INCIDENCE OF RHEUMATOID ARTHRITIS: DO THE OBSERVED AGE-SEX INTERACTION PATTERNS SUPPORT A ROLE OF ANDROGENIC-ANABOLIC STEROID DEFICIENCY IN ITS PATHOGENESIS?

Rheumatoid arthritis is a highly complex, systemic inflammatory disease of unknown etiology [1]. Its pathogenesis is multifactorial, involving mechanisms related to gender, immunogenetics, microvascularity, neurohormonal systems and sex hormones (e.g. pregnancy) [1, 2]. Major biological inter-relationships which are being discovered among such regulatory systems of the body [3] promise to elucidate essential biological and clinical characteristics of this mysterious disease. Additionally, analytical epidemiological investigations which are identifying distinguishing patterns of RA within populations may offer clues to its possible host, agent and environmental determinants [1].

In this issue, Symmons et al. [4] describe the incidence of RA in the Norwich Health Authority (NHA), utilizing data derived from a longitudinal population based register. The study represents an important effort to derive reliable incidence rates of RA in a large Anglo-Saxon population (around 485,000). The initial results [4] reveal significant age-sex interaction patterns which may reflect fundamental host determinants of disease. These and other incidence data (see below) may be consistent with a role of androgenic-anabolic (AA) steroid deficiency in the pathogenesis of RA.

Incidence of disease is defined epidemiologically as the rate of onset of a specified condition within a defined population during a particular time period. Prevalence of disease is more simply defined as the ratio or proportion of persons affected with the specified condition in a defined population at a particular time [1]. At equilibrium, the incidence (I) times mean duration (D) of disease equals prevalence (P), i.e.

\[ I \times D = P. \]

Both frequency statistics have advantages and limitations for their respective usages [1].

Analytically, incidence rates are more accurate and specific correlates of risk factors to ‘onset’ of disease than are prevalence ratios. Incidence data are proximate in time to the defined onset point and are not affected by either subsequent remissions or mortality from disease. Admittedly, the time of ‘onset’ of a chronic disease, e.g. RA, can be difficult to determine precisely. Accurately-performed incidence studies can offer valuable comparative data to infer onset risks of disease. Incidence rates can be determined by readily-available demographic factors, e.g. age, sex, race and social status. Furthermore, the new cases can be compared to controls in search of possible associations with genetic markers (e.g. HLA and others), agent factors (e.g. viral antibodies) and environmental exposures (e.g. diet, occupation and stress) [1, 5-7].

In the NHA study [4], a Norfolk Arthritis Register (NOAR) was established in order to identify new cases of inflammatory arthritis as they occur in the community and to follow these patients longitudinally in order to investigate the natural history. All practices (77 in 1989, comprising 286 general practitioners) and appropriate hospital clinics were asked to notify NOAR of all adults (aged over 16 yr) who fulfilled the defined polyarthritis criteria [4]. Soon after notification, patients were evaluated clinically in the home by metrologists and blood taken for RF testing. All patients were reviewed 1 year later at which point X-rays were taken if indicated.


The incidence figures are acknowledged to be minimum estimates [4]. Various reasons contribute to this belief, including incomplete physician ascertainment, failure of referral to NOAR as well as satisfaction of ARA criteria [8], only after presentation [4]. As the NHA study progresses, such methodologic influences on the incidence of RA are likely to be more precisely defined and more accurately interpreted.

Accepting the validity of these NHA incidence data [4] for the present, interesting age-sex interaction patterns are seen. Although RA was rare in men under age 45 yr, the incidence exceeded that of women in the oldest age group (i.e. 75 yr and older). The paucity of RA in younger adult males in the NHA study [4] supports previously derived incidence data.

From 1967 to 1977, a long-term, longitudinal survey was conducted of newly-diagnosed arthritis among residents under 45 yr of age in Memphis and Shelby County, Tennessee, USA (a racially-mixed population ca 500,000) [5, 6]. The 45 yr age limit was designed to minimize confounding effects of OA in this Arthritis Research Program (ARP). In that ARP Study [5-7], the incidence per 100,000 person-years (PY) of referred cases diagnosed as RA by the 1958 ARA criteria [9] increased in the younger women, i.e. from 20 (in ages 16 to 25 yr) to 50 (in ages 35 to 44 yr). However, in men, the incidence decreased slightly, i.e. from 15 (in ages 16 to 25 yr) to 8 (in ages 35 to 44 yr) [5-7].

In a preceding incidence study of atomic bomb survivors in Hiroshima-Nagasaki, Japan, performed by the Atomic Bomb Casualty Commission (ABCC) [10], no male case under age 50 yr was found during 4300 PY observation vs seven females cases during in 8500 PY. Among survivors age 50 yr and over, the respective frequencies were six male RA cases during 4400 PY and 10 female RA cases during 6400 PY. The absence of
FIG. 1.—Composite, age-specific incidence of rheumatoid arthritis per 100 000 person years in females (▲) and males (■). See text for referenced data and explanations.

The early incidence findings [5-7, 10] led to a hypothesis and later supporting studies [14] that AA steroid deficiency may contribute to the pathogenesis of RA, especially in women of child-bearing age. Those epidemiological [5-7] and metabolic [14] studies prompted an analysis of the age-specific F:M ratio of clinically-detected adult RA patients at *onset* of disease, conducted at the Arthritis Institute in Belgrade, Yugoslavia [15]. Exaggerated F:M ratios were found among the youngest adult seropositive RA patients, i.e. 38:3 cases at ages 16-24 yr and 70:13 cases at ages 25-34 yr vs 225:75 cases at ages 35+ yr. The F:M ratio was 6.8:1 under age 35 yr vs 3.0:1 from age 35 yr and older (*P*<0.001). No evident age-sex interaction at onset of RA was found among 100 females and 46 males with seronegative RA, who had an overall F:M ratio of 2.2:1 [15].

Further investigations utilizing the NHA population database, both with respect to cumulative age-sex specific incidence rates and other characteristics of the new RA cases, can further define the true age-sex interaction patterns in RA as well as the possible role of AA steroid deficiency in its pathogenesis [14, 16].

Controlled, prospective studies of RA have found decreased serum levels of dehydroepiandrosterone sulphate before onset of illness (mean 12 yr) in younger premenopausal, caucasian females [16; A. T. Masi et al., unpublished].

**Acknowledgements**

Sincere gratitude is expressed to Debbie Harper of...
EDITORIALS

UICOM-P for her outstanding contributions in preparing the manuscript and to Jon Spacht of the Methodist Medical Center of Illinois (MMC) for expert graphics. Michael Partridge, of Decision Resources, provided a helpful critique.

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REFERENCES

CLINICAL ACADEMIC RHEUMATOLOGY

Rheumatology training in Great Britain is in a ferment. Revisions will substantially decrease the time spent in training to bring us into line with European Community directives. Whether the brew will be worse than the original malt appears not to concern the Government. The masters of the National Health Service (NHS) emphasize flexibility about training, but impose guidelines of such rigidity that this will be impossible to achieve in the present framework of on-the-job training. Clinical academics in rheumatology met in Brighton prior to the British Society for Rheumatology’s Annual General Meeting to consider the implications of the Calman Report, and to berate the unfortunate representative from the Department of Health who presented it. All parties agree that the new proposals, together with the drastic reduction of junior doctor’s hours, will necessitate considerable expansion of the consultant grade. Since the Government has devolved the responsibility for this to Hospital Trusts without putting any more money in the pot, how it will be achieved is far from clear.

The basic skills which need to be imparted to trainees are not in doubt. These have been, and will be, determined by the Specialist Advisory Committee of the Joint Committee for Higher Medical Training of the Royal Colleges. Their acquisition will be more strictly monitored by a log book, annual appraisals and, very likely, an exit examination after 3 or 4 years (although that is stoutly resisted by the Colleges at the moment). It is the research component of such training which is likely to be squeezed out of existence. A thoughtful model for specialist training in rheumatology has been proposed [1]. Doherty suggests a core curriculum and standard methods of assessment. Individual centres could then add to that core, such as laboratory work, epidemiology, bioengineering, and clinical pharmacology. Trainees could opt to go where they wished to obtain this further training.

Another dilemma from these directives is the interface between academia and the National Health Service, and indeed, the training of academic rheumatologists. There is undoubtedly a sharpening of the