IMMUNZ

SNAPSHOTS

APRIL 2014

CONTENTS

OBITUARY

It is with much sadness that we record the passing of Dr. Margaret di Menna, an International Authority on Medically Important Yeasts. Margaret passed away in Hamilton on Monday 24th March aged 90 years. At the time of her passing she was planning her next review of Pathological Yeasts. She was active right up to this time.

WHAT'S NEW?

- We have witnessed many advances in the past 100 years. In 1914 the major diseases of concern were Consumption, Small Pox, Diphtheria, Infantile Paralysis, Typhoid, plus the enthusiasm for Radium treatment of cancer.
- More importantly perhaps is the recognition of Pathology Services: From a board meeting at Auckland Hospital in 1913 it was reported that *"The Pathological work was carried out with diligence and self-sacrifice… but it must be kept in mind the pathology plays an important role in diagnosis and treatment. The hospital cannot be considered as well equipped unless this department is developed."* (NZ Herald 13 Feb 1913)
- illumigene® BORDETELLA PERTUSSIS NOW CE MARKED AND FDA APPROVED

  Bordetella Pertussis is now available on the Illumigene platform. A low cost molecular method with results in one hour. There are now 5 assays available on the Illumigene System.
- In recent radio and TV news the low numbers of Group A strep that is being detected is target children is some concern. Reasons for the low detection rate are uncertain, and is an area that needs to be fully investigated to ensure detection and treatment programs can be effective in reducing this unwanted disease.

Philip Wyatt

RCPA MEETING: MELBOURNE 2014

Some highlights from the 2014 RCPA Meeting that was held in February at the Melbourne Convention Centre.

- The next couple of years may prove to be evolutionary for ANA testing.
- Anti-DFS70 is the hot topic of the moment.
- Questions raised on the importance of Ro52/TRIM markers.

- **Ro-52:** The most common specificity found in a cohort of 100 Canadian myositis patients, but is also associated with a variety of other autoimmune disease states. So what is the importance of Ro52? It is an important marker that indicates an AI disease, but to be of diagnostic use it should be supported by another positive specificity. (*Refer to publication below that summarizes the frequency of Auto-antibodies in Myositis in Canadian patients*).

- **DFS-70:** A topic that generated lively debate and mixed reactions. Key questions included:
  - How to use this assay, should it be reflex tested on positive samples?
  - Should it be run as an initial screen on all ANA requests?
  - How should the result be reported?
  - Should this result be reported in place of Fine Speckled?

  Looking Ahead: The RCPA QAP intends to implement a DFS pattern comment into the ANA program.

INOVA DIAGNOSTICS:

DFS-70

To augment the DFS-70 assay currently available on the BIO-Flash Analyzer, INOVA Diagnostics are releasing an IFA assay - **HEp-2 Select**: A new kit containing DAPI for the determination of ANA's (and exclusion of DFS-70) with manual microscopy or with the NOVA-View Automated Fluorescent Microscope.

DFS (Dense Fine Speckled) pattern is one of the most commonly seen IIF patterns in routine diagnostic laboratories performing ANA testing on HEp-2 substrates. Since first described, anti-DFS70 antibodies have been found in the sera of patients with a variety of chronic inflammatory conditions, and in healthy individuals. It has also been reported that none of the anti-DFS70 positive healthy individuals developed SARD over an average 4-year clinical follow-up.

The HEp-2 Select Kit with DAPI assay contains a special specimen diluent, which adsorbs DFS70 antibodies from patient samples and prevents their detection during ANA screening. This approach decreases the prevalence of ANA positive results in healthy individuals, thereby preventing unnecessary reflex testing or follow-up visits, as well as reducing associated costs and patient anxiety.

BIO-Flash Update

BIO-Flash reagent - **QUANTA-Flash tTg IgA** is now available in **100 test cartridges**. The on-board stability of this reagent has also been extended to 42 days. This new configuration also comes *WITH* improved pricing structure.

PUBLICATIONS: CLINICAL STUDIES

Heterogeneity of autoantibodies in 100 patients with autoimmune myositis: insights into clinical features and outcomes

M Koenig, MJ Fritzler, IN Targoff, Y Troyanov, JLSenécal

Arthritis Research & Therapy 2007:9 (R78)

Abstract:

The objective of this study was to determine the prevalence, mutual associations, clinical manifestations, and diagnoses associated with serum autoantibodies, as detected using recently available immunoassays, in patients with autoimmune myositis (AIM).

Sera and clinical data were collected from 100 patients with AIM followed longitudinally. Sera were screened cross-sectionally for 21 autoantibodies by multiplex addressable laser bead immunoassay, line blot immunoassay, immunoprecipitation of *in vitro* translated recombinant protein, protein A assisted immunoprecipitation, and enzyme-linked immunosorbent assay. Diagnoses were determined using the Bohan and Peter classification as well as recently proposed classifications. Relationships between autoantibodies and clinical manifestations were analyzed by multiple logistic regression. One or more autoantibodies encompassing 19 specificities were present in 80% of the patients. The most common autoantibodies were anti-Ro52 (30% of patients), anti- Ku (23%), anti-synthetases (22%), anti-U1RNP (15%), and antifibrillarin (14%).

In the presence of autoantibodies to Ku, synthetases, U1RNP, fibrillarin, PM-Scl, or scleroderma autoantigens, at least one more autoantibody was detected in the majority of sera and at least two more autoantibodies in over one-third of sera. The largest number of concurrent autoantibodies was six autoantibodies. Overall, 44 distinct combinations of autoantibodies were counted. Most autoantibodies were unrestricted to any AIM diagnostic

category. Distinct clinical syndromes and therapeutic responses were associated with anti-Jo-1, anti-fibrillarin, anti-U1RNP, anti-Ro, anti-Ro52, and autoantibodies to scleroderma autoantigens.

We conclude that a significant proportion of AIM patients are characterized by complex associations of autoantibodies. Certain myositis autoantibodies are markers for distinct overlap syndromes and predict therapeutic outcomes. The ultimate clinical features, disease course, and response to therapy in a given AIM patient may be linked to the particular set of associated autoantibodies. These results provide a rationale for patient profiling and its application to therapeutics, because it cannot be assumed that the B-cell response is the same even in the majority of patients in a given diagnostic category.

- ***Anti-DFS70 Antibodies in 597 Healthy Hospital Workers***

A Watanabe, M Kodera, K Sugiura, T Usuda, Eng M.Tan, Y Takasaki, Y Tomita, Y Muro

Arthritis & Rheumatism Vol. 50, No. 3, March 2004, Pg 892–900

Abstract

Autoantibodies against DFS70 (dense fine speckles 70) antigen (also known as lens epithelium–derived growth factor) have been recently identified among the antinuclear antibodies (ANAs) in patients with atopic disorders. We undertook this study to examine the frequency of anti-DFS70 antibodies in a large number of healthy people.

Sera of 597 healthy individuals working in a hospital (142 men, 455 women) were analyzed for ANAs and for anti-DFS70 antibodies by indirect immunofluorescence (IIF) with HEp-2 cells as a substrate and by immunoblotting using DFS70 recombinant protein and whole HeLa cell extract.

ANAs were present in 20% of all individuals by IIF. Nine percent of subjects were ANA positive at a serum dilution of 1:40, 4.0% at 1:80, 5.5% at 1:160, 1.0% at 1:320, and 0.3% at 1:640. There were 64 anti-DFS70 antibody–positive individuals. Surprisingly, this was 11% of the whole population and 54% of the ANA-positive population. The percentage of female anti-DFS70 antibody–positive subjects (86%; 55 of 64 subjects) was higher than the percentage of female anti-DFS70 antibody–negative subjects (75%; 398 of 533 subjects) ($P < 0.05$). The prevalence of anti-DFS70 antibody–positive sera decreased with increasing age ($P = 0.0017$).

Considering that anti-DFS70 antibody positivity is rare in patients with systemic autoimmune diseases, introducing the anti-DFS70 antibody examination as a screening test for ANA-positive persons could be used to rule out systemic autoimmune diseases, resulting in considerable cost-saving potential. In addition, this test defines a subpopulation of healthy people in whom long-term follow-up might reveal health-related implications of this finding, since anti-DFS70 antibodies have been shown to be associated with some illnesses.

- ***Autoimmunity to the Nuclear Autoantigen DFS70 (LEDGF): What Exactly Are the Autoantibodies Trying To Tell Us?***

Vidya Ganapathy and Carlos A. Casiano

ARTHRITIS & RHEUMATISM Vol. 50, No. 3, March 2004, Pg 684–688

Abstract:

The presence of circulating antinuclear autoantibodies (ANAs) is a key immunologic feature of systemic autoimmune diseases such as systemic lupus erythematosus and scleroderma. ANAs have also been detected, although generally with lower frequency and specificity, in many other human diseases, including cancer, atopic disorders, chronic fatigue syndrome (CFS), and interstitial cystitis (IC). ANAs target protein and nucleic acid antigens predominantly localized in the cell nucleus, facilitating their use as probes in the identification and characterization of a broad spectrum of nuclear proteins involved in key cellular processes, including RNA processing, mitosis, and apoptosis.

In the systemic autoimmune diseases, ANAs show a remarkable specificity in their target antigens, contributing to their use as markers in the differential diagnosis of these diseases and associated conditions. Understanding the mechanisms underlying the generation of ANAs in systemic autoimmune diseases and other chronic inflammatory conditions remains a challenge in the quest for advancing our knowledge of the aetiology and pathogenicity of these diseases.

A relatively common serum ANA pattern observed in many clinical and research laboratories around the world is that characterized by staining of dense fine speckles in the nucleus with strong staining of mitotic chromosomes. Human sera displaying this pattern by indirect immunofluorescence (IIF) microscopy normally react by Immuno-blotting (IB) with a band of ~70kd. The nuclear auto-antigen recognized by these sera was identified by Ochs et al and was designated dense fine speckles 70 antigen (DFS70). Analysis of protein sequence databases revealed that DFS70 is identical to a protein called transcription co-activator p75 and lens epithelium–derived growth factor p75

(LEDGF/p75). DFS70, most commonly known as LEDGF, is emerging as a common nuclear auto-antigen with important biologic functions, but without a clear-cut disease association.

In their original article, Ochs et al reported that DFS70 is the target of autoantibody responses in a variety of inflammatory conditions, including atopic dermatitis (AD), asthma, and IC. These investigators reported frequencies of anti-DFS70 autoantibodies in 64 Japanese patients with AD and 50 US patients with asthma of 29.7% and 16%, respectively, as determined by IIF microscopy and IB against the recombinant protein. They also detected autoantibodies to DFS70, although at relatively low frequencies, in US patients with IC (8.7%) and Sjögren's syndrome (SS) (6.9%).

- ***Importance of the dense fine speckled pattern on HEp-2 cells and anti-DFS70 antibodies for the diagnosis of systemic autoimmune diseases***

Michael Mahler, John G. Hanly, Marvin J. Fritzler

Autoimmunity Reviews: Volume 11, Issue 9, July 2012, Pages 642–645

Abstract:
The presence of anti-nuclear antibodies (ANA) is a hallmark of systemic autoimmune rheumatic diseases (SARD). The indirect immunofluorescence (IIF) assay on HEp-2 cells is a commonly used test for the detection of ANA and was recently recommended as the screening test of choice by a task force of the American College of Rheumatology. However, up to 20% of serum samples from healthy individuals (HI) have been reported to have a positive ANA test, the majority of which are directed to the dense fine speckles 70 (DFS70) antigen.

Even more important, the DFS IIF pattern has been reported in 33% of ANA positive HI, but not in ANA positive SARD sera. Since the intended use of the ANA HEp-2 test is to aid in the diagnosis of SARD, the reporting of anti-DFS70 antibodies and their associated pattern (DFS) as a positive test, significantly reduces the specificity and the positive likelihood of the ANA test. This has significant implications for diagnostic algorithms involving the detection of ANA.

We summarize the current knowledge of anti-DFS70 antibodies and their impact on ANA testing. We also suggest a test algorithm which considers the DFS pattern and the presence of anti-DFS70 antibodies. In addition, we describe a novel method based on immuno-adsorption of anti-DFS70 antibodies, which increases the specificity of the ANA HEp-2 test for SARD and which has the potential to overcome a significant limitation of the ANA HEp-2 assay.

- ***Anti-DFS70/LEDGF Antibodies Are More Prevalent in Healthy Individuals Compared to Patients with Systemic Autoimmune Rheumatic Diseases***

Michael Mahler, Todd Parker, Carol L. Peebles, Luis E. Andrade, Andreas Swart, Yvette Carbone, David J. Ferguson, Danilo Villalta, Nicola Bizzaro, John G. Hanly, Marvin J. Fritzler

Journal of Rheumatology; November *2012 39(11):2104-2110*

Abstract:
Antinuclear antibodies (ANA) are a serological hallmark of systemic autoimmune rheumatic diseases (SARD) such as systemic lupus erythematosus (SLE). While a number of ANA patterns detected by indirect immunofluorescence (IIF) have diagnostic significance, autoantibodies producing the dense fine speckled (DFS) pattern have been reported to be more prevalent in healthy individuals than in SARD.

Sequential samples submitted for ANA testing were screened for anti-DFS antibodies by IIF (n = 3263). Samples with the DFS pattern were tested for anti-DFS70/lens epithelium–derived growth factor (LEDGF) antibodies by ELISA and by a novel chemiluminescence assay (CIA, Quanta Flash DFS70). Sera from patients with various diseases and healthy individuals were tested for anti-DFS70/LEDGF antibodies by CIA. A cohort of 251 patients with SLE was used to analyze serological and clinical associations of anti-DFS70 antibodies.

The frequency of anti-DFS antibodies by IIF was 1.62%. The prevalence of anti-DFS70/LEDGF antibodies as detected by CIA in the different cohorts was 8.9% in healthy individuals, 2.8% in SLE, 2.6% in rheumatoid arthritis, 4.0% in asthma, 5.0% in interstitial cystitis, 1.7% in Graves' disease, and 6.0% in Hashimoto's thyroiditis. Of note, the prevalence of anti-DFS70/LEDGF antibodies was significantly higher in healthy individuals compared to patients with SARD (p = 0.00085). In SLE results, anti-DFS70/LEDGF antibodies were not significantly associated with clinical features or other autoantibodies typically found in SLE. Only 1/7 SLE sera showed anti-DFS70/LEDGF, but no other autoantibody reactivity.

"Monospecific" anti-DFS70/LEDGF antibodies may represent a biomarker for differentiating SARD from non-SARD individuals, but there is a need for a reliable assay to ensure reactivity to DFS70

- ***The Antinuclear Antibody Test: Last or Lasting Gasp?***

Marvin J. Fritzler

ARTHRITIS & RHEUMATISM Vol. 63, No. 1, January 2011, pp 19–22

Abstract:

Autoantibodies have been regarded as a serologic hallmark of systemic autoimmune rheumatic diseases (ARDs) for more than half a century. Two years following the landmark discovery of the lupus erythematosus (LE) cell and the LE cell phenomenon by Hargraves and colleagues at the Mayo Clinic in 1948, Coons and Kaplan described indirect immunofluorescence (IIF) as a useful approach to the detection of serum autoantibodies directed against intracellular antigens. This led to IIF applications designed to detect antinuclear antibodies (ANAs) as a key approach to the laboratory diagnosis of systemic lupus erythematosus (SLE) and eventually other systemic ARDs. After more than 50 years of widespread use, the ANA test and other IIF applications have enjoyed a favored position in diagnostic medicine, although they have been plagued by limitations and are now being challenged by newer diagnostic platforms and technologies. The advent and acceptance of the newer technologies has also been predicated on the appreciation that the ANA IIF test is not well suited to high-volume and high-throughput laboratories where the containment of medical health care costs has been a determining factor. Nevertheless, it has been recognized that many of these high-throughput technologies have limitations, most notably false-negative results, in the detection of ANAs.

To address these issues and concerns, the American College of Rheumatology (ACR) convened a committee to undertake an analysis and provide recommendations with respect to ANA testing as an approach to diagnosing systemic ARDs. In May 2010, a summary of the committee's findings and recommendations was published; among these was the recommendation that the ANA IIF test using cell substrates should be considered the "gold standard" assay to screen for autoantibodies in sera from patients with systemic ARDs.

For several decades, it has been well known that the ANA IIF test is compromised by the lack of universal standardization and by false-positive tests that lead (in some clinicians' opinions) to "unnecessary" referrals or even to inappropriate diagnoses. An interesting case in point are autoantibodies that produce a staining pattern referred to as nuclear dense fine speckled, and in this issue of *Arthritis & Rheumatism*, Mariz and colleagues elaborate on the nuclear dense fine speckled pattern and provide timely and provocative observations about its usefulness as a screening test for systemic ARDs. However, unlike the case with other ANAs, Mariz et al suggest that the detection of the nuclear dense fine speckled staining pattern can be used as a biomarker to rule out the diagnosis of SLE and/or other systemic ARDs. Two key points need to be made: first, it should not be concluded that all sera demonstrating the nuclear dense fine speckled staining pattern are from healthy individuals; second, before the observations and conclusions reached by Mariz and colleagues can be widely accepted and applied in clinics, a number of issues should be addressed.

VIRION\SERION:

- ***CSF/Serum Controls for CSF Diagnostics***

In the analysis of cerebrospinal fluid (CSF), the antibody index (AI) serves to demonstrate the intrathecal synthesis of pathogen-specific antibodies. The guidelines of the German Medical Association foresee the use of control samples in conjunction with laboratory tests in order to demonstrate compliance with the high mandatory standards also in the field of CSF diagnostics. Virion\Serion support customers by offering the new and innovative CSF/serum control sample pairs: **SERION ELISA AI Control**.

SERION ELISA AI controls are human CSF/serum control sample pairs for determination of the antibody index when using SERION ELISA classic immunoassays. They are lyophilized and - after reconstitution - to be treated as patient samples. SERION ELISA AI controls are additional controls to the reagents supplied with the SERION ELISA classic test kits with target values in pathologic or non-pathologic ranges. They are used to determine validity of test runs as well as precision and reliability of the method

- ***CSF/Serum Control Sample Pairs for Antibody Index (AI) Determination***

Significance of the Antibody Index in CSF Diagnostics: In the analysis of cerebrospinal fluid (CSF), the antibody index (AI) serves to demonstrate the intrathecal synthesis of pathogen-specific antibodies. The antibody index corresponds to the relationship between the quotient of the specific antibody activity in CSF and serum (Qspec. IgG) and the quotient of total immunoglobulin content in CSF and serum (QIgG or QLim IgG).

MERIDIAN BIOSCIENCES

illumigene® BORDETELLA PERTUSSIS NOW CE MARKED AND FDA APPROVED

Pre-release trials of this assay on the Meridian ***illumi****gene*® system in both New Zealand and Australia have shown the assay to be both highly sensitive and specific.

The ***illumi****gene*® Pertussis molecular assay targets Bordetella pertussis insertion sequence 481 (IS481)

- The ECDC reports that IS481 is a high copy number target
- The ECDC recommends that a positive IS481 result be considered as a probable B. pertussis infection. The ECDC and US CDC recognize molecular methods as important tools in diagnosis of Pertussis.
- Molecular assays are increasingly being used for detection of Pertussis because of its improved sensitivity and rapid turnaround time4
- Serology is not as yet included in the case definition of whooping cough
- There is an increased incidence of whooping cough
- ECDC confirmed that many European Countries have reported increased whooping cough cases in infants, adolescents and adults since 2011
- Bordetella pertussis should be considered in all adolescent and young adults with a prominent cough
- Young children often do not present with typical symptoms and over 50% are hospitalized
- Collect, test and treat for same day results, providing optimal patient management
- ***illumi****gene*® Pertussis provides rapid test results and does not require viable bacteria
- Decreased turn-around time vs. traditional bacterial culture or send-out requests
- Expedite appropriate antibiotic therapy for your patients

The ***illumi****gene*® platform allows a lab to run from one to ten samples in a single run, or two different assays, up to 5 samples of each simultaneously.
Time to result is approx 1 hour including preparation time.
Samples are direct antigen from swabs.

The Menu is GROWING

There are now 5 different assays available on *illumigene*®: *Clostridium difficile*
Strep Group B
Strep Group A
Mycoplasma pneumoniae
Bordetella Pertussis

MERIDIAN BIOSCIENCES: PUBLICATIONS

Clostridium difficile and inflammatory bowel disease: Role in pathogenesis and implications in treatment.

Orna Nitzan et al
World Journal of Gastroenterology 2013 Nov 21; 19(43) 7577-7585

Abstract:
The aim of this paper is to review recent data on CDI in IBD: role in pathogenesis, diagnostic methods, optional treatments, and outcomes of these patients.

Clostridium difficile (C.difficile) is the leading cause of antibiotic associated colitis and nosocomial diarrhea. Patients with inflammatory bowel disease (IBD) are at increased risk of developing C.difficile infection (CDI), have worse outcomes of CDI-including higher rates of colectomy and death, and experience higher rates of recurrence.

However, it is still not clear whether C.difficile is a cause of IBD or a consequence of the inflammatory state in the intestinal environment. The burden of CDI has increased dramatically over the past decade, with severe outbreaks described in many countries, which have been attributed to a new and more virulent strain. A parallel rise in the incidence of CDI has been noted in patients with IBD. IBD patients with CDI tend be younger, have less prior antibiotic exposure, and most cases of CDI in these patients represent outpatient acquired infections.

The clinical presentation of CDI in these patients can be unique-including diversion colitis, enteritis and pouchitis, and typical findings on colonoscopy are often absent. Due to the high prevalence of CDI in patients hospitalized with an IBD exacerbation, and the prognostic implications of CDI in these patients, it is recommended to test all IBD patients hospitalized with a disease flare for C.difficile.

Treatment includes general measures such as supportive care and infection control measures. Antibiotic therapy with oral metronidazole, vancomycin, or the novel antibiotic-fidaxomicin, should be initiated as soon as possible. Fecal macrobiota transplantation constitutes another optional treatment for severe/recurrent CDI.

- ***Multicenter Clinical Evaluation of the illumigene Group A Streptococcus DNA Amplification Assay for Detection of Group A Streptococcus from Pharyngeal Swabs***

Neil W. Anderson, Blake W. Buchan, Donna Mayne Joel E. Mortensen, Tami-Lea A. Mackey, Nathan A. Ledeboera,

J. Clin. Microbiol. 2013, 51(5):1474.

Abstract:
Acute pharyngitis is a nonspecific symptom that can result from a number of viral or bacterial infections. For most etiologies, symptoms are self-limited and resolve without lasting effects; however, pharyngitis resulting from infection with *Streptococcus pyogenes* (a group A *Streptococcus* [GAS]) can be associated with serious sequelae, including acute rheumatic fever and acute glomerulonephritis.

Rapid accurate detection of GAS in pharyngeal specimens from individuals suffering from pharyngitis aids in the management and selection of antibiotic therapy for these patients. A total of 796 pharyngeal swabs were collected at three separate clinical centers. Each specimen was analyzed using the *illumi*gene group A strep DNA amplification assay (Meridian Bioscience Inc., Cincinnati, OH). To confirm GAS identification, the results were compared to those from direct and extracted culture methods using Gram staining and a GAS-specific latex agglutination test. Discrepant results were resolved using an alternative nucleic acid amplification test. The prevalence of culture-detected GAS in this study was 12.8% (102/796 specimens).

The *illumi*gene assay detected GAS in 74/74 direct culture-positive specimens (100% sensitivity) and 100/102 extracted culture-positive specimens (98.0% sensitivity). GAS was detected by the *illumi*gene assay in an additional 42 specimens that were direct culture negative (94.2% specificity) and 16 specimens that were extracted culture negative (97.7% specificity). Discrepant analysis using an alternative molecular assay detected GAS nucleic acid in 13/16 (81.3%) false-positive specimens and 1/2 false-negative specimens, resulting in a final sensitivity of 99.0% and a specificity of 99.6% for the detection of GAS in pharyngeal swabs using the *illumi*gene assay

- ***Detection of Streptococcus pyogenes Using illumigene® Group A Streptococcus Assay***

Amanda M. Henson , Donna Carter, Kathleen Todd, Stanford T. Shulman , Xiaotian Zheng

J. Clin. Microbiol. *December 2013 51:12 4207-4209*

Abstract:
The performance of ***illumi****gene*® 28 Group A *Streptococcus* assay was evaluated by comparing to culture using 437 consecutive throat swabs. The ***illumi****gene*® 29 assay was also directly compared to PCR on 161 samples. This ***illumi****gene*® 30 assay is rapid and easy to perform. The assay also has 31 high sensitivity (100%) compared to culture or PCR, and high specificity (99.2%) compared to 32 PCR. 8.8% isolates were erythromycin resistant and 6.9% were clindamycin resistant.

UPCOMING MEETINGS

- **North Island Seminar**, May 3, Napier, NZ
- **ASM Meeting**, May 17-20, Boston, Massachusetts, USA
- **MSIG Seminar**, June 7, Christchurch, NZ
- **AACC Meeting**, July 27-31, Chicago, Illinois, USA

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