
UNIVERSITY OF NORTH TEXAS
HEALTH SCIENCE CENTER AT FORT WORTH
1970

Saad, Jill Moore., An Evaluation of Muscle Biopsies in a Managed Care Organization. Master of Science (Biomedical Sciences), May 2001, 16 pp., 7 illustrations, Reference List, 17 titles.

Abstract

Objective. The goal of this study was to assess the use of the percutaneous muscle biopsy in diagnosing inflammatory muscle diseases and to examine the benefit of centralizing inflammatory myopathies under one department - rheumatology - within a large health maintenance organization.

Methods. A retrospective review of 363 muscle biopsies and histopathology reports, spanning 25 years, formed the basis of this study. The databases used in this study were the medical record, an institutional rheumatology registry, and histopathology reports. Cytoarchitectural abnormalities, necrosis and regeneration formed the basis of muscle disease classification. The histopathology findings were interpreted against the patient's clinical history, examination, and clinical tests to develop a final diagnosis.

Results. Rheumatologists in this location performed two-thirds of the biopsies percutaneously using an intervetebral rongeur and surgeons performed one-third open biopsies. Over time open biopsies were phased out due to preference for the percutaneous method. The average age of all muscle biopsy patients was 45 (3 months to 88 years old) and 55% were male. Polymyositis was the most frequently identified myositis (62%), followed by dermatomyositis (19%), and inclusion body myositis (7%).

Conclusion. The use of percutaneous muscle biopsies using an intervertebral rongeur is the method of choice because of convenience, quality of specimen, low morbidity, and limited discomfort. Centralizing inflammatory muscle diseases within one organization contributes to the efficiency and effectiveness of inflammatory muscle disease management.

Key words. Muscle biopsy, management, registry, classification, managed care

AN EVALUATION OF MUSCLE BIOPSIES IN A

MANAGED CARE ORGANIZATION

Jill Moore Saad, B.S., PA-C

APPROVED:

Major Professor

Minor Professor

Committee Member

Chair, Department of Biomedical Sciences

Dean, Graduate School of Biomedical Sciences

AN EVALUATION OF MUSCLE BIOPSIES IN A MANAGED CARE ORGANIZATION

THESIS

Presented to the Graduate Council of the

Graduate School of Biomedical Sciences

University of North Texas

Health Science Center at Fort Worth

In Partial Fulfillment of the Requirements

For the Degree of

MASTER OF SCIENCE

By

Jill Moore Saad, B.S., PA-C

Fort Worth, Texas

May 2001

TABLE OF CONTENTS

LIST OF ILLUSTRATIONS

Page

An Evaluation of Muscle Biopsies in a Managed Care Organization

Introduction

Inflammatory myopathies are uncommon, but treatable diseases of muscles that can be clearly recognized and differentiated from other conditions that do not have a cure. The etiology of most inflammatory myopathies is not known but is thought to be of various causes. Studies have linked viruses such as influenza and rubella, particular toxins including ETOH, cocaine, and botulism, the combined use of corticosteroids and neuromuscular blocking agents, and other drugs including D-penicillamine, streptokinase, and phenytoin to the development of myopathies (Fischer 1996, Pascuzzi 1998, Ytterberg 1996). There are 22 defined types of inflammatory muscle disease, of which polymyositis (PMS) and dermatomyositis (DMS) are the most prevalent (Dalakas 1988).

The presentations of people with inflammatory muscle disease are variable. Patients with inflammatory myopathies frequently present with proximal muscle weakness and have elevated muscle enzymes in the serum. Brief polyphasic motor units and increased muscle irritability are seen on electromyography (EMG) (Bertorini 1998). A muscle biopsy and subsequent histopathological evaluation of a piece of affected muscle is often the defining diagnostic tool and are indicated after suspicion points to a possible neuromuscular disorder following the review of a patient's clinical presentation, but can not be confirmed by less invasive tests such as laboratory tests, EMG and nerve conduction studies. Typically, muscle biopsies will show evidence of fiber necrosis, atrophy and inflammation. Criteria have been developed for the

diagnosis of PMS, DMS and inclusion body myositis (IBM) to facilitate recognition of these unique muscle diseases and to facilitate clinical trials. Although in many instances the diagnosis can be made and therapy carried out in its absence, muscle biopsy places clinical evaluation on firmer ground. In addition to histopathologic evaluation, muscle biopsy also permits sampling of tissue for certain biochemical components or physiological properties (Kagen 1995).

Although there are many factors to consider in the diagnosis of inflammatory muscle diseases, the use of muscle biopsy seems to be the most reliable. Surgical biopsies have been limited in some degree because they are invasive and occasionally uncomfortable. In the past, the use of an open biopsy to obtain a muscle sample for the necessary histopathological evaluation was the method of choice, even though they are time-consuming and require general anesthesia in children (Magistris *et al.* 1998). However, in recent years, percutaneous needle muscle biopsy has gained favor, due to its convenience and less morbid technique. For example, proponents of an open biopsy believe this method confers a possible advantage of tissue inspection prior to sampling {Reynolds, Thompson, et al. 1999 18 /id}. However, because inflammatory myopathies may not uniformly involve all parts of all muscles and because evidence of this involvement may require microscopic evaluation, both procedures may share the disadvantage of being "blind" (i.e., difficult for the operator to be certain that the tissue being sampled will contain diagnostic findings). Another possible advantage often cited regarding open muscle biopsies is that it allows for larger samples to be obtained. However, percutaneous needle biopsies may permit sampling of deeper sites, only small amounts of tissue are needed for histopathology, and repeated or multiple samples may be obtained if needed {Kagen 1995 39 /id}. Percutaneous biopsy methods are more rapid, simpler, and less costly alternatives to open surgical methods, and have subsequently become the method of choice for many occasions.

Myositis is an integral part of rheumatology practice because of the systemic nature of these connective tissue diseases. Rheumatologists manage inflammatory muscle diseases such as PMS, DMS, and IBM, more than any other specialty (Villalba & Adams 1996). As a consequence rheumatologists often perform the muscle biopsy procedure. However, based on conversations with various rheumatologists the method of evaluation and obtaining muscle biopsies varies widely. Some practices send all patients to a general surgeon for open muscle biopsies. Other rheumatologists will attempt to obtain their own sample. In discussion with neuropathologists who examine many muscle biopsy specimens, they report that using a Bergström needle often produces varied and sometimes poor results (personal communication A. D'Agostino, 1994). As a result of suboptimal return using the Bergström needle, we set out in the mid-1980s to improve muscle biopsy results in a rheumatology service. The first step was to use an intervertebral rongeur, instead of a Bergström needle, described by Anderson (Anderson 1997), and modified by Hooker (Hooker 1997). This resulted in an improvement in the quality and quantity of the muscle biopsy, which helped to accurately diagnose, and therefore improve the management of muscle diseases by using more specific therapeutic regimens aimed at a particular disease. The results of all rheumatology diagnoses, including muscle diseases, were entered into a rheumatology registry maintained by the organization.

This is a descriptive study of one organization's muscle biopsy experience as a means of assessing the administrative efficiency of muscle disease management. We believe this presents an opportunity to examine techniques and trends in the utility of muscle biopsies when efforts to evaluate these diseases are concentrated within a department of a large health maintenance organization.

Methods

Setting

The study setting was the Northwest Division of Kaiser Permanente (KPNW), a not-for-profit group-model health maintenance organization (HMO) that has been in existence in the greater Portland, Oregon area since 1945 (Freeborn & Pope 1994). In 2000, the health plan contracted to provide health care services for 420,000 members. The medical staff was composed of approximately 1,000 providers who belonged to or were employed by the Permanente Medical Group.

KPNW is a vertically integrated prepaid group practice HMO. The health plan owns one hospital and contracts with six other hospitals for care of its members. Twenty-one medical offices and their providers (physicians, physician assistants, nurse practitioners) and support staff offer the full range of ambulatory services. (Hooker 1993). All medical providers are expected to perform a wide range of tasks and to treat most frequently seen general medical conditions. A wide range of specialized departments provides subspecialty care and four rheumatology specialists provide rheumatology services for the organization (Hooker & Freeborn 1991). While all rheumatologists were skilled in undertaking muscle biopsies, one person (RSH) performed most of the biopsies.

Data

Four databases were used for this study:

- the KPNW medical record,
- an institutional rheumatology registry,
- records from the KPNW pathology department, and
- histopathology reports from the neuropathology department at Oregon Health Sciences University (OHSU).

The search began with the rheumatology registry to identify all patients with a diagnosis of muscle disease or muscle biopsy. Both patient medical records

and Pathology Department muscle biopsies obtained within KPNW between January 1975 and December 1999 were identified using various search techniques. The OHSU neuropathology laboratory is a regional referral base for muscle biopsy specimens in the greater Oregon and Southwest Washington State area. This lab averages approximately 250 muscle biopsy specimens for histopathology analysis per year (personal communication A. D'Agostino, 1994). All muscle biopsies from KPNW were sent to this laboratory for histopathology evaluation. This database was also searched. A review of all four databases found 411 muscle biopsies reports linked to KPNW members. When pathology reports were reviewed, 48 were excluded for analysis due to duplications and missing information, leaving a total of 363 records available for analysis. This cohort of 363 histopathology reports and matched medical records spanning 25 years forms the basis of this study.

Categories

Biopsy reports included information on fiber size (presence of atrophy and/or hypertrophy), fiber type distribution, cytoarchitectural abnormalities (e.g. ragged red fibers, excess lipid, excess glycogen, central nuclei), necrosis and regeneration, and the interstitium (cellular infiltration, vasculitis, fibrosis). In addition, the presence of specific enzymes (e.g. myoadenylate deaminase, cytochrome oxidase, acid phosphatase), immunocytochemical staining (for glycogen, dystrophin, and adhalin), and electron microscopic findings, were provided where appropriate. Using published information by Anderson (1997), the biopsy results were placed into diagnostic categories: normal, denervation, inflammatory, atrophies, dystrophic, congenital, metabolic, and unspecified. The reports were then reviewed regarding correlation between common histopathological findings and subsequent disease processes (Anderson 1997). For example, the presence of fiber atrophy *and* inflammation and/or the presence of necrosis and regeneration *plus* inflammation often represent an inflammatory myopathy (e.g. PMS, DMS). Perifasicular atrophy is commonly

seen with DMS, especially juvenile and cytoarchitectural abnormalities such as rimmed vacuoles and cytoplasmic bodies are common findings in IBM. These histopathological findings were then interpreted against the background of the patient's clinical history and examination and results of less invasive procedures, (serum creatine kinase, and electromyogram data) to develop a final diagnosis.

Results

Information was available on 363 cases spread over 25 years. Gender and age grouped distribution of cases is shown in Exhibit 1. The average age of all patients at time of biopsy was 45 (age 3 months to 89 years) and 45% were female.

Three-quarters of the time, the major reason or complaint that brought the patient to the referring physician, rheumatologist or surgeon was weakness (46%), or pain or swelling of a limb (29%). Other symptoms such as stiffness, rash, movement disorder, birth defects or constitutional symptoms constituted the other 25 percent of symptoms (Exhibit 2).

Three types of providers performed all of the muscle biopsies: rheumatologists (64%), pediatric neurologists (19%), and surgeons (17%). Over the 25-year span, open biopsies were performed with decreasing frequency as the use of percutaneous biopsies increased (see Exhibit 3). The site of biopsy was the vastus lateralis 89 percent of the time. The upper arm (bicep, tricep, and deltoid) was sampled 5 percent of the time. Other biopsy sites were used in diminishing frequency (Exhibit 4).

The percutaneous muscle biopsies provided adequate sampling in all but four cases (1%). Histopathology reports identified muscle disease in 245 (67%) samples. Normal muscle was found in 108 (30%) samples and 14 (4%) showed abnormalities present but were not diagnostic (Exhibit 5).

The final diagnosis was obtained through comparison of the medical record and the results of the muscle biopsy. Occasionally the autopsy or death certificate report was obtained for confirmation. Inflammatory myopathies were the largest group of diseases (32%), followed by unknown or inconclusive pathology (21%), neuropathic diseases (17%), and no myopathy (14%). Congenital syndromes, metabolic myopathies and other myopathies made up the remaining 16 percent of cases (see exhibit 6).

A subanalysis of the 117 inflammatory myopathies, based on when inflammation was present or the diagnosis unequivocal, is displayed in Exhibit 7. This analysis reveals that PMS constitutes the greatest number (65 %) of myositis cases, followed by DMS (19%), IBM (7%), sarcoidosis (2%), and eosinophilia myalgia syndrome (2%). In a few instances, the diagnoses of PMS and DMS were made by clinical impression recorded in the medical record since the neuropathologist was unable to assist in sorting out the difference histopathologically. Descriptions characteristic of skin lesions in the medical records helped to confirm the diagnosis of DMS.

Discussion

Surprisingly, patients presenting for biopsy after the age of 64 were a small percentage of the whole (exhibit 1). This is in contrast to epidemiological studies which show the incidence and prevalence of muscle diseases increases with age whether it is inflammatory muscle disease or a degenerative form of muscle disease (Oddis *et al.* 1990;Silman & Hochberg 1993). We are not sure why our findings differ from epidemiological studies of myositis other than those studies tend to use clinical criteria for the diagnosis and rely on hospitalized cases. We suggest that most cases of inflammatory muscle diseases seen within KPNW are diagnosed and managed in the outpatient setting. As such they would not be included in hospitalized cases historically used for epidemiology studies.

The data collected regarding weakness and pain as the most common presenting complaints coincide to the most frequent clinical symptoms of myopathies, including polymyositis, and dermatomyositis. These clinical findings provide suspicion for involvement of muscle disease and if additional support is provided through serum enzyme tests, or EMG, a muscle biopsy should be the next step in obtaining an accurate diagnosis.

Patients with idiopathic inflammatory muscle disease may be managed by a range of specialists, including internists, family practitioners, pediatricians, neurologists, and rheumatologists. However, experience with this rare group of rheumatological disorders was seen as the domain of rheumatologists within this organization, as they performed the majority of the muscle biopsies.

The percutaneous method of muscle biopsy offers a number of advantages over the open muscle biopsy. It is easy to master, less morbid to the patient, no sutures are necessary, local anesthetic is used, it is less unnerving for parents when children are involved, it can be conveniently done in a typical examining room with little set-up, and it is more economical. In addition, our study showed that this method provided adequate tissue sampling in all but 4 cases, proving that it is a viable method for helping to diagnose muscle diseases (exhibit 5). It is believed that these advantages explain the increased use of this method over the 25 years, and help support the argument that the percutaneous muscle biopsy will become the method of choice among rheumatologists (O'Rourke *et al.* 1994).

The extent and distribution of any muscular weakness should determine the most appropriate site for biopsy (Anderson 1997). Since muscle weakness involving the lower extremities was the clinical presentation most often sited in our study (exhibit 2), and it was known that inflammatory muscle diseases affect proximal muscles over distal, the vastus lateralis was most often selected as the biopsy site. In addition, normal parameters are well established in the vastus lateralis, thus making samples from this site more informative and less misleading than biopsies taken from unusual sites. However, out of the 108 samples indentified as histopathologically normal, 56 represented patients that

were eventually diagnosed with a disease process, 32 of which had a type of muscle disease. In these cases, the disease process may have affected the muscles in a patchy distribution resulting in the collection of normal muscle that was adjacent to areas that had signs of a disease process. In addition, in a small percentage of cases, the disease may not have progressed far enough to show muscle involvement, or perhaps the site of biopsy may have been inadequate. Another more involved site, possibly identified through EMG testing or other imaging studies, should have been chosen. This information should raise questions regarding the method for choosing the site of the biopsy, and not whether the percutaneous muscle biopsy is a viable diagnostic tool. If improvements can be made in determining the biopsy site, the muscle biopsy can continue to provide an adequate sample for analysis. It is also important to note that the specimens labeled as normal, with no pathological diagnosis, are just as important in obtaining a diagnosis. In these cases, muscle diseases could be excluded and thus other causes could be investigated.

The data pertaining to the final diagnosis deserves some attention. As stated in the results, inflammatory myopathies were the largest group of diseases (32%), followed by the unknown category (21%). At first glance, this appeared to show that the muscle biopsy was not able to identify a final diagnosis in a large percentage of cases, therefore disproving the statement that muscle biopsies are able to place clinical evaluation on firmer ground. However, when reviewed in detail, the unknown category was made up of three separate groups. As stated above, there were 4 cases that actually did pertain to inadequate tissue sampling, resulting in the inability to make a final diagnosis. This is only 1% of the total biopsies undertaken. The remaining cases involved 36 that showed abnormalities either on laboratory testing, clinical exam, EMG, or on the histopathology report, but not enough information could be provided to accurately make a final diagnosis, 6 that pertained to missing biopsy reports, and 30 (8%) that were eventually diagnosed with no pathologic disease process at all.

Our results pertaining to the types of inflammatory myopathies, identifying polymyositis as the diagnosis in the majority of cases, parallels previous epidemiology research (Bohan 1975).

Conclusion

Our retrospective analysis of muscle biopsies was undertaken to evaluate the utility of performing percutaneous muscle biopsies, as well as to demonstrate the benefits of incorporating all muscle biopsies within a centralized department of a large health care organization. The majority of our patients were evaluated for the presence of muscle disease. Like other studies, we observed no complications from muscle biopsies (Edwards *et al.* 1980;Edwards 1983), and most patients were able to resume normal activity the following day. In most instances the muscle biopsy appeared to be definitive for either ruling in or ruling out a diagnosis.

The diagnostic yield of the intervertebral rongeur method of obtaining skeletal muscle specimens for analysis seems to offer a potential benefit to this organization. It is convenient, easy, reliable and economical. These advantages outweighed the use of open biopsies undertaken by surgeons (Reynolds *et al.* 1999). The threshold of comfort in undertaking a muscle biopsy is probably higher because of these attributes. Consequently, the benefit to the patient is probably enhanced as well. However, there were questions raised from this study pertaining to the methods used to chose the site of the biopsy. The data supports the need for better imaging studies to determine which muscle is more affected by the disease process to help ensure that the muscle tissue obtained through percutaneous biopsies contains the appropriate histopathology needed to make the appropriate diagnosis.

I acknowledge that there are a number of inherent limitations to a retrospective analysis of the sort undertaken here. I am not sure if undertaking a study for the purpose of definitively recommending one surgical procedure

over another is necessary. Enrolling patients with myopathic symptoms to be randomized for open or percutaneous procedures may be difficult in light of the mounting evidence of the benefits of the percutaneous technique and the fact it has become the method of choice for muscle researchers (O'Rourke, Blaivas, & Ike 1994;Magistris, Kohler, Pizzolato, Morris, Baroffio, Bernheim, & Bader 1998;Lilley *et al.* 1994;Edwards, Young, & Wiles 1980;Anderson 1997).

With the trend towards using the percutaneous method of muscle specimens, the biopsy-proven presence of muscle disease epidemiology may need to be revised. An interested rheumatology center; dedicated collaboration with a neuropathologist; and a large, defined population base may be the needed ingredients to undertake such a study.

EXHIBITS

Exhibit 1
Muscle biopsies by age groups and gender

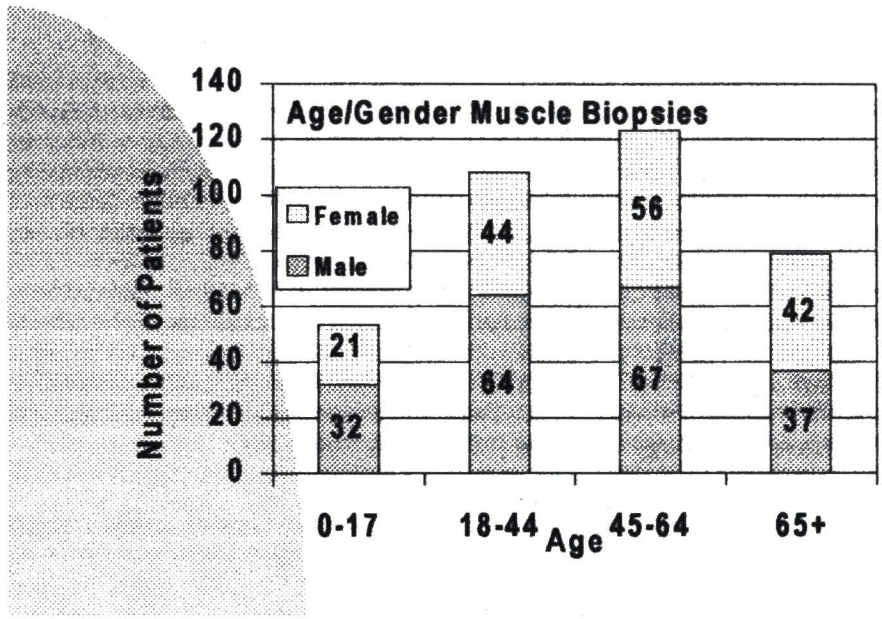


Exhibit 2

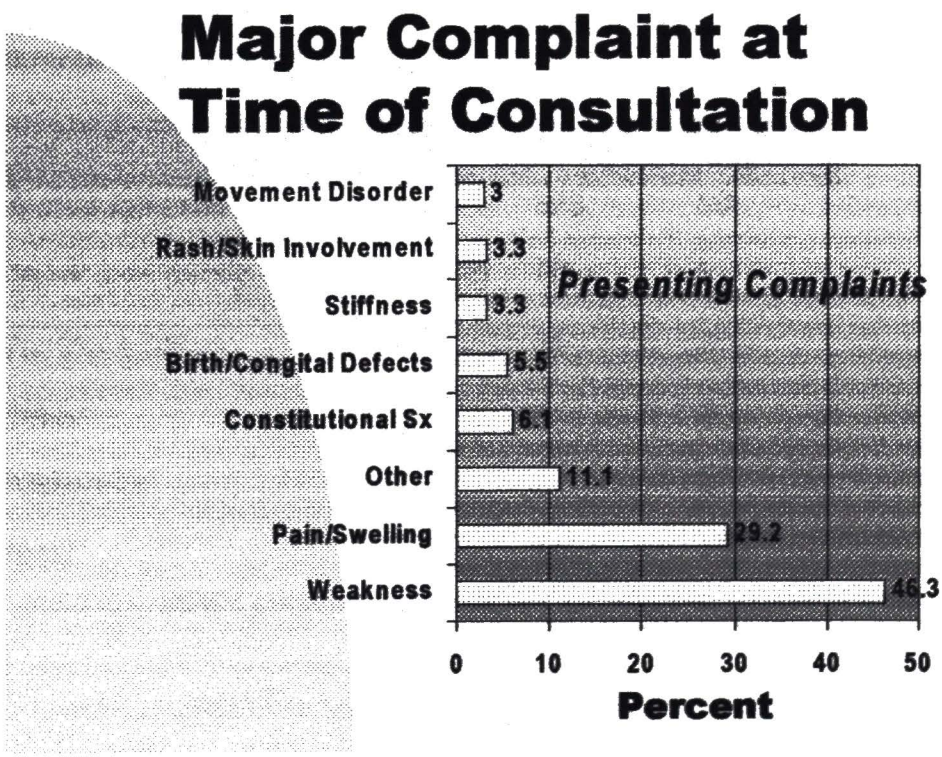


Exhibit 3

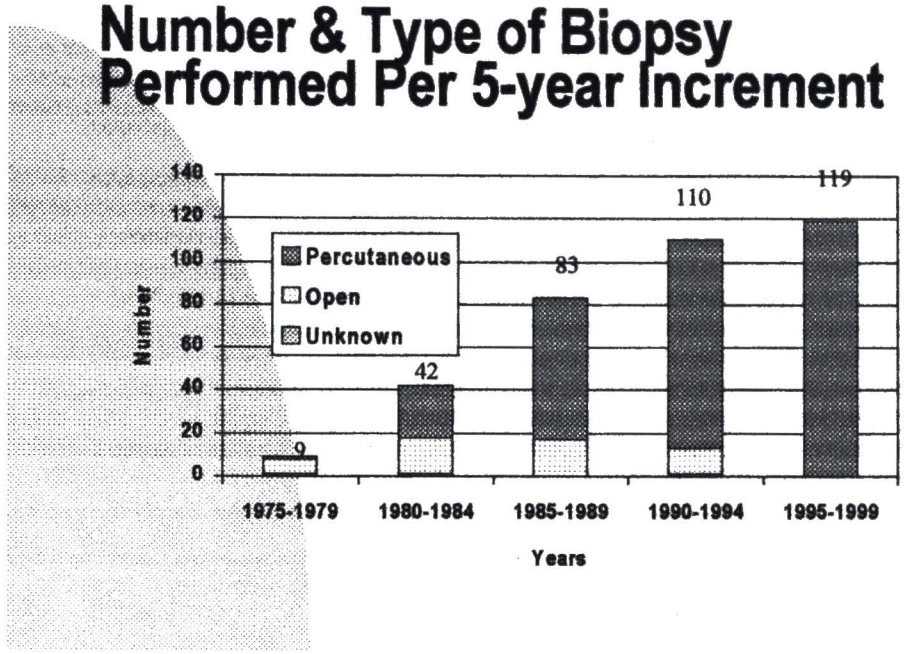


Exhibit 4

Muscle Biopsy Sites (n=363)

Site	*Number*	*Percent*
Vastus lateralis	323	89
Upper arm (bicep, tricep, deltoid)	19	6
Gastrocnemius	11	3
Other	9	2
Pectoralis	1	0
Total	363	100

Exhibit 5

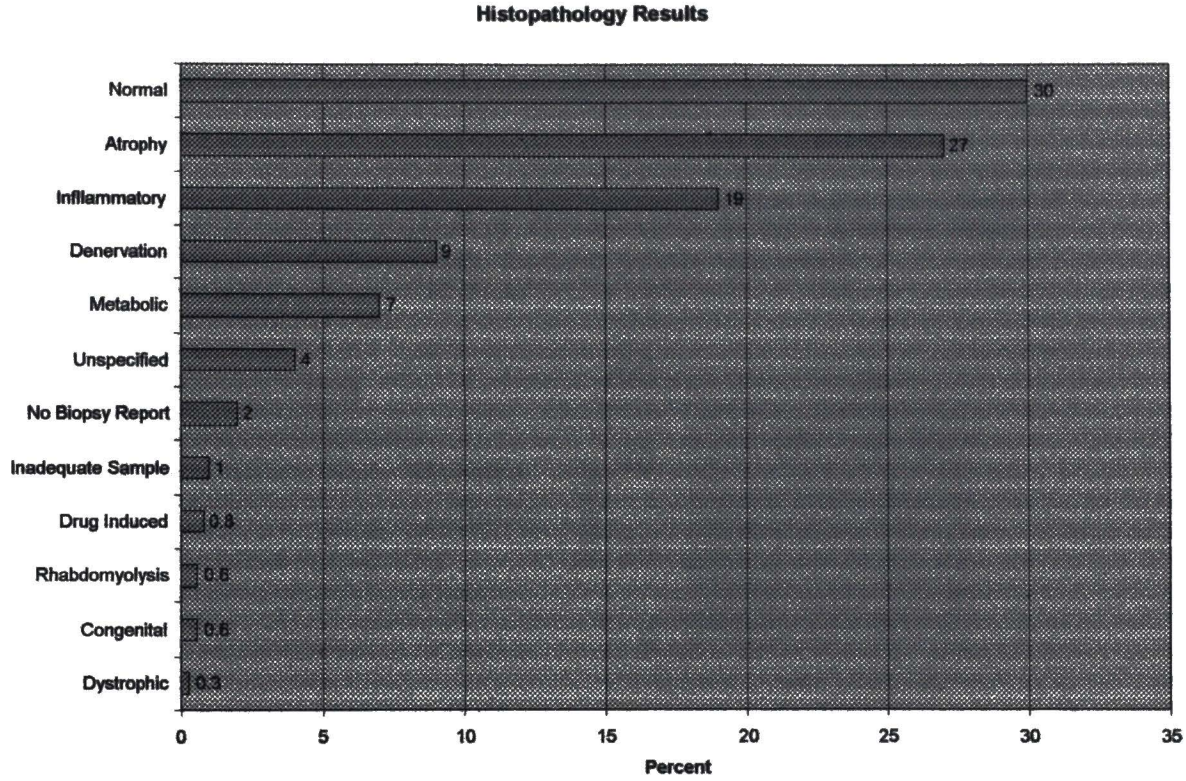


Exhibit 6

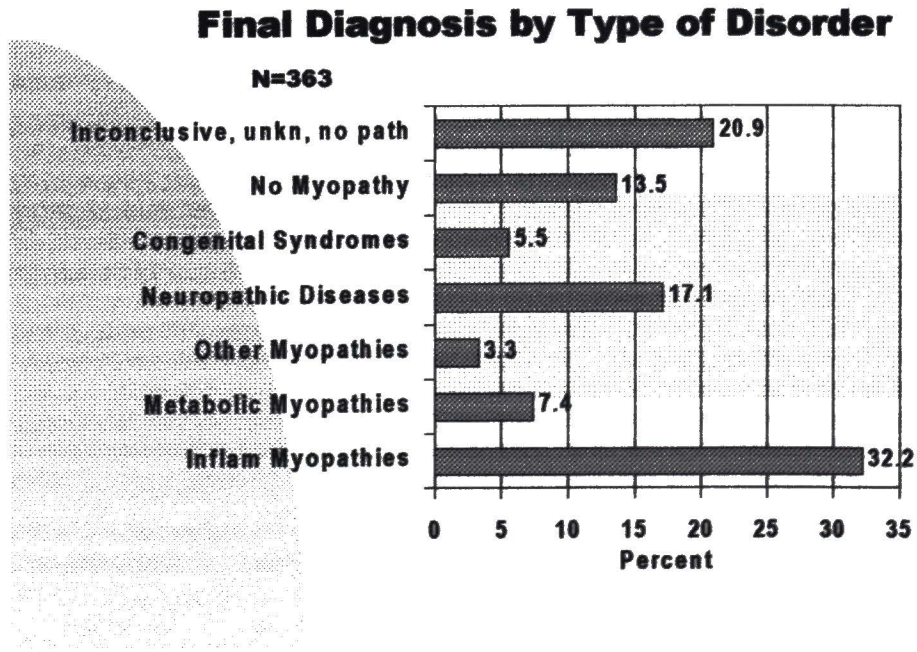
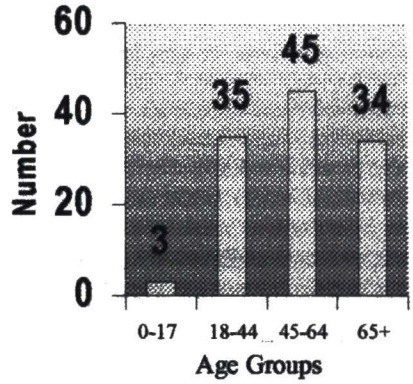


Exhibit 7

Inflammatory Muscle Diseases by Age Groups (1975-2000, N=117)

- Polymyositis
- Dermatomyositis
- Inclusion Body Myositis
- Inflammatory Myopathy
- Sarcoid Myopathy
- Eosinophilia Myalgia Syndrome



Reference List

1. Anderson,J.R. (1997) Recommendations for the biopsy procedure and assessment of skeletal muscle biopsies. *Virchows Arch* **431**, 227-233.

2. Bertorini,T.E. (1998) Inflammatory Myopathies (Polymyositis, Dermatomyositis, Inclusion Body Myositis). *Compre Ther* **24(10)**, 494-502.

3. Dalakas M.C. (1988) *Polymyositis and Dermatomyositis*. Buterworths, Boston.

4. Edwards,R., Young,A., & Wiles,M. (1980) Needle biopsy of skeletal muscle in the diagnosis of myopathy and the clincal study of muscle function and repair. *N Engl J Med* **302**, 261-271.

5. Edwards,R.H.T. (1983) Needle biopsy of skeletal muscle: a review of 10 years experience. *Muscle Nerve* **6**, 676-683.

6. Freeborn D.K. & Pope C.R. (1994) *Promise and Performance in Managed Care: The Prepaid Group Practice Model.* Johns Hopkins University Press.

7. Hooker R.S. (1993) The roles of physician assistants and nurse practitioners in a managed care organization. In: D.K.Clawson and M.Osterweis (Eds) *The Roles of Physician Assistants and Nurse Practitioners in Primary Care.* The Association of Academic Health Centers, Washington, DC.

8. Hooker R.S. (1997) Percutaneous muscle biopsy. In: J.Labus (Ed) *The Physician Assistant Surgical Handbook.* WB Saunders, Philadelphia.

9. Hooker,R.S. & Freeborn,D.K. (1991) Use of physician assistants in a managed health care system. *Public Health Rep.* **106**, 90-94.

10. Kagen,L.J. (1995) Myositis and myopathies. *Current Opinion in Rheumatology* **7**, 459-461.

11. Lilley,H., Dennett,X., & Byrne,E. (1994) Biopsy proven polymyositis in Victoria 1982-1987: analysis of prognostic factors. *J Royal Soc Med* **87**, 323-326.

12. Magistris,M.R., Kohler,A., Pizzolato,G., Morris,M.A., Baroffio,A., Bernheim,L., & Bader,C.R. (1998) Needle muscle biopsy in the investigation of neuromuscular disorders. *Muscle & Nerve* **21**, 194-2000.

13. O'Rourke,K.S., Blaivas,M., & Ike,R.W. (1994) Utility of needle muscle biopsy in a university rheumatolgy practice. *J.Rheumatol.* **21**, 413-424.

14. Oddis,C.V., Conte,C.G., Steen,V.D., & Medsger,T.A.Jr. (1990) Incidence of polymyositis-dermatomyositis: a 20-year study of hospital diagnosed cases in Allegheny County, PA, 1963-1982. *J.Rheumatol.* **17**, 1329-1334.

15. Reynolds,E.M., Thompson,I.M., Nigro,M.A., Kupsky,W.J., & Klein,M.D. (1999) Muscle and nerve biopsy in the evaluation of neuromuscular disorders: the surgeon's perspective. *J Pediatr Surg* **34**, 588-590.

16. Silman A.J. & Hochberg M.C. (1993) *Epidemiology of the Rheumatic Diseases*. Oxford University Press, Oxford.

17. Villalba,L. & Adams,E.M. (1996) Update on therapy for refractory dermtomyositis and polymyositis. *Current Opinion in Rheumatology* **8**, 544-551.