In May 1995, paediatric rheumatology was officially recognized as a speciality for training by the Royal College of Physicians in the UK. Since then, there has been a great deal of activity in terms of defining the provision of service within the speciality and training of doctors to provide the service. The General Medical Council now registers it as a sub-speciality of paediatrics. It is perhaps appropriate to consider the growth of the speciality and what to expect in the future from this speciality.

THE PAST

The first description of the symptoms and signs of arthritis in children is generally attributed to Thomas Phaire in 1545 [1] in his ‘boke of children’, where he noted the beneficial effects of warm, herbal baths, or hydrotherapy in modern terms. The first case report is attributed to Cornil in 1854 [2]. He described patients with polyarthritis, proteinuria and evidence of peri-carditis, osteoporosis and erosion of joints at autopsy. In modern terms, therefore, he described systemic juvenile chronic arthritis, with amyloidosis and osteoporosis. This was followed by a thesis from Diamantberger from Paris in 1891 [3]. On reviewing 35 cases from the literature and three of his own, he noted that they were heterogeneous and different from adult arthritis. This was reinforced by Sir George Frederic Still in 1897 [4] when he published his personal series of children with arthritis cared for by him when he was a registrar at Great Ormond Street Hospital, London. He distinguished them from adult rheumatoid arthritis and described the characteristic fever of the systemic form. The rash was noted in his own personal notes, but not mentioned in his paper, and it was left to Sir Harold Boldero at the Middlesex Hospital to point out this characteristic rash. He also noted growth retardation in these children. Thus, more than a century or more ago, the various types of arthritides in children had been described, including the complications that could arise out of the disease, such as amyloidosis, osteoporosis and growth retardation.

It was not until 1947, however, that rheumatology was given a research focus by the Medical Research Council (MRC) in the UK at the Canadian Red Cross Hospital in Taplow, Slough. More importantly, a focus was given for the first time to rheumatic diseases in childhood. The hospital was originally for rheumatic fever patients. However, it was soon apparent that more children suffered from chronic arthritis and other rheumatic diseases. One of Professor Bywaters’ registrars, Dr Barbara Ansell, became interested in this group of diseases and a proposal for disease classification was made by Drs Ansell and Bywaters in 1959 [5]. The classification of ‘Still’s disease’ was according to mode of onset, which is unusual in any type of disease classification; the rationale being that the presenting symptoms, the course of disease and prognoses of these broad groups appeared to be different. This form of classification was adopted by both the American Rheumatism Association in 1977 [6] and the WHO/EULAR in 1978 [7]. Unfortunately, these classifications were not exactly identical, creating a schism in nomenclature (reviewed in [8]).

Until 1975, expertise in treating these children in the UK was developed at one centre: the Canadian Red Cross Hospital. Subsequent to the retirement of its director, the MRC Rheumatism Unit was closed, and Dr Ansell started peripatetic clinics with local physicians within the UK, as well as maintaining a national unit at the MRC Clinical Research Centre at Northwick Park Hospital in Harrow. The British Paediatric Rheumatology Group (BPRG), consisting of 10 founder members, was established in 1985, affiliated to the British Paediatric Association. A European organization for paediatric rheumatology was also founded in 1979: the ‘EULAR Standing Committee for Paediatric Rheumatology’. Parallel developments also occurred in the USA, and the first international conference was held in Park City in 1977. The European Committee has an important function by allowing the sharing of clinical experiences, leading to new syndromes and new clinical entities being described. One of these was the chronic infantile neurological, cutaneous, articular syndrome (CINCA) as coined by Dr Prieur from Paris, concurrently described by Dr Ansell in the UK, and Dr Lovell in the USA [9]. The various clinical manifestations of vasculitides in childhood have also been recognized during the period up to 1985.

Between 1975 and 1985, collaborative clinical research within the UK and with its European partners was carried out on the management of juvenile chronic arthritis (JCA). More basic research was in the areas of genetics, amyloidosis and growth retardation. In the area of therapeutics, considerable advances have been made in terms of the number of non-steroidal anti-inflammatory drugs that can be used as a result of comparative or double-blind placebo-controlled studies (reviewed in [10]). With regard to second-line drug therapy, however, results were less hopeful up until 1985. The largest comparative study of second-line agents was performed between the USA and USSR collaborative study group. They showed that hydroxychloroquine, auranofin and penicillamine were no better than placebo in the treatment of polyarthritis [11, 12]. A review in the UK showed that the outcome of amyloidosis was significantly improved by chlorambucil [13] (Fig. 1), but there is an increase of leukaemia.

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from this treatment. Basic research has shown that the amyloid fibre is formed from polymers of an acute-phase protein, serum amyloid A, and that in the deposit there are a number of other molecules such as serum amyloid P component and glycosaminoglycans (reviewed in [14]).

As far as epidemiological studies are concerned, these were in their infancy and there were a number of studies performed in Northern American and European countries up to that point, giving an incidence of JCA of $1.3-18.2/100,000$.

An early twin study was incomplete due to lack of numbers, but highlighted that HLA-B27 was a marker; HLA association with different subgroups of JCA in part supporting the broad classification, but revealing heterogeneity and overlapping groups. There are also ethnic and regional differences. The main problem of most of these studies is that the numbers are not sufficiently large for definitive statements to be made.

In the field of growth retardation, the complication of steroid therapy was noted in the 1970s and alteration of the administration regimen of corticosteroids to maximize growth was advocated. However, the disease could cause growth retardation, as described by Cornil and Still. Low levels of somatomedin [insulin growth factors (IGFs)] were reported [15], but the results were controversial and varied between different studies due to assay difficulties.

The above is a very brief sketch skimming over the surface of the achievements of excellent clinicians in the past who have contributed substantially to the ground swell of knowledge in paediatric rheumatology.

THE LAST DECADE

The last decade saw an acceleration in the growth of paediatric rheumatology in the UK. The retirement of Dr Ansell in 1988 completed another cycle in the development of UK paediatric rheumatology. Up until then, the national unit was led by a rheumatologist who saw both adults and children. The regional clinics were staffed by an adult rheumatologist and a general paediatrician, i.e. part-time physicians with competing demands on their time. At the beginning of this decade, two paediatric rheumatologists were appointed (funded by the academic sector). Both elected to concentrate on practising only paediatric rheumatology allied to a programme of research. At the beginning of this decade, there was no health service appointment of paediatric rheumatologists as paediatric rheumatology was not recognized as a speciality. The need for services was unrecognized at all levels and there were a few parent support groups attached to individual clinics. As there was no speciality recognition, there were no trainees in paediatric rheumatology. In contrast, over the last decade, the membership of the BPRG has grown from 10 to over 100, consisting of consultants, trainees and allied health professionals. A national parent support group, the Children's Chronic Arthritis Association (with a current membership of over 400), was formed with regional representatives and hotlines.

In 1994, the British Paediatric Association Working Party published a report on paediatric rheumatology, defining the problems, the diseases, the burden on the health service and the service provision that was required, as well as the need for paediatric rheumatology research. Paediatric rheumatology was given academic recognition when I was appointed as the first Professor of Paediatric Rheumatology at London University in 1994, and moved the national referral unit to a more permanent home at Great Ormond Street Hospital. The recognition of the speciality by the Royal College for training in May 1995 was a crucial step to providing an important infrastructure so that paediatric rheumatology services can be provided across the UK, and also paediatric rheumatology research could flourish. In 1996, a new syllabus for training was produced, just in time for the revision of the whole of specialist training according to Calman recommendations. Now specialist paediatric rheumatology registrars have been appointed in two centres.

Over the last year, there has been increased collaboration between paediatric rheumatologists from North America and Europe, leading to a number of important international milestones. In 1994, a task force in paediatric rheumatology was convened by WHO/ILAR to consider the classification of the idiopathic arthritides in childhood. Prior to this, a number of articles had been published on the need for re-classification (reviewed in [16]). The result is a proposed revised classification which is currently being validated [17]. The next important milestone of international collaboration was the juvenile arthritis component of the International HLA Workshop in 1996. Over 2000 samples were collected. This was another impetus for us in the UK to optimize our resources, and the laboratory at the ARC Epidemiology Unit in Manchester undertook the HLA typing and storage of all DNA from JCA patients around the UK, provided by BPRG members. The third important milestone of international collaboration was in May of 1996. A consensus conference on core outcome measures for therapeutic trials in juvenile chronic arthritis was convened in Pavia under the leadership of...
Dr Martini (Italy) and Dr Gianinni (Cincinnati, USA). At that meeting, another important step was taken to establish co-ordination of future therapeutic studies in paediatric rheumatic diseases. An international organization (PRINTO) to undertake randomized open trials was born. The founders are Drs Martini (Italy), Prieur (France) and myself. These are significant steps in our management of JCA, which has been plagued by trials with small numbers, and uncontrolled studies. The fourth important international collaboration is the establishment of the paediatric rheumatology bulletin board on the Internet by Dr Dent from Canada.

The issue of adolescent care has been an active area of development on both sides of the Atlantic. The career development programme by Dr White in Washington DC is probably the pioneer programme for adolescents with chronic illnesses, but similar organizations are being set up in Canada and in the UK. A recent positive move is the appointment of a consultant physician in adolescent medicine at University College London/Great Ormond Street Hospitals.

GROWTH OF RESEARCH

Clinical and basic research in paediatric rheumatology in the last 10 yr has also gathered momentum. A national registry was established from 1989, and an estimate of the prevalence and incidence of rheumatic diseases was made possible [18]. In the area of therapeutics, the USA and USSR collaborative study group has shown the efficacy of methotrexate for polyarthritis [19]. A subsequent multicentre study (1992–6) was undertaken by us, involving centres within the UK as well as France, to address the question of whether methotrexate is also good for the therapy of polyarthritis with pauciarticular onset. The preliminary results were presented at the therapy workshop at the European Congress for Paediatric Rheumatology in Helsinki in August 1996, showing that methotrexate is also good for this subgroup (P. Woo, unpublished observations). The establishment of the trials co-ordinating centre (PRINTO) will accelerate knowledge on our therapeutic options.

Over the past 10 yr, scientists have begun to dissect the pathophysiology of different groups of JCA and demonstrate that, in terms of serum and synovial fluid cytokine profiles, there is certainly confirmatory evidence that the division of polyarticular JCA from systemic JCA was valid [20–22]. The concept of imbalance between pro- and anti-inflammatory cytokines has gained ground in inflammation research, e.g. in cerebral malaria the ratio of soluble tumour necrosis factor (TNF) receptor to TNF appears to affect the outcome and is related to a genetic variation of the TNF gene [23]. In our laboratory, studies using whole blood cultures in systemic JCA showed a possible imbalance in the reduced secretion of the anti-inflammatory cytokine interleukin-10 (IL-10) in the peripheral blood cells [24]. Examination of synovial fluid in different subgroups of patients, such as pauciarticular JCA, polyarticular JCA and spondyloarthopathies, yielded marked differences between the three groups, in particular the spondyloarthopathy group had a much higher ratio of TNF receptor to TNF, compared to polyarticular JCA or pauciarticular JCA [25]. These imbalances in response to the environment may be genetically determined, leading to pathology. In addition to the example quoted above [23], evidence for this hypothesis is accumulating. The ‘autoimmune haplotype’ HLA B8DR3 has been found to be associated with a number of autoimmune diseases in adults and children. Blood cells from these patients have a diminished capacity to produce pro-inflammatory cytokines with a normal capacity to produce anti-inflammatory cytokines such as IL-4 [26]. They are also high producers of TNF, and possess the rarer TNFA2 allele [27]. In a recent study, polymorphisms in the IL-1 gene locus have been associated with uveitis in early-onset pauciarticular JCA [28]. Other cytokine polymorphisms have now been described, and they are also in the regulatory regions of the genes. These observations suggest that these polymorphisms are important in the cytokine response to a given stimulus.

Another growing area of immunological research is the analysis of T-cell responses in different groups of arthropitides. In the B27-positive subgroup, T cells recognizing a conserved bacterial heat shock protein (HSP60) have been found [29, 30], giving a clue to the pathogenesis. Furthermore, cytokine gene polymorphisms can determine the T-cell responses to an infectious agent, as well as perpetuation of inflammation (as described above).

Current biomolecular investigations in inflammatory arthritis address primarily receptor molecules on cells, the signal transduction mechanism whereby these receptors transmit signals to activate genes, and gene regulation. Possible molecular targets have been identified for the development of new therapies. These include the generation of anti-receptor antibodies in the field of adult rheumatoid arthritis, e.g. anti-CD3, IL-1 receptor antagonist, and antibodies to cytokines themselves, such as TNF antibodies. Ironically, with the understanding of the signal transduction and transcription factor pathways, it is clear that some of the drugs we have used over the years, deemed to be effective in the treatment of arthritis, exert their effect precisely at these levels. A good example is glucocorticoid which inhibits a number of transcription factors such as NFkB and CEBP, both of which are responsible for IL-6, IL-8, ICAM, IL-1 receptor antagonist and a large number of acute-phase response genes. There is evidence that glucocorticoid inhibits the translocation of NFkB into the nucleus [31], and cyclosporin A inhibits the translocation of AP1 (another common transcription factor) into the nucleus [32]. Concurrent with these developments, research on gene delivery systems is growing apace. The rationale is that if one can tailor specific delivery to target cells of therapeutic genes, then side-effects could be considerably minimized. The use of genetic therapy by injecting controlling genes into appropriate cells and returning them to the animal, or injecting the joints with these genes carried by a viral vector, have
provided encouraging results. However, technology needs to be improved further in order to allow designer genes to be delivered to specific cell types.

In the field of amyloidosis, considerable advance has been made in the detection of amyloid deposits by a non-evasive scanning technique pioneered by Dr Hawkins and Professor Pepys at the Royal Postgraduate Medical School (RPMS) in collaboration with our unit and some members of the BPRG [33]. Fortunately, the incidence of amyloidosis during the last 10 yr in Scandinavia and Europe appears to be declining. This may be related to early diagnosis and more effective treatment of JCA. The genetic predisposition to amyloidosis is likely to be multifactorial. The frequency of the serum amyloid A alleles within the amyloid JCA population was significantly different from the non-amyloid JCA population [34]. Transgenic and knock-out mice are being prepared to evaluate the amyloidogenic potential of the SAA proteins. Other genetic factors include serum amyloid P component. Knock-out mice have been made at the RPMS and there are interesting differences between them and the wild-type mice (M. Pepys, personal communication).

In the field of growth retardation and osteoporosis, considerable work has been performed. Osteoporosis has been documented by bone densitometry in children suffering from JCA even though they have not been on steroids [35]. Examination of the growth factors, such as growth hormone and insulin growth factor 1 (IGF1), has shown that the growth hormone secretion of these patients is within normal limits, or at least the same as short/normal children, but IGFs levels were significantly below normal [36]. Moreover, we showed that the growth retardation, as well as the reduced IGF1 levels, are inversely proportional to measurements of disease activity such as C-reactive protein, suggesting that inflammatory cytokines may have a direct effect on IGF1. A recent report confirmed this by showing that IGF1 mRNA production from primary hepatocyte cultures is reduced by IL-1β and TNF-α, enhanced by the presence of growth hormone [37]. As far as osteoporosis is concerned, vitamin D levels have been documented as low, but probably due to steroid therapy. Of interest is that parathyroid hormone is low as well. This could be an adaptive response because of the leakage of calcium out of the bone into the serum to compensate for low serum calcium levels, and therefore inhibit parathyroid hormone. However, the mechanism is still unclear. Finally, our 1 yr trial of growth hormone has shown significant benefit to both height velocity as well as bone mineral density [38]. This has been confirmed recently by a similar study in Paris (A. M. Prieur, unpublished observation).

THE FUTURE

The natural evolution of a medical speciality or subject is that it can be divided into four stages. The first stage is descriptive, where keen observations by physicians allow a clinical syndrome to be defined and then subdivided into possible diseases for further study. The second stage is complementary to the first stage, in which laboratory investigations help further to define a disease and crystallize thoughts about possible pathogenesis. The third stage is more basic laboratory research into disease mechanisms and immunoregulation, as in the case of autoimmune diseases. The final stage should arise out of all three stages, where rational therapeutic strategies are carried out. From the previous description of the past and present, most of the work in paediatric rheumatology fits into the first two stages. In the next millennium, it is clear that the third and the fourth stages will be more prominent. The developments within the last 10 yr in molecular biology and molecular genetics would mean that the part of the human genome that codes for existing proteins will be sequenced by the year 2010, at which point all the information that has been gathered from linkage studies to define disease susceptibility loci (including JCA) will allow us to pinpoint the disease susceptibility genes with the aid of the completed genome map. The relative importance of the genes involved will need to be studied and would allow us to fine-tune our therapeutic targets. After the mapping of the genome, there will be even more work on the understanding of gene function and their interactions with each other, as well as with infectious agents. I foresee that this will be a major area of research which will elucidate the causes of the chronic arthritides which are currently termed 'idiopathic'. Novel molecular targets have already been mentioned and are by-products of this type of research. Future therapeutic trials using gene delivery systems, as well as using new drugs that are designed for specific molecular targets, would be the main thrust of therapeutic research. Hopefully, we will be able to find a drug that will replace glucocorticoids, which have been very beneficial but have far too non-specific an effect, leading to multiple undesirable side-effects.

International collaboration is the key to the advance of the understanding of the rheumatic diseases in children, as they are uncommon. The basis for such collaborations now exists and the randomized open trials centre will soon put evidence-based therapy on a firm basis. The collaborative nature of the European group will be strengthened further by a common training syllabus and its endorsement by the European Board of Paediatrics. Trainees, therefore, could move from country to country to fulfill their training requirements. Until such time as there is a 'cure' for rheumatic diseases in children, and even when there are cures, we still need paediatric rheumatologists to provide an informed quality service. Multidisciplinary work within the community will become more important. Issues such as adolescence, the transition into adulthood and career development will have more emphasis in the provision of care. Definition of outcome in the different connective tissue diseases, as well as arthritides, will allow sound comparison of different modalities of therapy and intervention.

In summary, therefore, I foresee that in the next millennium, paediatric rheumatology will come of age. Given that we have a very good start in terms of international collaboration, I anticipate that rational
and tested therapies will become the norm rather than something that we aspire to. The knowledge from basic science research into the mechanisms of disease will give us specific insight into the interaction between genes and their environment. Lessons from these will also have wider application to other inflammatory diseases of childhood.

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Knee pain is a common symptom and an important cause of morbidity [1]. The presence and severity of knee pain are risk factors for disability both in cross-sectional and longitudinal studies [2–4]. In the first National Health and Nutrition Examination Survey (NHANES-I), for example, baseline knee pain was associated with increased odds of difficulty walking 7–13 yr later, irrespective of baseline X-ray changes [2]. Knee pain is also a risk factor for radiographic progression of knee osteoarthritis (OA) and the need for total joint replacement [5].

The odds of knee pain clearly increase with the radiographic severity of OA [6–11]. In the NHANES-I study, among subjects aged 65–74 yr knee pain was reported by 8.8% of subjects with normal X-rays, 20.4% with Kellgren and Lawrence (K + L) grade 1 OA, 36.9% with grade 2 and 60.4% with grades 3–4 [12]. Despite this consistent association, community studies have produced another, less easily explained observation: there remain many subjects in whom X-ray changes and reported pain are discordant. On the one hand, pain may be reported in the absence of X-ray changes; alternatively, pain may be denied despite the presence of severe radiographic disease. We shall consider these groups separately.

The prevalence of self-reported knee pain with normal X-rays is ~10.0%. The Framingham Osteoarthritis Study [8] found a frequency of 4.4% for males and 9.6% for females; the NHANES survey results were 7.6% for males and 8.4% for females [12], and in the Baltimore Longitudinal Study of Aging (BLSA), a multidisciplinary research study of community-dwelling volunteers, 14% of subjects with normal X-rays reported ‘ever pain’ and 9% ‘current pain’ [11]. There are several reasons why subjects may complain of knee pain despite apparently normal X-rays. First, most studies utilized only supine or weight-bearing views of the tibiofemoral joint; failure to assess the patellofemoral joint could result in a subject being classified as ‘X-ray negative’ when in fact changes were present but not seen. Indeed, up to 24% of females reporting knee pain have isolated patellofemoral disease and if lateral views are included the predictive value of pain for radiographic change increases [13]. Second, a positive response to the NHANES-I knee question does not differentiate between isolated knee pain and widespread pain of which the knee is but a part. Recent studies in the USA [14] confirm findings from the UK of a prevalence of ‘widespread chronic pain’ of ~11% [15]. Such patients may answer affirmatively about knee pain, but this would not necessarily imply local pathology. Third, X-rays are relatively insensitive: they may be normal when other diagnostic studies such as arthroscopy show clear evidence of OA [16]. X-rays do not allow visualization of non-bony sources of pain, such as capsule, synovium or ligaments. Hence, clinical findings such as crepitus may also predict pain, at least in the presence of radiographic OA [2]. Finally, not all knee pain is due to OA: causes such as anserine bursitis, internal derangements and referred pain from hip or spine would not be identified on X-rays of the knees.

The second group (X-ray positive, pain negative) is larger. Pain reporting in grade 3–4 OA ranges from 40 to 79% [6–12]. Thus, up to half of the patients in the community with, by any standard, established radiographic OA, deny pain. How can this be explained? The K + L grading system is relatively crude: do individual radiographic features show a closer correlation with pain? At the knee, osteophytes appear to correlate best with pain reporting [10, 11, 17]. However, 44% of subjects in the BLSA cohort with grade 2+ osteophytes reported no current pain. Again, the precise question that is asked may affect the response in terms of pain reporting. Even though the NHANES-I question may produce greater reporting of knee pain than other questions [18], it may still underestimate prevalence: patients may have had pain, but not on ‘most days of a month’, or they may simply fail to recall previous episodes of pain. Further, OA may be a phasic condition with episodes of pain separated by remissions: the question may fail to capture the painful episode.

Our attempts to link radiographic changes to pain reporting stem from the belief that the cause of knee pain is visible on an X-ray. This may not be so. Risk factors for radiographic OA and for knee pain differ [9, 12]. Non-pharmacological interventions such as simply talking to patients by telephone [19], use of acupuncture [20, 21] or weight loss [22] and aerobic exercise programmes [23] can have significant effects on pain severity. Interventions on one knee may have a

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profound effect on pain perception in the other [24]. These, and other observations, strongly suggest that pain is not simply the result of structural changes but, rather, the outcome of a complex interplay between structural change, peripheral and central pain processing mechanisms, and subjective differences in what constitutes pain, in turn influenced by cultural, gender and psychosocial factors. Pain is, by definition, subjective and one person’s pain is another’s mere discomfort. There is no reliable way of assessing the severity or even the presence of pain by physical examination, but some clues may be provided by an examination of the role of psychosocial factors in knee pain reporting. ‘Psychological well being’, for example, was found in NHANES-I to be associated with knee pain irrespective of radiographic changes [6, 12]. A cross-sectional study of hospital out-patients found a relationship between anxiety and, to a lesser extent, depression and pain [25]. Less is known about the influence of stable traits or ‘personality’. It is known that neuroticism is associated with high levels of all forms of symptom reporting [26] and hypochondriasis is reported to be a powerful predictor of knee pain, at least in the elderly [27].

There are several areas which might lead us to a better understanding of the complex relationship between pain and structural change. In all community studies, pain has been treated as a dichotomous variable (present or absent); an alternative approach would be to look at the severity of pain as a continuous variable. The use of more sensitive imaging techniques, such as MRI, might allow earlier definition of OA through visualization of non-bony structures. Prospective studies would allow testing of the hypothesis that pain reporting is phasic. The relationship between pain reporting and psychosocial features needs to be addressed, both in the community and in patients who have elected to seek medical help. Prospective studies would allow separation of cause and effect in terms of psychological morbidity. Such studies may help us understand not only why the osteoarthritic knee can be painful, but why it is so often pain free.

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