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NTM-TB INSIGHTS

March 2016

Dr. Michael D. Iseman Honored with the Union NAR Lifetime Achievement Award

Dr. Michael Iseman is the epitome of a gentleman physician/scholar and someone who dedicated his entire career to studying mycobacteria and caring for patients with mycobacterial diseases. He is a true giant in the field.

Dr. Iseman was Chief of the Division of Mycobacterial and Respiratory Infections at National Jewish Health from 1982 to 2004. Dr. Iseman remained on faculty until 2014 when he became Professor Emeritus. He is still very active with National and International lectures as well as writing. Under his leadership, the Division of Mycobacterial and Respiratory Infections evolved from the leading multidrug-resistant tuberculosis treatment program to one of the premier clinical programs for treatment of nontuberculous mycobacterial infections. During his tenure, he taught many of us about mycobacteria and, just as important, how to be better people.

As a teacher, Dr. Iseman is unequalled. He ran the Denver TB Course from 1983 until his retirement. Thousands of people have taken this course, the longest-running TB Course in the U.S. He is the author of one of the most widely read texts on tuberculosis entitled *'A Clinician's Guide to Tuberculosis'*, a true classic in the field. He has published over 175 research manuscripts, book chapters, reviews and editorials. His 1993 publication in the New England Journal of Medicine on how to treat multidrug-resistant tuberculosis was the roadmap that the world followed.

Dr. Iseman served as Editor-in-Chief of *Tubercle and Lung Disease* and then the first Editor-in-Chief of the *International Journal of Tuberculosis and Lung Disease* from 1997 to 2002. His knowledge of mycobacteria, facilitated with the English language and perfect prose, are renowned.

Dr. Iseman has received numerous awards for his dedicated service including The James D. Bruce Public Health Award (American College of Physicians), Edward Livingston Trudeau Medal (American Thoracic Society, F. Murray Kornfeld Award (American College of Chest Physicians) and in 2010 the Lifetime Achievement Award at National Jewish Health.

Congratulations Dr. Iseman on your well-deserved Union North American Region Lifetime Achievement Award!

Global Scale-Up of the Programmatic Management of Multidrug-resistant Tuberculosis

Tuberculosis (TB) remains a major global health problem. Worldwide, there are an estimated 2 billion people infected with *Mycobacterium tuberculosis* from whom 9.6 million develop TB each year. A staggering 1.5 million people die from TB annually including over 400,000 with HIV infection. The emergence of drug-resistant strains of *M. tuberculosis* threatens to undermine TB control programs worldwide. Multidrug-resistant TB (MDR-TB) strains that are resistant to at least isoniazid and rifampin, and extensively drug-resistant TB (XDR-TB), MDR-TB strains that are also resistant to a fluoroquinolone and second-line injectable drugs, are more difficult to diagnosis and treat than other forms of TB.

The World Health Organization estimates that there are 480,000 cases of MDR-TB annually resulting in 190,000 deaths. Approximately 3% of new (untreated) TB cases and 20% of previously treated cases have MDR-TB. The estimated proportion of MDR-TB among new and retreated cases varies across the WHO regions with the highest proportion in the European region where approximately 50% of retreated cases have MDR-TB. By the end of 2014, XDR-TB was reported from 105 countries and accounted for an estimated 9.7% of MDR-TB cases. Given the significant morbidity and mortality associated with drug-resistant TB, it is imperative that we understand the barriers and gaps in the global control of MDR-TB.

Gaps in MDR-TB control

By the end of 2014, there were an estimated 480,000 patients with MDR-TB globally, which includes cases that have been notified, those that have been diagnosed but not notified and those that have yet to be diagnosed. Among already notified cases, there are estimated to be 300,000 (63% of estimated) patients with MDR-TB. The large gap between the estimated and notified cases is due in large part to lack of reporting and case detection. Unfortunately, only 123,000 patients (25% of the estimated) were actually notified to have MDR-TB: this gap between the notified TB cases and notified MDR-TB represents a lack of access to antimicrobial susceptibility testing. Among those identified as having MDR-TB, only 111,000 were enrolled into treatment, for whom outcome data are available on approximately 50%. Treatment success was reported in 48% of patients with almost a quarter being lost to follow-up. In order to scale up the programmatic management of MDR-TB, we must identify specific gaps in TB control and introduce targeted interventions to close the gaps.

The diagnosis gap – where are the missing cases?

Only 25% of patients estimated to have MDR-TB and 41% of notified TB cases are identified to have MDR-TB. These 350,000 "missing cases" result from a number of factors including poor access to and awareness of diagnostic facilities, low case detection, poor recording and reporting, as well as lack of appropriate infrastructure and human resources. Availability of antimicrobial susceptibility testing is greatly limited and culture-based methods lack standardization and reproducibility for many second-line drugs. Globally, only 12% of new cases and 58% of previously treated cases were tested for MDR-TB and only 24% of notified and confirmed MDR-TB cases had antimicrobial susceptibility testing performed for both fluoroquinolones and second-line injectable drugs. These figures fall short of the WHO End TB Strategy that calls for universal antimicrobial susceptibility testing.

Fortunately, antimicrobial susceptibility testing availability is increasing globally at a rapid pace in large part due to the availability of new molecular assays that offer the potential to identify genetic mutations that confer resistance in a fraction of the time that it takes phenotypic methods. Molecular methods have considerable advantages for scaling up programmatic management of MDR-TB and surveillance of drug-resistant TB because they offer speed of diagnosis, standardized testing, potential high through-put, and fewer requirements for laboratory biosafety.

Much of the scale-up activities related to antimicrobial susceptibility testing can be credited to the Global Laboratory Initiative that was established in 2008 as a Working Group of the Stop TB Partnership. The Global Laboratory Initiative, which consists of over 100 international partners, serves as an independent, technical expert advisory group to WHO, development and funding agencies, and countries. In collaboration with the WHO Supranational Reference Laboratory Network established in 1994, the Global Laboratory Initiative has helped to strengthen laboratory capacity and infrastructure in resource-limited areas, supported the global scale-up of rapid diagnostics, and improved quality of individual laboratories and laboratory networks.

The diagnosis-treatment gap

The number of MDR-TB cases started on second-line treatment increased from 30,492 in 2009 to 111,000 in 2014. However, this represents only 90% of the notified cases of MDR-TB and an abysmal 23% of all estimated MDR-TB cases. And unfortunately, the capacity to treat MDR-TB is lagging behind the capacity to diagnose MDR-TB so that "waiting

lists" are growing. There are many reasons for the diagnostic-treatment gap including a critical shortage of human resources, lack of availability of second line drugs, inadequate facilities for treatment and monitoring and ineffective TB control programs. Scale-up of treatment is further complicated by the prolonged duration of therapy (approximately 20 months) with regimens that are associated with many drug-related adverse events and poor treatment outcomes: the proportion of MDR-TB cases that were treated successfully was only 48% and this has not changed since at least 2007.

There is great optimism that treatment results will soon be improving with the introduction of new drugs and shorter regimens. Hoping to parallel the success of the Global Laboratory Initiative, the Global Drug Resistant TB Initiative, another working group of the Stop TB Partnership, was established approximately three years ago. The GDI evolved from The Green Light Committee Initiative that was established in 2000 as a subgroup of the MDR-TB Working Group within the Stop TB Partnership. The aim of the Green Light Committee Initiative was to help countries access quality-assured second-line anti-TB drug therapy for treatment of patients with MDR-TB. Between 2000 and 2010, the Green Light Committee approved the treatment of over 100,000 patients from 133 projects in 83 countries and conducted over 300 technical assistance missions. However, only approximately 30,000 patients were actually treated over this time frame.

Although enrollment into treatment was increasing, almost doubling between 2008 and 2009, the rate of enrollment was too slow. Therefore, a new framework was created that involved establishment of regional Green Light Committees and a global Green Light Committee. Over two years, each of the regional Green Light Committees was established and all are now up and running. In 2013, the MDR-TB Working Group and global Green Light Committee merged to become the Global Drug Resistant TB Initiative. This group works closely with the Stop TB Partnership, WHO, and regional Green Light Committees to continue the scale-up of programmatic management of MDR-TB worldwide, focusing on the high MDR-TB burden countries and working with the Global Laboratory Initiative and Global Drug Facility to link diagnosis with appropriate and effective treatment.

The concerted efforts of partners in the fight against MDR-TB will hopefully speed up access to antimicrobial susceptibility testing among TB patients and provide quality assured medications and effective regimens to all patients with MDR and XDR-TB.

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Mycobacterial Disease and In-born Inherited Errors of Interferon Gamma Mediated Immunity

Background

Loss or improper function of a part of the immune system results in immunodeficiency disorders. When impairment of the immune system is due to a genetic defect, the disorder is termed 'primary immunodeficiency'. Immune deficiency results in repeated infections, often with otherwise innocuous organisms and in cases of severe immune defects, such infections can be life threatening.

Immune deficiencies are generally classified into cellular and humoral or antibody deficiencies. While antibody deficiencies can be treated with supplemental immunoglobulin, cellular defects are much more difficult to treat and tend to be characterized by deep seated infections with intracellular organisms such as mycobacteria, fungi and viruses. Cellular defects leading to increased susceptibility to mycobacterial disease form a unique subset of immune deficiencies that predominantly affect the interferon gamma (IFNγ) and the interleukin-12 (IL-12) pathways that are key mediators of immunity to intracellular infection.

The immune response to mycobacterial infection involves a complex interplay of the innate and adaptive immune systems. Mycobacteria are phagocytosed by professional antigen presenting cells, such as macrophages and dendritic cells and survive and replicate within the phagosome. Infected macrophages produce cytokines including TNF-α and IL-12 and present mycobacterial antigens to CD4 and CD8 T cells, thereby driving the adaptive immune response. Upon antigen recognition and activation by IL-12, T cells are activated and produce key cytokines such as IFNγ that acts upon macrophages to further activate them. This cycle, the IL-12 – IFNγ cytokine loop, is critical to the control of mycobacterial infection (Figure 1).

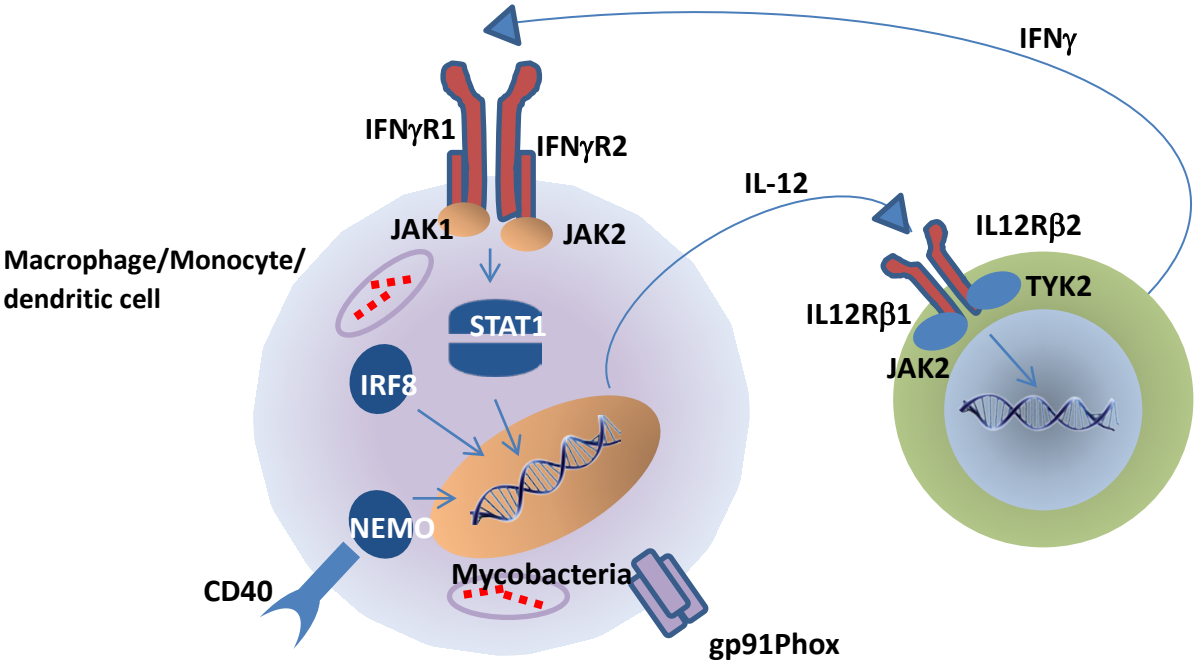

Figure 1. The immune response to mycobacterial infections

Mendelian Susceptibility to Mycobacterial Disease (MSMD) is caused by mutations in genes responsible for the various immune functions of T cells and phagocytes (monocytes, macrophages, dendritic cells) that are necessary for control of mycobacterial infections. Defects in these genes can lead to varying degrees of susceptibility to a variety of nontuberculous mycobacterial species of low pathogenicity, *M. bovis* BCG, as well as other intracellular pathogens such as *Salmonella typhimurium*, viruses such as Varicella-Zoster virus and fungi such as *Cryptococcus sp.* and *Histoplasma sp.* These genetic defects may be inherited in an autosomal dominant (AD), autosomal recessive (AR) or X-linked manner.

The clinical presentation varies with the extent to which the mutation affects protective immune processes. For example, AR defects of the interferon gamma receptor (IFNγR) that lead to complete loss of surface expression of the receptor, abrogate the interferon gamma response entirely. Similarly, AR mutations of STAT1 (Signal Transducer and Activator of Transcription 1), a molecule downstream of IFNγR and responsible for the transcription of IFNγ responsive

genes, also lead to a complete loss of the IFNγ response. Patients with these AR mutations of STAT1 and IFNγR are extremely susceptible to nontuberculous mycobacterial infections and tend to develop severe, disseminated disease in early childhood. Partial defects of the IFNγR that retain residual activity result in less severe infections that may be localized rather than disseminated. Mutations of the IL-12 receptor β1 chain (one of the two components of the IL-12R) or mutations of the IL-12p40 subunit of the functional IL-12 p70 molecule lead to less severe infections. Although relatively rare, mutations of IFNγR, IL-12R and IL-12p40 are observed more frequently than mutations in other IFNγ-related genes. These include: (1) interferon regulatory factor 8 (IRF-8) that plays a major role in antigen processing and presentation by mononuclear phagocytes, (2) interferon-stimulated gene 15 (ISG15) that induces production of IFNγ by Natural Killer (NK) and T cells and (3) STAT1. Genes that contribute to increased susceptibility to mycobacterial infection, but that are outside of the IFNγ-IL-12 loop include (1) GATA2 (MonoMac syndrome), a transcription factor that drives development of myeloid cells, (2) Nuclear factor-kappa-B essential modulator (NEMO) that activates NF-kB and thereby downstream genes that mediate essential immune functions, and the X-linked CYBB gene that encodes gp91phox, a component of the NADPH complex that mediates neutrophil and monocyte oxidative burst. Although rare, mutations in these genes predispose individuals to mycobacterial infections. The various genetic defects identified to date that are associated with chronic, often disseminated, mycobacterial infections are listed in Table 1.

Table 1. MSMD related genes

Gene	Protein	Inheritance	Functional impairment	Clinical features	Reference
IFNGR1	Ligand binding chain of IFNγR	AD, AR	Impaired interferon gamma response	AR presents with severe, disseminated infections. AD has a milder course.	[1, 2]
IFNGR2	Signal transducing chain of IFNγR	AR	Impaired interferon gamma response	Presentation occurs later in life, may be milder.	[3]
STAT1	STAT1	AD, AR	Impaired response to interferon gamma and interferon alpha	Increased susceptibility to both viral and mycobacterial infections.	[4, 5]
IL12RB1	IL-12 receptor beta 1 chain	AR	Defective IL-12 signaling thereby affecting T and NK cell function	Milder course of infection, susceptible to *Salmonella sp.* in addition to mycobacteria.	[6-8]
IL12B	IL-12 p40 subunit	AR	Loss of IL-12 production thereby affecting T and NK cell function	Milder course of infection, susceptible to mycobacteria and other intracellular organisms.	[9]
ISG15	Interferon stimulated gene 15	AR	Decreased interferon gamma production by T and NK cells.	Milder course of infection.	[10]
IRF8	Interferon regulatory factor 8 (IRF8)	AD, AR	Impaired priming of T and NK cells due to defective antigen presentation	Milder course of infection; disseminated *M. bovis* BCG-disease.	[11]
IKBKG	NEMO	X-linked	Affects the CD40-CD40L pathway; leads to impaired IL-12 production in monocyte/macrophages	Disseminated mycobacterial infections, increased susceptibility to viral infections.	[12]
GATA2	GATA2	AD and sporadic	Profound reduction in monocytes, dendritic cells, lymphopenia	Disseminated mycobacterial infections, HPV, EBV, increased susceptibility to fungal infections.	[13]
CYBB	gp91phox	X-linked	Selective defective monocyte/macrophage oxidative burst.	Disseminated *M. bovis* BCG or *M. tuberculosis* infection	[14]

Laboratory diagnosis and treatment

Laboratory diagnosis of IFNγR and IL-12R mutations includes analysis of surface expression of the receptors by flow cytometry along with demonstration of function by analysis of STAT1 and STAT4 phosphorylation, following stimulation with IFNγ and IL-12 respectively. Undetectable IL-12p40 and functional IL-12p70 as well as reduced IFNγ production by lymphocytes is seen in patients with mutations of the IL12Rβ1 or IL-12. Although phenotypic and functional analysis is helpful and can support diagnosis, sequencing is required for a definitive diagnosis for these and other genetic mutations listed in Table 1. Treatment of MSMD depends on the severity of infection. Severe cases such as AR complete IFNγR or STAT1 deficiency, MonoMac syndrome or NEMO mutations may be corrected by bone marrow transplant. Milder defects are treated with anti-mycobacterial therapy and supplemental IFNγ.

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The Doctor/Patient Relationship

Would we think of becoming involved in a business transaction leaving things to chance? Why do people allow the direction of their doctor's appointment to go forward on someone else's agenda?

Some people allow their medical providers to orchestrate their appointments, and then subsequently feel frustrated because they find themselves in a void as far as how to proceed. It is important for patients to take charge and plan well before our appointment. Under the current medical system, many doctors find they are unable to give us the time they would like, so it is essential to make the most of the time you are given. Your physicians are not mind readers, so communication from us is important. As you read further, you will find that doctors appreciate good planning on the part of their patients.

Methodology: A request for suggestions on how to make the most of your appointment was sent out to a physician database prior to a Nontuberculous Mycobacteria (NTM) support group meeting. In addition, we received input from our members as to their expectations from their doctors. The information from all the responses was merged and collated into this document. An attempt was made to include all the important points.

TIPS FOR MAXIMIZING THE EFFECTIVENESS OF PATIENT APPOINTMENTS

Before Your Appointment

Write your list of questions BEFORE your appointment with your physician. It is efficient to prepare no more than 3 of the most important questions, or if your list is longer, prioritize your questions.

Bring a current medication and supplements list, including dosage size in mg., how many times daily you take it, date started, relationship to meals or at bedtime if relevant. Also include medication allergies or side effects with date(s) and details of reaction, preferably typed. If this is not possible, bring all medication bottles. Believe it or not, it is easier to read names and dosages on the medicine bottle than handwriting. The medicine bottles also provide the phone number of the pharmacy. Some group members mentioned they keep a typed list of medications on their computer, which is easily modified and printed out for their doctor(s) appointments.

Some patients organize a diary. It can include some of the most important symptoms, changes to medications such as new antibiotics that may be necessary since your last visit, significant events that happened since the last visit, pneumonia, hospitalizations, any new procedures (surgical and otherwise) and their dates. The results of your ENT/sinus history, GI/reflux history/allergy history is also important to your respiratory history.

Bring a list of new doctors and other treating physician information including first and last names, addresses with phone and fax so that a report may be sent.

Prepare relevant CT scan and other imaging studies on CD including reports and either bring with you or send to office prior to your appointment. Prepare copies of relevant reports and lab data including copies to leave with the physician. Please do not ask your doctor to make copies for you during your appointment. If you cannot make your own copy, ask the doctor's receptionist to make you a copy prior to the consult with your doctor.

If possible, ask a family member, friend, caregiver or patient advocate to accompany you to the appointment to jot down notes or to provide extra listening. This is a complicated disease with lots of patient education. Often, it is difficult to comprehend all medical information provided at visits especially the initial and subsequent few visits.

At the Appointment

Find out how much time you will have with your doctor. This way, the patient and doctor alike can plan their time wisely. Give details of the specific symptoms and illness for which you came for this consultation.

Submit your list of questions to your physician at the beginning of the appointment. The physician is then able to guide the appointment keeping in mind the goals of the patient. The meeting should revolve around patient concerns that she/he needs answered before leaving the office.

Alert your doctor how many things are on the list of questions so the doctor can plan the time wisely. If you spend too long on item #1, you will never get to item # 10.

If you don't understand something (medical lingo), ask for clarification. So many patients don't want to feel stupid. Doctors sometimes forget they are speaking in "technicalities".

Provide the phone number in writing of any relative/friend you wish the doctor to call at a later time. HIPPA laws require patient approval since all personal medical information is confidential unless permission is given by the patient to release information.

If on NTM medications, provide information on side effects and report any new meds provided by other physicians since your previous visit.

Ask the doctor if there is a need for special assistance with auxiliary services. If so, have the nurse or support staff arrange for those visits at same appointment day (respiratory, meds/IV therapy, demo for special home equipment, social services, nutrition, etc.).

Ask about future appointments - date/time.

After Your Consultation

If possible, schedule your next appointment prior to leaving the office. Ask or remind support personnel to provide equipment or arrange for delivery prior to leaving the office. The doctor should provide special instructions prior to your next appointment such as sputum cups, etc.

Between Appointments

Prepare a list of questions in between visits. If you need answers between visits write everything down before calling the office.

PHYSICIAN REMARKS

** Physician must always show compassion! Very important**

Physician/patient meetings need to be timely meaning no extended waiting prior to and during appointments. Patients are weak and tired. And physician time is important. The doctor needs to stay on schedule for the benefit of all patients.

Be prepared for the physician to ask about details of your current and past related illnesses in an order that may be different from that which you are prepared to recite. Each physician organizes a history in his or her mind and that organization may not be similar to your planned presentation of your story.

Understand that aspects of your overall medical history that your/other physicians have not "connected" to your medical history may be relevant to your "new" consulting physician, e.g. rheumatologic history, past occupational/environmental exposure, etc.

A good consultant/detective starts “at the beginning” and may seem to dwell on aspects of the history, which to you may seem redundant or passé. He or she may seem to be “challenging” your statement of fact when the process of being certain of every aspect is critical to breaking a case that until now has been a mystery. For example, you may not in fact have asthma simply because other physicians in the past have told you that you have asthma.

Your physician relies on every aspect of the investigation in order to get it right for you. His or her diagnostic capability is “only as good as the weakest link” in that diagnostic process and thus he/she may ask you to see other physicians or have diagnostic studies at facilities that have, in his/her experience, “gotten it right” for that doctor in the past.

PATIENT COMMENTS

“I think the most important things for me regarding medical appointments is a list which clarifies my goal for the meeting and remembering that I am in charge of my own medical care and to sift out what is useful and discard the rest. This is particularly helpful when one’s doctors do not agree, or when the patient is balancing multiple maladies in which treatments conflict.”

“Be sure to clarify doctor’s questions and statements when not understood.”

“Make suggestions to your doctor and ask questions.”

“I keep a medical journal and write in it every day which I keep on my phone which syncs to my computer as a backup. I reread it when trying to figure out what may have contributed to specific medical symptoms.

“Ask for any forms that need to be filled out prior to your appointment. Often when filling out the forms, you may find it can trigger questions you may wish to ask your doctor at the appointment.”

“Ask that your test results and medical records be sent to your doctors. Do not assume they will be sent automatically. Some doctors charge patients for hard copy records, but will send records electronically at no charge.”

If the doctor’s office is located in a hospital, the support staff may have been hired by the hospital and may not be of the doctors’ choosing. Some of the patients in the group have been dissatisfied and frustrated with the competency of the support staff in their doctors’ offices. The support staff has to expedite such things as medical records, communicate with other doctors, arrange therapy, etc. Try to communicate your information or requests as simply as possible. Follow up when necessary in a courteous manner.”

“The doctor should consider, respect and comply with treatment choices for the patient. The doctor should consider alternatives for the patient when available if the patient does not agree with the one suggestion presented. Treatment should be worked out between doctor and patient”.

6 WARNING SIGNS THAT YOU MAY NEED A NEW DOCTOR - AARP Magazine, Aug.-Sept., 2013

Keep in mind that your doctor should be treating you with your best interests in mind. If you feel this is not the case, you have the ability and responsibility to see another doctor. In many cases, your present physician may lack an in-depth knowledge of NTM, so it is up to you to be proactive if you are dissatisfied with your care (not getting the attention you deserve, health not improving, etc.).

So how do you know if your doctor isn't "the one"? Your gut is often your best guide, experts say. But here are a few warning signs that you might need to give your doctor the boot, courtesy of geriatrician James Pacala, M.D., of the University of Minnesota.

Be wary of a physician who:

- Dismisses every complaint, blaming age.
- Insists that nothing can be done. There is always something to try.
- Spends too little time with you, or interrupts you frequently, especially if you're a patient with complex, multiple issues.
- Writes a prescription with minimum discussion.
- Recommends treatments without considering your lifestyle.
- Prescribes a variety of medications and procedures, or keeps referring you to more specialists without any improvement.

Remember, it is up to you to be your own advocate and find the best medical care. You, the patient, are an important member of your medical team.

Debbie Breslawsky

An NTM patient, Debbie Breslawsky is involved in NTM advocacy. She founded her first support group in New York in 2003, and has since founded one in Palm Springs, CA and another in Connecticut, as well as an on-line group. She serves on the National Jewish Health Board of Trustees as well as on the Board of NTM Information & Research.

March 24 – World Tuberculosis Day

World TB Day commemorates the discovery of the tuberculosis (TB) bacterium (*Mycobacterium tuberculosis*) by Dr. Robert Koch on March 24, 1882. World TB day is commemorated on this date each year to raise awareness among the public and policy makers that tuberculosis remains an epidemic in most parts of the world, and a public health problem in developed countries, causing the deaths of about one and a half million people each year. Koch's discovery opened the way towards diagnosing and curing TB.

World TB Day provides the opportunity to raise awareness about TB-related problems and solutions and to support worldwide TB-control efforts. While great strides have been made to control and cure TB, people still get sick and die from this disease in our country. Much more needs to be done to eliminate this disease.

50 years ago – Aspects of Bacterial Resistance in Tuberculosis

The J. Burns Amberson Lecture presented by George Canetti at the American Thoracic Society Conference in 1965 (*Am Rev Respir Dis* 1965. 92:687-703) Part 5 of 5.

There are so many more important things to say about drug resistance in tuberculosis that this lecture seems to me only a beginning. But time is up, and I must conclude. Nothing more useful can be done at the end of an Amberson Lecture than to point out a few promising directions for future research in the field.

Among such directions I do *not* place resistance-testing methods, at least for research without coordination. Improvements in the methods used in many places are undoubtedly needed. The basic lines along which the changes

should occur are known; testing methods must be quantitative. Techniques operating along quantitative lines are used in several places, and have been published. Those who propose new techniques are usually inclined to overstress their theoretical importance, and those who feel reluctant to use them are often tempted to minimize their practical importance. As new evidence is easily produced on both sides, much time is lost in such rear-guard action. What is really needed at the present stage, when so much knowledge has accumulated in the field of resistance-testing methods, is agreement of four or five competent laboratories *on a common protocol of strain testing,* with a few methodologic variations introducing graded amounts of progress. Within a year or two of cooperation, quantitative testing method *acceptable to everybody* would emerge and international agreement on resistance criteria would probably be settled at the same time. More than that is not needed. Testing methods are, after all, but a tool.

A most valuable field for future investigation is the *epidemiology* of primary resistance. Far too little use has been made, up to now, of the availability of strains labeled by drug resistance for exploring the pathways of tuberculous infection. In certain exceptional cases, the source of contamination can be traced as accurately as in the well-known airborne-infection experiments of the Riley group. Even if this is not the case, the type of primary resistance found, if correlated with the moment at which the corresponding drug was introduced into chemotherapy, permits inferences as to the earliest moment at which the infection of the patient may have occurred. This information is of special interest if the approximate moment at which the patient has acquired tuberculin hypersensitivity is known; clear-cut proof of exogenous superinfection may thus be provided in some cases. This type of epidemiologic research, based on histories of personal infection, is, of course, especially rewarding in countries where primary resistance is frequent.

Access to one of the most interesting parts of the field may be gained through systematic exploration of the *stability* of the drug resistance. As outlined above, loss of isoniazid resistance may explain certain differential features between acquired resistance and primary resistance. But more than that is probably at stake. Although drug resistance is fundamentally stable-through inheritability of the genetic apparatus of the resistant mutants from which resistant populations most probably derive - there exist types of drug resistance in tuberculosis which are *not* stable. They are observed especially easily in low-degree resistance (although a great part of it is, of course, stable). Low-degree resistance is frequent with *minor* drugs for reasons outlined above, and, as the drug concentrations used in resistance tests are chosen according to the average resistance level of the expected strains, these unstable types of resistance are more often *seen* with the minor drugs; but they can be produced as well with the others. Their characteristic is the rapid drop of resistance through subculture on drug-free medium, hence the greater frequency of such observations in *direct* resistance-test practice.

This unstable type of resistance is sometimes called *phenotypic*. It is often discarded from the field of "true" resistance with the contemptuous statement that cells growing on drug-containing media without being genetically resistant are only a selection of the "tougher" fringe of the susceptible population. It occurs to me that such a situation is worth more than verbal qualification. Familiarity with resistance, especially if gained through quantitative methods, shows many more situations which do not fit exactly into the framework of the usual explanations. To make a long story short, *plenty of work is waiting for microbial geneticists in the field of tuberculosis*. I have never understood why the only infection in which resistance acquired *in vivo* is so frequent has not attracted their attention. Is it because everything takes place at so slow a pace in tuberculosis? This certainly increases the amount of undesirable side changes occurring in the experimental systems. But, on the other hand, with such a slow-motion picture of the processes, what an opportunity for closer observation! I do not venture to say that tuberculosis offers for the study of basic drug-resistance mechanisms the same superb model as it does for the study of delayed hypersensitivity. But the possibilities are worth exploring.

On the whole, then, drug resistance in tuberculosis is a field of admirable diversity. This field has something to offer to almost everybody: the clinician, the pathologist, the pharmacologist, the biochemist, the epidemiologist, the geneticist. They all may take advantage of the world of phenomena linked with drug resistance, and they may in turn

make their own contribution to increased knowledge in the field. Such an opportunity for far-reaching research should not be lost.

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- **Microbiology, Tuberculosis & Pulmonary Infections (MTPI) Assembly at ATS 2016:**
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  Reception: Monday, May 16, 7 - 10 p.m.; Location: San Francisco Marriott Marquis, Room: Yerba Salon 1-3 - Lower B2 Level
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