Pleural effusion Pneumonia	10.4	16 300	-	+	+	Pen, Septran	-	A
91	GIT-15, Malaise-10	72	-	-	10.5	-	-	+	+	-	-	D
92	Chest pain-21 Jts-21, SOB-21	(i)30 Delay 78 (ii)13	+	-	11.0	6 100	ESR - 75	+	+	-	-	A
				Pulmonary & lymph node TB				+	-	Pen, Clox	Anti-TB	A
93	SOB-1, Grunt-1	8	-	Pneumonia	16.0	11 700	Blood urea - 71 Urine-Klebsiella	+	+	Amp, Clox	-	A
94	SOB-5, Cyanosis-5	(i)11 Delay 23 (ii)30	-	-	12.4	-	LP - NAD	+	+	-	-	A
				CCF				+	+			D
95	RT-14, SOB-1	22	-	-	11.9	7 300	-	+	+	Pen	-	A
96	RT-5	1	-	Cardio-respiratory arrest	9.8	-	-	+	+	Pen, Kan	Ipradol IPPV	D
97	Measles-4, Oedema-4	28	-	-	10.7	14 000	LP - NAD Sputum-Ps.aeriginosa	+	+	Pen, Kan, Clox	Blood T/F	A

CASE NO	HISTORY	ADMISSION	TEMP	COMPLICATIONS	INVESTIGATIONS			TREATMENT				OUTCOME
	Symptom & duration (days)	Duration* (days)	(>37°C)		Hb	WBC	OTHER	DIG	LASIX	A'BIOTICS	OTHER	ALIVE or DEAD
98	SOB-10	14	-	-	-	-	-	+	-	-	-	A
99	RT-21,SOB-1	21	-	Pneumonia	10.4	9 300	-	+	+	Pen, Kan	-	A
100	Herniorraphy -1, SOB-1	23	-	-	14.2	11 400	-	+	-	Pen, Kan	-	A
101	RT-14	(i)14 Delay 11 (ii)1	-	- CCF - ? off dig	8.4	7 400	LP - NAD Blood urea - 43	+	+	Pen	-	A D
102	RT-26,SOB-3	32	+	Pneumonia	12.5	12 200	-	+	+	Pen, Genta, Cloxacillin	-	A
103	SOB-4,fever	7	+	-	10.0	15 200	Blood urea - 38	+	-	Pen	-	A
104	RT-3,SOB-3	(i)24 Delay 49 (ii)50	-	Otitis media CCF,pneumonia	12.0	13 400	Blood urea - 61 Ear - staph, & D.pneumoniae	+ +	- +	Amp	Anti-TB (Heaf +ve)	A A
105	RT-21	25(+76)	-	-		-	-	+	+	-	-	A
106	RT-6,Rash-2, fever	23	+	Pneumonia	10.3	9 800	Sputum-Klebsiella	+	+	Pen, Kan, Clox,Erythro	-	A
107	RT-3,SOB-3	25	-	-	9.9	23 400	Blood urea - 53	+	-	Pen	-	D

CASE NO	HISTORY	ADMISSION	TEMP	COMPLICATIONS	INVESTIGATIONS			TREATMENT				OUTCOME
	Symptom & duration (days)	Duration* (days)	(>37°C)		Hb	WBC	OTHER	DIG	LASIX	A'BIOTICS	OTHER	ALIVE or DEAD
108	GIT-2	(i) 9 Delay 50 (ii) 2	-	- CCF - off dig	11.8	11 100	-	+ +	- +	Pen	-	A A
109	Malaise-4, SOB-4	1	-	-	-	-	-	+	+	+	-	D
110	RT-21,SOB-21	(i) 28 Delay 52 (ii) 59 Delay 76 (iii) 1	+	- Pneumonia Pneumonia + CCF	9.4	6 400	-	+ + +	+	Pen, Kana	-	A A D
111	SOB-12, Grunt-1	20	-	-	11.0	7 000	-	+	+	Pen, Kan	-	A
112	RT-7,fever	(i) 44 Delay 74 (ii) 16 Delay 168 (iii) 1	+	- CCF - off dig CCF - off dig	10.4	8 500	LP - NAD	+	+	-	-	A A A
113	RT-4,SOB-2	13	+	-	9.0	-	-	+	-	-	-	A
114	GIT-30,RT-10 Oedema-7	(i) 20 Delay 30 (ii) 10	-	- CCF - off dig	11.1	8 700	-	+ +	+ +	-	-	A A
115	SOB-7, Malaise-7, fever	24	-	-	11.7	9 100	-	+	-	-	-	A

CASE NO	HISTORY	ADMISSION	TEMP	COMPLICATIONS	INVESTIGATIONS			TREATMENT				OUTCOME
	Symptom & duration (days)	Duration* (days)	(>37°C)		Hb	WBC	OTHER	DIG	LASIX	A'BIOTICS	OTHER	ALIVE or DEAD
116	RT-1,fever	(i) 18	-	-	7.1	23 300	Urine-protein++ Sputum-E.coli	+	+	Pen, Kan	-	A
		Delay 61										
	RT-5	(ii) 27		Pneumonia Convulsions			LP - NAD	+	+	Pen, Kan	Steroids IPPV	A
		Delay 260										
		(iii) 21(+102)		Pneumonia Peripheral gangrene				+	+			A
117	RT-21,fever	5	+	-	7.0	-	-	+	+	-	-	A
118	RT-21, Oedema-21, fever	10	-	-	12.0	7 900	Blood urea - 60	+	+	Pen	-	A
119	SOB-2,GIT-1	9	-	-	6.3	20 900	Blood urea - 45	+	+	Pen	-	D
120	RT-7, Oedema-7, fever	15	-	Pneumonia	10.0	17 500	-	+	+	Pen, Septran	-	A
121	RT-4	44	-	-	10.0	18 400	Blood urea - 39	+	+	Pen	-	A
122	RT-1,SOB-1, Oedema-1	20	+	-	13.2	9 400	T/S-B Haemolytic streptococcus Urine-rbc's + granular casts	+	+	Pen	-	A

CASE NO	HISTORY	ADMISSION	TEMP	COMPLICATIONS	INVESTIGATIONS			TREATMENT				OUTCOME
	Symptom & duration (days)	Duration* (days)	(>37°C)		Hb	WBC	OTHER	DIG	LASIX	A'BIOTICS	OTHER	ALIVE or DEAD
123	SOB-2, Oedema-2	9	-	-	13.4	11 600	-	+	+	-	-	A
124	Malaise-4, Cyanosis-4, Fever	1	-	-	-	-	-	+	+	Pen, Kana	IPPV	D
125	GIT-1, SOB-1, Fever	1	-	-	-	-	PM. LP - 960 lymphocytes 28 polymorphs	-	-	-	-	D
126	Grunt-1, Fever-2	1	+	-	-	-	LP - NAD			Pen	Ipradol	D
127	RT-1, Convulsions -1	2	-	-	-	-	-	-	-	Pen	-	D
128	RT-1, SOB-1	1	-	-	9.0	-	-	-	-	Pen	-	D
129	RT-7, SOB-1, Fever	1	-	-	7.5	-	-	+	-	Pen, Genta	-	D
130	SOB-1	1	-	-	-	-	-	-	-	-	-	D
131	RT-3, GIT-1	1	+	-	8.0	-	LP - NAD	+	+	Pen	-	D
132	Malaise-14, SOB-4	17	+	-	8.0	-	Urine-protein++ LP - NAD	+	+	+	-	D

CASE NO	HISTORY	ADMISSION	TEMP	COMPLICATIONS	INVESTIGATIONS			TREATMENT				OUTCOME
	Symptom & duration (days)	Duration (days)	(>37°C)		Hb	WBC	OTHER	DIG	LASIX	A'BIOTICS	OTHER	ALIVE or DEAD
133	RT-7, GIT-7	1	-	-	7.9	13 200	Blood culture-	-	-	-	-	D
134	SOB-1,fever	1	-	-	11.0	-	-	-	-	Pen	Anti-TB (spine)	D
135	Grunt-1, Convulsions	1	-	-	7.0	-	-	-	-	-	-	D
136	SOB-1	1	-	-	-	-	-	-	-	-	-	D
137	SOB-2m GIT-2	1	-	-	9.6	8 000	Blood urea-78	+	+	Pen,Kan	-	D
138	SOB-2m Oedema-2 fever-2	(i)15(+24) delay 14	-	CCF-off dig pneumonia	9.7	8 500	-	+	+	Pen	-	A
	RT-4	(ii) 1	-	-	-	-	-	+	+	Pen	-	D
139	SOB-2m Oedema-2m	(i) 35 delay 330	-	Kwashiorkor Herpes Pneumonia	12	9 500	-	+	+	Pen,Genta, Clox	-	A
	SOB-1,fever	(ii) 1		-	-	-	-	+	+	-	-	D
140	SOB-14m Oedema-14m	28	-	-	12.6	4 900	-	+	+	-	-	D

Abbreviations: SOB = short of breath; RT = respiratory tract (mild); GIT = gastrointestinal tract; Grunt = grunting respiration; CCF = congestive cardiac failure; Br-pneum = bronchopneumonia; PCM = protein calorie malnutrition; LOC = level of consciousness; TB = tuberculosis; LP = lumbar puncture; NAD = nil abnormal detected; Salm = Salmonella; K = potassium; rbc's = red blood cells; E = Escherichia; Ps = Pseudomonas; C = Candida; Klebs = Klebsiella; L = left; ESR = erythrocyte sedimentation rate (mm per hour); H = Haemophilus; Pr = Proteus; T/S = throat swab; Staph = Staphylococcus; D = Diplococcus; PM = post-mortem; Pen = penicillin; Kan = kanamycin; Genta = gentamycin; Amp = ampicillin; Kef = keflex; Clox = cloxacillin; Chloro = chloramphenicol; Erythro = erythromycin; IPPV = intermittent positive pressure ventilation; T/F = transfusion; PEEP = positive end expiratory pressure; PAS = para amino salicylate; INH = isoniazid; Trachy = tracheostomy.

APPENDIX C

EVIDENCE OF INFECTION.

Signs indicative of infection and their absence or presence in each patient.

PATIENT NO.	HISTORY OF FEVER	ELEVATED TEMP	ELEVATED WBC	PNEUMONIA	CNS ABNORM	URAEMIA	URINARY ABNORM	POSITIVE VIROLOGY
1	-	-	-	-	-	-	-	-
2	-	-	+	-	-	+	-	+
3	-	-	+	-	-	-	-	-
4	+	-	+	-	-	-	-	+
5	-	-	-	-	-	+	-	-
6	-	-	-	-	-	-	+	+
7	-	-	+	-	-	-	-	-
8	+	-	+	-	-	-	-	-
9	+	-	-	+	-	-	-	-
10	+	-	+	-	-	+	-	-
11	+	-	-	-	-	+	-	-
12	+	-	-	-	-	-	-	-
13	-	-	+	+	-	-	-	-
14	-	-	-	-	-	+	-	+
15	+	-	+	+	-	+	-	-
16	+	-	-	-	-	-	-	-
17	-	-	-	-	+*	+*	-	-
18	-	+	-	-	-	-	-	-
19	-	-	-	+	+*	+*	-	-
20	-	-	-	+	-	-	-	-
21	+	-	-	+	-	-	-	-
22	+	-	+	-	-	-	-	-
23	-	-	-	-	-	-	-	-
24	+	-	-	-	-	-	-	-
25	-	+	+	+	-	-	-	-
26	+	-	-	-	-	+	-	-
27	-	+	-	-	-	+*	-	+

PATIENT NO.	HISTORY OF FEVER	ELEVATED TEMP	ELEVATED WBC	PNEUMONIA	CNS ABNORM	URAEMIA	URINARY ABNORM	POSITIVE VIROLOGY
28	-	-	+	-	-	+ *	+	+
29	+	+	+	+	+	-	-	-
30	+	-	-	-	+ *	+ *	-	-
31	+	+	+	+	-	+	-	-
32	-	-	-	-	-	-	-	+
33	+	+	+	-	-	+	-	-
34	-	-	-	+	-	-	-	-
35	-	-	-	-	-	-	-	-
36	-	-	+	+	-	-	-	+
37	-	+	-	+	-	-	-	-
38	+	-	+	+	-	-	-	-
39	-	+	-	-	-	+ *	+	-
40	-	-	+	-	-	+ *	+	-
41	+	-	+	+	-	+ *	-	-
42	-	-	-	-	-	+	-	-
43	-	-	-	-	-	-	-	-
44	+	+	-	-	+	-	-	-
45	+	-	-	-	-	-	-	+
46	+	-	+	+	+ *	-	-	-
47	-	-	-	-	-	-	-	-
48	-	+	+	-	-	+	-	-
49	-	-	+	-	-	-	-	-
50	-	+	-	-	-	+	-	-
51	-	-	-	+	-	-	-	+
52	-	-	-	-	-	-	-	+
53	+	+	-	-	-	-	-	-
54	-	-	-	+	-	-	-	+
55	-	-	-	-	-	-	-	-
56	+	-	+	-	-	-	-	-
57	-	+	-	+	-	-	-	-
58	-	+	+	+	-	+	-	+
59	+	-	+	+	+	-	-	-
60	-	-	+	-	-	-	-	-
61	-	-	+	-	+	-	-	-

PATIENT NO.	HISTORY OF FEVER	ELEVATED TEMP	ELEVATED WBC	PNEUMONIA	CNS ABNORM	URAEMIA	URINARY ABNORM	POSITIVE VIROLOGY
62	-	+	+	-	- *	+	-	-
63	+	-	+	+	+	-	-	-
64	-	-	-	-	+	-	-	-
65	+	-	-	+	-	-	-	-
66	-	-	-	+	-	-	-	+
67	-	+	-	-	-	-	-	-
68	-	-	-	+	-	-	+	-
69	-	-	-	-	-	-	-	-
70	-	+	+	+	-	-	-	-
71	-	+	-	-	+	-	-	+
72	-	-	-	-	-	+ *	+	-
73	-	-	+	+	-	+	-	-
74	+	-	+	-	-	-	-	-
75	-	-	+	-	-	-	-	-
76	-	-	-	-	+	-	-	-
77	-	-	-	-	+	+	-	-
78	+	-	-	-	+	+ *	-	-
79	-	-	-	-	-	-	-	-
80	-	+	+	-	-	-	-	-
81	-	-	-	+	+	-	-	+
82	-	+	-	-	-	+	-	-
83	-	-	-	-	-	-	-	-
84	+	-	-	+	-	+	-	-
85	-	-	-	+	-	+	+	-
86	-	-	-	-	-	+	-	-
87	+	+	-	-	-	-	-	-
88	-	+	-	-	-	-	-	-
89	+	+	+	-	-	-	-	-
90	+	+	+	+	-	-	-	-
91	-	-	-	-	-	-	-	-
92	-	+	-	-	-	-	-	-
93	-	-	-	+	-	+	-	-
94	-	-	-	-	-	-	-	+

PATIENT NO.	HISTORY OF FEVER	ELEVATED TEMP	ELEVATED WBC	PNEUMONIA	CNS ABNORM	URAEMIA	URINARY ABNORM	POSITIVE VIROLOGY
95	-	-	-	-	-	-	-	-
96	-	-	-	-	-	-	-	-
97	-	-	+	-	-	-	-	+
98	-	-	-	-	-	-	-	-
99	-	-	-	+	-	-	-	-
100	-	-	-	-	-	-	-	-
101	-	-	-	-	-	+	-	-
102	-	+	+	+	-	-	-	-
103	+	+	+	-	-	+	-	+
104	-	-	+	-	-	+	-	+
105	-	-	-	-	-	-	-	-
106	+	+	-	+	-	-	-	-
107	-	-	+	-	-	+	-	-
108	-	-	-	-	-	-	-	+
109	-	-	-	-	-	-	-	-
110	-	+	-	-	-	-	-	-
111	-	-	-	-	-	-	-	-
112	+	+	-	-	-	-	-	-
113	-	+	-	-	-	-	-	-
114	-	-	-	-	-	-	-	-
115	+	-	-	-	-	-	-	-
116	+	-	+	-	-	-	+	-
117	+	+	-	-	-	-	-	+
118	+	-	-	-	-	+	-	-
119	-	-	+	-	-	+	-	-
120	+	-	+	+	-	-	-	+
121	-	-	+	-	-	+	-	-
122	-	+	-	-	-	-	+	-
123	-	-	-	-	-	-	-	-

TEMP = temperature, WBC = white blood count, CNS = central nervous system, ABNORM = abnormality
* associated with shock

APPENDIX D.

ECG ABNORMALITIES

KEY TO ABBREVIATIONS (with limits of normality)

(ST) = SINUS TACHYCARDIA (beats/minute)

< 3 months	: > 190
3 to < 12 months	: > 180
12 to < 36 months	: > 160
36 to < 60 months	: > 140
⩾ 60 months	: > 120

(PR+) = PROLONGED PR INTERVAL (seconds)

< 1 month	: ⩾ 0.12
1 to < 12 months	: > 0.14
12 to < 60 months	: > 0.15
60 to < 96 months	: > 0.16
⩾ 96 months	: > 0.17

(LAD) = LEFT AXIS DEVIATION

(< lower limit)

(RAD) = RIGHT AXIS DEVIATION

(> upper limit)

Normal limits

7 days to < 1 month	: 0^{o} - 160^{o}
1 to < 3 months	: 20^{o} - 120^{o}
3 to < 12 months	: 20^{o} - 100^{o}
12 to < 60 months	: 0^{o} - 100^{o}
60 to < 96 months	: -20^{o} - 100^{o}
⩾ 96 months	: 0^{o} - 80^{o}

(P1a) = LEFT ATRIAL STRESS

Bifid or notched P waves in lead 2, V1 and/or other leads.

(Pra) = RIGHT ATRIAL HYPERTROPHY

Peaked P waves in lead 2 or right chest leads;

< 12 months	: > 2.5 mm
12 to < 36 months	: > 3.0 mm
⩾ 36 months	: > 2.5 mm

(Q) = PATHOLOGICAL Q WAVES

> 2 mm x > 0.03 seconds - any lead

or > 5 mm x > 0.02 seconds - leads I, AVL, V1-6

(T+) = DEFINITE T ABNORMALITY

T waves inverted and/or flattened (< 1 mm) and/or biphasic in <u>both</u> V5 and V6

($T^{\pm}$) = SUSPECTED T ABNORMALITY

T waves inverted and/or flattened (< 1 mm) and/or biphasic in <u>one</u> of V5 or V6

(ST+) = ST SEGMENT ELEVATION

$\geq$2 mm - limb leads
and/or $\geq$3 mm - praecordial leads

OR

$\geq$1 mm with coved ST segment
- limb leads
and/or $\geq$2 mm - praecordial leads
with other abnormalities
(i.e. Q, T or LVH)

(ST-) = ST SEGMENT DEPRESSION

(SV1) = LVH by S voltage in V1

$\leq$6 months : $\geq$20 mm
$\geqslant$6 months : $\geq$25 mm

(RV6) = LVH by R voltage in V6

$<$1 month : $>$20 mm
1 month to $<$6 months : $>$25 mm
$\geqslant$6 months $>$30 mm

(R/S) = Suspected LVH by R/S ratio in V1

1 to $<$36 months : $<$0.25
36 to $<$60 months : $<$0.20
$\geqslant$60 months : $<$0.10

(N) = NORMAL

(RVH) = RIGHT VENTRICULAR HYPERTROPHY

(BVH) = BIVENTRICULAR HYPERTROPHY

(ARY) = ARRHYTHMIA

(VPS) = VENTRICULAR PREMATURE SYSTOLE

(APS) = ATRIAL PREMATURE SYSTOLE

(WPW) = WOLF-PARKINSON-WHITE SYNDROME

CASE NO	ECG ABNORMALITIES AND TIMING OF ECG AFTER ADMISSION														
1	1d	1d	1d	2m	3m	7m	12m	15m	18m	21m	26m	29m			
	PR+ – P.1a Q T+	– RAD P.1a Q T+	– – P.1a Q T+	N	N	N	N	N	N	N	N	N			
2	1d	3d	5d		D										
	RAD P.1a –	RAD – ST+	RAD – –												
3	1d	1d	5d	7d	9d	16d	21d	23d	24d	28d	37d	41d		D	
	Q – – T+	– – – T+	– – – T+	– – – T+	– – – T+	– – – T+	– ST+ ST– T+	– ST+ ST– T+	– – – T+	– ST+ – T+	– – – T+	– – – T+			
4	1d	2d	3d	5d	8d	11d		D							
	– RAD – – T+ – –	– RAD – ST– T+ – –	– RAD – ST– T+ RVH –	– RAD – ST– T+ RVH –	PR+ RAD ST+ ST– T+ – RV6	RAD ST+ – T+ BVH –									
5	1d	4d	10d	19d	1m	2m	2.5m	3m	3.3m	3.5m	4m	4.3m	6m	7.5m	7.8m
	ARY – (LAD) – (ST–) T+	ARY – (LAD) (ST+) (ST–) T+	ARY – (LAD) (ST+) (ST–) –	ARY – (LAD) (ST+) (ST–) T+	ARY – (LAD) (ST+) (ST–) T+	– – – – – T+	– PR+ – – – RV6	ARY – (LAD) – (ST–) –	ARY – (LAD) – (ST–) –	ARY – (LAD) – (ST–) –	ARY – (LAD) – (ST–) –	– PR+ – – – –	N	ARY – (LAD) – (ST–) –	ARY – (LAD) – (ST–) –
	CONT.	8m	8.5m	12m	15m	19m	28m								
		ARY (LAD) (ST–)	ARY (LAD) (ST–)	ARY (LAD) (ST–)	ARY (LAD) (ST–)	ARY (LAD)	ARY (LAD) (ST–)								
6		8d	10d	24d	D										
		T+	–	–											
7	2d	5d	13d	3m	4m	5m	9m	15m	17m		59m.				
	P.1a T+	P.1a T–	P.1a T+	– T+	P.1a T+	N	N	N	N		N				
8	1d	1d	2d	3d	8d	10d	1m		D						
	– P.1a – T+	– P.1a – T+	– – ST+ T+	ST – ST+ T+	– – ST+ T+	– – – T+	– – – T+								

9	1d	4d	10d	11d	12d	17d	18d	19d	24d	25d	26d	27d	31d	33d	35d
	ARY	ARY	ARY	ARY	ARY	ARY	ARY	ARY	ARY	ARY	ARY	ARY	ARY	ARY	ARY
	–	–	–	–	T+	T+	T+	–	–	–	–	–	–	–	–
	–	–	–	–	–	–	–	–	–	SV1	SV1	–	–	SV1	–
	–	–	–	–	–	–	–	–	–	–	RV6	–	RV6	–	–
	39d		D												
	ARY														
	T+														
	–														
10	1d	9d	3m	6m	11m	15m	18m	22m							
	LAD	LAD	LAD	LAD	LAD	LAD	LAD	LAD							
	P.1a	P.1a	P.1a	–	–	–	–	–							
	P.ra	–	–	–	–	–	–	–							
	T+	T+	T+	T+	T+	T+	T+	–							
11	1d	1d	2d	3d	5d	6d	14d	1m							
	–	ARY	–	ARY	ARY	–	–	N							
	–	–	P.1a	–	–	P.1a	P.1a								
	ST+	–	ST+	–	–	ST+	ST+								
	ST–	–	–	–	–	–	–								
	T+	T+	–	–	–	–	–								
12	1d	5d	14d	4m	5m	9m	17m	29m							
	–	–	LAD	LAD	LAD	LAD	–	N							
	P.1a	P.1a	–	–	–	–	–								
	ST+	ST+	–	–	–	–	–								
	–	–	SV1	–	–	–	SV1								
13	1d		D												
	P.1a														
	ST+														
14		7d		D											
		P.1a													
		T^{+}_{-}													
15	1d	6d	14d	1m	4m										
	ST	–	–	–	ST										
	–	–	–	–	RAD										
	–	P.1a	–	P.1a	–										
	T+	T^{+}_{-}	T^{+}_{-}	–	–										
16	1d		D												
	T^{+}_{-}														
17	1d	1d	3d	3d	4d	6d	7d	10d	12d	1m	2m	4m	6m	9m	D
	–	ST	–	–	–	–	–	–	–	–	–	–	–	–	
	–	–	–	–	–	–	–	–	–	–	–	–	–	ARY	
	Q	–	–	–	–	–	–	–	–	–	–	–	–	–	
	ST+	ST+	ST+	–	–	–	–	–	–	–	–	–	–	ST+	
	ST–	ST–	–	–	–	–	–	–	–	–	–	–	–	ST–	
	T+	T+	T+	T^{+}_{-}	–	–	–	–	–	–	–	–	–	–	
	R/S	–	R/S	R/S	R/S	R/S	R/S	R/S	R/S	R/S	R/S	R/S	R/S	–	

18	1d	1d	3m	5m	7m		D								
	ST	–	–	–	–										
	LAD	LAD	LAD	LAD	–										
	P.1a	–	P.1a	–	P.1a										
	–	–	–	Q	–										
	–	ST+	–	–	–										
	–	ST–	–	–	–										
	T+	–	–	T+	T+										
	–	SV1	SV1	SV1	SV1										
	–	–	–	–	RV6										
19	1d	1d		D											
	–	ST													
	–	RAD													
	–	P.1a													
	–	P.ra													
	–	ST+													
	T+	T+													
	R/S	–													
20	1d	16d	26d	2.2m	2.5m	2.6m	5m	7m	16m	37m	42m	45m	51m	58m	
	–	LAD	–	–	–	–	–	N	–	–	–	–	–	–	
	–	–	–	–	–	–	–		–	–	PR+	PR+	PR+	PR+	
	–	–	–	P.1a	–	–	–		–	P.1a	–	–	–	–	
	–	–	–	–	–	–	–		–	ST+	–	–	–	–	
	T+	T+	T+	T+	T+	T+	T+		T+	T+	T+	T+	T+	–	
	–	–	–	R/S	R/S	–	–		–	R/S	–	–	–	–	
21	1d	14d	18d	28d	1.5m	1.8m	2.5m	4.5m	27m	33m					
	RAD	RAD	RAD	RAD	RAD	RAD	RAD	RAD	RAD	RAD					
	–	–	–	–	–	–	–	–	PR+	PR+					
	T+	T+	T+	T+	T±	T±	T+	T±	T±	–					
22	1d	2d	5d	9d	16d	2m	40m								
	RAD	–	–	–	–	–	N								
	–	P.1a	P.1a	P.1a	P.1a	P.1a									
	T+	T+	T+	T+	T+	T+									
	–	SV1	SV1	SV1	SV1	SV1									
	–	R/S	–	–	–	–									
23	1d	7d	15d	1.5m	2.5m	6m	8m	11m	13m	17m	19m	22m	25m	28m	63m
	–	–	–	–	–	–	–	–	–	–	N	N	N	PR+	N
	T+	T+	T±	T+	T+	T+	T+	T+	T+	T+				–	
	–	SV1	SV1	–	–	–	–	–	–	–				–	
	R/S	R/S	R/S	R/S	–	R/S	R/S	R/S	R/S	–				–	
24	1d		D												
	T+														
	R/S														
25	1d	1d	2d	10d	17d	2m	7m	10m	13m	22m	25m	29m	35m	50m	62m
	ST	–	–	–	N	N	N	ST	N	N	N	N	N	N	N
	ST+	ST+	–	–				–							
	T+	T+	T+	T+				–							
26	3d	6d	10d	4m	30m										
	P.1a	P.1a	P.1a	–	N										
	ST+	–	–	–											
	T+	–	T+	–											
	–	–	–	R/S											

27	1d	1d	2d	4d	6d	8d	20d	1m	1.3m	1.8m	9m				
	PR+ LAD P.1a – T+ –	– – P.1a – T+ –	– LAD P.1a – T+ –	– LAD P.1a ST+ T+ –	– LAD P.1a – T+ –	– LAD P.1a ST+ T+ –	– LAD P.1a – T+ R/S	– LAD P.1a ST+ T+ R/S	– LAD P.1a ST+ – –	– LAD – – – R/S	N				
28	1d		D												
	ST RAD T+														
29	1d	2d													
	P.1a T±	– T+													
30	1d		D												
	P.1a T± R/S														
31	1d	3d	5d	11d	4m	8m	11m	14m	19m	22m	25m	28m	31m	32m	33m
	ST – P.1a T+	– – P.1a –	– – P.1a –	– – P.1a T+	N	N	N	N	N	– PR+ – –	N	N	N	N	N
	CONT.	40m	46m	52m	60m	72m									
		N	N	– PR+	N	N									
32	1d	2d	3d	4d	7d	9d	15d	21d	1m	1.2m	2m	6m	9m	10m	11m
	– P.ra – – ST+ ST– T+ R/S	– – P.1a – ST+ – T+ R/S	– – P.1a – ST+ – T+ –	– – P.1a – ST+ – T+ –	– – P.1a Q ST+ – T+ R/S	– – – Q ST+ – T+ –	– – P.1a Q ST+ – T+ R/S	– – P.1a Q – – T+ –	PR+ – P.1a Q – – T+ –	– – P.1a Q – – T+ –	LAD – – Q – – T+ –	RAD – P.1a Q – – – –	N	– – P.1a – – – – –	– – P.1a – – – – –
	CONT.	15m	21m	26m											
		– P.1a –	– – T+	PR+ – –											
33	1d	15d	25d	2m	6m										
	RAD P.1a P.ra Q ST+ – T+ – –	– P.1a – – ST+ ST– T+ SVI R/S	– P.1a – – ST+ ST– T+ SVI –	– – – – ST+ ST– T+ – –	N										

34	1d		D												
	ST P.1a ST+ T+ R/S														
35	1d		D												
	ST Q ST+ ST− T+														
36	1d	1d	2d	3d	6d	7d	8d	13d	1m	1.7m	5m	9m	12m	15m	18m
	− P.1a T+ − −	RAD − T+ − −	− − T+ SV1 −	− − − SV1 −	N	N	N	− − − − RV6	N	N	− − − − RV6	N	N	N	N
	CONT.	20m	23m	27m	32m	35m	38m	44m	77m						
		N	N	N	N	N	N	N	N						
37	1d		D												
	ST Q ST− T+ R/S														
38	1d	3d	9d												
	T+	T+	T+												
39	1d		D												
	ST RAD P.1a T+														
40	1d	5d	8d	11d	3m	5m	8m	15m	21m						
	ST RAD − − T+	− − P.1a ST+ T+	− RAD − − −	− RAD P.1a − T+	N	N	N	N	N						
41	1d	1d	2d	1.5m	10m	16m	19m	22m	25m	28m	34m	40m	82m		
	ST RAD P.1a T+ −	− RAD P.1a T+ −	− RAD P.1a T+ R/S	− − P.1a T+ R/S	N	N	− − − T+ R/S	− − − − R/S	− − − − R/S	− − − − R/S	− − − − R/S	− − − − R/S	N		

42	2d	3d	4d	6d	9d	2m	2.5m	3m	4m	16m	34m	37m			
	ST	–	–	–	–	–	–	–	–	–	–	–			
	–	–	–	–	–	PR+	PR+	PR+	PR+	PR+	–	PR+			
	RAD	RAD	RAD	RAD	RAD	RAD	–	–	–	–	–				
	–	–	–	–	–	–	LAD	LAD	LAD	LAD	LAD	LAD			
	–	P.la	P.la	P.la	P.la	P.la	P.la	P.la	P.la	–	–	–			
	Q	Q	–	Q	Q	–	–	–	–	–	–	–			
	T+	T+	T+	T+	T+	T+	T+	T+	–	–	–	–			
43	1d	1m		51m	70m										
	RAD	RAD		N	N										
	T+	–													
44	1d	1d	2d	4d	8d	10d	21d	1m	2m	4m	11m	19m	22m	25m	29m
	ST	ARY	–	–	–	–	–	–	–	–	–	N	–	–	N
	RAD	–	–	–	–	–	–	–	–	–	–		–	–	
	–	–	–	–	–	LAD	LAD	LAD	LAD	LAD	LAD		–	–	
	–	ST+	ST+	ST+	ST+	ST+	ST+	ST+	–	–	–		–	–	
	T+	T+	T+	T+	T+	T+	T+	T+	T+	T+	T+		–	–	
	R/S	–	R/S	R/S	R/S	R/S	R/S	R/S	R/S	R/S	R/S		R/S	R/S	
	CONT.	32m	38m	/ 60m											
		–	–	N											
		R/S	R/S												
45	1d	1d	5d	7d	12d	2.5m	15m	17m	20m	25m	34m	/ 64m			
	ST	–	–	–	–	ST	N	N	N	N	N	N			
	ST+	ST+	–	–	–	–									
	–	ST–	–	–	–	–									
	T+	–	T+	T+	–	T+									
	–	SVI	SVI	SVI	SVI	–									
46	1d	2d	3d	8d	9d	11d	20d	2m	3m	5m	7m	9m	12m	14m	31m
	ST	–	–	–	N	–	–	–	–	–	–	–	–	–	N
	RAD	–	–	–		–	–	–	–	–	–	–	–	–	
	–	–	LAD	LAD		LAD	LAD	LAD	LAD	LAD	LAD	LAD	LAD	LAD	
	–	ST+	–	ST+		–	–	–	–	–	–	–	–	–	
	–	–	ST–	–		–	ST–	–	–	–	–	–	–	–	
	T+	T+	T+	–		–	T+	T+	T+	T+	T+	T+	T+	T+	
	–	–	SVI	SVI		–	–	–	–	–	–	–	–	–	
47	1d	9d	16d	1.5m	1.6m		D								
	ST	–	–	–	–										
	–	VPS	VPS	–	–										
	–	PR+	PR+	–	–										
	P.la	P.la	P.la	P.la	P.la										
	T+	T+	T+	T+	T+										
	–	SVI	–	–	SVI										
	R/S	R/S	R/S	R/S	R/S										
48	1d	2d	14d	21d	28d	30d	34d	4m	6m	30m					
	–	–	ST	–	–	–	–	–	–	–					
	–	–	–	APS	–	–	–	VPS	–	–					
	–	–	–	–	–	–	–	–	–	PR+					
	P.la	P.la	P.la	P.la	P.la	P.la	P.la	P.la	–	–					
	–	ST+	ST+	ST+	ST+	ST+	ST+	–	–	–					
	ST–	–	ST–	ST–	ST–	ST–	ST–	–	–	–					
	–	T+	T+	T+	T+	T+	T+	T+	T+	T+					
	R/S	R/S	R/S	R/S	R/S	R/S	–	–	R/S	–					

	1d	3d	4d	5d	12d	13d	14d	17d	18d	19d	24d	35d		D	
49	ARY	ARY	-	-	ARY	ARY	ARY	-	-	-	-	ARY			
	-	RAD	-	-	-	-	-	-	-	-	-	-			
	-	-	-	-	LAD	LAD	LAD	-	-	-	-	-			
	-	-	P.ra	-	-	-	-	-	-	-	-	-			
	-	Q	-	-	Q	Q	Q	-	-	-	-	-			
	ST+	-	ST+	ST+	ST+	ST+	ST+	ST+	ST+	ST+	ST+	ST+			
	-	-	-	-	ST-	ST-	ST-	ST-	ST-	-	-	-			
	T+	T+	T+	T+	T+	T+	T+	T+	T+	T+	T+	T+			
	-	-	R/S	R/S	-	-	-	R/S	R/S	R/S	R/S	R/S			
	-	-	-	-	-	-	-	-	-	-	-	SV1			
		7d	21d	3m	3.5m	4.5m	5m	6m	10m	/ 13m	19m	25m	33m	36m	
50		-	-	-	-	-	PR+	PR+	PR+	-	-	N	N	N	
		RAD	RAD	RAD	RAD	RAD	RAD	-	RAD	-	-				
		P.la	P.la	P.la	P.la	P.la	P.la	P.la	-	-	-				
		ST+	ST+	ST+	ST+	-	-	-	-	-	-				
		T+	T+	T+	T+	T+	T+	T+	T+	T+	T+				
		-	R/S	R/S	-	-	R/S	-	R/S	-	R/S				
		1.5m	2m	4.5m	8m	11m	17m	23m	26m	29m	32m	38m	50m	62m	/ 92m
51		ST	-	-	-	-	-	N	N	N	N	N	N	N	N
		-	PR+	PR+	PR+	PR+	-								
		P.la	P.la	P.la	P.la	P.la	P.la								
		ST+	-	-	-	-	-								
		T+	-	T+	T+	-	-								
		R/S	-	-	-	-	-								
		4d	10d	18d	21d	4.5m									
52		P.la	-	P.la	P.la	-									
		T+	T+	T+	T+	T+									
	2d	9d	15d	3m	5m	8m	11m	14m	17m	20m	/ 65m				
53	-	-	N	-	N	-	PR+	N	PR+	N	N				
	-	P.la		-		-	-		-						
	T+	-		T+		T+	-		T+						
	2d	3d	8d	9d	15d	20d	1m	1.3m	2m		D				
54	-	-	-	ST	-	-	-	-	-						
	T+	T+	T+	T+	T+	T+	T+	T+	T+						
	-	-	-	SV1	-	SV1	SV1	SV1	SV1						
	R/S	R/S	R/S	R/S	R/S	R/S	R/S	R/S	R/S						
	1d	1d	6d	1.8m	5.5m										
55	ST	ST	-	ST	-										
	LAD	LAD	LAD	LAD	LAD										
	T+	T+	T+	T+	-										
	R/S	R/S	R/S	R/S	-										
	1d	7d	1.8m	4m	7m	8m									
56	ST	-	-	-	-	N									
	T+	T+	T+	T+	-										
	-	-	-	-	R/S										
	1d	2d	8d	9d	10d	16d	6m								
57	P.la	-	P.la	P.la	P.la	P.la	N								
	ST+	-	-	-	-	-									
	T+	T+	T+	T+	T+	T+									

58		12d	27d	1.5m	2.5m	/ 16m	28m	30m	42m	51m	57m	72m			
		–	–	RAD	–	–	–	–	–	–	–	–			
		P.la	P.la	P.la	P.la	P.la	–	–	–	–	–	–			
		T+	T+	T+	T+	–	T+	T+	T+	–	–	–			
		–	–	SVI	SVI	–	–	–	–	–	–	–			
		R/S	R/S	R/S	R/S	R/S	R/S	R/S	R/S	R/S	R/S	R/S			
59	3d	16d	23d	30d											
	ARY	ARY	ARY	ARY											
	T+	T+	T+	–											
60	1d	1d	6d	12d	25d	3.5m	6m	11m	17m	26m	30m	36m	39m	42m	45m
	ST	ST	N	–	–	–	–	–	–	N	N	N	N	N	N
	–	–		P.la	P.la	P.la	P.la	P.la	P.la						
	ST+	ST+		–	–	–	–	–	–						
	ST–	ST–		–	–	–	–	–	–						
	–	–		T+	T+	–	–	–	–						
	CONT.	48m	51m	54m	63m	72m	/ 84m	96m							
		N	N	N	N	N	N	N							
61	2d	10d	16d	1.5m	1.8m	3m	3.2m	5m	8m	11m	14m	17m	26m	32m	41m/
	–	–	–	–	–	LAD	–	LAD	LAD	–	–	–	–	–	N
	P.ra	–	–	–	P.la	–	–	–	–	–	–	–	–	–	
	T+	T+	T+	T+	T+	T+	T+	T+	T+	–	–	–	–	–	
	–	–	–	SVI	–	SVI	SVI	SVI	–	–	–	–	–	–	
	R/S	R/S	R/S	R/S	R/S	R/S	R/S	R/S	R/S	R/S	R/S	R/S	R/S	R/S	
	CONT.	53m													
		N													
62	1d	1d	2d	3d	4d	5d	6d	12d	14d	16d	19d		D		
	ST	–	–	ST	ST	ST	ST	ST	ST	ST	–				
	LAD	LAD	–	–	–	–	–	–	–	–	–				
	Q	Q	Q	–	–	Q	–	–	–	–	–				
	–	–	–	P.la	P.la	–	P.la	–	–	–	–				
	–	–	–	–	–	–	–	–	–	P.ra	P.ra				
	ST+	ST+	ST+	ST+	ST+	ST+	ST+	ST+	ST+	ST+	ST+				
	ST–	ST–	–	–	–	ST–	ST–	ST–	ST–	ST–	ST–				
	T+	T+	T+	T+	T+	T+	T+	T+	T+	T+	T+				
	–	–	–	–	–	SVI	SVI	–	–	SVI	SVI				
	R/S	R/S	R/S	R/S	R/S	R/S	R/S	R/S	R/S	R/S	R/S				
63	1d		D												
	T+														
64	1d		D												
	ST														
	RAD														
	P.la														
	T+														
65	1d	4d	2m	3.5m	4m	5m	7m	37m	40m	/ 60m					
	–	–	–	ST	ST	ST	ST	–	–	N					
	LAD	–	–	–	–	–	–	–	–						
	–	RAD	–	RAD	–	–	–	–	–						
	T+	T+	T+	T+	T+	T+	T+	T+	–						
	–	–	–	R/S	R/S	R/S	R/S	R/S	R/S						

66	1d	4d	11d	13d	19d	24d	1.3m	1.5m	4m	9m	15m	38m	63m	/ 78m	93m
	–	–	PR+	PR+	–	–	–	–	–	–	PR+	N	N	N	N
	RAD	–	–	–	–	–	–	–	–	–	–				
	P.1a	P.1a	P.1a	P.1a	P.1a	P.1a	P.1a	P.1a	–	P.1a	P.1a				
	T+	T+	T+	T+	T+	T+	T+	–	–	–	–				
	R/S	R/S	–	–	–	R/S	R/S	–	–	–	–				
67	2d	10d	14d	3m	15m	21m	26m	32m	38m	39m	46m	47m	/ 59m		
	–	–	PR+	PR+	PR+	PR+	–	PR+	PR+	PR+	N	N	N		
	T+	T+	T+	–	–	–	–	–	–	–					
	–	–	–	–	–	–	RV6	–	–	–					
68	1d		D												
	LAD														
	ST+														
69	1d	10d	40d	2.5m	/ 12m	17m	23m								
	–	–	ST	ST	N	N	N								
	–	–	LAD	LAD											
	–	–	ST–	–											
	T+	T+	T+	T+											
70	1d	10d	18d	26d	1.2m	1.5m	3m	4m	9m	12m	15m	26m	30m	34m	/ 70m
	–	ST	–	–	ST	ST	–	N	N	N	N	N	N	N	N
	T+	T+	T+	–	T+	T+	T+								
71	4d	7d	10d	21d	1m	1.5m	4m	6m	21m	32m	40m	/ 56m			
	–	–	–	–	–	ST	–	N	N	N	N	N			
	–	–	ST+	–	ST+	–	–								
	T+	T+	T+	T+	T+	T+	T+								
	–	–	–	–	–	R/S	–								
72	1d	5d	8d	12d	15d	18d	/ 7m	13m	20m	24m					
	RAD	–	–	–	–	–	–	N	N	N					
	P.1a	P.1a	P.1a	P.1a	P.1a	P.1a	–								
	Q	–	–	–	–	–	–								
	–	–	ST+	ST+	–	–	–								
	T+	T+	T+	T+	T+	T+	T+								
	R/S	–	–	R/S	–	–	–								
73	1d	1d	3d	4d	5d	8d	11d	12d	15d	18d	29d	2m			
	–	ST	–	–	–	–	–	–	–	–	–	–			
	RAD	RAD	–	–	–	–	–	–	–	–	–	–			
	Q	Q	–	–	–	–	–	–	–	–	–	–			
	P.1a	P.1a	P.1a	P.1a	P.1a	P.1a	P.1a	P.1a	P.1a	P.1a	P.1a	–			
	ST+	ST+	–	–	–	–	–	–	–	–	–	–			
	–	ST–	–	–	–	–	–	–	–	–	–	–			
	T+	T+	T+	T+	T+	T+	T+	T+	T+	T+	T+	–			
	R/S	R/S	R/S	R/S	R/S	R/S	R/S	R/S	R/S	R/S	R/S	R/S			
74	1d	3d	7d	1m	12m										
	P.1a	P.1a	P.1a	N	N										
	T+	–	–												
75	1d	3d		D											
	P.ra	P.ra													
	ST+	–													
	T+	T+													
	R/S	–													

	1d	7d	13d	3m											
76	–	RAD	–	N											
	T+	T+	T+												
	R/S	R/S	R/S												
	1d	12d	17d	20d	1.7m	5m	16m	21m	24m	30m	33m	36m	39m	42m	45m
77	RAD	–	–	–	–	–	–	–	–	–	–	–	–	N	N
	P.la	P.la	P.la	P.la	P.la	P.la	–	–	–	–	–	–	–		
	–	P.ra	–	–	–	–	–	–	–	–	–	–	–		
	T+	T+	T+	T+	–	–	T+	T+	T+	T+	T±	–	T+		
	R/S	R/S	R/S	R/S	R/S	–	R/S	R/S	R/S	R/S	–	R/S	R/S		
	CONT.	48m	51m	54m	60m	/ 76m									
		N	N	–	N	N									
				R/S											
	1d	1d	2d	3d	7d	9d	11d	15d	21d	1m	1.5m	2.5m	3.5m	8m	/ 44m
78	–	–	–	–	–	–	–	–	–	–	–	ST	–	–	N
	RAD	–	–	–	–	–	–	–	–	–	–	–	–	–	
	Q	Q	Q	Q	Q	Q	Q	Q	Q	Q	–	Q	Q	–	
	ST–	–	–	–	–	–	–	–	–	–	–	–	–	–	
	T+	T+	T+	T+	T+	T+	T+	T+	T+	T+	T±	T+	T±	–	
	R/S	R/S	R/S	R/S	R/S	R/S	R/S	R/S	R/S	R/S	R/S	R/S	R/S	R/S	
	CONT.	70m													
		N													
	2d	3d	6d												
79	ST	–	–												
	RAD	RAD	RAD												
	P.ra	P.ra	–												
	T+	T+	–												
	R/S	R/S	–												
	1d	11d	2m	5m	8m	12m	18m	21m	27m	39m	/ 51m	63m			
80	ST	N	N	N	N	N	N	N	N	N	N	N			
	ST–														
	T±														
	2d	4d	17d												
81	–	LAD	N												
	P.la	P.la													
	P.ra	P.ra													
	ST+	ST+													
	T+	–													
	1d	3d	1m	8m											
82	ST	–	–	N											
	APS	–	–												
	LAD	–	–												
	–	–	RAD												
	–	P.ra	–												
	ST+	–	–												
	ST–	–	–												
	T+	T+	T±												
	3d	5d	6d	11d	2m	11m									
83	RAD	RAD	RAD	–	N	N									
	–	–	–	LAD											
	P.la	P.la	P.la	–											
	T+	T+	T+	–											
	–	R/S	R/S	–											

84	1d	1d	2d	3d	7d	10d	5m	10m	13m	17m	19m	22m	31m	45m	/ 60m
	–	RAD	RAD	RAD	–	–	N	N	N	N	N	N	N	N	N
	P.la	P.la	–	P.la	–	–									
	T+	T+	T+	T+	T+	T±									
85	1d	2d	5d	7d	14d	1.3m	12m								
	–	–	–	–	–	–	ST								
	RAD	RAD	RAD	RAD	–	–	RAD								
	–	P.la	P.la	P.la	P.la	–	–								
	–	P.ra	–	–	–	–	–								
	T+	T+	T±	–	–	T±	T+								
	–	–	RV6	–	–	–	–								
	–	–	R/S	–	–	–	–								
86	1d	2d	4d	6d	15d	28d	1.5m	2.5m	10m	17m	24m	30m	33m	40m	46m
	ST	–	–	ST	ST	–	–	–	N	N	N	N	N	N	N
	P.la	P.la	P.la	P.la	–	P.la	P.la	P.la							
	–	P.ra	P.ra	–	P.ra	P.ra	P.ra	–							
	T+	T+	T+	T+	T+	T+	–	–							
	–	–	R/S	–	R/S	–	–	–							R/S
87		17d	1.2m	2.5m	3.5m	5.5m	8m	9m	16m	32m	/ 57m				
		ST	ST	ST	ST	–	–	–	N	N	N				
		RAD	RAD	–	–	–	–	–							
		–	–	LAD	LAD	LAD	LAD	–							
		P.la	–	P.la	–	–	–	–							
		–	ST+	–	–	–	–	–							
		–	ST–	–	–	–	–	–							
		T+	–	T+	T+	–	–	–							
		–	–	–	–	SV1	–	SV1							
		R/S	R/S	R/S	R/S	–	–	–							
88	1d	12d	18d	24d	4.5m	12m	/24m								
	ST	ST	ST	–	–	N	N								
	P.la	P.la	P.la	P.la	P.la										
	T+	T+	T+	T+	T+										
89	1d	6d	7d	8d	21d	1.3m	6m	7m	/14m						
	ST	–	ST	–	ST	ST	–	–	N						
	–	P.la	P.la	P.la	P.la	–	–	–							
	T+	T±	T+	–	T±	T+	T+	T+							
90	1d	21d	1.3m	3m	6m	11m	18m								
	P.ra	N	N	N	N	N	N								
	T+														
91	1d	2d	11d	17d	22d	23d	24d	1m	1.5m	1.7m	2.2m		D		
	ST	ST	ST	ST	ST	ST	–	–	ST	ST	ST				
	–	–	–	–	–	–	PR+	PR+	PR+	PR+	–				
	P.la	P.la	P.la	P.la	P.la	P.la	P.la	P.la	P.la	P.la	P.la				
	Q	Q	Q	Q	Q	Q	Q	Q	Q	Q	Q				
	ST+	ST+	–	ST+	ST+	ST+	ST+	ST+	ST+	ST+	ST+				
	ST–	–	ST–	ST–	ST–	ST–	ST–	ST–	ST–	ST–	ST–				
	T+	T+	T+	T+	T+	T+	T+	T+	T+	T+	T+				
	–	–	RV6	RV6	–	–	RV6	RV6	–	–	–				
	R/S	R/S	R/S	R/S	R/S	R/S	R/S	R/S	R/S	R/S	R/S				
92	1d	4d	5d	1m	1.5m	3m	4.5m	6m	7m	8m	12m	15m	21m	40m	
	ST	–	–	–	–	N	N	N	N	N	N	N	N	N	
	T+	T+	T+	T+	T+										

93	1d	2d	4d	6d											
	ST	-	-	-											
	-	-	RAD	RAD											
	P.1a	P.1a	P.1a	P.1a											
	-	WPW	WPW	WPW											
	-	-	ST+	ST+											
	-	ST-	ST-	ST-											
	T+	T+	T+	T+											
	RV6	-	-	-											
94	2d	3d	4d	5d	21d	1m	1.5m	1.6m		D					
	-	-	-	-	ST	-	ST	-							
	-	APS	-	-	-	-	-	-							
	P.1a	-	P.1a	P.1a	-	P.1a	-	P.1a							
	ST+	-	ST+	-	ST+	-	-	-							
	ST-	ST-	ST-	ST-	ST-	-	-	-							
	SV1	-	SV1	SV1	SV1	SV1	SV1	SV1							
	RV6	RV6	RV6	RV6	-	RV6	RV6	RV6							
	R/S	-	R/S	R/S	R/S	R/S	R/S	-							
95	1d	3d	4d	5d	7d	8d	11d	14d	2m	3m	35m	36m	/ 65m		
	ST	-	-	-	-	-	-	-	ST	-	ST	ST	ST		
	-	-	-	-	-	-	-	-	-	-	-	-	RAD		
	-	-	-	-	-	-	P.1a	P.1a	-	P.1a	-	-	P.1a		
	T+	T+	T+	T+	T+	T+	T+	T+	T+	T+	T+	T+	T+		
	SV1	SV1	SV1	SV1	SV1	SV1	SV1	SV1	-	-	-	-	-		
	RV6	RV6	RV6	RV6	RV6	RV6	RV6	RV6	-	-	-	-	-		
	-	R/S	R/S	-	R/S	-	-	-	-	-	R/S	-	-		
96	1d		D												
	P.1a														
	T+														
	SV1														
	RV6														
97	1d	4d	7d	20d											
	P.1a	P.1a	P.1a	-											
	T+	T+	-	-											
	SV1	SV1	SV1	SV1											
98	1d	5d	8d	12d	1.5m	7m	13m	25m	37m	/ 71m	84m				
	-	-	-	-	-	-	N	PR+	PR+	N	N				
	-	-	-	-	RAD	-		-	-						
	P.1a	-	P.1a	P.1a	P.1a	P.1a		-	-						
	T+	T+	T+	T+	-	-		-	-						
	RV6	-	RV6	RV6	-	-		-	-						
	-	-	-	-	-	-		-	R/S	R/S	R/S				
99	1d	14d		D											
	ST	-													
	P.1a	-													
	ST+	-													
	ST-	-													
	T+	T+													
	SV1	SV1													
	R/S	-													

	1d	8d	10d	21d	2.7m	5.8m	6m	7m	7.5m	10m	12m	14m	17m	20m	29m /
100	–	–	–	–	N	–	ST	ST	ST	–	–	–	N	N	N
	–	P.la	P.la	P.la		–	–	–	–	–	–	–			
	T+	T+	–	–		T+	T+	T+	T+	T+	T+	T+			
	RV6	–	–	–		–	–	–	–	–	–	SV1			
	–	–	–	–		–	R/S	–	–	–	–	–			
	CONT.	41m	53m												
		N	N												
	1d	3d	8d												
101	P.la	P.la	P.la												
	–	P.ra	–												
	–	ST+	–												
	T+	T+	T+												
	SV1	SV1	SV1												
	RV6	RV6	–												
	1d	1d	3d	10d	21d	2m	5m	/ 13m	16m						
102	ST	ST	ST	–	–	–	–	–	N						
	–	LAD	–	–	–	–	–	–							
	P.la	P.la	P.la	P.la	–	P.la	–	–							
	ST+	–	–	–	–	–	–	–							
	T+	T+	T+	T+	T+	T+	T+	T+							
	SV1	SV1	SV1	SV1	SV1	–	SV1	–							
	RV6	–	RV6	RV6	RV6	RV6	RV6	–							
	–	–	–	–	–	R/S	–	–							
	1d	1d	2d	3d	4d	1.8m	6m	10m	/ 20m	32m	51m				
103	–	–	–	–	–	LAD	–	–	N	N	N				
	T+	T+	T+	–	T+	T+	T+	T+							
	SV1	SV1	SV1	SV1	SV1	–	SV1	SV1							
	–	–	–	–	–	–	–	RV6							
	2d	4m		D											
104	PR+	–													
	P.la	–													
	P.ra	–													
	ST+	ST+													
	–	ST–													
	T+	T+													
	SV1	SV1													
	1d	11d	20d	1.5m	1.7m	3m	8m	10m	15m	20m	24m	27m	35m	38m	41m
105	–	–	–	–	–	PR+	–	–	–	–	–	–	N	N	N
	–	RAD	–	LAD	–	LAD	–	–	–	–	–	–			
	P.la	P.la	P.la	P.la	P.la	P.la	P.la	P.la	P.la	–	–	–			
	–	Q	–	–	–	–	–	–	–	–	–	–			
	–	–	ST–	ST–	–	–	–	–	–	–	–	–			
	T+	T+	T+	T+	T+	T+	T+	T+	T+	T+	T+	T+			
	–	SV1	SV1	–	SV1	SV1	–	–	–	–	–	–			
	RV6	RV6	–	RV6	RV6	–	–	–	–	–	–	–			
	CONT.	44m	47m	50m	53m	56m	59m	68m							
		N	N	N	N	N	N	N							
	2d	6d	9d	16d	1.5m	2m	5m	8m							
106	–	–	PR+	N	–	N	–	N							
	–	–	ST+		–		–								
	T+	T+	–		T+		T+								
	SV1	SV1	SV1		SV1		–								

	1d	1d	2d	5d		D									
107	ST	ST	ST	–											
	–	–	P.1a	P.1a											
	Q	Q	Q	Q											
	ST+	ST+	ST+	ST+											
	ST–	ST–	ST–	–											
	T+	T+	T+	T+											
	SV1	SV1	SV1	SV1											
	1d	3d	2m												
108	ST	–	ST												
	LAD	LAD	LAD												
	P.1a	P.1a	P.1a												
	T+	–	T+												
	–	–	SV1												
	RV6	–	RV6												
	1d		D												
109	ST														
	P.1a														
	ST+														
	T+														
	RV6														
	1d	6d	21d	1m	2.8m	3m	3.3m	4m	6m		D				
110	ST	–	–	–	ST	–	–	–	–						
	P.1a	–	–	P.1a	–	P.1a	P.1a	P.1a	P.1a						
	ST–	ST–	–	–	–	–	–	–	–						
	T+	T+	T+	T+	T+	T+	T+	T+	T+						
	–	SV1	–	–	SV1	SV1	SV1	SV1	SV1						
	RV6	RV6	RV6	RV6	RV6	RV6	RV6	RV6	RV6						
	–														
	1d	12d	1.5m		D										
111	ST	–	–												
	–	PR+	–												
	–	–	RAD												
	–	–	P.1a												
	–	ST–	–												
	–	T+	T+												
	SV1	SV1	–												
	–	RV6	RV6												
	1d	2m	3m	5m	8m	11m		D							
112	ST	ST	–	ST	ST	–									
	P.1a	P.1a	P.1a	P.1a	–	P.1a									
	P.ra	–	–	P.ra	–	–									
	T+	T+	T+	T+	T+	T+									
	–	–	–	–	SV1	–									
	RV6	RV6	RV6	–	RV6	RV6									
	–	–	–	–	R/S	R/S									
	1d	1d	1.5m	2.5m	3.5m	7m	11m	15m	19m	27m	/ 37m	55m			
113	ST	–	–	–	ST	–	–	–	–	–	–	–			
	–	–	–	–	–	RAD	–	RAD	RAD	RAD	RAD	RAD			
	P.1a	P.1a	–	–	–	–	–	–	–	–	–	–			
	–	–	Q	–	Q	–	–	–	–	–	–	–			
	T+	–	–	T+	T+	–	T+	–	–	–	–	–			
	SV1	SV1	BVH												

	1d	2d	3d	4d	8d	15d	1.5m	1.6m	3m	7m	10m	13m	16m	19m	28m
114	ST	ST	–	–	–	–	ST	–	–	–	–	–	–	–	–
	–	–	–	–	LAD	LAD	–	–	–	–	–	LAD	LAD	LAD	–
	P.1a	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	ST+	ST+	ST+	–	–	–	–	–	–	–	–	–	–	–	–
	T+	T+	T+	T+	T+	T+	T+	T+	T+	T+	T+	T+	T+	T+	–
	SV1	SV1	SV1	SV1	SV1	SV1	SV1	SV1	SV1	SV1	SV1	SV1	SV1	SV1	SV1
	–	–	–	–	–	–	–	–	–	–	RV6	–	–	–	–
	R/S	R/S	R/S	R/S	R/S	R/S	R/S	R/S	R/S	–	R/S	R/S	–	–	–
	CONT.	38m	58m												
		SV1	–												
		R/S	–												

	1d	3d	10d	11d	12d	13d	6m	8m	11m	12m	17m	18m	19m	22m	26m
115	–	–	–	APS	–	APS	–	–	–	–	–	ST	ST	N	N
	–	–	P.1a	P.1a	–	–	–	–	–	–	–	–	–		
	Q	Q	Q	Q	Q	Q	–	–	–	–	–	–	–		
	T+	T+	T+	T+	T+	T+	T+	T+	T+	T+	T+	T+	T+		
	SV1	SV1	–	SV1	–	–	–	–	–	–	–	–	–		
	RV6	RV6	–	–	–	–	–	–	–	–	–	–	–		
	R/S	–	–	–	–	–	–	–	–	–	–	–	–		
	CONT.	29m	35m	42m	53m										
		N	N	N	N										

	1d	12d	16d	20d	1.5m	3.5m	6m	6.5m	6.8m	7m	7.5m	8.5m	9m	9.5m	10m
116	ST+	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	T+	T+	T+	T+	T+	T+	T+	T+	T+	T+	T+	T+	T+	T+	T+
	SV1	SV1	SV1	SV1	SV1	SV1	SV1	SV1	SV1	SV1	SV1	SV1	SV1	SV1	SV1
	–	–	–	–	–	–	RV6	RV6	–	RV6	RV6	–	–	–	–
	R/S	R/S	R/S	R/S	–	R/S	R/S	–	–	–	–	–	–	–	–
	CONT.	11m	12m	18m	45m	50m	59m								
		T+	T+	T+	N	T+	N								
		SV1	SV1	SV1											

	2d	5d	12d	13d	1m	2.2m		D							
117	–	ST	ST	–	ST	ST									
	P.1a	P.1a	P.1a	–	P.1a	–									
	BVH	BVH	–	BVH	BVH	–									
	–	–	–	–	–	SV1									
	–	–	–	–	–	RV6									

	1d	7d													
118	P.1a	P.1a													
	ST+	ST+													
	T+	T+													
	SV1	SV1													

	1d	3d		D											
119	P.1a	P.1a													
	T+	–													
	RV6	–													
	–	SV1													
	R/S	R/S													

120	1d	1d	5d	1.5m	7m	/ 30m	32m								
	ST	–	–	–	N	N	N								
	P.ra	–	–	–											
	ST–	ST–	–'	–											
	T+	T+	T+	T+											
	–	SV1	SV1	SV1											
	RV6	–	–	–											
	R/S	R/S	R/S	R/S											
121	1d	2m	5m	5.2m	6m	12m	16m	21m	26m	34m	/ 37m	52m			
	ST	–	–	–	–	–	–	–	–	–	–	–			
	LAD	LAD	LAD	LAD	LAD	LAD	LAD	LAD	LAD	LAD	LAD	LAD			
	P.la	P.la	–	–	–	–	–	–	–	–	–	–			
	–	Q	Q	Q	Q	Q	Q	Q	–	–	–	–			
	–	ST+	–	–	–	–	–	–	–	–	–	–			
	–	ST–	–	–	–	–	–	–	–	–	–	–			
	T+	T+	–	T+	T+	T+	T+	T+	T±	T±	–	–			
	SV1	SV1	SV1	SV1	SV1	SV1	SV1	SV1	SV1	–	–	–			
	RV6	–	RV6	–	–	–	–	–	–	RV6	–	–			
	R/S	R/S	R/S	R/S	R/S	–	–	–	–	–	–	–			
122	1d	2d	22m												
	APS	APS	–												
	RAD	RAD	–												
	T+	T+	T+												
	SV1	SV1	–												
	R/S	R/S	–												
123	1d	2d	5d	11m	17m	31m	/ 43m	55m							
	–	–	ST	–	–	–	–	–							
	P.la	P.la	P.la	–	–	–	–	–							
	–	P.ra	P.ra	–	–	–	–	–							
	T+	T+	T+	–	–	–	–	–							
	SV1	SV1	SV1	SV1	SV1	SV1	SV1	SV1							
	R/S	R/S	R/S	–	–	–	–	–							

APPENDIX E.

SERUM ENZYMES

Serum enzyme values (u/L) of patients in the clinical series.

LDH = lactate dehydrogenase
HBDH = alpha hydroxybutyrate dehydrogenase
CPK = creatine kinase

CASE NO	LDH TIME-PERIOD (days)						HBDH TIME-PERIOD (days)						CPK TIME-PERIOD (days)					
	1-2	3-7	8-14	15-21	22-28	28	1-2	3-7	8-14	15-21	22-28	28	1-2	3-7	8-14	15-21	22-28	28
1	2480	-	-	-	-	-	1023	-	-	-	-	-	178	-	-	-	-	-
2	-	-	420	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3	1860	1540	-	-	780	-	868	579	-	-	304	289	108	25	-	-	-	-
4	440	-	-	-	-	-	192	-	-	-	-	-	16	-	-	-	-	-
5	-	-	415	-	-	-	-	-	328	-	-	-	-	-	21	-	-	-
6	-	-	-	1000	640	-	-	-	-	434	251	-	-	-	-	73	50	-
7	980	-	-	-	-	-	386	-	-	-	-	-	130	-	-	-	-	-
8	700	1160	-	-	-	-	299	270	-	-	-	-	29	31	-	-	-	-
9	360	360	-	-	-	-	169	227	-	-	-	-	26	23	-	-	-	-
10	4940	-	454	-	-	-	3110	-	381	-	-	-	253	-	-	-	-	-
11	3617	4244	3732	1292	-	-	2459	3280	2344	796	-	-	1500	1675	80	1375	-	-
12	357	386	309	-	-	-	275	328	261	-	-	-	-	-	-	-	-	-
13	3260	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
15	4632	1110	-	454	483	-	4580	-	-	-	-	-	334	5	17	22	-	-
17	1200	-	-	800	-	-	487	-	-	338	-	-	55	-	-	18	-	-
18	580	-	-	-	-	-	232	-	-	-	-	-	24	-	-	-	-	-
19	598	-	-	-	-	-	443	-	-	-	-	-	755	-	-	-	-	-
20	660	520	-	-	-	-	289	226	-	-	-	-	97	21	-	-	-	-
22	440	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
23	-	-	820	-	-	-	-	-	338	-	-	-	-	-	58	-	-	-
25	-	-	1360	-	-	-	338	-	569	-	-	-	24	-	18	-	-	-
26	424	-	270	-	-	-	280	-	236	-	-	-	30	-	35	-	-	-

CASE NO	LDH TIME-PERIOD (days) 1-2	3-7	8-14	15-21	22-28	28	HBDH TIME-PERIOD (days) 1-2	3-7	8-14	15-21	22-28	28	CPK TIME-PERIOD (days) 1-2	3-7	8-14	15-21	22-28	28
27	878	531	357	-	-	-	723	410	314	-	-	-	-	-	-	-	-	-
28	540	-	-	-	-	-	202	-	-	-	-	-	52	-	-	-	-	-
29	965	1370	-	-	-	-	854	1196	-	-	-	-	1357	953	-	-	-	-
30	637	-	-	-	-	-	627	-	-	-	-	-	-	-	-	-	-	-
31	1400	-	-	-	-	-	631	-	-	-	-	-	-	-	-	-	-	-
32	760	900	-	760	-	-	294	338	-	-	-	-	24	21	-	24	-	-
33	637	-	-	-	-	-	593	-	-	-	-	-	35	-	-	-	-	-
34	511	-	-	-	-	-	366	-	-	-	-	-	225	-	-	-	-	-
35	1860	-	-	-	-	-	554	-	-	-	-	-	-	-	-	-	-	-
36	800	820	-	320	-	-	313	280	-	128	-	-	21	13	-	16	-	-
38	599	-	-	473	-	-	555	-	-	381	-	-	14	-	-	21	-	-
40	367	405	280	-	-	-	347	289	275	-	-	-	-	-	60	-	-	-
41	1820	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
42	3100	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
44	1140	-	-	-	-	-	675	-	-	-	-	-	102	-	-	-	-	-
45	820	-	-	-	-	-	338	-	-	-	-	-	23	-	-	-	-	-
46	1100	1000	-	1140	-	-	453	427	482	-	-	-	23	26	-	21	-	-
47	170	-	-	-	-	-	-	-	-	-	-	-	16	-	-	-	-	-
48	1129	-	-	512	502	550	420	-	-	463	460	-	213	-	-	32	21	39
49	150	-	1160	660	580	520	651	-	483	304	328	328	26	-	52	26	52	50
50	463	-	-	-	-	-	531	-	-	-	-	-	17	-	-	-	-	-
52	260	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
53	-	183	782	329	-	-	-	377	560	261	-	-	-	50	24	21	-	-
54	760	-	-	-	-	-	130	-	-	-	-	-	-	-	-	-	-	-
55	600	-	-	-	-	-	280	-	-	-	-	-	26	-	-	-	-	-
56	2620	-	-	-	-	-	859	-	-	-	-	-	-	-	-	-	-	-
57	676	-	-	-	-	-	603	-	-	-	-	-	53	-	-	-	-	-
58	-	-	-	-	-	-	-	-	-	-	-	-	12	11	-	-	-	-
62	-	-	-	-	-	-	289	-	371	-	-	-	25	-	28	-	-	-
63	1600	-	-	-	-	-	677	-	-	-	-	-	314	-	-	-	-	-

CASE NO	LDH TIME-PERIOD (days) 1-2	3-7	8-14	15-21	22-28	28	HBDH TIME-PERIOD (days) 1-2	3-7	8-14	15-21	22-28	28	CPK TIME-PERIOD (days) 1-2	3-7	8-14	15-21	22-28	28
66	222	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
67	590	–	–	–	–	–	227	–	–	–	–	–	23	–	–	–	–	–
69	–	251	241	–	–	434	–	232	227	–	–	367	–	35	30	–	–	69
70	920	–	–	560	–	–	627	–	–	391	–	–	26	–	–	16	–	–
71	480	600	–	–	–	–	347	434	–	–	–	–	123	118	–	–	–	–
72	–	–	–	309	–	–	3376	1734	–	280	–	–	–	–	–	17	–	–
73	480	–	–	–	–	–	159	–	–	–	–	–	–	–	–	–	–	–
74	940	–	760	–	–	–	424	–	332	–	–	–	39	–	23	–	–	–
75	1680	–	–	–	–	–	643	–	–	–	–	–	30	–	–	–	–	–
76	–	290	212	251	193	174	–	–	178	207	179	154	–	402	131	96	53	48
78	1320	1560	1000	–	–	–	579	584	347	–	–	–	–	–	–	–	–	–
79	1620	1320	–	–	–	–	–	916	796	–	–	–	–	–	–	–	–	–
80	760	–	–	–	–	–	415	–	–	–	–	–	–	–	–	–	–	–
81	–	–	–	–	–	–	–	–	–	–	–	–	21	–	–	–	–	–
83	405	463	–	–	–	–	–	309	318	–	–	–	–	60	55	–	–	–
84	440	340	–	–	–	–	159	130	–	–	–	–	70	–	–	–	–	–
85	4800	1760	–	1000	–	–	1206	675	–	386	–	–	–	47	–	–	26	–
86	180	–	–	–	–	–	135	–	–	–	–	–	–	–	–	–	–	–
88	–	–	270	–	–	–	–	–	251	–	–	–	–	–	8	–	–	–
89	–	299	–	–	193	–	–	192	–	–	–	–	–	50	–	–	6	–
90	377	–	–	–	–	–	328	–	–	–	–	–	21	–	–	–	–	–
92	340	800	400	–	–	–	250	250	183	–	–	–	21	11	26	–	–	–
93	3185	–	–	–	–	–	2654	–	–	–	–	–	45	–	–	–	–	–
94	680	800	–	–	–	–	347	304	–	–	–	–	–	39	–	–	–	–
95	700	580	–	–	–	–	389	328	–	–	–	–	92	31	–	–	–	–
97	1303	–	936	782	–	–	1042	–	907	632	–	–	380	76	39	–	–	–
99	820	820	–	172	–	–	338	304	–	–	–	–	52	13	–	80	–	–
100	860	–	880	–	–	–	342	–	342	–	–	–	24	–	21	–	–	–
101	1023	–	–	–	–	–	666	–	–	–	–	–	42	–	–	–	–	–
102	–	415	–	309	405	–	–	313	–	299	208	–	–	171	–	70	90	–
103	740	640	–	–	–	–	270	337	–	–	–	–	18	16	–	–	–	–

CASE NO	LDH TIME-PERIOD (days)						HBDH TIME-PERIOD (days)						CPK TIME-PERIOD (days)					
	1-2	3-7	8-14	15-21	22-28	28	1-2	3-7	8-14	15-21	22-28	28	1-2	3-7	8-14	15-21	22-28	28
104	270	-	-	-	-	-	241	-	-	-	-	-	67	-	-	-	-	-
106	-	1148	-	-	-	620	-	579	-	-	-	288	-	39	-	-	-	31
107	386	-	-	-	-	-	347	-	-	-	-	-	47	-	-	-	-	-
108	-	290	-	-	-	309	-	232	-	-	-	208	-	27	-	-	-	32
109	848	-	-	-	-	-	564	-	-	-	-	-	280	-	-	-	-	-
110	560	-	540	-	-	-	235	-	209	-	-	-	23	-	13	-	-	-
111	540	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
113	-	-	-	-	-	-	-	-	-	-	-	-	59	-	-	-	-	-
114	560	460	420	-	-	-	241	202	150	-	-	-	24	8	13	-	-	-
115	-	-	720	740	-	-	-	-	309	333	-	-	-	-	-	-	-	-
116	640	-	-	-	-	-	236	-	-	-	-	-	13	-	-	-	-	-
118	1080	960	-	-	-	-	400	347	-	-	-	-	13	10	-	-	-	-
119	620	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
120	680	-	-	-	-	-	274	-	-	-	-	-	24	-	-	-	-	-
121	560	-	-	-	-	-	241	-	-	-	-	-	23	-	-	-	-	-
122	1020	-	-	-	-	-	463	-	-	-	-	-	73	-	-	-	-	-
123	780	760	-	-	-	-	295	371	-	-	-	-	48	35	-	-	-	-

APPENDIX F.

SPECIMENS SENT FOR VIRAL STUDIES, AND RESULTS.

(-ve = negative)

CASE NO	THROAT SWAB CULTURE	URINE CULTURE	STOOL CULTURE	BLOOD CULTURE	ANTIBODY TITRE	OTHER
2		-ve	-ve	Cytomegalovirus	CMV - 1:8	
3	-ve		-ve	-ve	-ve	
4			Echovirus - ? Type			
5	-ve	-ve	-ve x2	-ve	-ve	
6	-ve	-ve	-ve	-ve	Rubella - 1:8	CSF -ve
9	-ve	-ve	-ve	-ve	-ve	
10	-ve	-ve	-ve	-ve	-ve	
12				-ve x2	-ve x2	
13	-ve	-ve	-ve	-ve	-ve	
14						Tracheal aspirate: Para influenzavirus T.III
17	-ve	-ve	-ve	-ve	-ve	
18	-ve	-ve	-ve	-ve	-ve	
20	-ve x3		-ve x3	-ve	-ve	
25		-ve		-ve x2	-ve x2	
27	Enterovirus		Enterovirus			Sputum -ve
28	-ve		Coxsackievirus B4	-ve	-ve	
29		-ve	-ve			Sputum -ve
31	-ve x3		-ve x3	-ve x3	-ve x3	
32	Poliovirus Type II x2	-ve	Poliovirus Type II x3	-ve	-ve	
35	-ve			-ve	-ve	PM organs -ve
36	-ve x2		Coxsackievirus A			
38	-ve	-ve	-ve			
40		-ve				

CASE NO	THROAT SWAB CULTURE	URINE CULTURE	STOOL CULTURE	BLOOD CULTURE	ANTIBODY TITRE	OTHER
41				-ve	-ve	
42		-ve	-ve	-ve	-ve	
45	-ve		-ve	-ve	-ve	
				Adenovirus (repeat)	-ve	
46	-ve		-ve	-ve	-ve	
47				-ve	-ve	
48			-ve			
49	-ve			-ve	-ve	
50		-ve				
51	-ve	-ve	Echovirus Type 9			
52	Herpes hominisvirus		-ve	-ve	-ve	
54	-ve		-ve x3	-ve x2	-ve x2	PM stool and spleen - Enterovirus
58	-ve		-ve	-ve	Measles 1:640 (CFT)	
61	-ve		-ve			
62	-ve		-ve	-ve	-ve	
66			Echovirus - ? Type			
68						PM organs -ve
70	-ve	-ve	-ve	-ve	-ve	
71	-ve		Adenovirus	-ve	-ve	
73	-ve x3		-ve	-ve x2	-ve x2	
76	-ve		-ve	-ve	-ve	CSF -ve
78	-ve x3		-ve x3	-ve x3	-ve x3	
81						Sputum: Herpesvirus simplex x2
83			-ve			
84	-ve			-ve	-ve	
86	-ve	-ve	-ve x2	-ve x2	-ve x2	
87	-ve	-ve	-ve	-ve	-ve	
90				-ve	-ve	
91				-ve x2	-ve x2	
92	-ve	-ve		-ve	-ve	

CASE NO	THROAT SWAB CULTURE	URINE CULTURE	STOOL CULTURE	BLOOD CULTURE	ANTIBODY TITRE	OTHER
93				-ve	-ve	
94	-ve		Adenovirus x2	-ve	-ve	
95	-ve		-ve	-ve	-ve	
96						PM organs -ve
97				-ve	Measles 1:1024	Sputum: Adenovirus
98		-ve		-ve	-ve	
100	-ve	-ve x2	-ve	-ve	-ve	
101	-ve		-ve	-ve	-ve	PM organs -ve
102		-ve				Sputum -ve
103	-ve	Cytomegalo-virus		-ve	CMV 1:32	
104			Coxsackievirus B	-ve	-ve	
108		Adenovirus	Adenovirus			
110				-ve	-ve	
112	-ve	-ve	-ve	-ve	-ve	
113			-ve			
114	-ve	-ve	-ve	-ve x2	-ve x2	
115	-ve		-ve	-ve	-ve	
116	-ve		-ve	-ve	-ve	
117	Herpes hominisvirus			-ve	-ve	
119	-ve	-ve	-ve	-ve	-ve	
120	Herpes hominisvirus			-ve	Herpes hominisvirus 1:10 x2	
121				-ve	-ve	
123	-ve	-ve	-ve x2	-ve	-ve	
126						PM organs -ve
131						PM organs -ve
133						PM organs -ve, bronchus-para-influenzavirus Type 3 or 4

APPENDIX G

DURATION OF FOLLOW-UP AND OUTCOME

Key: Clinical - A = alive, N = normal, (N) = probable normal, D = dead, / = no further follow-up or transferred

X-ray - N = normal, ±N = probable normal (CTR 55% to <60%), C = cardiomegaly (CTR > 60%)

ECG - N = normal, "N" = minor changes, i.e. residual QRS axis deviation or increased R/SV1 ratio, Abn = persistent LVH, atrial abnormality, ST-T wave changes or arrythmias

ON DIG = duration, (x) intermittent, / = patient discontinued treatment, - = treatment continuing

d = days, m = months

CASE	DURATION			OUTCOME			
NO	CLINICAL	X-RAY	ECG	CLINICAL	X-RAY	ECG	ON DIG
1	50m/	25m	29m	A-N	N	N	15m
2	49d	42d	5d	D	N	"N"	42d
3	45d	37d	41d	D	C	Abn	45d
4	13d	9d	11d	D	C	Abn	13d
5	43m	31m	28m	A-N	C	Abn	43m-
6	164d	53d	24d	D	C	N	5m
7	59m	49m	59m	A-N	±N	N	31m
8	46d	44d	1m	D	C	Abn	46d
9	39d	39d	39d	D	C	Abn	39d
10	30m/	14m	22m	A-N	±N	"N"	24m
11	3m/	27d	1m	A-N	C	N	3m-
12	29m/	18m	29m	A-N	±N	N	9m
13	26d	21d	1d	D	C	Abn	26d
14	8d	1d	7d	D	C	Abn	8d
15	12m/	12m	4m	A-N	±N	"N"	6m
16	2d	1d	1d	D	C	Abn	2d
17	268d	6m	9m	D	±N	Abn	9m
18	210d	7m	7m	D(>270d)	C	Abn	9m
19	1d	1d	1d	D	C	Abn	1d
20	76m	53m	58m	A-N	N	"N"	(43m)
21	32m	23m	32m	A-RVH*	C	"N"	16m
22	80m	80m	40m	A-N	N	N	(14m)
23	63m	29m	63m	A-N	N	N	25m
24	1d	1d	1d	D	C	Abn	1d
25	63m	29m	63m	A-N	N	N	(35m)
26	31m	31m	31m	A-N	N	N	31m
27	10m/	7m	9m	A-N	±N	N	10m-
28	1d	1d	1d	D	C	Abn	1d
29	9m/	9m	2d	A-N	±N	Abn	29d/
30	4d	2d	1d	D	C	Abn	4d
31	72m	52m	72m	A-N	±N	N	31m
32	26m/	23m	26m	A-LVH	±N	"N"	26m-
33	6m/+	6m	6m	A-N	N	N	6m-
34	1d	1d	1d	D	N	Abn	1d
35	1d	1d	1d	D	C	Abn	1d
36	77m	77m	77m	A-N	N	N	44m
37	1d	1d	1d	D	C	Abn	1d
38	23d/	23d	9d	A-LVH	±N	Abn	23d/
39	1d	-	1d	D	-	Abn	-
40	21m	21m	21m	A-(N)	N	N	21m-

CASE	DURATION			OUTCOME			
NO	CLINICAL	X-RAY	ECG	CLINICAL	X-RAY	ECG	ON DIG
41	82m	65m	82m	A-N	N	N	25m
42	37m/	32m	37m	A-N	N	"N"	11m
43	70m	59m	70m	A-N	N	N	5m/
44	70m	70m	60m	A-N	N	N	35m
45	64m	64m	64m	A-N	N	N	31m
46	39m/	6m	31m	A-N	±N	N	39m-
47	60d	48d	48d	D	C	Abn	60d
48	35m	30m	30m	A-N	N	Abn	34m
49	68d	38d	35d	D	C	Abn	68d
50	36m	33m	36m	A-N	±N	N	33m-
51	92m	50m	92m	A-N	N	N	29m
52	6m/	26d	4.5m	A-N	±N	Abn	6m-
53	65m	53m	65m	A-N	±N	N	20m
54	70d	63d	2m	D	C	Abn	70d
55	30m/	30m	5.5m	A-N	C	"N"	2m/
56	9m/	7m	8m	A-N	C	N	9m/
57	21m/	7m	6m	A-N	N	N	9m
58	104m	43m	72m	A-N	N	"N"	54m
59	49m	49m	30d	A-N	±N	Abn	-
60	96m	93m	96m	A-N	N	N	48m
61	64m	64m	53m	A-N	N	N	31m
62	22d	19d	19d	D	C	Abn	22d
63	1d	1d	1d	D	C	Abn	1d
64	1d	1d	1d	D	C	Abn	1d
65	60m	60m	60m	A-N	N	N	8m/
66	95m	95m	93m	A-N	N	N	14m
67	59m	40m	59m	A-N	N	N	29m
68	1d	1d	1d	D	C	Abn	1d
69	31m	30m	23m	A-(N)	N	N	(32m)
70	70m	52m	70m	A-N	N	N	28m
71	70m	33m	56m	A-N	±N	N	(25m)
72	28m	24m	24m	A-(N)	C	N	16m
73	2m/+	29d	2m	A-(N)	±N	"N"	2m-
74	40m	12m	12m	A-N	N	N	2m/
75	7d	1d	3d	D	±N	Abn	7d
76	4m/+	3m	3m	A-N	±N	N	4m
77	88m	88m	76m	A-N	±N	N	(65m)
78	71m	71m	44m	A-N	±N	N	16m/
79	34d/+	30d	6d	A-N	N	"N"	34d-
80	63m	39m	63m	A-N	N	N	27m
81	14m	6d	17d	A-N	±N	N	9d/
82	16m/	13m	8m	A-N	N	N	16m
83	52m	13m	11m	A-N	±N	N	20m
84	73m	49m	60m	A-N	N	N	22m
85	33m	13m	12m	A-N	±N	Abn	38d/
86	56m	30m	46m	A-N	±N	"N"	50m
87	57m	32m	57m	A-N	N	N	35m
88	24m	24m	24m	A-N	±N	N	10m/
89	18m	7m	14m	A-N	±N	N	18m
90	18m	18m	18m	A-N	N	N	10m

CASE NO	DURATION			OUTCOME			
	CLINICAL	X-RAY	ECG	CLINICAL	X-RAY	ECG	ON DIG
91	72d	66d	66d	D	C	Abn	72d
92	40m	14m	40m	A-N	±N	N	15m
93	19d/	4d	6d	A-(N)	±N	Abn	.19d/
94	64d	48d	1.6m	D	C	Abn	64d
95	65m	65m	65m	A-N	N	Abn	3m/
96	1d	1d	1d	D	C	Abn	1d
97	47m	3m	20d	A-N	±N	Abn	3m-
98	84m	84m	84m	A-N	N	"N"	±14m
99	62d	2m	14d	D	C	Abn	±30d/
100	65m	23m	53m	A-N	N	N	23m
101	26d	24d	8d	D	C	Abn	26d
102	18m	8m	16m	A-N	C	N	18m-
103	51m	41m	51m	A-N	±N	N	41m-
104	152d	4m	4m	D	C	Abn	(5m)
105	78m	56m	68m	A-N	±N	N	68m
106	8m/	54d	8m	A-LVH	N	N	8m/
107	41d	20d	5d	D	C	Abn	25d
108	32m/	32m	2m	A-LVH	C	Abn	32m/
109	1d	1d	1d	D	C	Abn	1d
110	216d	6m	6m	D	C	Abn	7m
111	42d	40d	40d	D	C	Abn	42d
112	386d	11m	11m	D	C	Abn	(13m)
113	55m	46m	55m	A-N	N	"N"	27m
114	58m	58m	58m	A-N	N	N	(20m)
115	53m	33m	53m	A-N	N	N	27m
116	61m	61m	59m	A-N	N	N	25m/
117	71d	25d	2.2m	D	C	Abn	71d
118	19m/+	11m	7d	A-N	C	Abn	19m-
119	9d	7d	3d	D	C	Abn	9d
120	68m	68m	32m	A-N	N	N	20m
121	52m	35m	52m	A-SM^{o}	±N	"N"	(33m)
122	22m/	22m	22m	A-N	N	Abn	(13m)
123	55m	55m	55m	A-N	N	Abn	2m/

* Clinical signs of atrial septal defect.

\+ Transferred to referral centre (Richmond, Transkei, Posmasburg, Namaqualand and Transkei, respectively).

o Apical systolic murmur of trivial mitral incompetence.

APPENDIX H .

CARDIOTHORACIC RATIO

The admission, maximal, minimal and final cardiothoracic ratio (as a percentage) for each patient, and the time after presentation when obtained.

CASE NO	ADMISSION	MAXIMAL	MINIMAL	FINAL	NO. OF X-RAYS
1	61.0	61.0 - 0/A	49.4 - 25m	49.4 - 25m	9
2	64.2	66.7 - 10d	54.6 - 42d	54.6 - 42d	5
3	65.0	66.9 - 36d	62.5 - 37d	62.5 - 37d	7
4	71.6	71.6 - 0/A	68.2 - 9d	68.2 - 9d	3
5	77.2	77.2 - 0/A	59.4 - 13m	61.0 - 31m	7
6	54.3	63.3 - 10d	54.3 - 0/A	60.9 - 53d	7
7	60.8	63.5 - 9m	57.4 - 49m	57.4 - 49m	6
8	84.7	84.7 - 0/A	62.7 - 11d	73.0 - 44d	7
9	67.9	67.9 - 2d	63.1 - 10d	65.5 - 39d	4
10	61.7	63.3 - 51d	54.2 - 9d	58.3 - 14m	11
11	63.1	68.8 - 4d	57.0 - 7d	60.6 - 27d	13
12	65.6	65.6 - 0/A	57.3 - 18m	57.3 - 18m	7
13	62.1	67.2 - 21d	62.1 - 0/A	67.2 - 21d	5
14	66.3	66.3 - 0/A	66.3 - 0/A	66.3 - 0/A	1
15	57.4	61.2 - 5d	56.7 - 12m	56.7 - 12m	5
16	64.7	64.7 - 0/A	64.7 - 0/A	64.7 - 0/A	1
17	58.9	58.9 - 0/A	54.4 - 17d	56.8 - 6m	5
18	68.2	79.7 - 7m	68.2 - 0/A	79.7 - 7m	5
19	66.9	66.9 - 0/A	64.3 - 1d	64.3 - 1d	1
20	59.6	68.9 - 70d	49.7 - 53m	49.7 - 53m	22
21	62.5	64.9 - 10m	61.1 - 10m	61.9 - 23m	6
22	72.8	72.8 - 0/A	52.9 - 80m	52.9 - 80m	4
23	65.9	65.9 - 0/A	50.0 - 29m	50.0 - 29m	6
24	67.9	67.9 - 0/A	66.4 - 1d	66.4 - 1d	2
25	73.2	73.2 - 0/A	51.4 - 25m	52.9 - 29m	7
26	75.0	75.0 - 0/A	53.2 - 31m	53.2 - 31m	4
27	60.4	60.4 - 0/A	58.0 - 34d	58.7 - 7m	5
28	60.3	60.3 - 1d	60.3 - 1d	60.3 - 1d	1
29	57.8	66.2 - 12d	55.0 - 12d	55.6 - 9m	9
30	59.5	62.5 - 2d	59.5 - 0/A	62.5 - 2d	3
31	66.2	66.2 - 0/A	54.4 - 4m	56.9 - 52m	10
32	61.2	61.2 - 0/A	59.1 - 23m	59.1 - 23m	2
33	64.6	64.6 - 0/A	54.4 - 6m	54.4 - 6m	4
34	60.1	60.1 - 0/A	51.6 - 1d	51.6 - 1d	2
35	69.2	69.2 - 0/A	69.2 - 0/A	69.2 - 1d	1
36	75.0	75.0 - 0/A	51.8 - 30m	54.8 - 77m	15
37	60.9	60.9 - 0/A	60.9 - 0/A	60.9 - 1d	1
38	61.7	61.7 - 0/A	50.7 - 4d	57.1 - 23d	4
39	- *	-	-	-	-
40	56.6	61.2 - 5d	53.6 - 21m	53.6 - 21m	4
41	62.8	63.3 - 28m	51.0 - 65m	51.0 - 65m	16
42	73.2	73.2 - 0/A	53.2 - 32m	53.2 - 32m	2

CASE NO	ADMISSION	MAXIMAL	MINIMAL	FINAL	NO. OF X-RAYS
43	56.4	56.4 - 0/A	49.2 - 37m	52.9 - 59m	6
44	61.1	63.9 - 5m	53.7 - 70m	53.7 - 70m	7
45	62.2	65.6 - 12d	52.6 - 64m	52.6 - 64m	5
46	63.1	63.1 - 0/A	56.3 - 6m	56.3 - 6m	5
47	65.6	65.6 - 0/A	61.7 - 48d	61.7 - 48d	3
48	57.9	64.5 - 4m	52.6 - 30m	52.6 - 30m	15
49	63.9	63.9 - 0/A	61.3 - 38d	61.3 - 38d	4
50	74.7	78.5 - 15m	59.5 - 33m	59.5 - 33m	11
51	61.3	64.5 - 40d	48.7 - 50m	48.7 - 50m	11
52	56.4	63.3 - 11d	49.1 - 12d	57.2 - 26d	7
53	64.5	64.5 - 0/A	57.6 - 58d	59.0 - 53m	3
54	67.3	69.2 - 63d	67.3 - 0/A	69.2 - 63d	2
55	68.5	68.5 - 0/A	60.0 - 30m	60.0 - 30m	2
56	70.9	70.9 - 0/A	58.9 - 7m	58.9 - 7m	4
57	51.5	56.8 - 17d	51.5 - 0/A	52.3 - 7m	7
58	63.7	66.9 - 64d	52.4 - 43m	52.4 - 43m	15
59	62.1	68.4 - 30d	59.9 - 49m	59.9 - 49m	5
60	56.7	56.7 - 0/A	50.8 - 81m	50.8 - 93m	2
61	68.0	68.2 - 80d	53.2 - 64m	53.2 - 64m	9
62	60.4	70.5 - 14d	58.9 - 2d	61.5 - 19d	6
63	67.4	67.4 - 0/A	67.4 - 0/A	67.4 - 0/A	1
64	71.9	71.9 - 0/A	68.5 - 1d	68.5 - 1d	2
65	71.2	71.2 - 0/A	49.7 - 58m	50.8 - 60m	5
66	63.1	63.1 - 0/A	49.2 - 78m	52.8 - 95m	3
67	65.8	65.8 - 0/A	46.2 - 40m	46.2 - 40m	8
68	67.7	67.7 - 0/A	67.7 - 0/A	67.7 - 0/A	1
69	72.0	72.0 - 0/A	49.7 - 30m	49.7 - 30m	8
70	59.3	61.7 - 6d	52.2 - 52m	52.2 - 52m	7
71	60.0	62.9 - 6m	56.0 - 12m	56.8 - 33m	9
72	68.3	68.3 - 0/A	60.4 - 24m	60.4 - 24m	9
73	64.6	64.6 - 0/A	59.6 - 29d	59.6 - 24d	6
74	61.9	63.5 - 28d	54.1 - 12m	54.1 - 12m	8
75	59.1	59.1 - 0/A	59.1 - 0/A	59.1 - 0/A	1
76	60.8	60.8 - 0/A	48.2 - 9d	59.8 - 3m	7
77	63.0	64.5 - 51d	53.3 - 70m	55.1 - 88m	8
78	65.1	65.1 - 15d	47.8 - 44d	56.7 - 71m	9
79	63.4	66.5 - 2d	58.8 - 21d	61.5 - 30d	7
80	59.4	59.6 - 1d	50.6 - 80m	50.6 - 80m	8
81	64.3	64.3 - 0/A	55.6 - 6d	55.6 - 6d	4
82	63.5	64.6 - 25d	53.4 - 13m	53.4 - 13m	8
83	73.9	73.9 - 0/A	50.3 - 11m	55.6 - 13m	9
84	67.8	67.8 - 0/A	50.0 - 19m	54.7 - 49m	3
85	67.8	67.8 - 0/A	55.3 - 7d	57.9 - 13m	10
86	56.9	62.2 - 2d	53.3 - 10m	55.5 - 30m	7
87	62.0	65.6 - 3m	51.7 - 22m	52.9 - 32m	6
88	66.3	66.3 - 0/A	56.7 - 38d	57.7 - 24m	5
89	66.9	69.7 - 41d	55.7 - 7m	55.7 - 7m	7
90	64.4	64.4 - 0/A	50.0 - 0/A	51.5 - 18m	3
91	57.8	72.0 - 43d	57.8 - 0/A	68.6 - 66d	9
92	62.9	63.3 - 6m	53.0 - 5m	57.1 - 14m	6
93	67.8	67.8 - 0/A	57.3 - 4d	57.3 - 4d	3

CASE NO	ADMISSION	MAXIMAL	MINIMAL	FINAL	NO. OF X-RAYS
94	72.1	72.1 - 0/A	61.1 - 21d	64.6 - 48d	5
95	66.4	66.4 - 0/A	54.9 - 65m	54.9 - 65m	6
96	68.3	68.3 - 0/A	68.3 - 0/A	68.3 - 0/A	1
97	59.4	59.4 - 0/A	49.6 - 43d	55.2 - 3m	10.
98	65.7	66.9 - 1d	47.1 - 84m	47.1 - 84m	12
99	68.1	69.4 - 2m	68.1 - 0/A	69.4 - 2m	2
100	69.2	69.2 - 0/A	52.6 - 23m	52.6 - 23m	6
101	68.6	68.6 - 0/A	67.9 - 24d	67.9 - 24d	2
102	71.9	71.9 - 0/A	59.3 - 21d	62.1 - 8m	9
103	62.2	62.7 - 2d	58.4 - 41m	58.4 - 41m	6
104	70.2	70.9 - 4m	55.8 - 3m	70.9 - 4m	3
105	71.9	71.9 - 0/A	53.2 - 44m	55.3 - 56m	14
106	56.0	56.3 - 40d	50.8 - 9d	53.9 - 54d	6
107	61.3	62.8 - 9d	60.0 - 20d	60.0 - 20d	3
108	70.7	75.2 - 8m	69.7 - 4m	71.1 - 32m	4
109	63.8	63.8 - 0/A	63.8 - 0/A	63.8 - 0/A	1
110	68.7	78.7 - 6m	67.7 - 27d	78.7 - 6m	8
111	57.6	68.2 - 4d	57.6 - 0/A	62.3 - 40d	4
112	78.3	80.0 - 11m	69.2 - 5m	80.0 - 11m	5
113	62.2	62.2 - 0/A	47.9 - 11m	53.7 - 46m	4
114	71.3	71.3 - 0/A	54.1 - 57m	54.1 - 57m	11
115	72.6	72.6 - 0/A	48.3 - 27m	51.9 - 33m	8
116	69.2	70.6 - 6m	54.6 - 61m	54.6 - 61m	17
117	68.4	68.4 - 0/A	62.4 - 25d	62.4 - 25d	2
118	79.3	79.3 - 0/A	61.1 - 11m	61.1 - 11m	5
119	71.5	71.5 - 0/A	65.2 - 3d	69.1 - 7d	3
120	68.9	68.9 - 0/A	51.4 - 12m	52.4 - 68m	9
121	67.8	67.8 - 0/A	56.3 - 35m	56.3 - 35m	3
122	67.2	67.2 - 0/A	51.1 - 16m	53.5 - 22m	3
123	55.1	64.8 - 1d	53.6 - 55m	53.6 - 55m	5

d = days; m = months; 0/A = on admission.
* = No x-ray taken (see page

APPENDIX I

AUTOPSY FINDINGS

A. CARDIAC FEATURES

CASE No. (DIAG)	MORPHOLOGY				HISTOLOGY		
	APPEARANCE	WEIGHT (Gms)	CHAMBER HYP.&/or DIL.	MYOCARDIUM (cut-surface)	MYOFIBRES	INTERSTITIUM	SUBENDOCARDIUM
9 (M)	Flabby Peric-petechiae -effusion	-	-	Mottled ++	Degeneration Fragmentation necrosis	Diffuse lymphos++	-
14 (M)	- ASD	72	LA++, RA++, RV++	-	fragmentation	lymphos++	-
19 (M+F)	Enlarged EFE++	70	LV++	-	Patchy degeneration& fragmentation	Diffuse mononucs++; Oedema+++	-
28 (M)	Congested Mottled Peric-effusion Dilated MV	76	LV+++	Mottled ++	Fragmentation & patchy necrosis	lymphos+++	-
30 (M)	Enlarged globular	82	-	Mottled ++	-	Diffuse mononucs+++; Oedema++	-
34 (M)	Enlarged,dilated pale with patchy conges-tion	-	-	Mottled ++	Necrotic +++	Diffuse lymphos+++	-
35 (M)	Pale, flabby with petechiae & area of thin-ning peric-effusion	66	LV++	Mottled ++, congested	Degeneration fragmentation & necrosis Sub-epicardial haemorrhage	lymphos+++; plasma cells++; oedema+++	haemorrhage

CASE NO (DIAG)	MORPHOLOGY				HISTOLOGY		
	APPEARANCE	WEIGHT (Gms)	CHAMBER HYP.&/or DIL.	MYOCARDIUM (cut-surface)	MYOFIBRES	INTERSTITIUM	SUBENDOCARDIUM
37 (M)	Enlarged, congested	86	-	-	Degeneration Fragmentation	lymphos++ oedema++	-
39 (M)	Enlarged, flabby, pale	88	LV++	Mottled+	-	mononucs++	-
54 (M+F)	Enlarged EFE++ (LA LV and RV) Peric-effusion	84	LV+++, RV++	streaky fibrosis	degeneration, fragmentation, focal fibrosis	lymphos++ histios++, plasma cells+; congestion++	collagen+++ elastin++ (LA LV)
62 (M)	Enlarged ante-mortem thrombus LV & aorta	102	LV++	Mottled+	degeneration & necrosis+++	lymphos+++	-
63 (M)	Enlarged, pale, congested	68	-	-	-	lymphos++; congestion+++	-
64 (M)	Dilated, pale, somewhat opaque	94	-	Mottled++	necrotic++, Fatty infiltration	Patchy areas of lymphos, monos, plasma cells++	No increased collagen or elastin
68 (M)	Enlarged Pale, flabby; Peric-effusion	88	LV++, RV+	Mottled+	Focal necrosis++ Fatty change	mononucs+++	-
96 (M)	Peric-effusion	50	LV++	Mottled++, petechiae	Degeneration	Occasional lymphos & plasma cells+ congestion+++	-

CASE NO (DIAG)	MORPHOLOGY				HISTOLOGY		
	APPEARANCE	WEIGHT (Gms)	CHAMBER HYP.&/or DIL.	MYOCARDIUM (cut-surface)	MYOFIBRES	INTERSTITIUM	SUBENDOCARDIUM
99 (F)	Pale EFE+++	82	LV+++, RV++	-	"Ischaemic"	-	Thickened+++ Collagen+++
101 (F)	EFE++ (LV and LA) Dilated MV	93	LV+++, RV+ LA++, RA+	-	Hypertrophy+++	-	Collagen++ Elastin++
109 (M+F)	Enlarged, flabby, pale EFE++	-	LV++	Mottled+++	-	Patchy cells+	Collagen & elastin++
117 (M+F)	Enlarged, Thin, opacified endocardium	134	LV++	Mottled+	-	Focal mononucs ++	Collagen+++ Elastin++
119 (M)	Enlarged+++, with white patches	118	LV++, RV++	Diffuse petechiae	Hypertrophy	Diffuse mononucs++ Congested++	-
124 (F)	EFE++ Peric-effusion -petechiae	-	LV+++, LA+	-	Hypertrophy	Congestion++	Thickened and disorganised
125 (M+F)	Enlarged, globular; EFE++	-	LV++	-	-	Area of cell infiltration+	Early changes
126 (F)	Enlarged; EFE++; peric-effusion	62	LV+++, RV++	Mottled++	Fat infiltration	-	Collagen+++ Elastin+++

CASE NO (DIAG)	MORPHOLOGY				HISTOLOGY		
	APPEARANCE	WEIGHT (Gms)	CHAMBER HYP.&/or DIL.	MYOCARDIUM (cut-surface)	MYOFIBRES	INTERSTITIUM	SUBENDOCARDIUM
127 (M)	Enlarged, flabby, Congested+++	-	LV++, RV+++	-	Degeneration, fatty change	Diffuse lymphos ++	-
128 (M)	Enlarged, dilated, Petechiae++	-	LV+++	Congested	Degeneration, fragmentation & necrosis+++	Intense lymphos+++	-
129 (M)	Dilated, flabby, ante-mortem throm-bus (LV)	58	-	Bulky, soft	Necrosis++	Cells+++	-
130 (M)	Normal size	76	-	-	-	lymphos, histiocytes & plasma cells+++	-
131 (M)	Normal size	68	RV+, RA	-	Necrosis+	lymphos++ ; congestion+	-
132 (M+F)	Enlarged EFE++(left & right) Peric-effusion	84	LV+++, RV++	-	Fatty change	Patchy mono-nucs++	Collagen+++
133 (M+F)	Enlarged; EFE++ (LV&LA)	92	-	Mottled++	-	Diffuse cells++	-
134 (M)	Enlarged, flabby Peric-effusion	88	LV++ RV+	Mottled++	Degeneration++	lymphos+++	-

CASE NO (DIAG)	MORPHOLOGY				HISTOLOGY		
	APPEARANCE	WEIGHT (Gms)	CHAMBER HYP.&/or DIL.	MYOCARDIUM (cut-surface)	MYOFIBRES	INTERSTITIUM	SUBENDOCARDIUM
135 (M)	Enlarged+++, pale, Pericarditis + effusion	80	LV++	Congested+++	Degeneration++ (including AV node)	lymphos++ Congestion++	-
136 (M)	Small	64	-	-	Focal necrosis	Diffuse lymphos+++	-
137 (F)	Enlarged Congested+ EFE++	142	LV+++, RV+, LA+	-	Hypertrophy++ Degeneration+	Few eosinophils	Collagen++ Elastin++
138 (F)	EFE++ Peric-effusion MV - thickened	152	LV++, LA+, RV+	-	Hypertrophy++	Congested+	Collagen+++
139 (F)	EFE++	-	-	-	Focal degeneration	-	Thickened, cellular Elastin++
140 (M+F)	Enlarged+++ EFE+++ MV distorted	198	LV+++, RV+++, LA+++, RA+++	-	Hypertrophy	Mononucs+, - diffuse	Collagen++ Elastin

DIAG = diagnosis; HYP = hypertrophy; DIL = dilatation; Peric = pericardial; ASD = atrial septal defect; MV = mitral valve; LA = left atrium; RA = right atrium; RV = right ventricle; LV = left ventricle; + = mild; ++ = moderate; +++ = severe; AV = atrio-ventricular; lymphos = lymphocytes; mononucs = mononuclears; histios = histiocytes; monos = monocytes.

B. NON-CARDIAC FEATURES

CASE NO. (PM DIAG)	LUNGS				LIVER		LYMPHOID HYPER-PLASIA	OTHER
	VIRAL		BACT PNEUM	CONG or OEDEMA	FATTY INFIL	CONG		
	PNEUM	BRONCH						
9 - M	-	-	-	-	-	-	-	Ascites
14 - M	+	-	+	-	-	-	+	Renal infarcts; Cerebral anoxia
19 - M+F	+	+	-	+	+	-	+	Viral meningitis
28 - M	+	+	-	+	+	+	+	-
30 - M	+	-	-	+	+	+	+	Cerebral oedema; Congested lungs
34 - M	+	-	+	+	+	+	-	Cerebral oedema
35 - M	+	-	-	-	-	-	+	Cerebral oedema; Acute glomerulo-nephritis
37 - M	+	-	-	-	-	-	+	-
39 - M	+	-	-	-	+	+	+	Congested spleen & kidneys; Cerebral anoxia
54 - M+F	+	+	-	-	+	-	+	Cerebral anoxia
62 - M	+	-	-	+	-	+	+	Infarcts right cerebrum, spleen, kidneys; Viral meningitis
63 - M	+	+	-	-	+	+	+	-
64 - M	+	-	-	+	+	+	+	Myositis; Cerebral oedema
68 - M	+	+	-	-	+	+	+	Acute tubular necrosis; Adrenal and pancreatic atrophy; Tongue ulcers; Cerebral anoxia
96 - M	+	-	-	-	+	+	+	-
99 - F	-	-	+	-	-	+	+	Acute glomerulonephritis
101 - F	+	-	+	+	+	-	-	-
109 - M+F	+	-	-	+	-	-	+	-
117 - M+F	-	-	-	-	-	-	-	-

CASE NO. (PM DIAG)	LUNGS				LIVER		LYMPHOID HYPER-PLASIA	OTHER
	VIRAL		BACT PNEUM	CONG or OEDEMA	FATTY INFIL	CONG		
	PNEUM	BRONCH						
119 - M	-	-	-	+++	-	-	+	Pulmonary haemorrhages
124 - F	-	-	+	+	-	+	-	Cerebral anoxia; Congested spleen
125 - M+F	+	-	-	-	-	-	+	Viral meningitis; Cerebral oedema
126 - F	+	+	-	+	+	-	+	Cerebral anoxia
127 - M	-	-	-	+	+	+	-	Cerebral oedema
128 - M	+	+	+	-	-	+	+	-
129 - M	-	+	-	+	+	+	+	Cerebral oedema and brain stem compression
130 - M	+	+	-	-	-	+	+	Congested kidneys & spleen; Cerebral anoxia
131 - M	+	+	-	-	-	+	+	Congested organs; Cerebral oedema
132 - M+F	+	+	-	+	+	-	+	Cerebral anoxia
133 - M+F	+	-	-	+	+	-	+	Acute tubular necrosis
134 - M	+	+	-	+	+	+	+	Kwashiorkor
135 - M	+	-	-	+	+	+	+	Cerebral oedema & brain stem compression; Congested spleen & kidneys
136 - M	-	-	+	-	-	-	-	Kwashiorkor; Bronchiectasis; Ulcers tongue and oesophagus
137 - F	+	-	-	-	-	+	+	-
138 - F	-	-	-	+	+	+	-	Congested kidneys and spleen
139 - F	+	+	-	-	+	-	+	Septicaemia; Peritonitis - amoebic; Kwashiorkor
140 - M+F	+	-	-	+	-	-	-	Cardiac cirrhosis; Congested organs

PM = post-mortem; DIAG = diagnosis; PNEUM = pneumonitis; BACT PNEUM = bacterial pneumonia; CONG = congestion; INFIL = infiltration; M = myocarditis; F = fibroelastosis.

STATISTICS

The following statistical methods were extensively used throughout the treatise.

1. CHI-SQUARE TEST (X^2)

For testing the significance of differences between expected and observed frequencies. Since only 2 frequencies were compared in all instances, the so-called 2x2 format was applied, i.e.

$$X^2 = \frac{(bc - ad)^2 \, k}{efgh},$$

where a,b, and c,d are the variables, and e,f,g,h and k are the totals, in the following table

a	c	e
b	d	f
g	h	k

Yates's correction was applied in all analyses, whereby 0.5 was added to each compartment less than expected, and subtracted from each compartment greater than the expected value. X^2 tables were consulted, at 1 degree of freedom, to assess probability (p) of significance.

2. STUDENT'S T-TEST FOR UNPAIRED DATA

For testing the significance of differences of means of 2 unpaired series of data.

The t-statistic was derived as follows,

$$t = (\bar{X}_1 - \bar{X}_2) \; / \; SE$$

where $$SE = \sqrt{\frac{\left[\Sigma X_1^{\,2} - (\Sigma X_1)^2 \; / \; N_1\right] + \left[\Sigma X_2^{\,2} - (\Sigma X_2)^2 \; / \; N_2\right]}{(N_1 - 1) + (N_2 - 1)} \times \left(\frac{1}{N_1} + \frac{1}{N_2}\right)}$$

Student's t tables were consulted at $(N_1 - 1) + (N_2 - 1)$ degrees of freedom to assess probability (p) of significance.

VARIANCE RATIO TEST was applied to confirm that standard deviations of the 2 populations were not significantly different.

3. LINEAR REGRESSION (Chapter 10 only).

Line of identity correlating 2 sets of paired samples was derived from the formula,

$$y = Ax + B,$$

where $$B = \frac{\Sigma xy - \frac{(\Sigma x)(\Sigma y)}{n}}{\Sigma x^2 - \frac{(\Sigma x)^2}{n}}$$

4. CORRELATION COEFFICIENT (Chapter 10 only).

The correlation coefficient was derived from the formula,

$$r = \frac{\Sigma xy - \frac{(\Sigma x)(\Sigma y)}{n}}{\sqrt{\left\{\left[\sum x^2 - \frac{(\Sigma x)^2}{n}\right]\left[\sum y^2 - \frac{(\Sigma y)^2}{n}\right]\right\}}}$$

References:

1. Moroney, MJ. Facts from Figures. Penguin Books, Middlesex, 2nd ed, 1953, p 249.
2. ibid. p 227.
3. Sprent, P. Statistics in Action. Pelican Books, Middlesex, 1977, p 137.
4. ibid. p 129.