RHEUMATOLOGY: MADE IN INDIA
(Camps, COPCORD, HLA, Ayurveda, HAQ, WOMAC and Drug Trials)
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Abstract:
This coveted oration describes my clinical and research career. The focus is on ‘Indian-ness’ and contributions to Indian Rheumatology.

Methods: This oration will focus on clinical profile, camps, HAQ, Community oriented program for control of rheumatic diseases (COPCORD) Bhigwan, Ayurveda, drug trials, ANA, HLA, BJD, New Millennium Indian Technology Leadership Initiative (NMITLI), MAI, database & CRD.

Results: The clinical profile of Indian arthritides is different and Caucasian population based classification criteria do not suffice. Comparative data from free arthritis camps is presented. Validated versions of HAQ and WOMAC suitable for Indian use were developed and are presented. The maiden Indian WHO COPCORD, an ongoing rural population program in Bhigwan (Pune), has provided statistics on prevalence, incidence, risk factors. The Bhigwan model, unlike any other COPCORD, provides free clinical services. The Bhigwan longitudinal observational seven year data from RA patients (unpublished) showed that (i)regular DMARD use had lower HAQ scores (better functional ability) (ii)chloroquin was safe (iii)steroids had higher HAQ scores. The HLA DR profile in RA, both from Bhigwan and hospital referrals, was remarkably different. We have demonstrated the efficacy and safety of certain standardized Ayurvedic drugs in RA and OA knees through several controlled randomized drug trials; one of these drugs is now marketed worldwide. These trials also showed an unprecedented robust placebo response. A multicentric NMITLI arthritis program, funded by Government of India, has been launched to identify evidence based Ayurvedic medicinal plants and will be co-ordinated from CRD, Pune. The Bone and Joint Decade (BJD) 2000-2010 India program, also run from CRD, has launched several national research programs.

Conclusion: As clinicians, we can do significant research, especially pertaining to community needs. Arthritis camps are useful. But we also need population studies such the WHO COPCORD Bhigwan. BJD has begun to measure the national disease burden. Ayurvedic medicines can treat arthritis and need further scientific exploration. Rheumatology needs to be recognized both as a specialty and a research area.

Key words: Ayurveda, BJD, Clinical Research, COPCORD, Drug Trials, Epidemiology, Quality of Life, Rheumatology

I thank the Indian Rheumatology Association for awarding me the IRACON AVENTIS Oration 2003. My oration title is rather unconventional but the aim is to stir ‘Indian-ness’ in our specialty. I shall focus on the scientific aspects of my work related to clinical and laboratory studies in patients with rheumatic diseases. Clinical studies include profile of patients with rheumatic complaints in hospital and community (camps), COPCORD (Community oriented program for control of rheumatic diseases) Bhigwan, validation of HAQ (Health Assessment Questionnaire- for RA) and WOMAC (Western Ontario McMaster’s University, an OA Index), Ayurvedic drug trials. Lab studies include ANA and HLA. I shall take this opportunity activity to introduce The Bone and Joint Decade...
(BJD) and the New Millennium Indian Technology Leadership Initiative (NMITLI).

1981-1989:

Clinical Profile:

In 1980, I joined Armed Forces Medical College (AFMC), Pune, for my post-graduation in general medicine. Brig AR Subramanian, the then Head of the Department of Medicine and my guide allotted me “A study of polyarthritides” for my MD dissertation. Evaluation of 50 patients suffering from chronic polyarthritides was a fascinating exercise with observation of some diseases that we rarely see now—syphilis, Jaccoud’s arthritis, and infective polyarthritis. A lower prevalence of rheumatoid factor was observed in Rheumatoid arthritis. The prevalence of RA in the young servicemen population was reported to be 0.06%. An overlap between RA and SSA (seronegative spondarthritis) in several young servicemen was observed. Caucasian population based criteria were not suitable for our community. The concurrent presence of RF and B27 led some credence to my earlier observation of RA-SSA overlap. The frequency of B27 in the servicemen cohort (Table 2) was compared that from other Indian and Caucasian data. The Association of Physicians of India awarded Dr Berry Memorial Award 1987 and E Merck Award 1988 to our research presentations.

<table>
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<th>Subset</th>
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<th>AIIMS, Delhi</th>
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<td>RA(+)</td>
<td>73</td>
<td>26</td>
<td>92</td>
</tr>
<tr>
<td>RA(-)</td>
<td>67</td>
<td>20</td>
<td>80</td>
</tr>
<tr>
<td>Total RA</td>
<td>130</td>
<td>46</td>
<td>172</td>
</tr>
<tr>
<td>Unclassifiable</td>
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<td>1</td>
<td>5</td>
</tr>
</tbody>
</table>

Note: (+): RF positive; (-): RF negative

Table 2: Frequency and relative risk of B27 locus antigen in SSA

<table>
<thead>
<tr>
<th>Subset</th>
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<th>Caucasians</th>
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<tbody>
<tr>
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<td>73</td>
<td>26</td>
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<tr>
<td>RS</td>
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<td>20</td>
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<tr>
<td>SSA-U</td>
<td>41</td>
<td>7</td>
<td>84</td>
</tr>
<tr>
<td>Reactive</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Arthritis Controls</td>
<td>9</td>
<td>6</td>
<td>9</td>
</tr>
</tbody>
</table>

Note: f: frequency percent; R: relative risk; AS: Ankylosing Spondylitis; RS: Reiter’s Syndrome; SSA-U: Seronegative Spondarthritis Undifferentiated.

1990-1999:

Arthritis Camps:

The socio-economic viability of medical camps was appealing. Under guidance of Dr KH Sancheti, Director and Chief orthopedic surgeon, Sancheti Institute for Orthopedic and Rehabilitation (SIOR), Pune, a senior mumbai, a

Figure 1: Arthritis Camps: Percent distribution of patients classified in to major disease category
nostic break-up (percent) of the patients seen in the two camp series with different background. The 1989 data was collected from 8 camps, held monthly, in SIOR with free clinical services and subsidized investigations. The 1994 data (unpublished) was collected from 26 camps, held every 2-3 weeks, at another center, Medinova, Pune; with free of cost clinical and lab services. These camps provide good platform for public education and provide useful clinical data but cannot replace population based studies.

**Fellowship:**

I completed a three month advanced APLAR training fellowship in the Dept of Rheumatology, The St George Hospital, Sydney, Australia, in 1992 under the supervision of Prof John Edmonds. He initiated me into community research. On return to Pune, I organized a rheumatology team and the ‘Center for Rheumatic Diseases’ (CRD).

**HAQ (Health Assessment Questionnaire):**

The HAQ brought back into focus issues connected with ‘quality of life’ and ‘disability’. It was realized that the HAQ would have to modified in the Indian setting. Both the community and the patients were interviewed and surveyed to obtain data and views on the critical functional elements related to our habits and traditional life styles (e.g. sitting cross legged on the floor) for the Indian HAQ. A HAQ research team, with suitable community and patient representation, to finalize the Indian version through a consensus approach was established. It was ensured that the basic concept and structure of the Stanford HAQ was not lost during the several cross cultural adaptations and language translations. Finally, reinforced with validation statistics, the Indian HAQ (see Appendix A) came into being. The instrument was presented for the first time in the national conference of the Indian Rheumatology Association in 1992. Till date, HAQ continues to be an essential component of our rheumatology assessment, be it referral practice, drug trials, arthritis camps or the WHO COPCORD Bhigwan.

**Laboratory:**

I was inspired by the study of Malaviya et al to determine the lupus population prevalence using filter paper blood clots (FPBC) collected during an urban malaria survey. Using FPBC, a pilot study was carried out to validate the ANA detection using color enzymes instead of the gold standard immunofluorescent (IF) technique. Color enzyme patterns are visualized under light microscope. The technique was fine tuned subsequently, to enhance its sensitivity and specificity. HLA DR typing in patients with RA was done with collaboration of Prof John Edmonds (Australia) and Prof Alan Silman (UK) both from referral practice and the COPCORD rural population. An ongoing program to collect classification and HLA data in juvenile inflammatory arthritis is underway.

**Ayurveda:**

Prof B Patwardhan, Director, School of Health Sciences, Pune University, initiated a project in early 90s to determine the lupus population prevalence using filter paper blood clots (FPBC) collected during an urban malaria survey. Using FPBC, a pilot study was carried out to validate the ANA detection using color enzymes instead of the gold standard immunofluorescent (IF) technique. Color enzyme patterns are visualized under light microscope. The technique was fine tuned subsequently, to enhance its sensitivity and specificity. HLA DR typing in patients with RA was done with collaboration of Prof John Edmonds (Australia) and Prof Alan Silman (UK) both from referral practice and the COPCORD rural population. An ongoing program to collect classification and HLA data in juvenile inflammatory arthritis is underway.
Faculty, Harvard Medical School, at the Arthritis Unit of Massachusetts General Hospital, Boston. A 16 week randomized, double blind, placebo controlled, parallel efficacy clinical drug trial study to evaluate RA-1 in patients with RA. The randomized phase of 182 patients was followed by a year long open label phase; almost one-third patients were evaluated at five year follow-up. The RA-1 trial was published\(^\text{14}\) with an editorial\(^\text{22}\) commending the work and highlighting an integrated approach towards alternative and complementary medicines. Recently, a systematic analysis reviewed this trial\(^\text{21}\). The Indian modification of the WOMAC index for OA was validated (Appendix B) for OA hips and knees and used it to evaluate efficacy of RA\(^\text{11}\) in OA knees\(^\text{24}\). The result of the Ayurvedic drug trials were presented at the ACR meetings\(^\text{25,26}\). RA-1/11 is now marketed Worldwide (in India by Dabur under the trade name of Artrex). Ayurveda needs to be understood in the context of modern medicine\(^\text{27,28,29}\) with particular reference to rheumatology. An overview of Ayurveda therapeutics on the American College of Physician’s PIER website\(^\text{30}\) was posted by me.

**Increased placebo response:**

A robust placebo response was observed in our patients from randomized controlled drug trial studies. Fig 2 & 3 demonstrates a significant placebo effect in patients with active RA from RA-1 study\(^\text{14}\) and a recently completed SIRO trial (unpublished). The ‘percent change from baseline’ with respect to the joint count for swelling and HAQ is being shown. The joint count for swelling and HAQ are amongst the ACR core set efficacy measures\(^\text{31}\) for drug trials in RA. However, ACR 20\(^\text{32}\) can differentiate an active drug response from that of the placebo, as shown in Fig 4. The data on leflunomide (unpublished) in Fig 4 is derived from

![Figure 2: Percent change from Baseline in the joint count for swelling in the placebo group from two randomized controlled drug trial studies over time (weeks)](image1)

![Figure 3: Percent change from Baseline in HAQ in the placebo group from two randomized controlled drug trial studies over time (weeks)](image2)

![Figure 4: ACR 20 improvement in patients (percent) of RA by placebo, RA-11, & Leflunomide over time (weeks)](image3)
the referral clinical practice in CRD, Pune. However, there was an almost 30% ACR 20 improvement response in the placebo group at week 16 (Fig 4). There are several reasons for the strong placebo response due to over caring attitudes of the investigator to the cultural and traditional belief of an Indian patient in the doctor.

Besides carrying out several drug trials on anti-arthritic Ayurvedic medicines, we have carried out controlled evaluations of the COX-2 inhibitors.

COPCORD (Community oriented program for control of rheumatic diseases):

Population studies are uncommon in our setting largely because of economics and logistics. The maiden Indian rural population based WHO-ILAR COPCORD was launched in Bhigwan in Feb 96 and is the only program of its kind in the World that has continued till date. It has been a novel experiment in community rheumatology. Beyond the one time COPCORD population survey rhetoric, the Bhigwan program has fulfilled the long term COPCORD objectives (identifying risk factors, health education and preventive strategies) and provided free clinical services, including medicines and assist devices for the needy, to the community at large. Today, COPCORD Bhigwan provides cover to about 40,000 rural population spread over 120 villages or so. Prof HA Valkenburg, The Netherlands, a distinguished epidemiologist & founder of the WHO-ILAR COPCORD, wrote in his official report “Remarkable that the whole data sampling (of COPCORD Bhigwan) could take place in 5 weeks time as the result of a very well prepared and punctually executed organization in which apparently all team members actively and enthusiastically participated. The survey itself was an amazingly well oiled, concentrated and highly organized operation in which the local medical community participated”. The COPCORD Bhigwan data has been presented and published several times. Yet, it gets misinterpreted in important reviews with a mix up of prevalence & proportion statistics.

The prevalence of RA (ACR classified) in rural Bhigwan was reported to be strikingly high. Some new data that are unpublished on the long term evaluation of these RA patients are being presented using the CRD Pune HAQ (Appendix A). Some of the key steps in this treatment evaluation (Fig 5 & 6) were (i) the

Figure 5: Mean HAQ score over time in different treatment categories in the RA Bhigwan COPCORD RA Chohort

Figure 6: Mean HAQ score over time in the Bhigwan COPCORD RA Chort in patients on long term steroid use
entire Bhigwan RA cohort (n=51; includes old and new) was selected, (ii) patients were followed up every 3-6 weeks, (iii) HAQ was completed by trained rural health workers though interview in home/work place/COPCORD village clinic every 6-8 weeks, (iv) patients not attending COPCORD or taking unsupervised therapy were also followed up, (v) the HAQ collection dates were converted into weeks and rearranged at 3 monthly interval bins, starting from the time of initial population survey. Sometimes the HAQ data week had to be shifted to the nearest 3 monthly bin, (vi) the higher of the 2 or more qualifying HAQ values were preferred, (vii) the nearest HAQ value was used to fill the missing value, (viii) Patients qualified as ‘long term steroid user’ when documented steroid exceeded 3 months per year or when the depot methylprednisolone preparation had been injected more than 3 times per year or when the period of cumulative steroid use exceeded half of the follow up period (ix)HAQ score ranges from 0 to 24. A score less than 9 is generally considered low/mild. The mean HAQ score of each of the treatment groups was computed at predetermined 3 monthly bin end-points and plotted over time. At least data from 9 patients was required in the 3 monthly bin before computing the mean HAQ. There were 3 treatment Groups [Irregular/unknown therapy (mostly NSAID &/or steroid use) and poor follow-up =13 patients; Chloroquine=15 patients; methotrexate=18 patients (these patients also received prior or concurrent chloroquin)]. Fig 2 shows that several patients of RA have been followed up to 7 years or so using HAQ for evaluation. Patients on long term DMARD did reasonably well with respect to HAQ derived functional ability.

We have recently observed that a low HAQ score 38 may fail to capture the severe functional disability arising out of a single or few joints e.g knees (in our setting). The long term COPCORD Bhigwan treatment data (Fig 5) also endorses the long term safety of chloroquin. We have prescribed the cheap chloroquin sulfate to the Bhigwan patients rather than the expensive hydroxychloroquin. And except for mild-moderate skin pigment changes due to Chloroquine that were easily managed, we did not encounter any other serious clinical concerns, including ocular. It is also likely that the more severe RA patients received a combination of methotrexate and chloroquin but we have not yet analyzed the groups for their baseline measures. Fig 6 shows that only one third patients in the RA cohort were prescribed long term steroids and their HAQ scores were higher as compared to the remaining patients (not on long term steroids).

In a recent WHO-Bone and Joint Decade publication 40, COPCORD Bhigwan data was used to project prevalence statistics of RA and OA in the subcontinent. COPCORD Bhigwan has now set the stage for national statistics and a national program for rheumatic diseases.

2000 ONWARDS:
New Millennium Indian Technology Leadership Initiative (NMITLI):

CSIR, Government of India, launched a fully funded NMITLI project in 2002 to enable India to occupy a global leadership position in certain niche areas, including Ayurveda. Based on Ayurvedic knowledge and experiential base, evidence based Ayurvedic medicinal plants’ derived drugs to treat arthritis, diabetes and hepatitis will be identified. The project is for a four year period. Modern medicine scientists would exercise their core competence to test and validate the various procedures, processes and applications. A parent protocol was developed for the ‘arthritis component. As the group Clinical Co-ordinator, I am privileged to have premier medical institutions working along
with CRD, Pune in this very exciting and ambitious project– AIIMS (New Delhi) NIMS(Hyderabad), KEM Hospital (Mumbai) & SPARC (Mumbai). The project was begun on 01 April 2002. We have translated the Indian versions (see above) of HAQ and WOMAC into several Indian languages. Several multicentric controlled drug trials are now in progress. Our initial focus is on OA knees but we will carry out early phase II evaluation in RA as well.

Bone and Joint Decade BJD India:

The WHO supported Bone and Joint Decade (BJD) 2000-2010 was launched in Jan 2000. I participated in the workshops leading to the launch. BJD aims to curb the growing but under recognized menace of the rheumatic-and- musculoskeletal diseases (RMSD). IRA is one of the founder members of BJD India NAN (National Action Network). I hold the office of the national secretary. The membership is steadily increasing and there is a liaison officer in several states to organize and coordinate BJD CME and public education activities. This year, BJD India has sponsored five major research programs that include a COPCORD Bhigwan model based multiregional urban population based survey for RMSD. To begin with, surveys will be completed in Jammu, Chennai and Pune. Recognizing the BJD India effort, the Dept of Science and Industrial Research (DSIR), Govt of India, has recently endorsed it with the prestigious research status of a Scientific and Industrial Research Organization (SIRO).

Mission Arthritis India:

Mission Arthritis India (MAI) is a patient support group that operates from Pune. MAI is one of the founder members of BJD INDIA: NAN. CRD, Pune, has endorsed the programs of MAI and provides all logistic and professional support.

CRD:

Center for Rheumatic Diseases (CRD), Pune, is now run by Arthritis Research Care Foundation, a private registered charitable society and trust. University of Pune has recognized it as a ‘research center’ for doctorate and post-doctorate studies. Based on the performance of the COPCORD Bhigwan & NMITLI programs, Govt of India has recently conferred upon CRD the status of a SIRO. This has been made possible by a dynamic and dedicated team that includes rheumatologist, research doctors, Ayurvedic physicians, microbiologist, soft ware & data-base experts, statistician and a drug trial coordinator. 3 students are doing their doctorate studies on osteoporosis, immunogenetics and Ayurvedic RA therapy. A large clinical and lab database is maintained at CRD. Several indigenously designed user friendly software programs with Visual Basic at the front end and Microsoft access at the back end have been created. Case record forms of all patients including the trial patients and COPCORD, are being entered since 1996.

I am indeed proud to be an Indian rheumatologist. Our rheumatology practices must cater for our masses. We have our own unique set of situations and problems. The very diversity that sometimes divides us is also our biggest scientific medical asset, both in terms of clinical challenge and research. Our rheumatology must be continuously made in India.

ACKNOWLEDGEMENT:

Several colleagues, friends and family have helped me transform my vision into reality. I remain indebted to each one of them. Anuradha V (in charge lab) & Manjit Saluja (co-ordinator, CRD & trials) have played a key role with exceptional responsibility and
dedication. I would not have achieved this measure of success without the personal sacrifices, generous support and deft finance management of Mehernaz Chopra. And finally, I bow to my late parents in eternal gratitude for having set me on this path.

References:
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33. Chopra A, Bichile L, Rajadhyaksha A et al. Randomized Double Blind Clinical Drug Trials of Meloxicam in Rheumatoid Arthritis and Osteoarthritis Knees: An Indian Experience. APLAR J Rheumatology 2003 (accepted for publication)
Appendix A

Health Assessment Questionnaire (Modified – Crd Pune Version)

NAME:_________________________________________________AGE:____SEX:____DATE:________

We are interested in learning how your illness affects your daily life. Please feel free to add any comments on the back of this page. Please check the response which best describes your abilities over the past week.

ARE YOU ABLE TO:

<table>
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<tr>
<th>Score</th>
<th>Without Difficulty (0)</th>
<th>With some Difficulty (1)</th>
<th>With much Difficulty (2)</th>
<th>Unable (3)</th>
</tr>
</thead>
</table>

I: DRESSING
1) Dress yourself, plus doing buttons ?
2) Wash your hair ?
3) Comb your hair ?

II: ARISING
4) Stand up straight from a chair ?
5) Get in & out of bed ?
6) Sit cross-legged on floor & get up ?

III: EATING
7) Cut vegetables ?
8) Lift a full cup /glass to your mouth ?

IV: WALKING
9) Walk outdoors on flat ground ?
10) Climb up five steps ?

V: HYGIENE
11) Take a bath ?
12) Wash & dry your body ?
13) Get on & off the toilet ?

VI: REACHING
14) Reach & get down a 2 kg. object (such as bag of sugar) from just above your head ?

VII: GRIP
16) Open a bottle previously opened ?
17) Turn taps on and off ?
18) Open door latches ?

VIII: ACTIVITIES
19) Work in office / house ?
20) Run errands and shop ?
21) Get in & out of a bus ?
22) Get in & out of a car / Autorickshaw ?

TOTAL SCORE________

Please check any AIDS or DEVICES that you usually use for any of these activities:

- Cane
- Walker
- Crutches
- Wheelchair
- Special Built Up Chair
- Raised Toilet Seat

Categories for which you need HELP FROM ANOTHER PERSON:

- Dressing & Grooming
- Eating
- Arising
- Walking
- Hygiene
- Reach
- Grip
- Errands
Appendix B  
Womac Index (Modified - Crd Pune Version)

STUDY JOINTS: $ RT KNEE $ LT KNEE $ BOTH

Please tick (✓) in the appropriate column

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<th>NONE</th>
<th>MILD</th>
<th>MODERATE</th>
<th>SEVERE</th>
<th>EXTREME</th>
<th>SCORE</th>
</tr>
</thead>
</table>

HOW MUCH PAIN DO YOU HAVE?
1. In walking on flat surface
2. Going up or down stairs
3. At night while in bed
4. Sitting or lying
5. Standing upright

HOW MUCH IS YOUR STIFFNESS?
6. After first wakening in the morning
7. After sitting, lying or resting later in the day

HOW MUCH DIFFICULTY DO YOU HAVE?
8. Descending stairs
9. Ascending stairs
10. Standing up from a chair
11. While standing
12. Bending to floor (to pick up objects)
13. Walking on flat ground
14. Getting in and out of Autorickshaw/Bus/Car
15. Going shopping
16. On rising from bed
17. While lying on bed
18. While sitting on chair
19. Going on/off toilet –Indian/Western
20. Doing heavy domestic duties (moving heavy boxes, scrubbing floor, lifting shopping bags)
21. Doing light domestic duties (cleaning room/table/cooking/dusting)
22. While sitting cross legged on floor
23. Rising from cross legged position
24. While squatting on floor

TOTAL