Correspondence

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 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 and fax number (if available). Financial associations or other possible conflicts of interest should always be disclosed. To expedite receipt of letters, we encourage authors outside Canada to communicate by fax (416-967-7556).

IgG Anti-ß$_2$-Glycoprotein I Antibodies in Adult Patients with Systemic Lupus Erythematosus

To the Editor:

I read with interest the article by Tubach, *et al*[1]. The suggestion that analysis of anti-ß$_2$-glycoprotein antibody (anti-ß$_2$-GPI) is redundant has major clinical implications — if it is a valid assessment method. Such a perspective could afford major cost-savings. A challenge immediately arose.

There appears to be a discrepancy between the number of anticardiolipin positive individuals who also had anti-ß$_2$-GPI (9 of 11) and the number of anti-ß$_2$-GPI positive individuals who also had anticardiolipin antibodies (12 of 91). Analysis of the data, assuming that the anti-ß$_2$-GPI numbers were correct, revealed the chi-square analysis of Table 1. Assumption is made that the apparent inconsistency in the anticardiolipin group with associated antibodies was erroneous. The anti-ß$_2$-GPI data were assumed to be correct and utilized as such in Table 1. These data do indeed yield a chi-squared value of 20.379, significant at the p level presented by Tubach, *et al*[1].

Table 1. The 19 and 24 were derived directly from the number of positives listed for each antibody[1]. The total number of patients was 102. The number of individuals with both anti-ß$_2$-GPI was 12. Direct information was lacking for 2 blocks. Those were calculated by subtracting the known values from the totals.

	Anticardiolipin Antibody		
Anti-ß$_2$-GPI	Positive	Negative	Total
Positive	12	7	19
Negative	12	71	83
Total	24	78	102

However, one-third of the individuals at risk for antiphospholipid syndrome would have been missed if only anticardiolipin antibodies had been examined. While the association of anti-ß$_2$-GPI with anticardiolipin antibodies is statistically significant, I would disagree with the suggested interpretation. Given the importance of both antibodies for antiphospholipid syndrome, I am concerned with the clinical implication of overlooking the problem in one-third of patients. I do not believe that a case has been made for eliminating analysis of anti-ß$_2$-GPI.

Arthritis Center of Northeast Ohio,
Northeastern Ohio Universities College of Medicine,
Youngstown, Ohio 44512, USA. Bruce M. Rothschild, MD.

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Dr. Meyer replies

To the Editor:

In reply to Dr. Rothschild, we must say that only 1/19 patients with systemic lupus erythematosus (SLE) with anti-ß$_2$-GPI did not have a history of IgG anticardiolipin antibody (aCL) positivity (Table 1). It is correct to say that 3 patients were considered negative for IgG anticardiolipin (12, 15, and 18 GPL units), but positive for anti-ß$_2$-GPI (8, 11, and 27 units) on the same sample. In 2 of these cases, the patient was positive for lupus anticoagulant (LAC; data are missing for the third patient). Since determination of anti-ß$_2$-GPI antibody is not yet standardized, we consider that the assumption that "determination of anti-ß$_2$-GPI in addition to anticardiolipin *and* LAC is unlikely to improve the diagnosis of antiphospholipid syndrome in patients with SLE" is valid.

Table 1. Contingency table between anticardiolipin and anti-ß$_2$-GPI antibody in 102 patients with SLE.

	History of aCL		
	Positive	Negative	Total
Anti-ß$_2$-GPI			
Positive	18	1	19
Negative	6	77	83
Total	24	78	102

Hôpital Bichat,
75018 Paris, France. Prof. Olivier Meyer

Epidemiologic and Clinical Features of Behçet's Disease

To the Editor:

I read with interest the report by González-Gay, *et al*[1]. Behçet's disease (BD) is commonly observed in Japan, the Middle East, and Mediterranean countries. Its incidence ranges roughly from 1 in 1000 in Japan to 1 in 500,000 in Europe and North America[2]. These figures might change in different series; however, it is apparent that the disease mostly affects people living in countries located on the ancient Silk Road.

Just as the incidence differs among different parts of the world, there are also regional differences in clinical manifestations of this disease[3]. In their study, González-Gay, *et al* state that neurologic involvement was frequently observed (31.3%), whereas this figure is much higher compared to the Turkish population, where neurologic involvement is less than 10%[2]. Also in their study population, gastrointestinal (GI) findings were found in about 20% of the patients, where again in Turkish patients with BD, GI findings are exceedingly rare. The reason for these differences is unknown. However, I would like to draw attention to 2 points possibly related to each other. First, the time to diagnosis of BD in the study of González-Gay, *et al* is around 10 years. This delay to diagnosis is unusual in regions were the disease is more prevalent and many more clinicians are experienced with the manifestations of the disease. Second, such a delay in diagnosis means that therapy has been delayed for about the same period. If diagnosis had been established earlier, then a treatment would have been instituted before certain clinical manifestations developed. I assume that a delay in diagnosis might allow the develop-

ment of some devastating complications such as ocular and neurologic involvement.

I believe that if a diagnosis is made at initial stages of the disease and an effective treatment begun, the development of serious findings might be prevented. In a recent study from Turkey, interferon (IFN) based regimens proved effective in the prevention of many of the manifestations including ocular and neurologic disease[4]. In that study, it was reported that earlier institution of therapy not only prevented the most dreadful complication, ocular manifestations, but also minimized the damage such involvement might cause. There is growing evidence that IFN is an acceptable mode of treatment for the prevention of many of the complications of this disease[5]. I believe that early institution of an effective treatment, preferably with IFN, might change the natural course and improve the prognosis of Behçet's disease.

Süleyman Demirel University Medical School,
Isparta, Turkey.

Yavuz Bardak, MD.

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Dr. González-Gay, *et al* reply

To the Editor:

We thank Dr. Bardak for his interest in our work. As Dr. Bardak points out the long delay to the diagnosis in many of our patients may be due to the fact that Behçet's disease (BD) was classically considered to be uncommon in Europe. However, there was a significantly shorter delay in diagnosis in our patients with neurological complications (median 2.5 vs 10 yrs in the patients without neurological complications). This observation may have a different meaning to that suggested by Dr. Bardak. We feel that patients with neurological manifestations constitute a subgroup of BD with more severe manifestations that occur relatively early after onset of initial manifestations. Due to this, Dr. Bardak's assumption on an inappropriate delay to the diagnosis in some patients with BD, specifically in those with neurological BD, cannot be supported.

As we have a very small number of cases, we are unable to confirm whether early therapy may prevent the development of ominous complications. Indeed, all our patients with neurological BD were seen by us for the first time when neurological complications had just occurred. However, in our limited experience, colchicine seems to be effective in reducing new flares of oral or genital ulcers. Also, although interferon-α (IFN-α) has been found useful in preventing complications of BD, the study discussed by Dr. Bardak in the *Lancet*[1] is related to 135 patients, and we think that more prospective double blind controlled studies are needed to further support the routine use of IFN-α in BD. In addition, the positive results described in that paper were mainly related to ocular complications, but not enough information about neurological manifestations was provided. In our view this therapy should specifically be considered in and restricted to groups of patients with high risk of severe complications.

Hospital Xeral-Calde,
Lugo, Spain.

Miguel A. González-Gay, MD, PhD;
Carlos García-Porrúa, MD, PhD;
Francisco Brañas, MD,
Ignazio Olivieri, MD.

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Classification of Chronic Arthritides of Childhood (Juvenile Idiopathic Arthritis): Criticisms and Suggestions to Improve the Efficacy of the Santiago-Durban Criteria

To the Editor:

In the late 1970s two classification schemes for primary forms of chronic rheumatism in children were proposed, with different names and different exclusion criteria: the North American (American College of Rheumatology, ACR, formerly American Rheumatism Association) classification system, which used the term juvenile rheumatoid arthritis (JRA), and the EULAR classification system, which used the term juvenile chronic arthritis (JCA). Both systems recognized different subtypes mainly on the basis of the disease onset: systemic, polyarticular, or pauciarticular (oligoarticular).

The development of the concept of seronegative spondyloarthropathies by Moll and Wright and the recognition of similar conditions in childhood, together with the awareness of the immunogenetic heterogeneity of the chronic forms of childhood arthritis, further revealed the inadequacy of the old systems of classification. The critical point was reached at the Round Table on Nomenclature and Classification of Juvenile Chronic Arthritides in Barcelona in July 1993 during the XVIII Congress of the International League Against Rheumatism (ILAR). While the Americans were faithful to their ACR nomenclature and criteria, the Europeans (Huppertz, Fantini, Southwood and Woo) were in favor of splitting the disease into several distinct forms. The need for a controlling mechanism for nomenclature and classification criteria, ideally international, was widely acknowledged: ILAR was considered appropriate to operate this mechanism. In Barcelona a Standing Committee for Pediatric Rheumatology was established, with Dr. Chester W. Fink as chairman. A task force of 12 pediatric rheumatologists representing all 4 regional leagues was convened to propose new sets of classification criteria for the diseases formerly termed JRA or JCA.

The task force first met in September 1994 in Santiago, Chile. A document was published in 1995: the Proposal for the Development of Classification Criteria for Idiopathic Arthritides of Childhood[1]. This proposal was to be considered a framework, needing formal evaluation in populations from a wide variety of ethnic backgrounds. According to the so-called Santiago criteria, 7 diseases with onset before the 16th birthday were classified: systemic arthritis, rheumatoid factor (RF) negative polyarthritis, rheumatoid factor positive polyarthritis, oligoarthritis, extended oligoarthritis, enthesitis related arthritis, and psoriatic arthritis. Classification is

made 6 months after the onset of the disease, on the basis of specified criteria. For each disease the following standardized structure was proposed: definition, descriptors (information for further subclassification), and specific exclusions. One of the principles underlying these classifications was that there should be no overlap between the 7 diseases: patients who fulfilled the criteria for 2 or more classifications should be excluded from any of the listed classifications, but would be given ongoing consideration as part of the evaluation process.

The Classification Task Force of the ILAR Pediatric Standing Committee held its second meeting in Durban, South Africa, in March 1997, with Dr. Ross E. Petty as chairman. The Revision of the proposed Classification Criteria for Juvenile Idiopathic Arthritis (JIA) was published in 1998[2]. The goal of the Committee was to develop criteria that would enable the identification of homogeneous groups of children with chronic arthritis to facilitate research in immunogenetics and other basic sciences, epidemiology, outcome studies, and therapeutical trials.

The main points in which the Durban criteria differ from the Santiago criteria are the following: (1) the different forms of JIA are referred to as categories and not as diseases; (2) the category of "probable systemic arthritis" is no longer considered; (3) both persistent and extended oligoarthritis are grouped in the same overall category of "oligoarthritis"; (4) the new category of "other arthritis" is proposed to accommodate children with idiopathic arthritis who fit either into no category or into 2 or more categories.

In the words of the chair of the ILAR Task Force, Ross E. Petty[3], the criteria, as they now stand, should be viewed as "a work in progress." Members of the pediatric rheumatology research community are urged to participate in the process by making their opinion known, particularly by evaluating the proposed criteria.

One major criticism can be raised to the Santiago-Durban classification criteria: the system doesn't consider the established nomenclature for adult rheumatology. One principle should be recognized to avoid confusion and to facilitate the communication among both clinicians and basic scientists: whenever possible, the same disease should be called by the same name in children and in adults. While some of the chronic arthritides affecting children seem to be diseases typical of childhood and rarely (as in the case of adult Still's disease) or exceptionally (as in the case of oligoarthritis associated with uveitis) affecting adults, other diseases (such as rheumatoid factor positive rheumatoid arthritis and the spondyloarthropathies, SpA) affect both children and adults. For the latter diseases, clarity and coherence would require the use of the same nomenclature, in the case of children preceded by the term "juvenile" (as when we speak of juvenile SLE, etc.).

Another weak point of the Santiago-Durban criteria concerns the concept of enthesitis related arthritis, which covers all the recognized SpA, exception made for psoriatic arthritis. The group of generally accepted seronegative SpA includes ankylosing spondylitis, Reiter's syndrome and reactive arthritis, psoriatic arthritis, arthritis associated with inflammatory bowel disease (IBD), and forms that fail to meet criteria for definite categories, which are designated as undifferentiated SpA. In the early 1990s, 2 sets of classification criteria were proposed with the aim of encompassing the whole clinical spectrum of SpA, including undifferentiated SpA: the Amor[4] and the European Spondylarthropathy Study Group (ESSG) criteria[5]. In the ESSG study, the sensitivity and specificity of the Amor and ESSG criteria were compared and were found to be similar (sensitivity 85 and 87%; specificity 90 and 87%, respectively). The high sensitivity and specificity of these criteria have been confirmed in validation studies in several populations. Although the Amor and ESSG criteria were derived from a population of adult patients with SpA, their performance has also been found to be good in a large European multicenter study of patients with juvenile onset SpA (sensitivity 73.5 and 78.7%, respectively; specificity 97.6 and 92.2%)[6]. Although the frequency of the various SpA is different in children in comparison to adults (more undifferentiated forms and less ankylosing spondylitis), all the SpA are easily recognizable in children and adolescents; consequently, there is no need to denote the same diseases with different names. Since reactive arthritis cannot be considered an arthritis of unknown cause, it shouldn't enter the scheme of the juvenile idiopathic arthritides, while all the other SpA, that is, ankylosing spondylitis, psoriatic arthritis, IBD associated arthritis, and undifferentiated SpA, can easily be categorized within the general group of SpA.

The Durban Classification Criteria for JIA were tested on a cohort of 683 patients in the database of the Center for Rheumatic Children of the Gaetano Pini Institute in Milan. As shown in Table 1, 157 cases (roughly 23%) fell into the category of "other arthritis," a number unacceptable for a system of classification.

The high number of patients falling in the category of "other arthritis" can be explained by 2 main factors, one intrinsic to the system, the other presumably bound to the characteristics of the patient cohort.

In the Durban system of classification, while the presence of systemic arthritis is an exclusion for all other categories, the presence of either psoriasis or enthesitis is not an exclusion criterion for oligoarthritis and RF seronegative polyarthritis. Consequently, by crudely applying the criteria, all children with arthritis associated with either psoriasis or enthesitis inevitably fulfill the criteria of at least 2 categories, unless other exclusions are present. Moreover, arthritic children with spiking fever but without any of the other systemic features (namely evanescent, nonfixed, erythematous rash; generalized lymph node enlargement; hepatomegaly or splenomegaly; serositis) cannot fulfill the criteria for systemic arthritis and fall into one or more of the other categories.

As far as the characteristics of our patient cohort are concerned, the high prevalence of oligoarticular onset among the Italian children with chronic arthritis and the high prevalence of psoriasis in our population cannot be ignored.

To reduce the number of cases falling into the category of "other arthritis," 2 main ways can be suggested: (1) to reduce the exclusions, and (2) to consider a hierarchy of the categories.

According to our patient data, the exclusions that more frequently hamper an obvious classification are: (a) family history of psoriasis in at least one first or second-degree relative (for oligoarthritis); (b) psoriasis confirmed by a dermatologist in at least one first or second-degree relative (for enthesitis related arthritis).

This suggestion is founded on the evidence that psoriasis is significantly more frequent in families of patients with typical chronic oligoarthritis or juvenile SpA[7]. The exclusion of cases with a family history of psoriasis from these 2 categories not only impoverishes them, but deliberately ignores one of the most interesting even if unclear features of all these disorders, which run in the same families, probably sharing some pathogenetic mechanism. According to our experience, oligoarthritic children with a family history of psoriasis and those without it do not present any signifi-

Table 1. Categorization of the cohort of 683 cases of juvenile idiopathic arthritis in the Gaetano Pini Institute database according to the Durban criteria.

	No. of Cases
Systemic arthritis	75
Oligoarthritis	326
Persistent	245
Extended	81
Polyarthritis (RF negative)	76
Polyarthritis (RF positive)	14
Psoriatic arthritis	13
Enthesitis related arthritis	22
Total of categorized cases	526
Other arthritis	
Fit no category	98
Fit more than one category	59
Total of noncategorized cases	157

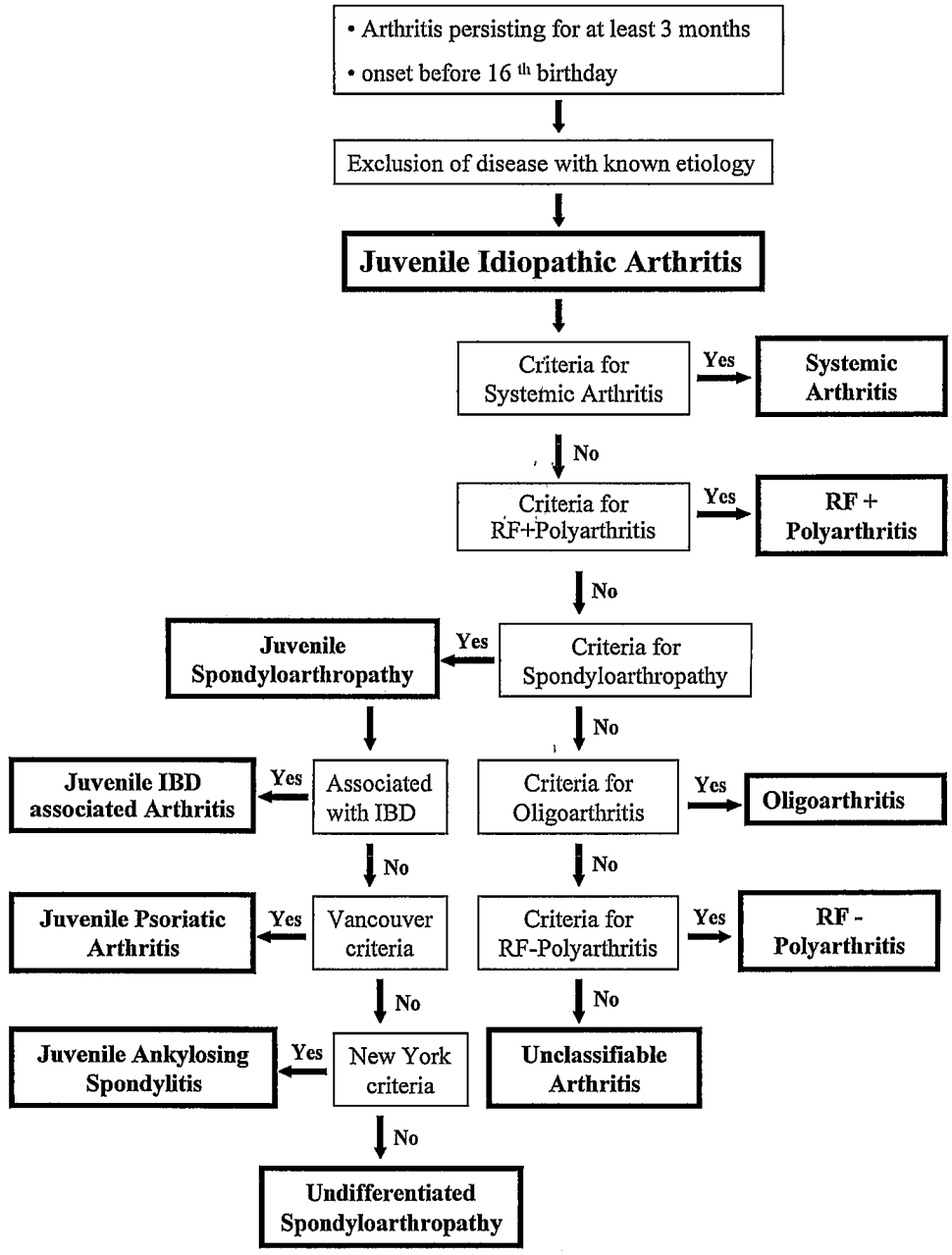

Figure 1. The classification tree.

cant difference concerning immunogenetic background, ANA positivity, arthritis course, and eye complications.

Another point is the definition of rheumatoid factor (RF) positive polyarthritis. Oligoarticular onset of disease with subsequent polyarticular course is not rare in childhood, so the number of joints affected during the first 6 months of disease could be also less than 5. The amended definition would be: arthritis symmetrically affecting 2 or more joints during the first 6 months of disease, associated with positive RF tests on 2 occasions at least 3 months apart.

As we observed in our cohort, it is not rare that children with chronic arthritides satisfy more than one set of criteria. From a clinical and prognostic point of view, however, there is a hierarchy among the different categories, so that if a patient fits into more than one category, he or she should be attributed to the category with the highest rank. In attributing ranks, 2 general principles could be taken into account: (1) the more severe form should be preferred to the less severe one; and (2) the more differentiated form (that is, better characterized biologically and/or clinically) should be preferred to the less differentiated one.

Following these principles, a classification tree has been devised (Figure 1), where the different categories of JIA are considered following a predefined sequence: if a case doesn't satisfy the criteria of a category, it is confronted with the criteria of the following, and so on. According to our experience, for the categorization of patients with juvenile idiopathic arthritides we suggest this classification tree, in which the Santiago-Durban criteria are modified and integrated according to the above comments.

The application of the classification tree to our cohort would yield the results shown in Table 2.

In conclusion, if the hierarchy principle were accepted and the classification tree were adopted using as sets of criteria those of Durban slightly modified and integrated with other validated criteria (such as those of

Table 2. Categorization of the cohort of 683 cases of juvenile idiopathic arthritis in the Gaetano Pini Institute database according to the proposed classification tree.

	No. of Cases
Systemic arthritis	88*
Polyarthritis (RF positive)	22
Spondyloarthropathies	59
IBD associated arthritis	3
Psoriatic arthritis	17
Ankylosing spondylitis	10
Undifferentiated SpA	29
Oligoarthritis	427
Persistent	327
Extended	100
Polyarthritis (RF negative)	87
Total of categorized cases	683

*Including 13 cases without any other systemic feature but spiking fever. IBD: inflammatory bowel disease.

Vancouver for psoriatic arthritis and those of New York for ankylosing spondylitis) all the patients could be satisfactorily classified and each category (disease) would maintain a fruitful and valuable homogeneity.

Gaetano Pini Institute,
University of Milan,
Milano, Italy. Flavio Fantini, MD.

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Correction

Nagashima M, Asano G, Yoshino S. Imbalance in production between vascular endothelial growth factor and endostatin in patients with rheumatoid arthritis. J Rheumatol 2000;27:2339–42. In the Results summary in the Abstract, page 2339, the Results section, page 2340, and in the labels and legends for Figures 1 and 2, all values for endostatin should be nanograms per milliliter, not picograms. We regret the error.

THE 45TH ANNUAL MEETING OF JAPAN RHEUMATISM ASSOCIATION
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Correspondence:
Shigeto Kobayashi, M.D.,Ph.D.
Department of Rheumatology,
Juntendo University, School of Medicine,
2-1-1 Hongo, Bunkyo-ku,
Tokyo 113-8421
JAPAN
TEL: +81-3-5802-1067, FAX: +81-3-5800-4893