

Separations

Co-tenancy model: Thinking outside of the box can earn you dollar\$ and cent\$

By: Bonny Champagne, Marketing Product Specialist

If you had an opportunity to read the previous Separations, issue 1 volume 4, you are probably on the edge of your seat to find out which Michigan lab has been referred to as "the nation's most unique collaborative regional laboratory organization".¹ We at Sebia are always pleased to call attention to our most outstanding customers! Drum roll please...

The organization to receive the much deserved praise is Michigan Co-Tenancy Laboratories (MCL), which operates in parallel with Warde Medical Laboratories (WML). MCL/WML is headquartered in Ann Arbor, MI, is owned by 17 hospitals, and involves 30 hospital labs in four Midwestern states.

"MCL evolved out of Warde Medical Laboratories to meet the changing needs of the hospitals it served," noted Dennis R. Hodges, Manager of Business Development. "It was David Keren, M.D., Warde's Medical Director, who recognized that Warde had only begun to tap the regional demand for specialized testing services. Many hospitals did not want to completely outsource a service as critical as laboratory testing. Co-tenancy was a solution that allowed these hospitals to achieve economies of scale while maintaining control of their laboratory operations."

The premise of co-tenancy: Cooperate with your competitors to achieve a common goal. You may ask how this particular business model (co-tenancy) benefits the participating hospitals.

- A broad menu of reference and esoteric tests are provided to participating hospitals, along with high quality results and fast turnaround times.
- MCL has provided continued yearly reductions in lab testing costs – cost-per RVU (Relative Value Unit) or internal cost per test declining 21.7% in the past five years.
- Competition between participating hospitals is preserved. (Read more below!)

In the co-tenancy model, all owners are not-for-profit health systems or hospitals and share a cost center in common. "What the hospital owners choose to charge their customers for the lab testing services is beyond the scope of the co-tenancy," states Dr. Paul N. Valenstein, M.D., Chief Operating Officer. "Our job is to run the shared lab operation with high quality and efficiency." This is a very important concept, due to the fact that Michigan has a law which forbids a provider, including a laboratory, to mark up the price of a test performed by another lab. "However, under the co-tenancy agreement, all participating hospitals are owners of the shared lab operation," states Hodges. "Because testing done in the central reference lab is an intrinsic part of a hospital's own operation, it can price tests based on its own business economics." The marketing and billing (to include Medicare reimbursement) for lab tests is the responsibility of the owners (or co-tenants) under their own names.

MCL is only one of three co-tenancy laboratories in the United States and is a first-class example of just what can be created and accomplished when hospital CEOs, lab administrators, and pathologists come together and think outside of the box! The co-tenancy model, by its very design, is a match for any national lab competitor!

Maintaining control of laboratory testing is the key to a laboratory's economic success with reimbursement dollars playing a key role.

Are you interested in receiving reimbursement information specific to your laboratory? Simply complete (in full) and return the Reimbursement Info Card. In return, you will receive a customized report to include financial projections for your laboratory.

¹ Smart, June. Hospitals in Michigan Build Unique Shared Lab. The Dark Report, Volume IX, Number 15.

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Creativity is encouraged at Sebia, which is why we asked for your input last year at the CLMA and AACC tradeshows in submitting haikus (simple three-line poems). We were truly overwhelmed by all of your participation! The result...a published book, *Clarity – Laboratory Haikus*, written by laboratory professionals such as yourself! Drop by the Sebia Electrophoresis booth at the AACC 2003 in Philadelphia, PA (Booth 1935) to receive a copy of *Clarity – Laboratory Haikus* and enter in the drawing for a full-day spa treatment !

We have many new products that we are excited to preview for you at the AACC 2003. New products include innovative assays such as Hydragel® CSF Isoelectric Focusing, the ultimate in oligoclonal banding detection, and Comprehensive Urine Profile, which combines total kidney assessment and Bence Jones free light chain detection into one simple test. We'll see you in Philly!

Please circle number 1 5 3 if you would like a call from your Sebia representative to discuss automating electrophoresis testing in your laboratory or implementing our new assays in your lab!

Ask Borek (continued)

liquid that allows for easy dosage. It is important to follow closely the prescribed procedures. Under stronger reducing conditions, e.g., increased concentration and incubation time, and temperature above 30°C, protein denaturation may result. Denatured proteins are often nearly insoluble; application marks and possibly additional bands may appear.

CRYOGLOBULINEMIA

Cryoglobulins are immunoglobulins that can aggregate and become reversibly insoluble. They either precipitate or gel, hence they are referred to as cryoprecipitate or cryogel, respectively. The intermolecular bonds responsible for the aggregation are weak and highly dependent on temperature and pH. The transition is usually observed at low temperatures (e.g., under refrigeration) but may occur at much higher temperatures (<37°C). Therefore, cryoglobulins can also precipitate *in vivo* in blood vessels with very serious consequences. Cryoglobulins may cause severe cold sensitivity mimicking that caused by high titer agglutinins (cold agglutinin disease) or by cryoprecipitates of monoclonal IgM with specificity for the surface of RBC antigen I. Various primary conditions can be responsible for the presence of cryoglobulins, e.g., multiple myeloma, Waldenström's macroglobulinemia, autoimmune disease and infections (hepatitis C). The severity of the primary problem is further exacerbated by the propensity of cryoglobulins to precipitate *in vivo*. Cryoglobulins are usually classified into three types:

Type I – These are composed of a single component monoclonal immunoglobulin; IgG is the most common; IgM, IgA and free light chains are less frequent. The monoclonal protein is usually present in high concentrations (>0.5 g/dL). Monoclonal IgG cryoglobulins have unique primary, secondary and tertiary properties that invite self-association at lowered temperatures into gelatinous or crystalline structures. These can form obstructive wads causing small vessel occlusions. Type I account for approximately 25% of cryoglobulinemia cases. They are mostly present in patients with lymphoproliferative diseases, particularly multiple myeloma and Waldenström's macroglobulinemia.

Type II – These mixed type cryoglobulins are immune complexes formed in cold by monoclonal IgM antibodies [with rheumatoid factor (RF) activity] to either IgG or IgA. The antigenic Ig's are either polyclonal (type IIa) or oligoclonal (type IIb). As in idiopathic cold agglutinin diseases, >95% of IgM are with k light chain. Type II cryoglobulins are present at much lower concentrations than the Type I. *Type II are most often associated with lymphoproliferative diseases, infections (mostly hepatitis C) and a broad assortment of autoimmune and connective tissues disorders, such as systemic lupus erythematosus, Sjögren's syndrome (a complex condition including inflammation of the cornea, pharynx and joints), rheumatoid arthritis and scleroderma.*

Type III – These mixed type cryoglobulins are composed of polyclonal RF (typically IgM) and a polyclonal IgG (sometimes IgA). Polyclonal IgM antibodies possess enhanced affinity for IgG complexed to an antigen. Type III represent about 50% of cryoglobulinemia cases and are present in low concentrations (<0.1 g/dL). The Type III cryoglobulins are seen in a variety of autoimmune systemic rheumatic diseases and persistent chronic infections with immune complexes (e.g., bacterial endocarditis, hepatitis).

Type I and II may lead to Raynaud's syndrome, vasculitis, cold agglutinin hemolytic anemia, peripheral neuropathy or immune complex disease. When the mixed type II and III cryoglobulins are not associated with autoimmune or lymphoproliferative diseases, or if the primary condition is Sjögren's syndrome, such conditions are termed "essential" mixed cryoglobulinemia. The monoclonal and polyclonal RF in type II and type III cryoglobulins, respectively, is often associated with immune complexes, and might be stimulated by them. Fifty percent of the patients with type II or type III have lymphoproliferative disease or suffer from vasculitis. Hepatitis C antibodies are found in about 90% of type II and type III cases combined. The individuals with cryoglobulins that precipitate in superficial vessels suffer from a variety of symptoms, alone or in combination, such as purpura (confluent intradermal or submucous hemorrhage), pain in joints, leg ulcers, renal and hepatic damage, and Raynaud's syndrome (vasospasms of the digital arteries with dermatological sequelae).

If you would like to receive information concerning Sebia's Fluidil product (1 4 8) or Immunofixation assay (1 4 9), please circle the corresponding number on your Reader Response Card.



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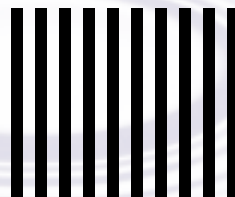
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CRYOGLOBULINS AND CRYOGLOBULINEMIA

Over the years, a number of people asked me various questions about cryoglobulins. "How do we know they are present in serum?", "How do we analyze them?", "Why do they precipitate in cold?", "What can they do to the patient?", etc. Although I briefly wrote about cryoglobulins in this column about three years ago, I feel the time has come to discuss them in greater depth.



Cryoglobulins have the nasty habit of precipitating in cold regardless of whether they are in a test tube or circulating in a body. The following story (from a reliable source) illustrates their nastiness *in vivo*. Once upon a time, an old lady used to live alone somewhere in Michigan or Minnesota (such a story could not happen in Florida). During winter months, each time she went to retrieve her mail from a curbside mailbox, she passed out. Her neighbors (apparently not with a CLS or MT degree) dutifully brought her back to her house each time wondering about her habitual drunkenness. To their surprise she recovered shortly thereafter. Eventually, she was taken to local Dr. Welby who realized it was not schnapps but the exposure to cold that caused her to pass out.

SAMPLE COLLECTION, HANDLING AND STORAGE

- Special procedures are needed when collecting or treating samples for cryoglobulin testing. Collect blood and keep it at 37°C during transportation and clotting. The blood collection tubes should also be pre-warmed to 37°C.
- Cryoglobulins should precipitate or gel when the serum sample is kept at 4°C. If no precipitate forms within 72 hours at 4°C (some recommend one week) the sample may be considered cryoglobulin free. The precipitation of cryoglobulins is reversible. Dissolution of the precipitate upon re-heating to 37°C confirms the presence of cryoglobulins.

- For electrophoresis, the cryoglobulin preparation must be clear without any turbidity or particulate matter since these might hinder diffusion of the sample into the applicator teeth. To clear turbidity due to cryoglobulins, add Fluidil (Sebia PN 4587). Particulates other than cryoprecipitate (e.g., RBC, stroma) should be removed by centrifugation. Cryoglobulins may associate with serum lipids and remain suspended during centrifugation. Opacity in such sera should clear by brief re-heating to 37°C.
- Serum cryoglobulins may form a cryogel or cryoprecipitate particularly upon storage at 2 to 8 °C and possibly even at room temperatures. The serum sample may then become too viscous to diffuse effectively into the sample applicator tooth. Or, when precipitation occurs, often seen as sample's turbidity, the particulates also may hinder the diffusion and some of them may be deposited on the gel and stay at POA. As the result, electrophoregrams will be lightly stained and marked decrease in albumin may be observed. Problematic samples have to be treated with Fluidil that solubilizes both the cryogels and cryoprecipitates. When polymerized IgM is involved reducing de-polymerization with 2ME (2-mercaptoethanol) may have to be performed.
- Apart from the cases where the presence of cryoglobulins is obvious, e.g., high serum viscosity or presence of a precipitate, the following comments may aid in deciding whether or not cryoglobulins might be present, the sample should be treated, and what could happen when no treatment is performed:
 - Monoclonal Type I cryoglobulins generally precipitate within 24 hours at 4°C.
 - Type II and III mixed cryoglobulins that are often in low concentrations require longer low temperature incubation times. Such samples do not require any treatment if the electrophoresis is performed prior to low temperature incubation. Generally, presence of small amounts of cryogel (e.g., with no apparent increase in viscosity) will not adversely affect the results of electrophoresis.
 - Very small amounts of cryoprecipitate settled at the bottom of the test tube may become unnoticed. Swirl the test tube. If a small amount of precipitate is noticed, heat the sample to 37°C and perform electrophoresis.
 - When cryoglobulins are suspected, the evidence of their presence is inconclusive, or are present in small amounts, heat the sample to 37°C prior to electrophoresis.
 - The heating itself might not suffice. Use Fluidil to prevent gelling and precipitation that may possibly take place as the sample diffuses into the applicator teeth (at room temperature) or in the course of electrophoresis (at 20°C on the Sebia system).

PROCESSING OF SAMPLES FOR ELECTROPHORESIS AND IMMUNOFIXATION

Solubilization of cryoglobulins for electrophoresis
Most immunoglobulin aggregates that form cryoglobulins can be dissociated with Fluidil. To dissociate cryoglobulins, add 25 µL Fluidil to 75 µL serum, vortex for 15 seconds, and then follow with the standard electrophoretic procedure. Fluidil, a

chaotropic agent, disrupts hydrophobic interactions by allowing water molecules to solvate nonpolar groups. Consequently, it disrupts the native conformation of proteins and dissociates molecular aggregates and non-covalent complexes.

Identification of cryoglobulin components by immunofixation

Sebia immunofixation procedures offer a convenient way for the identification of the immunoglobulin components of cryoglobulins. This requires isolation of the cryoprecipitate or cryogel, its solubilization and immunofixation with appropriate antisera. Collect, transport and clot blood at 37°C. Divide the serum from each sample into two test tubes and store at 4°C. For complete precipitation, usually 72 hours are prescribed. Type I cryoglobulins usually precipitate within 24 hours. Type II and particularly type III, at low concentrations, might require prolonged time. Confirm the presence of cryoglobulin by re-heating one of the test tubes to 37°C and observing dissolution of the precipitate. Centrifuge the second tube at 4°C and discard the supernatant. Wash the precipitate three times with icy saline (centrifuge after each wash at 4°C) and dissolve it in a minimum volume (100 µL) of warm saline (≥ 37°C). Vortex to promote solubilization. If a noticeable amount of precipitate is not dissolved, add more saline. Just before electrophoresis, add 10 µL of Fluidil to the dissolved cryoprecipitate, mix well and keep at 37°C for a few minutes. Perform the immunofixation procedure without any further sample dilution using the Bence Jones migration program for increased sensitivity. If the results indicate the presence of polymerized IgM in the cryoprecipitate, add 10 µL of 1% 2ME in Fluidil to 100 µL of the dissolved cryoprecipitate. Mix and incubate for 15 minutes at ≤ 30°C and re-run the immunofixation. To prevent the reaction from going too far in the dilute cryoglobulin solutions, the 2ME concentration, 0.09%, in the final reaction mixture is lower than that prescribed for any other de-polymerization.

Reducing de-polymerization

This procedure is prescribed for cryoglobulins containing polymerized IgM. It can be also used with serum samples that have formed a POA artifact or where a presence of polymerized IgA or IgM is suspected. (i) Prepare 10% 2ME in water, (ii) mix 5 µL of the 10% 2ME solution with 45 µL Fluidil; this mixture is stable for 1 week in a closed container at room temperature, (iii) add 25 µL of the mixture to 75 µL of neat serum, vortex, incubate at least 15 minutes (maximum 30 minutes) and then follow with the standard IF procedure. The final reaction mixture contains 0.25% 2ME.

NOTE on 2ME and reducing depolymerization conditions

For many assays, the intermolecular disulfide bond linkages that hold large molecular entities together have to be first cleaved to release the constituting subunits and allow solubilization or to access hidden antigenic determinants. The reducing agent that is commonly used to cleave the disulfide bonds (-S-S- → 2 -SH) is 2-mercapto-ethanol (2ME, hydroxy-1-ethanethiol, b-mercapto-ethanol, BME). In spite of its unpleasant odor, which requires the use of a hood, 2ME is preferable. It is a

continued on back

Customer Focus



University medical center has acute eye for electrophoresis efficiency

Sebia HYDRASYS® creates another point of distinction for Iowa healthcare system

The University of Iowa has a rich history of groundbreaking medical discoveries and firsts.

Its nickname, the Hawkeyes, means "keen vision."

So then, it's no surprise that one of its labs found a leading-edge solution to cut electrophoresis time considerably.

In 2001, the University of Iowa Hospitals and Clinics — renown worldwide for solving some of the mysteries of Alzheimer's disease, muscular dystrophy, macular degeneration and other complex disorders — made a breakthrough in solving the challenges of a consolidated lab environment. In an effort to accommodate increased electrophoresis workflow and create greater efficiency, the lab went live on the Sebia HYDRASYS instrument.

The change to automation was spurred by more practical reasons than just the quest to be leading-edge. The previous manual method required a fair chunk of technologist time...and since University of Iowa had combined multiple laboratory testing into one location, it needed to maximize personnel tasks to the fullest.

"We reorganized our labs and combined workloads to help control costs," explains Marlene Loonan, medical technologist in the main chemistry lab. "As a result, our team's responsibility has expanded beyond just protein electrophoresis to also include urine immunopathology, serum immunofixation, and screening of spinal fluid for multiple sclerosis. CSF screening in particular is more of a specialty service that few labs offer."

Also on the radar screen was the larger industry issue of staffing. "The number of medical technologists is decreasing nationwide, so it was important that we had a solution in place to deal with impending personnel shortages," Loonan adds. "We needed something that would work with minimal coverage."

The lab performed its own system comparison and found the Sebia HYDRASYS best met its needs in a number of categories: ease of use, efficiency, gel quality and the ability to handle many different types of testing. The end result is what seems like rocket-fast speeds in processing time; staff can now process protein electrophoresis in a quarter of the time it took previously.

"The good reproducibility of the Sebia gels means there's less need to repeat tests," says Dr. Charles Lutz, pathologist. "This contributes to faster response to our colleagues and clients, while ensuring accuracy of test results."

University of Iowa Hospitals and Clinics

Iowa City, Iowa

"With Sebia, orders are filled right away. Their support team is a major asset"

Marlene Loonan, Medical Technologist

Designed as a "walkaway" system, the HYDRASYS handles everything from sample application to migration to incubation, staining, destaining and drying.

"Because it's fully automated and less technique-dependent than our old system, we don't have to worry about little nuances in the way different people perform a process," notes Mary Droll, medical technologist in the chemistry lab. "This makes for easier training too; some of us had never done immunofixation before the consolidation of our labs, so simplicity of the system — and the patience of the Sebia staff — was critical to a smooth transition."

Something else that caught the attention of these Iowa Hawkeyes was the flexibility of the HYDRASYS and its extensive assay menu. For example, the lab can now offer multiple sclerosis testing on the same instrument, enabling it to meet demand and boost revenue potential. And because Sebia offers a cerebrospinal fluid assay that can be performed on unconcentrated or even diluted CSF, the cost and logistical challenges associated with this type of assay have been reduced.

Flexibility also comes into play with Sebia gels; a choice of gel sizes means that there's never any waste with smaller workloads. "And orders for new kits are filled right away," Loonan adds. "If we order Monday through Wednesday, kits arrive the next day."

She and her colleagues praise Sebia's support team as a major asset, citing numerous anecdotes whereby Sebia specialists helped resolve an operational challenge or technical issue. For example, when the lab techs were encountering problems generating "clean" gels, their Sebia rep made an onsite visit to help them perfect the blotting process — ensuring maximum clarity and readability of the test results.



Dr. Charles Lutz and Dr. Michelle Barry examining Sebia's 9 IF gel.

"Overall, the Sebia HYDRASYS has allowed us to process tests faster and with greater confidence in the results," says Dr. Lutz. "Given that personnel time represents a large portion of lab expenses, an automated system is often the best way to achieve greater efficiency".

Are you interested in learning more about the benefits of automating electrophoresis testing in your laboratory? Simply circle 150 on your Reader Response Card. If you would like to learn more about Sebia's unique Cerebrospinal Fluid (CSF) Immunofixation assay or Sebia new CSF Isoelectric Focusing assay please circle 151 or 152, respectively.

We Need Your Feedback

In order to better serve you, we constantly update our Sebia Separations Mailing list. Please complete this card and return to us.

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Results interpreted on-site? YES / NO

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