

athies. In only two patients had the arthritis syndrome developed one to two weeks after a short spell of diarrhea. No infective agent responsible for these enteric symptoms could be demonstrated. Three other patients had spells of diarrhea one to six years after the occurrence of the initial synovitis. The 11 other patients never had gastrointestinal symptoms. Eight patients were subjected to routine gastrointestinal investigation (included proctoscopy with biopsy), with a normal result. All 16 HLA-B27-positive patients in whom ileocolonoscopy was performed had microscopical evidence of inflammation in the terminal ileum or in the ileocecal valve. In nine patients the macroscopical examination of the ileal mucosa showed signs of edema or ulceration. Results of histologic examination were abnormal in all cases and demonstrated inflammation in the lamina propria and in the epithelium, with infiltration of lymphocytes and plasmacytes widening, flattening, and destruction of the villi. In six cases, formation of microgranulomas, suggestive of chronic inflammatory bowel disease, was present. Ileocolonoscopy was also performed in a control group of eight HLA-B27-negative patients (four men and four women; mean age, 35 years; range, 23 to 50) with polyarthritis (rheumatoid arthritis or systemic lupus erythematosus) and in two HLA-B27-positive patients with ankylosing spondylitis without peripheral synovitis. The terminal ileum and ileocecal valve were normal in all these patients.²

These findings suggest that an asymptomatic inflammatory infection of the ileum can be important in the pathogenesis of reactive arthritis in HLA-B27-positive patients who have no signs of genitourinary or bowel infection. The hypothesis can be advanced that enteric lesions are responsible for the release of mediators — immunologic or otherwise — into the circulation to provoke a recurrent reactive arthritis. These data may also have therapeutic implications. Since it is generally accepted that sulfasalazine exerts some beneficial effect on the symptoms of chronic inflammatory bowel disease, this drug was given to 12 of the patients with the typical clinical pattern of reactive arthritis (all HLA-B27-positive and all with asymmetrical pauciarthral involvement and enthesopathies). These patients had not responded permanently to nonsteroidal antiinflammatory drugs. Clinical remission of all articular and paraarticular symptoms (enthesopathies) was obtained in eight patients after three to six months of sulfasalazine treatment. In the four other patients, marked improvement of these symptoms was observed. These findings must still be confirmed in a controlled study.

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To the Editor: Keat reviewed the role of microbial infection in the pathogenesis of reactive arthritis and Reiter's syndrome as well as the relation of these diseases to ankylosing spondylitis and anterior uveitis and their close association with the HLA-B27 antigen, but he failed to address the crucial question of the relation between such microbial agents and the HLA-B27 antigen in the pathogenesis of these diseases.

As Keat comments, *Chlamydia trachomatis* has repeatedly been implicated in the pathogenesis of Reiter's syndrome. We have recently reported the association of a heightened cell-mediated immune response to *C. trachomatis* in HLA-B27-positive patients with anterior uveitis.¹ Several of these patients had Reiter's syndrome and all had a marked lymphocyte-transformation response to chlamydial antigen. Further studies² on this group of patients have revealed that antibodies to chlamydiae (serotypes D and L-2) cross-react with, and show increased percentage binding to, the HLA-B27 lymphocytes of patients with sacroiliitis. These antibodies also bind human conjunctiva and may thus have a role in localizing the immune response to extraarticular sites such as the eye. Similar studies by Geczy et al.³⁻⁵ and Ebringer et al.⁶⁻⁸ on several gram-negative bacteria, particularly klebsiella species, have shown analogous findings,

with antibodies to gram-negative bacteria selectively lysing the cells of patients with HLA-B27-associated ankylosing spondylitis and Reiter's syndrome and the lymphocytes of patients with anterior uveitis, and cross-reacting with the vitreous of bovine eyes.

These studies suggest an important functional relation between certain microorganisms and the immune response of patients with HLA-B27-related syndromes. Furthermore, the observed differences between normal persons with HLA-B27 antigens and HLA-B27-positive patients with ankylosing spondylitis, anterior uveitis, and Reiter's syndrome appeared to have been acquired.⁵ It has been proposed that plasmids may be transferred from certain microorganisms to the cells of HLA-B27-positive subjects, subsequently altering their genome in such a way as to express "nonself" surface antigens. This is an interesting hypothesis for which there is preliminary evidence.⁹

Why HLA-B27 cells should be preferentially altered or infected by certain microorganisms is not known. Preliminary data from our laboratory indicate that the phagocytic response (as measured by chemiluminescence) of HLA-B27 macrophages to several gram-negative bacteria and *C. trachomatis* is significantly reduced when compared with that of non-HLA-B27 macrophages.¹⁰⁻¹² This may be the fundamental defect in HLA-B27-positive persons that allows prolonged exposure to particular microorganisms with the subsequent generation of an aberrant immune response, leading to the disease patterns we recognize as ankylosing spondylitis, anterior uveitis, and Reiter's syndrome.

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The above letters were referred to Dr. Keat, who offers the following reply:

To the Editor: The letter of Mielants and Vey's is of great interest but requires no reply.

Dr. Wakefield and colleagues draw attention to the phenomenon of cross-reactivity between microbial antigens and the HLA-B27

antigen in patients with B27-related diseases. I would certainly not take issue with their implications that the findings of several groups in this respect, including their own, are intriguing and important and that these should be widely discussed and debated. In my view, however, this debate could not be adequately presented in a more general review and does not belong there.

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GRADUATES OF FOREIGN MEDICAL SCHOOLS AND MEDICAL MANPOWER

To the Editor: Drs. Stimmel and Graettinger (Jan. 26 issue)¹ assert that foreign-medical-school graduates, including U.S. citizens, "are once again playing a larger part in the provision of medical care in this country." This statement cannot be derived from analyses of the data they provide. It is critical to clarify this issue, since their assertion has far-reaching policy impact.

The authors translate a 312 per cent increase over the past four years in applications from foreign nationals to the National Resident Matching Program (and a 273 per cent increase in applications from U.S. citizens from foreign schools) into concomitant increases in the practitioner pool. A distinction must be made between applicants for positions and those who eventually enter graduate medical education. Because of a leveling off in the number of entry-level positions, particularly those in the match, and a high match rate for U.S. graduates, the match rates of foreign graduates remain relatively low. In contrast to what the authors assert, graduates of foreign medical schools over the past three years have represented about 19 per cent of residents across all years of training.² Although the number of Matching Program applications has risen markedly, participation by foreign graduates in accredited residency training has not increased.

Indeed, there is documentation of a dramatic reduction in the entry of foreign nationals through physician-exchange visitor programs. Over the past decade, new-entrant visiting exchange physicians sponsored by the Educational Commission for Foreign Medical Graduates declined from a high of 2917 in academic year 1973-1974 to only 544 in 1981-1982. Of these 544, over 20 per cent were graduates of Canadian schools (i.e., schools accredited by the Liaison Committee on Medical Education [LCME]). Only 370 foreign nationals from schools not accredited by the LCME were in residency or fellowship training.³ Increased numbers of alien physicians participating in the Matching Program may be more a function of their exploring multiple entry pathways than an indication of dramatic increases in the physician pool.

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To the Editor: Stimmel and Graettinger's article concerning the extent and implications of the entry of foreign-medical-school graduates into house-staff training programs in the United States serves to underscore the concerns voiced by the Resident Physician Section of the American Medical Association (AMA) over the past year.

The leadership of the Resident Physician Section has contended that the medical-education system in the United States is unprepared to ensure that graduates of medical schools in this country can complete their education to the point of licensure. If financial pressures continue to erode the number of first-postgraduate-year positions and the number of graduates of U.S. medical schools re-

mains at its present level, we could begin to see a serious shortage of first-postgraduate-year positions. Since most states require at least one year of postgraduate training for a new physician to obtain licensure, inability to obtain an internship would prove very costly to the affected physician and to the society that helped fund his or her education. Should this shortage affect graduates of U.S. medical schools, a condition of "deficit enrollments" would occur: more students would be entering the system than there are positions available to allow them to enter the profession. In a sense, medical education would become pyramidal, with people being dropped between their fourth year of medical school and the first postgraduate year. The Resident Physician Section is striving to have the medical-education system acknowledge its obligation to its students to enable them to complete their basic training to the point of licensure. We have submitted resolutions to the AMA House of Delegates calling for the adoption of the principle that the number of entering first-year positions at U.S. medical schools be at least equal to the number of first-postgraduate-year positions, thus avoiding the condition of deficit enrollment. Thus far, the House of Delegates, bolstered by strong opposition from the Medical Schools Section, has refused to adopt this concept.

Clearly, the issue is complex. Although it is true that some states do not require an internship as a condition of licensure, they number less than the 14 claimed by Stimmel and Graettinger. According to recent AMA statistics, seven states do not require graduates of U.S. medical schools to serve an internship in order to obtain licensure, and only three states allow this option to graduates of foreign schools (AMA Department of Medical Education: personal communication). It is our impression that licensure without postgraduate training is not in the public interest.

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To the Editor: The controversy regarding foreign-medical-school graduates is unquestionably linked to the findings of the Graduate Medical Education National Advisory Committee's report, which predicted a surplus of 90,000 doctors by the year 1990 and of over 200,000 by the year 2000. The report recommended a cutback in funding for U.S. medical schools and a 10 per cent reduction in the size of graduating classes.

Meanwhile, 12,000 to 16,000 U.S. citizens are studying medicine at unknown and unaccredited medical schools, which in many cases were developed for profit in nations that lie close to the continental United States.

Stimmel points out that foreign-medical-school graduates who participate in Fifth Pathway programs do better in residency matching and score better on state licensing examinations. This observation serves as an indictment of the poor quality of medical education that many of these students receive. It would seem obvious that a remedial educational year at a Fifth Pathway educational program would improve performance, and such improvement is only to be expected.

Anecdotal statements in the article, such as, "Compelling evidence does indicate, however, that Fifth Pathway students entering the system are making meaningful contributions to medical care," are meaningless. What proof is there for such a statement?

The most important question to ask must remain, Why should we reduce the number of graduates of U.S. medical schools while at the same time looking for ways to make it easier for U.S. citizens to beat the established system by attending offshore medical schools not accredited by the LCME? The open-admission policy of many of these schools and the relatively easy access by their graduates to the licensure process in most states will serve only to sabotage the entire system of premedical and medical education. If allowed to continue, this sabotage will destroy the morale of many of the premedicine