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REVIEW

Return to clinical in contrast to serologically-based diagnoses

Bruce M Rothschild

Bruce M Rothschild, Department of Medicine, Ohio Medical University, Rootstown, OH 44272, United States

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Correspondence to: Bruce M Rothschild, MD, FACR, Professor of Medicine, Department of Medicine, Ohio Medical University, 5500 Market Street, Rootstown, OH 44272, United States. spondylair@gmail.com
Telephone: +1-785-6151523
Fax: +1-724-4272707

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Abstract

The future of rheumatology is predicated upon a return to basics. The advent and facile availability of laboratory testing led to reduction of emphasis on clinical skills. Recognition that immunologic abnormalities are not limited to individuals who clearly have related pathology provides new motivation for reorientation of training programs to assure that graduates have appropriate information gathering, diagnostic and procedural skills. Inadequate accessibility to rheumatologic care requires innovative approaches and especially training and educating those individuals who provide primary care. While the rheumatologist can elicit the patient's history remotely, telerheumatology will be feasible only when the individual interacting physically with the patient has confidence in their examination skills and when those skills have been validated. Named syndromes or diseases will be modified to avoid impugning the individual or compromising their future access to health, disability and life insurance. Interventions will be pursued in a more cost-effective, evidence-based manner. The future of rheumatology is dependent upon the rheumatologist's ability to amortize the inadequate reimbursement for direct patient interaction, depending on skills of interpretation of standard X-rays, ultrasound performance and results.

Key words: Laboratory test; Immunology; Procedure; Telerheumatology; Nomenclature; Radiology; Ultrasound

Core tip: Rheumatology started as a clinical practice, dependent on skills of eliciting pertinent history, performing complete physical examination and recognition and interpretation of radiologic findings. Laboratory testing has distracted from those origins and it is time to return to those basic skills.

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INTRODUCTION

Rheumatology is undergoing a number of transitions, with the future representing a return to basics. Training programs will reemphasize development and validation of clinical skills. Serologic diagnostic approaches are being reevaluated with emphasis on clinical diagnosis.

Limitations of serology-based diagnosis

Significance of serologic test results has been a source of controversy ever since. Sharp *et al*[1] recognized anti-RNP antibodies and identified them as the arbiter for diagnosis of mixed connective tissue disease (MCTD). The MCTD that he associated with anti-RNP antibodies presented as a well-defined syndrome, consisting of a mixture of symptoms attributable to various connective tissue/collagen vascular diseases. That combination did not represent co-occurrence of more than one connective tissue disease, and was insufficient in character and associated phenomena to define a single (up until then) recognized entity.

Sharp *et al*[1] had clearly identified a previously unrecognized syndrome. As the characteristics of the phenomenon he recognized were promulgated, rheumatologists started recognizing it in the absence of anti-RNP antibodies. Thus, some perceived presence of anti-RNP antibodies as unnecessary to the diagnosis of MCTD. More widespread testing revealed that those antibodies had less specificity than originally thought[2-4]. Clinical diagnosis of Sharp's disorder has become the more common approach.

Dr. Sharp's was but one of many attempts at standardization in rheumatology. It must be remembered that such efforts were intended to create more uniform/homeogeneous groups for scientific studies, not for clinical diagnosis[5,6]. His is not unlike DRGs, developed for a similar research purpose but subsequently "hijacked" for a national clinical coding system by non-clinicians. These attempts to establish uniform groups make the assumption that disease/symptom classifications have validity and are not simply conventions, philosophical categorizations made to help guide therapeutic approaches.

Practice of rheumatology started with establishing our own laboratories for performance of sophisticated tests, declining to accept as valid any test results performed at other facilities. At some point, such tests were delegated to various outside laboratories, with loss of oversight by the ordering physician. Whether this was a manifestation of inadequate familiarity with the techniques involved or unappreciated "interference" by insurance companies designating where tests could or could not be performed, interpretation of those tests became more complicated.

Original performance of antinuclear antibody assessment on rat or mouse liver or kidney slices had well-established normal ranges, known frequency of false positives and interpretable patterns[7]. When replaced by microscopic examination of tissue culture Hep-2 cells, similar validation of pattern implications was less stringent[8]. It can no longer be specifically attributed to the originally-associated disorders. Even presence of a positive ANA can be misleading, as it is present in 5% of the general population. Given the prevalence of lupus, 95% of individuals with a positive ANA don't actually have lupus. And 5%-30% of individuals with lupus do not have a positive ANA[9].

Similarly, serology-based practitioners have used presence or absence of rheumatoid factor as defining whether an individual is suffering from rheumatoid arthritis. The titer-based nature of the test reflects the need for sufficient sensitivity to indicate greater than normal amount of rheumatoid factor in the blood (noting that antibodies reacting with components of other antibodies are routinely present in normal individuals). This reduces specificity - for abnormal amounts in the blood, not actually for diagnosis of rheumatoid arthritis. Rheumatoid factor is elevated in other connective tissue disorders, other forms of inflammatory arthritis, malignancy, chronic infections (*e.g.,* endocarditis, rheumatic fever, tuberculosis, syphilis, viral disease, parasitic disease), rheumatic fever, pulmonary fibrosis, sarcoidosis and chronic renal disease). The tradeoff between sensitivity and specificity results in a titer cutoff that has a 5% false positive result. While that cutoff may be 1:40, it is not unusual to have 1:160 titers in normal healthy individuals. The former impression that presence of rheumatoid factor has specificity for diagnosis of a specific variety of inflammatory arthritis probably derives from lumping of all inflammatory arthritis as rheumatoid, as described below.

Perhaps the most eggarious of the serologic approaches is to diagnoses ankylosing spondylitis simply because the HLA-B27 histocompatibility antigen is present. HLA-B27 is present in 90% of individuals with ankylosing spondylitis and 50% of individuals with other forms of spondyloarthropathy, but is also common in healthy individuals. A recent Turkish study found HLA-B27 present in 18% of the general population, while the prevalence in Caucasians is 13% and in African Americans, 4%[10]. Given that ankylosing spondylitis is only present in 0.2% of the population, 98% of HLA-B27 positive individuals will not have the disease. Thus, the reversion from serologic to clinical diagnostic approaches will eliminate the patient's psychic trauma resulting from receiving such a misdiagnosis and facilitate the clinician who must subsequently disabuse that patient of the perceived life-style and morbidity implications of a disease they don't have.

Reinvestment in clinical skills

In the transition from clinical diagnoses to those based on testing by outside laboratories, a standard rheumatology procedure became similarly outsourced, actual examination of joint fluid. Examination by the rheumatologist originally provided an approximation of white and red blood cell content, allowing verification of

outside laboratory actual counts[11]. Loss of cells in clots or other handling misadventures were recognized and the reliability of results provided by outside laboratories, independently assessed. This was a "side benefit" of rheumatologist-performed polarizing examination for crystals. It was also difficult to find a reference laboratory with acceptable reliability[12-15]. Concern with this issue apparently fell by the wayside, perhaps related to changes in training program priorities. Clinically oriented individuals recognize the importance of their performance of this evaluation, but serologically-oriented individuals have delegated this to outside laboratories. The future of rheumatology involves restoration of its practice by rheumatologists and re-establishing their expertise in its performance[13].

Perhaps one of the major factors stimulating renewed attention to clinical evaluation is the availability of so many effective biologic agents (*e.g.,* acting on tumor necrosis factor, interleukins 1 and 6, T cells)[16-18]. These target the inflammatory process, but have no direct effect on mechanical sources of pain and morbidity. It has become much more critical for the rheumatologist to be able to distinguish inflammatory components of a patient's complaints and limitations from those of mechanical origin[11,19]. Pain and limited ambulation (and sometimes swelling) resulting from ligamentous laxity producing knee instability may be misinterpreted as a component of the patient's inflammatory arthritis, if the responsible knee instability is not recognized. Similarly, distinguishing wrist pain related to tendonitis [often of mechanical origin (*e.g.,* DeQuervain's tenosynovitis)] is critical in its resolution, and in avoiding more aggressive anti-inflammatory and biologic therapies - for a problem that will not yield to such intervention[11,19], but will subject the patient to potential toxicity.

One of the most important lessons is for the clinician to have the patient point to the site of pain[11]. The complaint of hip pain is a classic example. This term is commonly used to identify pain in the buttock, back or lateral aspect of the pelvis, rarely for the groin - which is actually the anatomical location of the hip. While pain in the buttock or back may lead to investigation for fibromyalgia or sacroiliitis, it is pain in the lateral aspect of the pelvis which affords the rheumatologist the rare opportunity to safely provide immediate relief. That area is home to a series of bursae[20]. Previously referred to simply as trochanteric bursitis, it has now been realized that there are actually four bursae that are typically involved as a group - and that treatment of only one usually is ineffective. All four bursae (gluteus medius, gluteus minimus, subgluteus medius and subgluteus minimus) need to be injected with a water insoluble corticosteroid. Water soluble steroids simply diffuse to the whole body, while non-soluble ones remain localized to the affected area. They expose the patient to less systemic complications. The lidocaine in the injection provides immediate relief and verifies the accuracy of the diagnosis, while the corticosteroid provides lasting benefit. Of course, for this disorder and for others (*e.g.,* epicondylitis, DeQuervain's tenosynovitis), it is important to examine clinical history for activities of daily life and occupational derivations - issues which need resolution, if recurrence is to be avoided.

Clinical skills of physical examination are also being reemphasized, especially the importance of assuring the examination is complete and inclusive[11]. Uniformity is critical, to reduce interobserver variability[21,22]. This includes assuring ability to perform arthrocentesis of all joints. The "no touch" joint aspiration technique was recognized and promoted a third of a century ago. It is predicated upon understanding joint anatomy, a subject typically not addressed in medical school. Renewed access to the anatomy laboratory provides the opportunity to dissect and identify surface markers that allow facile joint access joint[11]. Much of this has been relegated to utilization of ultrasound for needle placement, allowing clinical skills to deteriorate, rather than utilizing ultrasound images to refine those clinical skills.

Role of procedures

Rheumatology has been a field badly in need of a procedure. Reimbursement for time spent with patients has been woefully inadequate, while procedures are typically well compensated. Closed muscle biopsies, fat and synovial membrane biopsies have been pursued, but are not major revenue generators. Rheumatologists will have difficulty maintaining the level of our services if we cannot amortize the inadequately reimbursed clinical examinations.

An early consideration was developing endoscopy (gastroscopy) skills, as it was thought that rheumatologists should be able to evaluate the ulcers caused by the medications we prescribe. Assessing significance of gastrointestinal complaints is complicated as most symptomatic individuals actually do not have endoscopic evidence of damage, while many non-steroidal anti-inflammatory drug-related ulcers are not symptomatic. A mechanism existed in the 1980's to establish just such training. It was, however, abandoned because hospital credentialing at that time was usually limited to those who had completed a gastroenterology training program, with general surgeons grudgingly allowed to perform the procedure. Rheumatologists were not getting credentialed, despite appropriate training.

Infusions have been touted as revenue-generators, leading to a potential conflict of interest between patient and practice revenue. Performance and examination of X-rays would seem the most appropriate procedure for rheumatologists to add to the armamentarium. Thus, training in radiologic techniques will be emphasized as well as developing skills necessary for skeletal radiologic evaluations[11]. Because some rheumatologists practice in an environment where the organization/hospital has an agreement with a radiology group for sole performance of X-ray examinations, there has been a perception that stream of revenue is totally lost. However, training in skeletal radiology provides the opportunity to bill for

reexamination of X-ray images, whenever there are findings that general radiologists have not recognized. The generalist has a search image and pattern of review that is different than that of the skeletal radiologist (*e.g.,* rheumatologist trained in skeletal radiology), so each has significant contributions to patient care and it is appropriate for both to bill.

Attempting to find a fully billable procedure has led rheumatologists to consider diagnostic ultrasound. While an excellent and informative technique[23-25], it is quite time-expensive, although shortcuts with limited examinations have been pursued[26]. It has been used for needle localization for arthrocentesis for those without confidence in their clinical skills to localize the joint[27-29], but does have a value in recognizing calcium pyrophosphate deposition disease and gout, as well as distinguishing synovial effusions from synovial proliferation and recognizing erosions[27,28,30,31]. There has been significant controversy as to whether it is more sensitive than the clinical examination for recognition of effusions, most of which seems to relate to examination skills. It may be one of the best radiologic techniques for recognizing and identification of shoulder pathology[32], a 20 min examination which unfortunately is not sufficiently recompensed for that time allocation.

Diagnostic appellations

We've also learned to examine what's in a name: An identification helpful to patients or a diagnosis that can be used to discriminate (*e.g.,* by insurers). Names often have unintended deleterious effects, stigmatizing people, industries or communities and can misdirect therapy[33,34]. This is exemplified by changes in utilization of the diagnostic appellation, rheumatoid arthritis. The criteria originally proposed by Ropes *et al*[5] were modified by a committee of what was then the American Rheumatism Association modification of criteria for rheumatoid arthritis in 1987[35].

Diagnosis of rheumatoid arthritis has been predicated on committee-derived criteria which subsequently expanded its purview and deleted past exceptions[36-39]. The resulting patient cohort may be more inclusive, but specificity is problematic. This has commonly resulted[40-42] in lumping as rheumatoid arthritis additional patients with predominantly non-axial disease[43-45]. Expansion of these criteria was accompanied by the requirement that there be no "alternative diagnosis that better explains the synovitis". The latter assumes adequate diagnostic skills to recognize other disorders. Spondyloarthropathy and calcium pyrophosphate deposition disease are the major disorders that share clinical presentations with that of rheumatoid arthritis[46-48], It is critical to recognize the symmetrical pattern, marginal localization of and axial joint sparing characteristics of rheumatoid arthritis[49-51], if these alternative diagnoses are to be recognized.

Examination of the archeologic record reveals two distinct patterns, thus challenging the specificity incurred when utilizing the 1987 criteria for diagnosis of rheumatoid arthritis. Predominant metacarpal phalangeal joint involvement, distribution of erosions to the bare areas of peripheral joints and periarticular osteopenia characterizes the arthritis present in seven populations, with joint ankyloses conspicuously absent[38,39,49,52].

Erosions in skeletons from other archeologic sites involved fewer joints and were typically localized to the areas originally covered by cartilage (subchondral)[53-57]. Joints were often fused[46,48,50,54,56,58-62]. Radiologic examination revealed periarticular osteopenia in less than half, in contrast to its universal presence in the first gro up[46,48,50,54,56,58-62]. Why are the patterns and distribution of joint involvement so different in these populations? "Osseotropism" and "rheumotrophism" have been suggested to help characterize the phenomena[57]. It seems useful to examine how individuals with this second pattern of arthritis compare with those more universally recognized as having spondyloarthropathy, those with axial joint disease[46,48,54,57,62,63]. Vertebral centra bridging in the form of syndesmophytes and sacroiliac joint and zygapophyseal erosions or fusion through their articular surfaces are definitive for the diagnosis of spondyloarthropathy[46,48,54,57,62,63]. It is the latter form of fusion through the articular surface of sacroiliac joints that provides insights to the subchondral propensity of erosion localization in peripheral joints. Fusion requires that the integrity of the subchondral cartilage be compromised, such that trabeculae can bridge what was originally a synovial lined space. This propensity is not found in individuals with rheumatoid arthritis.

The biomechanics of the two diseases are also quite different[53,64]. As might be expected, a disorder that disrupts articular surfaces should produce joints which glide less easily than one in which the joint surface is smooth. One method to quantify such variation is use of an accelerometer, which characterizes as vibration intensity/power the joints resistance to transitional movement[64,65]. High vibration/power was noted in individuals with subchondral erosions, independent of presence or absence of peripheral joint fusion or axial joint disease, in contrast to low vibration/power in individuals with marginal erosions lacking peripheral joint fusion or axial joint disease, the group classically recognized as having rheumatoid arthritis[64,65]. There was no overlap of vibration/power "signatures" between the groups.

Critical examination of the zoologic record also provides clarity. Previous diagnosis of rheumatoid arthritis in pigs and dogs[66-69] was apparently related to lack of familiarity with alternative (to rheumatoid arthritis) diagnoses, as the classic subchondral erosions and peripheral joint fusion of spondyoarthropathy were present[51,54,62,70,71]. Systematic assessment revealed frequent evidence of the above-noted patterns associated with spondyloarthropathy, but none of those associated with rheumatoid arthritis, among more than 30000 mammals examined in zoological collections around

the world[46,50,72]. The animals have a disorder clearly distinguishable from classic rheumatoid arthritis.

Peripheral joint fusion clearly represents a pathophysiology distinct from that of natural course of rheumatoid arthritis[38]. The term "natural" is used, as corticosteroid therapy has many complications, including altering disease course to allow joint fusion. The biomechanics and epidemiology (both archeologic and zoological) of erosive arthritis clearly separate rheumatoid arthritis and spondyloarthropathy. Those studies further note that isolated wrist and ankle affliction is indicative of spondyloarthropathy and not rheumatoid arthritis. The lumper-splitter controversy, wherein lumpers considered most inflammatory arthritis as part of the rheumatoid arthritis syndrome, is being superceded by the splitters[6,73,74].

Therapeutic intervention

While methotrexate and tumor necrosis factor inhibitors might be considered the "boutique" treatments for inflammatory arthritis[75], because of less insurance company obstruction to their use and expansion of available biologic agents, therapeutic intervention also is returning to the basics and perhaps more cost-effective agents. Use of one of the older agents, hydroxychlorquine (plaquenil), is undergoing resurgence, with renewed recognition of its efficacy[76]. Sulfasalazine is another example. It originally was developed specifically for treatment of rheumatoid arthritis because of the perspective that it was infectious in origin[77,78]. At the time of its conception, antibiotics were predominantly sulfa-based. Combining that antibiotic with the anti-inflammatory effect of salicylate was therefore logical but proved to be ineffective - in the short term. It was subsequently recognized that sulfasalazine had delayed benefit, requiring months for its efficacy to manifest. Renewed consideration of sulfasazine therapy resulted from recognition of inflammatory arthritis of the spondyloarthropathy variety in gorillas[79]. How do you treat a 600 pound individual with an attitude? Eye contact is considered a threat gesture and they don't cooperate in the same manner as chimpanzees for the vascular access necessary to assure medication safety. Anesthetizing gorillas at frequent intervals is not an option, because of anesthesia-related mortality. A medication was required which did not require the close laboratory monitoring so necessary with methotrexate and the ophthalmologic evaluations required with hydroxychloroquine use[80,81]. Sulfasalazine seems the safest of the disease modifying (DMARD), has documented efficacy in gorillas, and is actually now standard veterinary treatment for the disease (except perhaps in dogs, where some develop dry eyes from the drug)[79]. Recognition of its efficacy across the vertebrate spectrum[79], led to reexamination of its use in humans and recognition that it offers a safe alternative (without the cancer risk) to methotrexate.

Telerheumatology

Telemedicine or remote provision of services has been suggested as a new approach, especially in underserved areas[82]. Working with physicians and physician extenders, this has proven a useful approach in Alaska[83]. If needed for cardiology (for which extensive education and experience are provided in medical school and residencies), how much more so that might seem for rheumatology. However, that very difference in training and experience is fundamental to the difficulty of providing rheumatology services in such a manner[84]. It would require establishment and validation of physical examination (not limited to the joints) and history taking skills, assurance that those skills are maintained

Those history taking skills require attention to nuances and vocabulary variation in different geographic and ethnic populations. There are major discrepancies between patient-completed questionnaires and their verbal response to essentially the same questions (*e.g.,* attention to hesitancy in responses, suggesting they are thinking about the question. If so, it is useful to have patient verbalize what they are considering and often dismissing - precluding access to important diagnostic information. "Absenting substantial revision of medical school and post-graduate education and training, telerheumatology does not seem feasible"[84], not ready for prime time.

CONCLUSION

The future of rheumatology is predicated upon patient advocacy as always, but now more proactive with those who make the laws/regulations that insurance companies are obligated to follow[81]. This derives from insurance companies with oxymoronic names stonewalling evidence-based appeals and even FDA-approved usages in favor of medicines unapproved for a given indication. The future direction is illustrated by the change in the American College of Physicians' journal name from Arthritis and Rheumatism to Arthritis and Rheumatology. Rheumatism was an old term for aches and pains. Rheumatology deals with much more than arthritis and now recognizes derivation of those aches and pains. It has changed from simply recording symptoms to identifying their causes. That is the future of rheumatology, pursuing a more scientific, evidence-based approach, examining and testing preconceived notions to provide appropriate care with an approach that maximizes efficacy and safety.

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