INSTRUCTIONS FOR LETTERS TO THE EDITOR

Editorial comment in the form of a Letter to the Editor is invited; however, it should not exceed 800 words, with a maximum of 10 references and no more than 2 figures (submitted as camera ready hard copy per Journal Guidelines) or tables and no subdivision for an Abstract, Methods, or Results. Letters should have no more than 3 authors. Full name(s) and address of the author(s) should accompany the letter as well as the telephone number, fax number, or E-mail address.

Contact. **The Managing Editor, The Journal of Rheumatology, 920 Yonge Street, Suite 115, Toronto, Ontario M6J 3G7, CANADA. Tel: 416-967-5155; Fax: 416-967-7556; E-mail: jrheum@jrheum.com Financial associations or other possible conflicts of interest should always be disclosed.**

Diagnostic Relevance of Antibodies to Serotonin and Phospholipids in Fibromyalgia Syndrome

To the Editor:

In their communication, Werle, *et al* reported that antibodies to serotonin can be detected in patients with fibromyalgia syndrome (FM) in a significantly higher incidence (20%) than in healthy controls (5%; $p < 0.003$); nevertheless they state that "antibodies against serotonin have no diagnostic relevance in patients with fibromyalgia syndrome"[1]. We do not agree with this interpretation, and would like to add further data.

Indeed, in 1992, we reported that antibodies to serotonin could be detected in 74% of 50 FM patients[2], and in 1994 we described for the first time the association of antiserotonin antibodies with antibodies to phospholipids. Among 100 FM patients 73% had antibodies to serotonin and 54% to phospholipids[3]. These patients had been followed in our outpatient department for 6–10 years (P.A. Berg), and several serum samples were available from these patients during that time. As mentioned by Werle, *et al*[1], in the meantime several point analysis studies have been performed by us and other authors observing an incidence of antiserotonin antibodies in the range of 20–61% and of antiphospholipid antibodies in the range of 26–36%. To clarify these discrepancies with respect to our previous findings, we started another point analysis in 1997 in 72 additional patients seen in our outpatient department (R. Klein). The incidence of the antibodies to serotonin was low, reaching only 28% (Table 1). However, following these patients in a longitudinal study, i.e., testing sera at different time intervals during a period of 4 years, we observed that up to 58% have been found positive (unpublished observation). Therefore, one has to postulate that antibodies to serotonin in particular can fluctuate. Analyzing more than 200 controls, only 11–15% were found to be positive, and this was statistically significant compared to the patients with FM ($p < 0.01$).

Concerning the incidence of antiphospholipid antibodies (aPL), our previous finding[3] was confirmed by the group in Heidelberg, who detected aPL in 43% of their patients with FM[1]. These observations are of interest with respect to a recent report demonstrating a hypercoagulable state in 92% of 54 patients with FM and chronic fatigue syndrome (CFS) similar to that in patients with antiphospholipid antibody syndrome[4].

Considering the concept that FM may belong to a wider syndrome, labelled "functional somatic syndrome"[5], we tested, using a different approach, sera from patients with other disorders that have been attributed to this syndrome, such as CFS or irritable bowel disease. We also included patients with disorders representing single symptoms of FM such as depression, migraine, endometriosis, restless legs syndrome, or inner ear diseases (reference 6 and unpublished observations). Interestingly, also in these patients we found antibodies to serotonin in 25–68% and aPL in 25–50%. In contrast, in patients with inflammatory rheumatic disorders, the antibodies to serotonin were detected in only 11–15%[2,6], and this frequency was similar to that in healthy individuals (Table 1). Taken together these data argue in favor of the diagnostic relevance of antibodies to serotonin and phospholipids.

As for many autoantibody associated diseases, the triggering events responsible for these characteristic serological phenomena remain unknown. One explanation often discussed is molecular mimicry leading to the loss of tolerance towards autoantigens[7]. That FM and especially CFS can be precipitated also by infectious agents[8] fits this concept.

It is well documented that autoreactivity is a physiological condition[9], and therefore it is not surprising that the FM associated antibodies are also found in healthy individuals, although at a low incidence. The concept of the existence of a physiological autoimmune reaction towards serotonin is substantiated by our recent finding that also autoreactive T lymphocytes recognizing tryptophan and serotonin can be detected in healthy individuals and in an enhanced incidence in FM patients[10]. It seems therefore most likely that the antibodies are part of the pool of naturally occurring antibodies, which are mainly involved in the first line defence to bacterial or viral infections or chemical xenobiotics[9].

Further, it is not at all unlikely that FM is a heterogeneous disease, and that the demonstration of autoantibodies may reflect a subgroup with a possible autoimmune origin. This would also explain variations in the incidence of FM associated antibodies reported by different authors. In any case, the observation of a defined group of antibodies in association with specific clinical manifestations is considered in many instances as an indicator for a particular autoimmune disorder[10], and therefore there is no reason to reject the significantly increased antibodies to serotonin as diagnostically relevant for FM.

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Table 1. Incidence of antibodies to serotonin and phospholipids in patients with FM analyzed in 2 university hospitals (Heidelberg and Tübingen) in the last 10 years, based either on point analysis or longitudinal studies. Antibodies were found in only 9–15 % of healthy controls.

Hospital	Type of study	No. of Patients	Antibodies to Serotonin, %	Antibodies to Phospholipids, %	Antibody Positive, Total	Reference
Tübingen	Longitudinal (1994)	100	72	54	79	3
	Point analysis (1997)	72	28	26	44	Unpublished
	Longitudinal (2001)	72	58	47	67	Unpublished
Heidelberg	Point analysis (2001)	203	20	43	?	1

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Drs. Werle, *et al* reply

To the Editor:

We appreciate the investigations of our colleagues Klein and Berg in the field of fibromyalgia (FM), and their sophisticated pathophysiological considerations. From our point of view, the results of the different studies cited in their letter are not contradictory; however, the interpretation and clinical conclusion are quite different and conflicting.

The question we discussed in our paper[1] was: What is the diagnostic power of antiserotonin antibodies? Is the detection of these autoantibodies *clinically* useful for decision making? Should we routinely measure these antibodies? How can these results influence the treatment of our patients?

In their letter, Klein and Berg summarize that the prevalence of antiserotonin antibodies varies in a broad range of 20–61%. They state that this is due to a high level but considerable fluctuation of antiserotonin antibodies over time. A similar gap of antibody prevalence (25–68%) was observed by Klein and Berg in patients with other functional disorders.

These data strengthen our opinion that a positive antiserotonin antibody test result has no clinical relevance for differential diagnosis of FM. These antibodies are not useful to discriminate patients from nonpatients in FM or to identify clinically relevant subgroups of FM patients, since there is no evidence that the variation of concentration of antiserotonin antibody over time is related to progression of symptom severity. The clinician has to decide on diagnosis and therapy, and antibody testing offers no help in this respect.

Figure 1 illustrates the association of disease prevalence and the positive predictive value of antiserotonin antibodies for the diagnosis of FM based on a sensitivity of 20% and a specificity of 95% based on the data of our study. This plot demonstrates that, for example, at a prevalence of about 5%, which has been reported for females at an age of about 50 years[2], the positive predictive value is 0.17. This means that only one of 5 positive test results is likely to indicate an FM patient, and vice versa 4 out of 5 positive results were received from non-FM subjects. At a given prevalence of 30%, which might occur only in very specialized outpatient clinics, the probability to obtain a positive test result in FM patients would still be only about 50%. Moreover the negative predictive value is not a useful criterion for decision making.

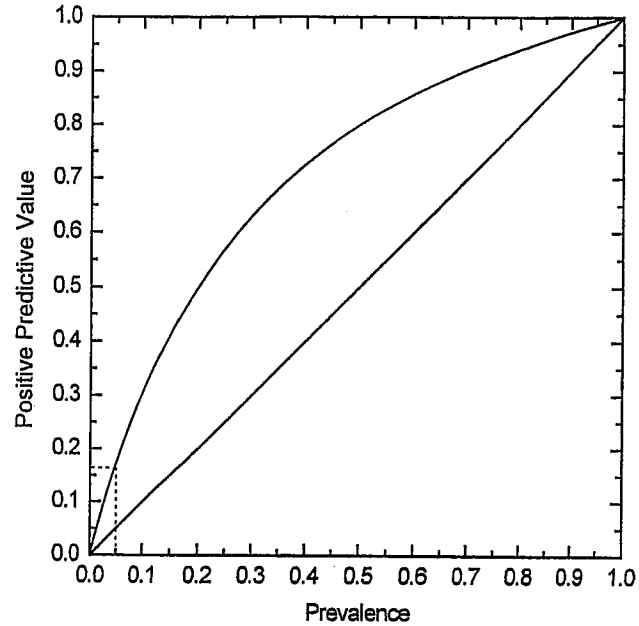

Figure 1. Association of disease prevalence and positive predictive value (PPV) of antiserotonin antibodies for the diagnosis of FM based on sensitivity of 20% and specificity of 95%. At a prevalence of 0.05 the PPV is 0.17 (broken line).

However, the scientific question of why there are significant differences in autoantibody patterns between FM patients and normal controls needs further clarification.

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Is Hypermobility a Factor in Fibromyalgia?

To the Editor:

I read with great interest the comments by Dr. Fitzcharles regarding hypermobility and its possible association with fibromyalgia[1] (FM). Unfortunately, evaluation and documentation of hypermobility is difficult in uncomfortable patients with a tendency toward deconditioning and generalized muscle spasm from nonrestorative sleep. Beyond improving our ability to recognize hypermobility in this challenging patient subset, considering other associations with hypermobility may provide different insight into this question.

Hypermobility is associated with specific, important mechanical stresses at the joints and entheses, often resulting in a presentation of migratory, nondeforming musculoskeletal pain in children and adults. Overuse syndromes, possibly more common due to altered local enthesopathic stresses during

repetitive or transient microtrauma from joint hyperflexion and hyperextension under duress, may account for some of these presentations. "Repeated minor traumatic episodes" may be an important consideration and a treatment focus, but I suspect that a larger issue underlies the hypothesis that FM is associated with hypermobility.

Evidence of altered autonomic function, whether primary or secondary, in patients with FM is building[2,3]. Also, the relevance of autonomic regulation[4] as it relates to many maladies has not yet been fully explored. Hypermobility is associated with anxiety[5], panic attack[6], and unexplained chest pain, which may all be linked by dysregulation of autonomic function. Patients with FM often exhibit many stimulatory issues interfering with sleep quality, such as nighttime restlessness[7], racing thoughts, and busy dreams. Options to decrease this nighttime restlessness with lorazepam, clonazepam[8], and pramipexole[9] in doses used for restless legs syndrome, all decreased FM pain scores, at least in preliminary open label analyses of 166–202 consecutive patients. Posttraumatic stress disorder commonly accompanies FM[10], and may be another manifestation of excessive sympathetic tone. This fight-or-flight response should be expected to inhibit deep, restorative sleep through hypervigilance, i.e., a fundamental, primitive, survival mechanism.

Why hypermobility would cluster with or be a marker for a tendency to have excessive sympathetic tone is unclear. If one believes that FM is an expected and predictable consequence of significant, persistent stage IV sleep disturbance, whether through torture or experimentally induced, then an effective inhibitor of deep sleep, such as excessive sympathetic tone, may be important. If so, it is interesting that hypermobility may simply be a musculoskeletal marker for a potential to develop autonomic dysregulation especially in the setting of intense or prolonged sympathetic/fight-or-flight stimuli. Hypermobility may be difficult to document, but understanding its implications as an important risk factor for more than local mechanical enthesopathic stress may provide meaningful insight into prevention and treatment of autonomically mediated gastrointestinal, cardiac, psychiatric, and musculoskeletal disorders.

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Dr. Fitzcharles replies

To the Editor:

Dr. Holman's interesting comments regarding fibromyalgia (FM), hypermobility, and recent findings indicating altered autonomic function in this group of patients are appreciated.

We agree with Dr. Holman that the role of the central nervous system (CNS) is increasingly recognized in FM. The focus towards dysregulation of central pain processing mechanisms, including changes in autonomic function, is seemingly more plausible in the light of recent research[1]. The puzzling mechanisms of function of the CNS are slowly becoming clearer as variables such as autonomic function, levels of neuromodulators, and even changes in cerebral blood flow are now measurable. The findings of autonomic dysregulation in illnesses not manifesting prominent chronic pain such as severe liver disease[2], Parkinson's disease[3], and postmyocardial infarction[4], as well as other conditions commonly associated with pain such as irritable bowel syndrome[5], chronic headaches[6], and recently FM[7] calls into question the precise role of the autonomic nervous system in pain perception and expression. We do not yet know whether these observations represent simply an associated finding or have influence upon the expression of the condition. We should therefore exercise caution in not too readily attributing a single factor such as autonomic dysfunction as a cause of pain in FM.

Our current understanding of FM suggests that multiple factors are likely operative. To date, there are two measurements that appear to show consistent abnormality: abnormalities of substance P in the cerebral spinal fluid and reduction of thalamic regional blood flow as measured by resting single photon emission computed tomography (SPECT) brain scan, with precise anatomical localization by superimposition of magnetic resonance imaging (MRI) scan[8,9]. Autonomic dysregulation likely represents some component of this central pain mechanism, and further study is needed to clarify the importance of this finding.

The sleep disturbance in FM is also perplexing. Great hopes were held for the effect of the tricyclic antidepressants on the sleep disorder in FM and therefore relief of symptoms. The modification of the sleep abnormality has, however, not proved successful in relieving the symptoms of pain in the majority of patients with FM, and these agents are often discontinued by patients over time. In addition, FM was found to occur at the same rate as in population studies when patients attending a sleep disorders clinic were examined, suggesting that sleep disturbance alone is not a major factor in the expression of FM[10].

The notion of hypermobility associating with panic disorders and anxiety is intriguing and difficult to understand. The studies from Barcelona have described a strong association of hypermobility in patients with anxiety disorders, and also a high rate of anxiety disorder in rheumatology patients exhibiting hypermobility[11,12]. These findings from a single tertiary care center require confirmation in other patient populations. The association between physical changes of connective tissue and disordered psychological status defies our current understanding. We have, however, learned that the psyche does have important influence upon physical manifestations in humans, such as stress induced bronchospastic disease or possibly even the diffuse pain of FM.

Needless to say there are likely many compounding factors influencing the expression of FM. Among the numerous factors being explored, physical changes such as hypermobility, neuroendocrine abnormalities, the effect of previous pain experience, overall deconditioning, and possibly even some genetic components are currently in vogue. The exact role of each of these factors may soon be elucidated.

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Warfarin and Azathioprine: Clinically Significant Drug Interaction

To the Editor:

Warfarin and azathioprine (AZA) is a combination of drugs that is often encountered in patients with rheumatological conditions such as systemic lupus erythematosus (SLE). A drug interaction between warfarin and AZA is not a commonly recognized event and the mechanism for such an interaction is incompletely understood. A review by Wells, *et al*[1] presents level 3 evidence for an interaction between AZA and warfarin in which AZA induces an apparent resistance to warfarin anticoagulation. Level 3 evidence suggests a possible association on the basis of case reports in which the timing is pharmacologically plausible. The basis of the claim is a single case report in which bleeding occurred in a patient receiving anticoagulation with warfarin upon discontinuation of AZA[2]. Since this review, 2 more case reports have been published[3,4] providing additional level 3 evidence of a possible association. The authors describe international normalized ratio (INR) levels remaining subtherapeutic despite increasing doses of warfarin in patients also taking AZA. In addition, an abstract has been published describing a retrospective study of patients with primary and secondary antiphospholipid antibody syndrome, where there was an increased requirement for warfarin in those patients receiving AZA[5].

We describe an additional case of AZA induced warfarin resistance that further supports the contention of a significant interaction between these 2 drugs.

A 41-year-old woman with a 3 year history of SLE with a strongly positive anticardiolipin antibody test, complicated by a pulmonary embolus, presented with increasing shortness of breath for 2 weeks. She had to sleep propped up, was unable to walk 5 m without becoming dyspneic, and reported sharp pleuritic pain in the posterior chest wall. She had been taking warfarin since the time of diagnosis, with a stable INR in the therapeutic range, and a daily dose in the order of 5 mg. Her SLE symptoms, including bronchiolitis obliterans organizing pneumonia (BOOP) and pericarditis, had been reasonably controlled with 50 mg/day prednisolone for 3 months, and longterm hydroxychloroquine 200 mg/day.

During a quiescent phase of her illness, AZA was added as a steroid-sparing agent and hydroxychloroquine was stopped. The dose of AZA was gradually increased over a period of 6 months, from 25 mg daily to the present dose of 150 mg daily. The increased shortness of breath developed 3.5 months after commencement of AZA. She was admitted for investigation and management, and on admission her INR was found to be 1.8.

During the admission, her warfarin dose was increased steadily, until an INR of 3.5 was achieved with a daily dose of 12 mg warfarin. She was then discharged. Her dose of prednisolone and AZA remained unchanged throughout the admission and discharge.

Warfarin is a drug that is frequently associated with clinically significant drug interactions, particularly those in which the anticoagulant effects are potentiated. Drug interactions in which the effects of warfarin are inhibited are less frequent, and standard texts make very little mention of a drug interaction between warfarin and AZA[6-8]. To date, this phenomenon has been described in only 3 individual case reports and one abstract[2-5].

From Figure 1, it can be seen that the INR of our patient remained within the therapeutic range for a long period, dropping to subtherapeutic levels for a sustained time only when AZA was introduced. Concurrently reducing doses of prednisolone may also be implicated in this case of warfarin resistance; however, a literature review failed to identify a drug interaction between any of the corticosteroid drugs and warfarin. In our patient the drug interaction did not become apparent until the dose of AZA reached 100 mg. In all 3 case reports documenting interaction, the patients were taking between 100 and 200 mg AZA when the problem was noted. Taken together, this would seem to indicate that the interaction is dose dependent.

To definitively prove that a drug interaction exists, rigorous scientific method would demand that we withdraw AZA from the patient, with subsequent rechallenge to document the changes in INR and required warfarin dose. However, in the case of our patient, clinical judgment dictates that such a course of action would be unethical. In 2 of the case reports, AZA was withdrawn and rechallenged, with commensurate increases in daily warfarin requirements[3,4].

Without measuring blood levels of warfarin in these patients, it is only possible to speculate on the nature of the interaction between warfarin and AZA. Impairment of the anticoagulant effects of warfarin in the presence of AZA could arise from pharmacodynamic or pharmacokinetic factors. Subtherapeutic responses may be caused by ingestion of vitamin K-containing substances or the concurrent administration of agents that are known to reduce the absorption or enhance the metabolism of warfarin, either by inducing tissue resistance to the anticoagulant effects or by enhancing biotransformation of the S-isomer of warfarin to the less pharmacologically active R-isomer.

This is the fourth published report of a clinically significant drug interaction between warfarin and AZA. The introduction of AZA to the drug regimen of patients taking warfarin results in a higher dose of warfarin being required to maintain therapeutic INR levels. We feel it is important that this interaction

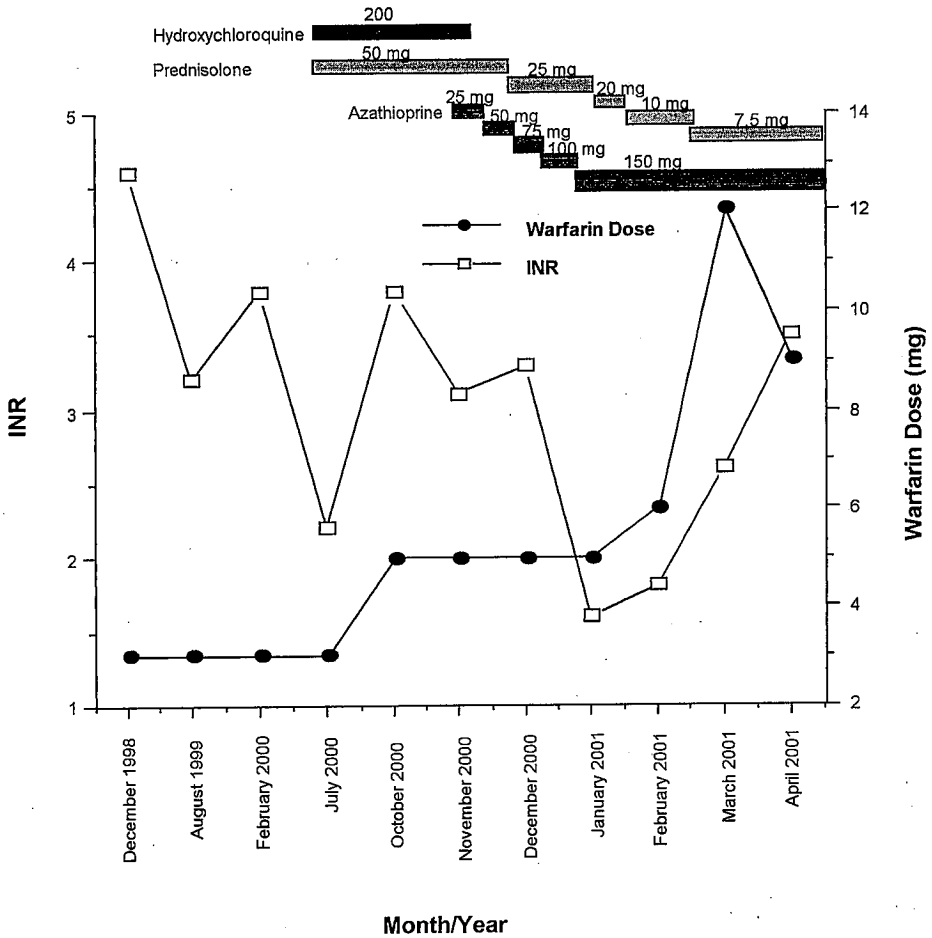

Figure 1. Drug therapy in this patient.

is more widely recognized among clinicians, and that the INR be carefully monitored in patients taking warfarin when the AZA dosage is modified.

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Obesity Does Not Impair Rehabilitation Outcome in Spondyloarthropathy

To the Editor:

Seronegative spondyloarthropathies (SpA)[1,2] involve spinal and extraspinal joints and entheses, frequently leading to increasing limitation of spinal mobility. The body mass index (BMI) has no or limited influence on the range of motion in the spine in a healthy population[3,4]. Both obesity and underweight have been found to have an association with an increased risk in functional status decline[5]. We have found no publications dealing with the influence of BMI on spinal movement measures, functional indices, or rehabilitation outcome in patients with SpA; it might nonetheless be assumed that obesity would have a negative effect on these. We tested this hypothesis.

The series consisted of 122 consecutive patients (71 men, 51 women) who had SpA with spinal involvement. The diagnoses were mostly idiopathic ankylosing spondylitis: 82 patients; 40 patients had other SpA (i.e., reactive arthritis, enteroarthritis due to colitis ulcerosa or morbus Crohn, psoriatic and nonspecific spondyloarthritis). Their health condition was otherwise fairly good: 60% had no other disease, 25% had some other disease in stable condition, e.g., hypertension, and 15% had some other back or joint complaint, e.g., degenerative disease; but symptoms were mostly attributable to spondyloarthritis. BMI is calculated as follows: body weight (kg)/body height (m) × body height (m). Obesity was defined from a cutoff BMI > 25 kg/m². There were 54 patients (28 men, 26 women) with BMI < 25 kg/m² and 68 patients (43 men, 25 women) with BMI > 25 kg/m². Age, disease duration, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and body height did not differ between the groups.

Table 1. The adjusted results (age, disease duration, and actual entry value of the variable) of rehabilitation short-term effects of spinal measurements and functional indices BASFI (Bath Ankylosing Spondylitis Functional Index) and DFI (Dougados Functional Index) in male patients with spondyloarthropathy.

Variable	Baseline		Mean Difference in Change		p-value Between Changes
	BMI < 25 Mean (SD)	BMI ≥ 25 Mean (SD)	BMI < 25 Mean (95% CI)	BMI ≥ 25 Mean (95% CI)	
Spinal mobility measurements, mm					
Thoracolumbar flexion S1-C7	60 (22)	57 (29)	–9 (–4 to –14)	–7 (–3 to –10)	0.40
Thoracolumbar rotation, tape	26 (16)	22 (14)	–4 (–1 to –6)	–5 (–2 to –8)	0.41
Finger-floor distance	145 (162)	168 (152)	43 (13 to 74)	54 (20 to 89)	0.62
Functional indices as score values					
BASFI (0–10)	2.6 (1.8)	3.5 (2.3)	0.5 (0.1 to 1.0)	0.7 (0.3 to1.1)	0.57
DFI (0–40)	7.8 (5.1)	11.4 (6.9)	1.5 (–0.4 to 3.4)	2.3 (0.9 to 3.7)	0.46

The patients participated in a 3 week inpatient rehabilitation course based on intensive physiotherapy and exercise; the treatment program has been described[6]. Spinal mobility and functional ability were measured at the beginning and at the end of the course. The spinal mobility measurement methodology has been described in detail[7,8]; the 11 movement measures were Schober S1 test, whole thoracolumbar flexion from S1 to C7, thoracolumbar lateral flexion, thoracolumbar rotation as mean value for right and left side with a tape as in the Pavelka method, occiput to wall distance, cervical rotation, cervical lateral flexion, cervical extension, finger to floor distance, chest expansion, and intermalleolar distance. Patients filled in self-administered questionnaires for the functional indices: the Bath Ankylosing Spondylitis Functional Index (BASFI)[9] and the Dougados Functional Index (DFI)[10]. The Finnish versions of these indices have been validated[11]. The questionnaires were sent to the patients 6 months after the rehabilitation, and 78% of them fulfilled the indices.

Without adjustments, the range of motion measures and BASFI at baseline did not differ between groups; DFI was a little poorer in obese patients (mean DFI 10.6 in obese and 7.4 in other patients). All 11 spinal movement measures (except occiput to wall distance in the group with BMI < 25 kg/m²) and both functional indices improved highly significantly ($p < 0.01$) during the course in both the obese and the non-obese groups, and there were no significant differences between the groups in the short-term effects of rehabilitation.

Adjusting according to sex, age, disease duration, and the value for the variable at entry, the data on short term rehabilitation effects are given in Table 1. This adjusted analysis includes only men (n = 16 in the BMI < 25 kg/m² group, and n = 18 with BMI > 25 kg/m²), whose demographic data were the following (mean/range): age 46 years (29–70), disease duration since diagnosis 9 years (0–30), ESR 16 mm/h (2–66), CRP 12 mg/l (1–51), and BMI 25.8 kg/m² (18.9–35.5, SD 4.1). There were no differences in the adjusted results between the obese and non-obese groups.

Six months after the course the functional indices had worsened from the end values of the course and the changes between the BMI groups did not differ significantly; however, the BASFI values had a tendency to worsen more in obese patients during the followup. There were no differences in BMI values between participating and nonparticipating patients.

In the Finnish population (1997) 67% of men and 51% of women aged 25–54 years had BMI ≥ 25[12], and the BMI distribution seems to be about equal in patients with SpA: 62% of men and 51% of women aged 25–64 years with SpA had BMI ≥ 25.

Although the BMI has no association with ranges of spinal movements, obesity otherwise has a negative influence on health condition. It is encouraging that obese patients with SpA benefit from rehabilitation no less than the non-obese. If obese patients can be motivated to continue the exercises taught during the rehabilitation course, they may benefit from rehabilitation even more than those of normal weight, since continuous exercise may serve to alleviate possible comorbidity, e.g., hypertension and diabetes.

Thus BMI has no effect on spinal mobility mesurements and obesity does not impair short term rehabilitation effects in SpA. We recommend rehabilitation equally for obese and for non-obese patients with spondyloarthropathy.

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Validation of a German Version of the Disabilities of Arm, Shoulder, and Hand Questionnaire (DASH-G)

To the Editor:

In 1994 the American Academy of Orthopedic Surgeons Outcome Research Committee developed and validated a functional outcome questionnaire, the Disabilities of Arm, Shoulder, and Hand questionnaire (DASH)[1]. This instrument covers symptoms of the upper extremity, hand and wrist function, heavy and high performance of the upper extremity, and general upper extremity function. The objective of our study was to translate the DASH into German and to evaluate its reliability and validity for German speaking patients with shoulder pain.

Included in our study were 52 consecutive patients with shoulder pain attending our department. Inclusion criteria were: (1) informed consent; (2) age 18 or older; (3) ability to complete questionnaires; (4) shoulder pain originating from within shoulder girdle (no known neurological or vascular disorders, neoplasm, referred pain from internal organs, or systemic rheumatic condition); and (5) no fractures or dislocation.

Participants underwent a standardized clinical examination and were provided with a questionnaire. Active range of motion of the shoulder using a plurimeter[2] was assessed in a sitting position: forward flexion, abduction, external rotation, and internal rotation in 90° abduction.

The patients had to rate their level of current pain (numerical rating scale)* and the global effect the shoulder problem has on their shoulder function (5 point scale).

The DASH consists of 2 components: the function/symptom/social role component and the optional high performance sport/music or work section. We used the function/symptom/social role component only in the validation process.

Further instruments included German versions of the Stanford Health Assessment Questionnaire (HAQ)[3] and the Medical Outcomes Study Short Form-36 (SF-36)[4]. The HAQ was chosen because it has a larger number of questions dealing with upper extremity function than other arthritis-specific instruments[5]. Only the components covering limitations of the upper extremity were used in the validation process.

The SF-36 consists of 8 health concepts: limitation in physical activities, limitation in usual role activities, bodily pain, general health perception, vitality (energy and fatigue), limitation in social activities, limitations in usual role activities because of emotional problems, and mental health (psychological distress and well being).

Three patients who completed the DASH with more than 10% missing items were excluded from analysis. The mean age of the remaining 49 patients was 58.7 years (SD ± 8.3) and mean current pain level 5.6 (SD ± 2.8). The distribution of self-rated global effect of shoulder problem was as follows: none 6%, slight 13%, moderate 27%, severe 41%, and very severe 13%. The mean overall DASH score was 43.4 (SD ± 21.3).

Table 1. Correlations (Spearman) of the German version of the DASH with different scales, current pain, and global impact of the shoulder problem.

Different Scales and Patient Ratings	DASH
HAQ	0.88**
SF–36	
Limitation in physical activities	–0.58**
Limitation in usual role activities	–0.58**
Bodily pain	–0.79**
General health perception	–0.35*
Vitality (energy and fatigue)	–0.46**
Limitation in social activities	–0.26
Limitation in role due to emotional problems	–0.21
Mental health (physical distress and well being)	–0.19
Current pain	0.81**
Global impact	0.76**

DASH: Disabilities of ARM, Shoulder, and Hand Questionnaire.
HAQ: mean of upper extremity subscales of the Health Assessment Questionnaire.
SF-36: Medical Outcomes Survey Short Form-36. * $p < 0.05$, ** $p < 0.01$.

Table 2. Correlations (Spearman) of clinical data with the overall DASH score and the mean of the upper extremity subscales of the HAQ.

Range of Motion of Painful Shoulder	DASH	HAQ
Flexion	–0.49**	–0.63**
Abduction	– 0.57**	–0.66**
External rotation in 90° abduction	–0.34*	–0.38*
Internal rotation in 90° abduction	0.04	–0.1

* $p < 0.05$, ** $p < 0.01$.

The internal reliability (Cronbach's alpha) of the physical function component was 0.95 and of the overall DASH 0.96. Cronbach's alpha of the symptom and social role component were lesser in magnitude (0.80 and 0.87). Test-retest reliability (18 patients filled out the questionnaire 10 days later) as measured with Spearman correlation coefficient was 0.90 ($p < 0.01$) for the overall scale.

The correlations (Spearman) of the DASH with pain variables and the patient global assessment, the subscales of the SF-36, and the upper extremity item score of the HAQ are shown in Table 1. Correlations of the range of motion measures in different planes and the overall DASH were low to moderate (Table 2).

The translation and adaptation of the DASH for a German context required no major cultural adaptation. We found the overall DASH to have a high internal consistency similar to the American version[6]. The test-retest results are comparable to other patient-administered instruments measuring shoulder function[7,8].

The overall DASH correlated strongly with the HAQ subscales relating to the upper extremities, indicating that both questionnaires measure a similar construct. Correlations of the HAQ with the 3 components of the DASH were smaller, especially with the symptom and social role component. This indicates that the DASH contains additional information in comparison with the HAQ, suggesting the DASH has some discriminant validity.

The lower association of the DASH with SF-36 physical functioning scale can be explained by the dominance of lower extremity items. Pain as measured with the SF-36 pain scale and current pain levels were highly associated with the DASH, suggesting that function, as determined with the DASH, is strongly influenced by pain levels.

The association of the DASH with measures of range of motion of the painful shoulder were generally only moderate in size. This could be explained in several ways. Some people with shoulder pain may not have restrictions of shoulder movements[9]. On the other hand the DASH also captures arm and hand function in addition to shoulder function.

Our data confirm that the German version of the DASH retains the characteristics of the American original and is a reliable and valid instrument to measure functional disability in German speaking patients with shoulder pain. A full length version of our study has been submitted to a German journal (*Zeitschrift fur Rheumatologie*).

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Acute Inflammation at the Site of Calcinosis in Limited Cutaneous Scleroderma

To the Editor:

Soft tissue calcifications due to hydroxyapatite deposits involving the skin or subcutaneous tissues occur in scleroderma and in a variety of connective tissue diseases[1-7], and they may be palpable as subcutaneous nodules[6]. Acute calcific periarthritis is a disorder characterized by acute periarticular inflammatory episodes associated with juxtaarticular deposits of calcium hydroxyapatite and other related basic calcium phosphate crystals[2,5,8-11]. Surprisingly few patients with scleroderma have been described who experienced episodes of such acute calcific periarthritis[1]. We describe a woman with limited cutaneous scleroderma and attacks of inflammation typical of acute calcific periarthritis, which were initially confused with infection.

A 35-year-old woman had frostbite in 1995. This was followed by episodes of Raynaud's phenomenon, and then she gradually developed thickened skin in her hands with general limitation of the range of motion. She had smoked one pack of cigarettes per week and had bipolar disorder that was being treated with lithium.

We first saw the patient in early 1999. She had a blood pressure 100/70 mm Hg, telangiectasia on her face and chest, and sclerodactyly of the fingers of both hands. There was an eschar and blanching on the tip of the second right finger, which she could not fully extend. There was a minimally tender nodule on her left olecranon area. Nailfold capillaries examined microscopically revealed dilated loops with hemorrhages distal to some loops and loss of other capillaries. Radiographic examination of the left elbow showed 2 tiny calcifications adjacent to the olecranon, but hands were normal. Barium swallow showed diminished distal esophageal motility.

Her erythrocyte sedimentation rate was 16 mm/h, and she had a normal blood count. There was a high titer antinuclear antibody (1/5120) with a nucleolar pattern. Urinalysis was normal. Cryoglobins were not detected in her serum. She had normal thyroid function tests. Serum creatinine was normal. Anticentromere antibodies were negative and Scl-70 was not done. She was felt to have limited scleroderma.

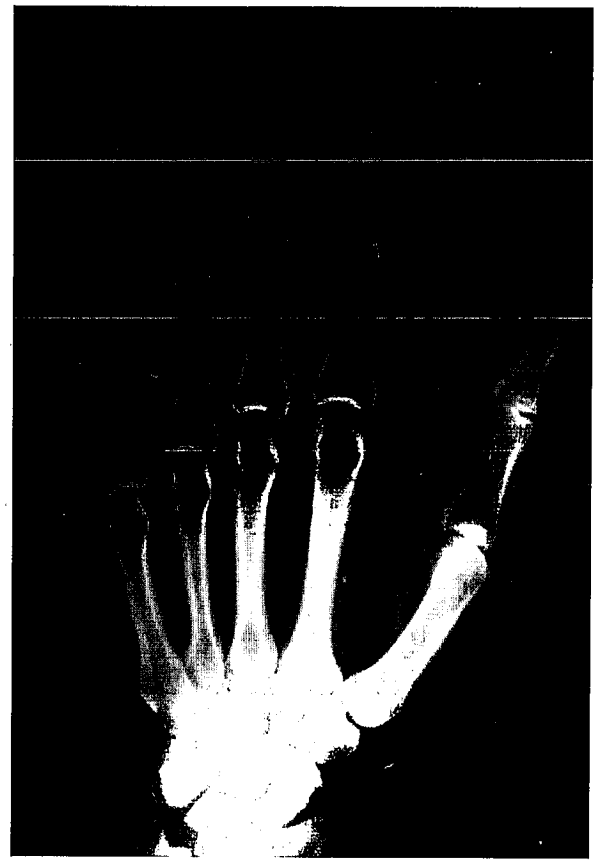

Figure 1. Radiograph showing calcification in the soft tissue adjacent to the thumb interphalangeal joint on the palmar side. The round ossification adjacent to the metacarpal phalangeal joint is a sesamoid bone.

A calcium channel blocker was started with caution, as she had low blood pressure. She was advised to wear gloves and cease smoking and caffeine intake. A digital block to the right second finger was given, with little benefit. She began using warm soaks on her own to alleviate symptoms and to allow her to work on her range of motion. On March 17 she reported acute pain, erythema, and tenderness in the right thumb that was felt by the referring physician to be infected. She was seen by a dermatologist, who prescribed antibiotics and stopped the warm soaks. The swelling slowly resolved.

On April 12 she began range of motion exercises for the fingers and received 3–4 sessions of paraffin baths to both hands. She reported increased manipulation skills and increased flexibility. She obtained a home paraffin bath unit, which she started using in May. On June 7 she developed acute red tender swelling in the volar aspect if the right thumb for the second time. On examination there was swelling, warmth, and tenderness of the right thumb. Radiographs showed calcification at the site of inflammation (Figure 1). Treatment with colchicine in a dose of 0.5 mg PO TID then BID along with indomethacin 5 mg PO TID was started. She developed gastrointestinal distention and some diarrhea, but swelling did decrease although pain persisted. Colchicine was decreased and indomethacin was replaced by rofecoxib 25 mg/day for 10 days. Resolution continued, and she did well until September 16, when she developed pain in the subcutaneous tissue at the dorsal aspect of the olecranon of her left elbow. This was very tender to palpation and painful with repetitive activities. A small nodule 2 cm distal to the tip of olecranon was the site of tenderness to palpation. On repeated radiograph this still appeared as very small soft tissue calcifications. The nodule was excised and revealed scattered subcutaneous calcifications. Some were encapsulated

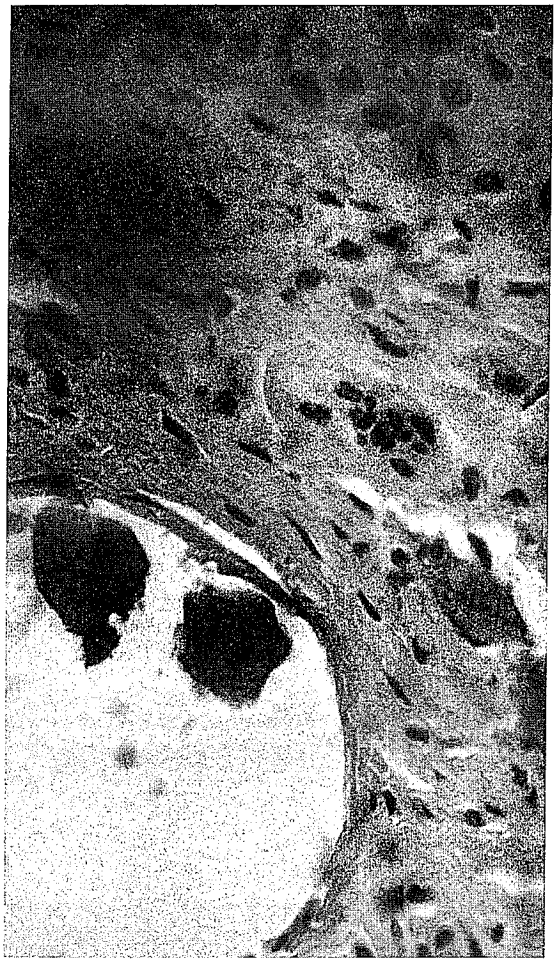

Figure 2. Dark hematoxyphilic calcified material with adjacent chronic inflammation containing lymphocytes and histiocytes in the surgical biopsy from the olecranon are a tender calcific deposit. H&E stain, ×400.

by fibrous tissue and others had adjacent chronic inflammation (Figure 2). On November 8 she had discontinued all medications. The site of the removed nodule at the left elbow showed only a scar.

We found only one report of inflammation with acute calcific periarthritis in patients with scleroderma[1]. Fam and Pritzker[1] described 3 cases including one with acute inflammation of the prepatellar bursa of the right knee. The diagnosis of the bursitis was made radiologically by dense prepatellar calcification, and the mineral was confirmed to be hydroxyapatite by electron microscopy and x-ray diffraction. The patient was treated with indomethacin 50 mg TID for 21 days and intrabursal injection of dexamethasone phosphate. We were surprised that similar inflammation has not been reported more frequently in scleroderma, given the propensity for the apatite to cause inflammation in other situations. Are cases simply not reported, or is inflammation rare in these scleroderma patients?

The clinical presentation of our patient was so severe that she initially was prescribed antibiotics for suspected infection, as has occurred in other reports of acute calcific periarthritis[8,10,11]. Diagnosis is made clinically and by radiograph, but calcification may not be seen on standard views; oblique views may be necessary. One report has described the coexistence of acute calcific periarthritis and infection[12]. Gout might also be considered in scleroderma patients with acute inflammation and does occur in systemic sclerosis[13]. This could be missed if appropriate radiology and synovianalysis is not performed.

The 2 attacks of inflammation of the right thumb in our patient followed institution of local applications of heat; the second while using paraffin baths. Might local heat be a factor that could precipitate attacks of inflammation in scleroderma patients? The painful episode at the left elbow was not preceded by any hot applications or overuse. Frequently involved sites of calcification include points of chronic irritation like the extensor surface of elbows and radial aspects of fingers that oppose the thumb[14,15].

Our patient had been effectively treated with colchicine and then indomethacin, followed by switching to rofecoxib. Episodes of acute inflammation at other calcifications have been treated with nonsteroidal antiinflammatory drugs and colchicine[1,2,13] as well as aspirations and local steroids.

If acute inflammation is uncommon in the calcinosis associated with scleroderma, it could be important to determine why this might be. One possibility is decreased vascularity in these areas. If acute inflammation is found, inquiry might be made into possible precipitating factors such as heat or mechanical trauma.

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Book Reviews

Arthritis and Allied Conditions. A Textbook of Rheumatology, 14th Edition.

William J Koopman, Editor. Philadelphia: Lippincott, Williams and Wilkins, 2001. Volumes I and II, 2848 pages, price $299.00 U.S.

What started as a single authored edition in 1940 (Bernard I. Comroe), later edited by Joseph Lee Hollander, and then Daniel J. McCarty and collaborators, now has 190 contributing authors in 2 large volumes. My first purchase, the 6th edition, (Hollander, 1960) was read and reread cover-to-cover as befits a good textbook. The present 14th edition has 131 standalone chapters, each expansively documented and extensively referenced. I could pick up and read comfortably my 6th edition. Volume I of this 14th edition is 7 lb 8 oz, (3.45 kg), volume II is 6 lb 9 oz, (3.9 kg) both quite heavy to hold.

The job of a textbook editor surely is daunting. Remarkable advances to the study and treatment of rheumatic diseases occur steadily in the 4–5 years between editions. Many chapters from previous editions have undergone extensive revision. This edition has 7 chapters addressing new topics and 37 chapters authored by new contributors. The first 665 pages deal with the scientific basis for the study of rheumatic diseases, and the next 400 on therapeutic approaches. This is followed by 1700 pages dealing with inflammatory and connective tissue disorders, other miscellaneous rheumatic diseases, regional disorders of joints, osteoarthritis, metabolic bone and joint diseases, and infectious arthritis.

There are many stellar chapters, well written and easy to understand, such as "The Epidemiology of Rheumatic Diseases" and "Clinical Evaluation in Rheumatic Diseases" (which more appropriately should be titled "Anti-Rheumatic Drug Trial Design"). Other examples of chapter content include the structure of the joint and its constituent molecules, the inflammatory response and effective pathways, proteoglycans, apoptosis, cytokines, immune complexes, nitric oxide, and eicosanoids. Several chapters document the molecular basis of immunoglobulin and T cell receptor diversity, the cellular basis of the inflammatory response, and the importance of the HLA complex in the pathogenesis of rheumatic diseases. There is documentation of many new therapeutic modalities, biologic agents, immunomodulatory agents, gene therapy and bone marrow transplantation, COX–Z, and the role of bacteria in the pathogenesis of rheumatic disease.

A real disappointment, however is the poor reproduction of radiographs. Trainees in rheumatology, a specialty that prides itself on the ability to interpret bone and joint radiographs, will have to look elsewhere for their education in musculoskeletal radiology. Line drawings are good. Histological specimens are poorly reproduced, difficult to interpret and are poorly labeled. As an example, Figure 122.6, "The histology of major metabolic bone diseases", is reproduced in black and white and yet the caption describes bright red, dark red and yellow (paratrabecular, trabecular and marrow). The excellent chapter on inflammatory myopathies is weakened by the absence of any meaningful description of electromyography. One contributing author claims that electrodiagnostic tests are the "gold standard" for carpal tunnel syndrome and yet there is no description of these neurophysiological tests. This stands in marked contrast to the 36 pages on magnetic resonance imaging and 90 pages on surgery. Both these chapters contain redundant and extraneous material.

Joe Hollander, planning for his 6th edition, claimed that " The effort has been to obtain an outstanding contributor on each subject, not necessarily chosen for the neutrality of his point of view." With above reservations aside, I believe that Koopman for this 14th edition has been as focused and just as successful. These reference volumes are recommended for the excellence of the written material. It is hoped that in later editions more care is given to editing histology and radiograph reproduction.

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Primary Care Rheumatology

Edward D. Harris, MD, and Mark C. Genovese, MD, editors. Philadelphia: WB Saunders Company, 2000, (Harcourt Health Sciences), 413 pages, price $52.00 US

It is always very difficult for me to say, especially in view of the growing knowledge in rheumatology, how much one should expect the primary care physician to know about musculoskeletal system disease. This 413 page text contains information delivered in 3 parts: *"General Approach to Musculoskeletal Disroders," "Approach to the Patient with Musculoskeletal Pain,"* and *"Recognition and Management of Patients with Specific Rheumatologic Problems."* The authors represent different disciplines of medicine and many of them are well known experts in their fields.

This book contains very well organized algorithms and tables, with information that would be useful for any physician involved in the management of musculoskeletal disorders. Many radiographs and graphic presentations of diagnostic tests are featured. A section entitled *"Aspiration and Injection of Joints and Soft Tissues"* describes indications and techniques of aspiration and injection of joints. I would like to see a notation that only experienced operators should be involved in this form of therapy and that prior training should be considered essential.

A section *"Pain – Its Origin, Consequences and Management"* is very interesting but probably a little too complicated for the everyday clinical use of this book. Some recommendations for the management of chronic pain are consistent with the American College of Rheumatology guidelines, but not necessarily in accord with the consensus among Canadian rheumatologists (e.g., acetaminophen as the drug of choice for relieving mild to moderate musculoskeletal pain and considering nonsteroidal antiinflammatory drugs treatment only).

In Part I, Chapter 9, *"Drugs that Relieve Pain and Inflammation,"* oral gold and d-penicillamine are described among other effective and quite acceptable medications such as hydroxychloroquine, sulfasalazine, and methotrexate. Some information on the efficacy of those drugs in the treatment of rheumatoid arthritis would be useful to the reader. In the Appendix, the *"Protocols for the Medical Management of Musculoskeletal Complaints"* are not going to be easily followed by the primary care physician, especially when higher than average dosing is advised, (i.e., hydroxychloroquine, 600 mg per day). It is quite useful to have geriatric medicine covered as well as musculoskeletal diseases of children. I found quite interesting the sections dealing with musculoskeletal problems involving orthopedic surgeons, as well as primary care physicians and dermatologists.

In summary, this text contains very solid basic information about musculoskeletal disorders but not necessarily for the primary care physician. This will be an excellent review for rheumatologists, orthopedic surgeons, and medical residents in training. I expect that there is a significant amount of knowledge in this book that is beyond the scope of the primary care physician, but it can always serve as a useful reference book. Finally, but maybe not so important, it is good value for the money.

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Textbook of the Autoimmune Diseases

Robert G. Lahita, Nicholas Chiorazzi, Westley H. Reeves, editors, Philadelphia: Lippincott Williams and Wilkins, 2000, 912 pages, price $169 US

This textbook was written to present rheumatologists and other specialists managing autoimmune diseases with authoritative and up-to-date information on the basic science and clinical aspects of these disorders. The book is divided in 3 sections dealing with the basic mechanisms of the immune system, autoimmune diseases of organ systems, and disorders of unknown etiology, among which are the autoimmune connective tissue diseases.

Included are other interesting topics such as chapters on how to interpret autoimmune tests and environmental autoimmunity.

The level of language used in the basic sciences section makes it easy to understand for someone who is not familiar with basic immunology. This review of knowledge is systematic and complete. The second part of this section succinctly presents the pathogenesis of autoimmune diseases. The third section, which concerns most of the connective tissue diseases and systemic autoimmune diseases that are of interest for rheumatologists, is concisely presented in short chapters with many summarizing tables that can be useful for quick reference. In the section entitled *"Possible Autoimmune Syndromes"*, I was disappointed, as a rheumatologist, to see that a full chapter had been devoted to fibromyalgia. This disorder definitively does not have an autoimmune basis and does not justify provision of this space in the book. Black and white pictures are not always graphically interesting but they are clear and efficiently supportive of the text. There is an interesting section of color plates.

This textbook presents a summary of knowledge on the pathogenesis of autoimmune diseases and an interesting and practical overview of clinical aspects of these disorders. The price is not high considering the amount of information it contains and it would certainly be a good acquisition for a rheumatologist.

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Rheumatoid Arthritis

J.J. Goronzy and C.M. Weyand, editors. Basel: Karger, 2001, 282 pages, price $170.50 US

This multi-authored volume is the third in a series on current directions in autoimmunity. It focuses exclusively on rheumatoid arthritis (RA) and addresses both genetic and immunobiology themes in the pathogenesis of the disease.

The first 3 contributions cover the genetics of RA as well as the structural basis for the HLA-DR association of RA. The subsequent sections are devoted to immunologic aspects of RA pathogenesis. The role of T cells is explored by 2 different investigators, and leukocyte homing to the synovium is examined by another. There are 2 sections that review the role of molecular mimicry, in RA and Lyme arthritis. The role of the unique synovial microenvironment in rheumatoid synovitis is examined through reviews of lymphoid microstructures and the regulation of apoptosis (programmed cell death) in synovial fibroblasts. The contribution of cytokines to RA pathogenesis is dealt with by 2 investigators, one focusing primarily on tumor necrosis factor-α and interleukin 1 (IL-1) and the other on IL-15. Finally, the role of biologic therapy in the treatment of RA is addressed.

The editors of this volume, Goronzy and Weyand, with their own expertise and research focus in RA pathogenesis, have put together a comprehensive review of the basic mechanisms in RA. Although some aspects of disease pathogenesis are not covered, the selection of articles and organization of topics flow well, and address some major issues in understanding the evolution of rheumatoid synovitis. The contributions are all well written, each having a helpful introduction to the topic and clear text that is not overly scientific. Thus, for most sections, the information is accessible to clinicians. That being said, there is an assumption that the reader has an elementary understanding of immunobiology and genetics.

This volume will be valuable for anyone with an interest in genetics and basic mechanisms in RA pathogenesis. It is an excellent resource for clinical trainees in rheumatology, rheumatologists with an interest in biologic therapies, or investigators studying RA or other autoimmune diseases.

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Muscle Pain: Understanding Its Nature, Diagnosis and Treatment

S. Mense, D.G.Simons, I.J. Russell, editors. Hagerstown, MD: Lippincott Williams and Wilkins, 2001, 385 pages, price $54.05 US

This text is a comprehensive overview of the biology and clinical features of muscle pain. The 3 authors are recognized authorities in this field and have made many contributions to the topic of muscle pain over the years. The authors' stated purpose in producing this book was "to present an overview of the clinical diseases and syndromes associated with muscle pain and to combine the clinical view with new concepts based on neuroanatomic and electrophysiologic research."

The first 7 chapters deal with the neurobiology of muscle pain including local and spinal mechanisms as well as central modifying mechanisms. Each chapter focuses on different aspects of biology and how the basic science relates to various clinical features such as local muscle disorders, neuropathic muscle pain, and various referred pain syndromes. The authors point out frequently that many traditional concepts of pain mechanisms are unsupported by research based evidence and are only unconvincing theories.

A recurring comment in this text is that investigators who seek to understand pain mechanisms often overlook the concept of myofascial pain. The largest chapter addresses the subject of myofascial pain and gives a detailed discussion of current understanding, clinical features, and management strategies of this common problem. The final chapter is an up-to-date review of fibromyalgia with several pages outlining the disturbed physiology that underlies this disorder. The author discusses various treatment strategies for fibromyalgia.

In summary, this is an excellent book. It is well written, has excellent illustrations, and includes a large up-to-date reference base. I would highly recommend this text as a resource for physicians who treat pain disorders.

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