Introduction and objectives. Myxomas are the most common type of primary cardiac tumors. The aim of this study was to analyze the clinical forms of presentation of cardiac myxoma, the postoperative evolution, and the possibility of recurrence and tumoral embolism.

Patients and method. From July 1992 to March 1999, 31 patients with myxoma were studied. Cell cycles (ploidy pattern of the tumoral DNA) were studied in 12 patients to evaluate the risk of recurrence and tumoral embolism.

Results. The most frequent clinical manifestations were constitutional symptoms (74%), dyspnea (45%), and embolism (41%). Smaller-diameter myxomas correlated independently with tumoral embolism (45%). The in-hospital mortality was 3.2%, no deaths were observed during follow-up (mean: 4.8 years). No patients had clinical or echocardiographic signs of tumoral recurrence. Patients with tumoral embolism (n = 8) were compared with patients without embolism (n = 4). Patients who suffered embolism had higher S phase > 7 and/or DNA index > 1.2 (4/4 patients [100%], p = 0.061) than patients without embolism (2/8 patients [25%]). Cytometry of the only recurrent tumor (second operation) revealed a diploid tumor with a significantly more frequent S phase (10%) than in sporadic myxomas (4.27 ± 2.32%, p = 0.039).

Conclusions. Constitutional symptoms, dyspnea, and tumor embolism were the most frequent clinical manifestations. Clinical and anatomicopathologic characteristics and the cell cycle were not significantly related to tumoral embolism, but there was a tendency toward a higher proportion of cells in S phase and a higher DNA index in tumors associated with embolism. The S phase was significantly more frequent in the only case of recurrent myxoma and could be a potential marker of recurrence.

Key words: Myxoma. Cardiac tumors. Embolism.

Mixomas cardíacos: correlación anatomoclínica

Introducción y objetivos. Los mixomas son los tumores cardíacos más frecuentes. El objetivo del presente trabajo fue estudiar las formas de presentación clínica de los mixomas, la evolución postoperatoria y las probabilidades de recidiva y embolia tumoral.

Pacientes y método. Entre 1992 y 1999 fueron sometidos a cirugía 31 pacientes portadores de mixomas. A un subgrupo de ellos se les realizó un estudio del patrón de ploidía del ADN tumoral con el objetivo de identificar pacientes con posibilidad de recidiva y/o embolias tumorales.

Resultados. Las manifestaciones clínicas más frecuentes fueron los síntomas constitucionales (74%), la disnea (45%) y los episodios embólicos (41%). El diámetro menor más pequeño de los mixomas se correlacionó de forma independiente con embolia tumoral (p = 0.007). La mortalidad operatoria fue del 3.2%. A largo plazo ningún paciente falleció ni presentó recidiva tumoral. En 12 pacientes se realizó un estudio del ciclo celular para determinar la posibilidad de recidiva y embolia tumoral. Se comparó a los pacientes sin embolias (n = 8) con un grupo (n = 4) que tuvo manifestación embólica. El estudio de citometría de flujo reveló una fase S > 7 y/o un índice de ADN > 1.2 en 2/8 pacientes (25%) del grupo sin embolias, en cambio en 4/4 (100%) de los pacientes con embolia (p = 0.061). La citometría en el único caso de tumor recurrente (era su segunda intervención quirúrgica) puso de manifiesto un tumor diploide con una fase S (10%) significativamente mayor que en los mixomas esporádicos (4.27 ± 2.32%; p = 0.039).

Conclusiones. Los síntomas constitucionales, la disnea y los episodios embólicos fueron las manifestaciones clínicas más frecuentes. El estudio de ploidía celular puede ser útil en los pacientes con antecedentes heredofamiliares para predecir recidivas. Hubo una tendencia a una cantidad más elevada de embolias en los mixomas con un mayor porcentaje de células en fase S del ciclo celular.

Palabras clave: Mixoma. Tumores cardíacos. Embolia.
INTRODUCTION

Primary cardiac tumors occur infrequently. The most common are myxomas, which tend to have a varied clinical presentation, and for this reason they are called the «great impostors» of cardiovascular nosology.1

Years ago, myxomas were rarely recognized due to the scarcity of diagnostic measurements. It was difficult to sort them out therapeutically due to the fact that the best way to discover and eradicate myxomas was by surgical intervention, and cardiac surgery was still in an inadequate state of development for this at the time.

Swiss surgeon Clarence Crafoord 2 successfully performed the first cardiac bypass surgery for extirpation of a myxoma of the left atrium. Beginning in the 1960s, a growing number of studies were published regarding patients cured by surgical resection of myxoma. Nevertheless, In 1967 Gerbode et al3 reported the recurrence of myxomas, including in patients who had undergone a protracted surgical extirpation and who were considered «cured».

The primary aim of this study was to evaluate the clinical manifestations and long-term hospital course of 31 patients who underwent surgical resection of cardiac myxomas. Second, a study of cellular ploidy pattern with the intention of identifying those patients with a possibility of tumor recurrence or a tumor embolism was undertaken. The study included patients from July 1992 to December 1999. Followup extended until March 2000, which provided a post-operative followup period of more than 7 years.

PATIENTS AND METHODS

This was a respective study of all patients diagnosed with myxomas who underwent surgery during the period from July 1, 1992 to December 31, 1999. In order to establish the incidence of patients with myxomas in our institution, we reviewed 112 280 clinical histories and 14 449 cardiovascular surgery files.

A transthoracic echocardiogram was obtained on all patients using a 2.5 MHz transducer and a Hewlett-Packard Sonos 2500, with 2-dimensional M-mode real time recording, in accordance with our usual laboratory technique.4 Intraoperative transesophageal echocardiography was also performed on all patients in accordance with the techniques conventionally used in our laboratory.4 The transesophageal recordings were performed with an 5 MHz omniplanar transducer. Serial echocardiography studies were performed to establish the presence of recurring tumors.

In those patients in whom associated heart disease was either suspected or needed to be ruled out, cineangiography was performed prior to surgery. Angiography was again performed each time the diagnosis needed to be confirmed and when more detailed information was needed regarding the anatomy of the tumor, particularly if requested by the surgeon performing the surgery.

Surgery technique

The surgery consisted of a wide resection of the tumor base followed by closure of the remaining interatrial communication. When it was not possible to identify the base of the tumor, electrocoagulation of the surrounding area was performed to avoid tumor recurrence.

Anatomicopathologic study

The smallest and largest tumor diameters were determined by macroscopic examination, as was the presence of hemorrhage, necrosis, and tumor base. Samples to be studied were processed with an optical microscope using the following protocol: they were fixed on a formol pad, embedded in paraffin, and stained with hematoxylin-eosin, Mason trichome, Alcian blue dye, and periodic acid-Schiff stain.

Flow cytometry

In order to correlate the possibility of recurrence or embolization with tumor ploidy and the S-phase of cellular synthesis, 12 cases of primitive myxomas located in the atria and right ventricle were studied to determine the content of cell DNA by flow cytometry. The ploidy and S-phase were determined by a modified Hedley method,5 reserving the material fixed in formol in some cases, or 50μ sections of the material included in others; we processed these with 0.5% pepsin, tripsin, providone iodine stain, 35μ porosity monofilament filter, FACScan argon laser flow cytometry study of the samples, and a CellFit mathematical analysis of the histograms.

Statistical analysis

The continuous numerical values were expressed by mean and standard deviation. The Student t test and the Pearson linear correlation coefficient were used to analyze the association between numerical data. The category variables were expressed in percentages and compared by exact Fisher test and χ² test. Logistical regression analysis was used for the multivariant analysis. Values of P<.05 were considered statistically significant. The SPSS 3.1® statistical package was used for all calculations.

RESULTS

Patient median age was 53.4±18.3 years (range 14

to 82 years). A total of 17 patients (54.8%) were women and 14 (45.2%) were men.

Clinical characteristics. Forms of presentation

Some patients presented with a symptomatic picture as the beginning of their illness. One was asymptomatic and the diagnosis of myxoma was made on casual echocardiography.

A total of 23 of the 31 patients (74.2%) presented with general symptoms such as asthenia, weight loss, slight fever, and palpitations. The existence of familial myxomatous illness could be corroborated in only 1 patient (3.23%). This patient had also previously undergone surgery (recurrent tumor) for a myxoma in the same site as that which motivated the current consultation.

Table 1 shows the most common forms of presentation in the 31 study patients. Stress dyspnea was the second most frequent (45.16%) manifestation at the start of symptom occurrence, following the category of general symptoms.

Systemic embolisms were the third most frequent form of presentation (in a total of 13 patients [41.93%]; cerebral embolism in 9 patients, coronary embolism in 1 patient, pulmonary embolism in 1 patient, 1 patient with an embolism in the right upper extremity, and retinal embolism in 1 patient). In 1 patient the symptoms began with an acute myocardial infarct of the inferior surface, interpreted as an embolism of a coronary artery caused by tumor material or a thrombus of the tumor surface. In a right atrial myxoma, a pulmonary thromboembolism was found to be the first manifestation of the disease.

On auscultation or echocardiography, left atrial tumors, a total of 25, showed signs of mitral stenosis in 6 patients, mitral insufficiency in 4 patients, and in 15 cases the mitral transvalvular flow was not compromised.

Electrocardiographic findings

A total of 18 patients (58.06%) had normal electrocardiographic tracings, and 13 (41.93%) had pathologic changes, including left atrial enlargement in 3 patients, right atrial enlargement in 1 patient, biatrial overload in 1 patient, complete block of the right branch in 2 patients, complete block of the right branch plus hemiblock of the left anterior branch in 1 patient, left anterior hemiblock in 1 patient, complete block of the left branch in 2 patients, grade 1 atroventricular block in 1 patient, and 1 patient presented with non-specific changes in ventricular repolarization. A total of 27 patients (87.10%) were in sinus rhythm and 4 (12.9%) presented with chronic atrial fibrillation with a preserved ventricular response.

Echocardiography study

Different types of echocardiography (2-dimensional, color Doppler and transesophageal) were successful in establishing the presence of myxomatous cardiac tumors (mobile, dense, globular masses) in 29 (93.5%) of 31 patients (Figures 1 and 2).

In 1 patient, the preliminary diagnosis of vegetation located on the mitral sub-valve due to infectious endocarditis was made; histological examination finally revealed the presence of a myxoma. In another patient, electrocardiogram could not discriminate between a thrombus and an atrial myxoma.

In all patients, pathologic anatomy confirmed the diagnosis of myxoma, while surgical anatomy was similar to the echocardiography findings concerning
the location and size of the tumor.

**Location of myxomas**

Tumor location was as follows: left atrium in 25 patients, right atrium in 3 patients, left ventricle in 1 patient, right ventricle in 1 patient, and bi-atrial in 1 patient. In 30 patients (96.8%) there was intracavity tumor growth, 19 myxomas of the left atrium presented with a tumor base in the interatrial septum with growth toward the left atrium; in only 1 patient the tumor developed in the tendinous chords of the mitral sub-valve.

The mean age of patients with atrial myxomas was 56.3±15.8 years, while the mean age of those with myxomas located in the right and left ventricles was 18.5±6.36 years (P=0.002).

**Surgical procedures performed**

The average amount of bypass time was 67.2±27.4 min (range 27 to 140 minutes) and the average aortic interruption time was 46.6±24.9 min (range 18 to 115 minutes). The average volume of cardioplegia solution used was 800 mL.

Table 2 shows the associated surgical procedures that were performed along with the resection of each myxoma.

The most frequently performed procedure for atrial myxomas was a wide resection of the tumor base, which was nearly always in the septum, with subsequent closure of the communication in 16 patients either by autologous pericardial patch or with simple closure. In 5 patients, in whom the resection of the tumor base was not wide for anatomical reasons, electrocoagulation was performed.

Of note, mitral valvuloplasty was performed on 1 patient with a left ventricular myxoma because the anterior ventricular valve had previously been removed in order view the tumor mass more clearly.

**Surgical mortality-morbidity**

There were no post-operative complications in 14 out of 31 patients (45.16%) on whom surgery was performed. One patient (3.23%) died 10 days following surgery due to sepsis. Sixteen of 31 patients (51.61%) developed a non-fatal complication during their post-operative hospital stay (Table 3). Three patients who developed a nodal rhythm and required the placement of a temporary pacemaker; 2 of these subsequently required permanent pacemaker implantation.

Followup lasted an average of 1496.13±871.83 days (range 2736 to 100 days) and no deaths were recorded during that time period.

In addition, during this period none of the patients presented with clinical or echocardiography manifestations of tumor recurrence.

**Anatopathological study. Analysis of tumor ploidy and S-phase of cardiac myxoma embolization**

Tumor size varied; the largest mean tumor diameter was 46.9±22.73 mm (range 10 mm to 105 mm) and
the smallest mean diameter was 30.55±13.03 mm (range 10 mm to 70 mm). All the tumors consisted of soft polyplody masses with a smooth surface, and were papilla derived and irregular or mixed. On dissection, the majority had alternating areas of hemorrhagic material and whitish gelatinous areas; on a few occasions focal calcified resistance was encountered on resection.

The histological picture was uniform for all cases and consisted of an abundant myxoid matrix with myxoma cell characteristics. There was neither mitotic evidence nor significant change in size, shape, or intensity of nuclear stains. The number of tumor cells varied from histological field to field in various sample areas of the same tumor and in different tumors. There were also variations in the inflammatory mononuclear component, vascular density, and superficial endothelial cover of the tumor. In 22 of the 31 cases (71%), the implantation of the myxoma base in the endocardial surface was established histologically, and the edges of the surgical section were free of tumor.

Table 4 lists the principal anatomopathological characteristics that were observed.

The mean age of patients with myxomas located in the atrium was 56.38±15.84 years, while for those patients with myxomas located in the right or left ventricle it was 18.50±6.36 years (P=0.002).

There was a positive correlation between the largest tumor diameter and patient age (r=0.4734; P=0.007).

Table 5 shows the association between embolic presentation and the variables analyzed; an inverse correlation was seen between the smallest tumor diameters and the clinical form of presentation. There was no statistically significant relationship between the other variables studied (age, sex, largest tumor diameter, necrosis, hemorrhage, and location of the tumor).

**Flow cytometry studies**

In a subgroup of 12 patients from the original group of 31 patients, the contents of cell DNA was determined by flow cytometry.

The median age of this group was 46.50±16.83 years (range 14 to 70 years). Seven of 12 patients (53.84%) were male. One patient (8.33%) presented with familial and recurrent myxoma, while the remaining 91.67% (11 of 12 patients) had sporadic myxomas. Four of 12 (33.33%) had cerebral emboli. The most frequent location of the myxomas was the left atrium (10 out of 12 patients) (Figure 3); in 1 patient the tumor was located in the right ventricle and in the 1 patient in the right atrium. All underwent
surgery and there were no deaths or major complications reported. A comparative study was made between those patients who did not have emboli \((n=8)\) and those who did \((n=4)\). All patients were in sinus rhythm, and the size of the left atrium did not differ significantly \((42.50±20.2\) vs \(35.37±10.5\)). Table 6 summarizes the comparative analysis of the 2 groups.

The flow cytometry study showed an S-phase >7 or a DNA index >1.2 in 2 of 8 patients \((25\%)\) in the group without emboli, and in the total patients with emboli \((P=.061)\). Of this group of 12 patients, 8 had a normal diploid pattern and 4 showed a significant increase (>10% of all nuclei) at the 4C peak and were designated as aneuploids. The average S-phase was 4.75±2.76 (range 1.5 to 10.0). The cytometry performed on the only patient with recurrent tumor (who underwent prior surgery at another institution) revealed a diploid tumor with an S-phase significantly greater \(10\%)\) than that found in sporadically-occurring myxomas \((4.27±2.32\%); \(P=.039\))

### DISCUSSION

Primary heart tumors are rare. Various studies on autopsies performed on non-selected populations have shown that the incidence varies between 0.0017% and 0.19%. It has also been determined that three-quarters of cardiac tumors are benign, and that approximately half are myxomas; the other half are lipomas, rabdomiomas, fibroelastomas, and other more rare types. In our institution, the incidence was 0.21% of all patients who underwent various types of cardiac surgery.

Although they can occur at any stage of life, myxomas occur much more frequently between the ages of 30 years and 60 years. Hudson observed a myxoma in an individual of 95 years of age, the oldest person found to have this type of tumor. In our series, the average age of tumor occurrence was similar to that found in most studies. In addition, as other authors have observed, patients with recurrent myxomas and familial antecedents are younger; the only patient in our group with recurrent, familial disease was 24 years old, an age considerably younger than the average age of the rest of our cases. The patient had cutaneous lesions (lentiginosis), a 3-chamber (both atria and the right ventricle) myxoma as revealed by the first surgery, tumor recurrence and emboli, and of all the myxomas studied by cytometry, was the 1 who presented with the greatest percentage of S-phase cells.

The genetic studies performed on this particular subgroup of patients shows the existence of autosomal dominant patterns with variable phenotypes among family members. Karga et al showed the accumulation of ras p 21 protein in myxomas. In spite of the low incidence, it seems reasonable to include oncogene ras mutations in the pathology of myxomas.
The presence of microsatellite instability is an indicator of the increased incidence of genome mutations of neoplastic cells due to defective DNA repair. This is the first published description of microsatellite instability in sporadically-occurring myxomas as a possible pathological mechanism for their development. The majority of myxomas develop in the left atrium, followed in order of frequency by the right atrium and then the ventricles. This distribution was also evident in our series (of the 31 cases, 25 corresponded to the left atrium, 3 to the right atrium, and 1 to each of the ventricles; the other 2 cases were bi-atrial). As in previous studies, the most frequent location within the left atrium was the interatrial septum, more specifically the oval fossa area; a smaller number originated in the posterior wall, and in only 1 case tumor growth originated in the anterior wall.

Only 6.45% of the myxomas in our group were ventricular, 3.23% in each ventricle. The clinical manifestation of the patient with the left ventricular tumor was an acute myocardial infarct of the inferior surface. This type of unusual presentation was probably due to the coronary embolus of a thrombus originating from either the myxoma surface or a fragment of the tumor tissue. On the other hand, it is interesting to note that, in this case, the technical method used for tumor resection constituted a surgical variant, de-insertion of the anterior mitral valve to enable a better view of the interventricular septum where the myxoma was implanted, and the subsequent plastic repair. Only 1 patient presented with multiple myxomas in both atria. Previous studies have shown a low incidence of tumors compromising more than 1 chamber of the heart, which is a slightly higher incidence than that of myxomas with familial antecedents. One case (3.23%) that stands out is that of a myxoma originating in the tendinous chords of the mitral valve, which has rarely been encountered in previous studies.

A cardiac myxoma is a neoplasm of uncertain histogenesis that occurs only on the endocardial surface, usually located in the atria. Histological diagnosis is based on the discovery of typical myxoma cells in a matrix rich in mucopolysaccharides. The cells of a cardiac myxoma are histologically and histogenetically different from the fusiform cells of soft tissue myxomas. It has been postulated that the cells from which these tumors originate are the so-called reserve totipotential sub-endothelial cells capable of forming vascular structures that express endothelial and neural markers. The existence of an aneuploid cell population in a tumor is generally considered evidence that the lesion is neoplastic. The presence of aneuploidy, as well as the finding of chromosomal abnormalities in the case of myxomas, support a neoplastic origin for this type of tumor.

Conventional histological evaluation is not useful for differentiating between sporadically-occurring and recurrent myxomas, which may support the possible usefulness of a pattern ploidy analysis of cell DNA to predict the risk of recurrence and tumor emboli.

The DNA contents and proliferation characteristics of myxomas have been the object of few studies. Those studies concluded that the majority of sporadically-occurring myxomas are diploid, with a small percentage of tetraploid cells insofar as the total group of recurrent and familial myxomas include tetraploid populations; a single published study disagrees with these figures. In our study, the determination of the S-phase and the proliferation fractions by flow cytometry revealed that the majority of myxomas were diploid and had low proliferation rates. The only patient who had a history of a previous recurrence was the patient who presented with a larger S-phase within the group of diploid myxomas.

As has been described, the clinical forms of tumor presentation, particularly of myxomas, are diverse and depend basically on the size and location of the tumor. The usual manifestations are generalized symptoms such as those resulting from embolic phenomenon and obstruction of intracardiac blood flow.

What are considered generalized symptoms (fatigue, weight loss, and low grade fever), were those most frequently encountered in this study, but these symptoms did not form the basis for diagnosis. In our series, dyspnea was the second most frequently occurring symptom after generalized symptoms.

Embolic episodes reached a frequency of 41.3% in our study, a value which coincides with those of previous studies, in which the percentage of emboli ranged from 28% to 40%. Although difficult to interpret, an interesting finding was that, of the anatomopathological characteristics analyzed, the smallest myxoma diameter was independently associated with tumor emboli. In the subgroup where ploidy was analyzed, a tendency was observed toward a greater number of embolic episodes in myxomas with a higher percentage of cells in S-phase, inasmuch as a positive correlation between larger tumor diameter and age suggested a prolonged period between the origination of the tumor and symptomatic manifestations, as is the case with a slow-growing neoplasm.

Embolic events are unusual in right chamber myxomas. Nevertheless, there is evidence confirming not only the phenomenon of pulmonary embolism, but also the subsequent development of pulmonary hypertension, and even sudden death by massive pulmonary embolism from tumor tissue. In this study, of the 4 cases of myxomas of the right cavities, 1 initially presented as a pulmonary thromboembolism.
The size and location of myxomas determines the clinical manifestations of obstruction of the intracardiac blood flow, with simulation of different types of valvulopathy, particularly mitral narrowing. The size of the tumor and location in the body can determine the seriousness of the valve obstruction. The symptoms vary from dyspnea due to cardiac insufficiency or syncope to sudden death due to complete obstruction.

The treatment of choice for cardiac tumors, especially myxomas, is surgery.\textsuperscript{6,22}

The majority of published studies agree on the complete cure of patients who undergo surgery for myxoma of both atria, after more than 10 years of post-operative followup. Recurrence is considered rare, as it occurs in only 1% to 5% of patients according to different studies. Nevertheless, there are patient subgroups with a higher probability of recurrence. The greatest risk factors are familial antecedents, the coexistence of cutaneous lesions (lentiginosis) and the simultaneous appearance of myxoma.\textsuperscript{10} In these cases, the probability of the occurrence of a second tumor ranges from 12% to 22%, while in sporadically-occurring myxomas the incidence is 10 times lower. The only case of re-operation (performed at another center) recorded in our study was that of the young patient, who had all 3 of the previously-mentioned characteristics.

The possible causes of recurrence include incomplete resection of the myxoma, the proliferation of a second tumor focus, or the original tumor having an intracardiac base. The surgical technique used to avoid recurrences is the wide resection of tissue surrounding the base of the tumor; in the case of atrial myxomas, this creates a true interatrial communication (resection of the interatrial septum near the oval fossa) that is preferably closed with a pericardial patch or a simple suture. When tumor location does not permit wide resection, laser photocoagulation is habitually performed in an area of 1 cm around the tumor peduncle. Both procedures are aimed at eliminating residual tumor cell groups that are capable of generating new proliferation.

Although the number of patients included in this study does not permit definitive conclusions regarding noscomial death, this could be considered reduced, as it was 3.23% (1 of 31 patients). The only patient who died had a multiple myxoma requiring more complex surgery including the reconstruction of both atria with an autologous pericardial patch due to the extension of the tumor and its firm adhesion to the cardiac chambers.

With regard to more relevant hospital complications, we must mention transient supraventricular arrhythmias caused by atrial manipulation during tumor resection. Although the arrhythmias resolved spontaneously with anti-arrhythmia treatment, in 2 patients it was necessary to implant permanent pacemakers because they presented with a low frequency nodal rhythm that caused cerebral oligohemia symptomatology. During long-term followup (average 4.1 years), all patients remained asymptomatic, without echocardiography evidence of tumor recurrence. Given that several patients were followed for more than 6 years, these patients were considered definitively cured.

The positive correlation between larger tumor diameter and age suggests a prolonged period of time between the occurrence of the tumor and symptomatic manifestations, as is the case with a slow growing neoplasm.

In accordance with the results obtained in our series of cases, it would be useful to perform a study of cell ploidy, particularly in patients with familial antecedents, in order to predict recurrences or neoplastic emboli.

CONCLUSIONS

The incidence of myxomas in the present series, although it included only a small number of patients, was low. Nosocomial mortality-morbidity could be considered reduced. During followup (average 4 years), there was no tumor recurrence, so that surgery can be considered a cure for myxomas. The wide resection of the area surrounding the tumor base is important to avoid tumor recurrence. In accordance with the results obtained in this series, a study is needed of cell ploidy in patients with familial antecedents in order to predict recurrence. Of the anatomo-pathological characteristics analyzed, smaller tumor diameter was the only independent variable with predictive value associated with tumor emboli. It was also observed that there was a tendency toward a greater proportion of cells in S-phase in the embolizing tumors.

REFERENCES

5. Hedley DW, Friedlander ML, Taylor IW, Rugg CA, Musgrove


