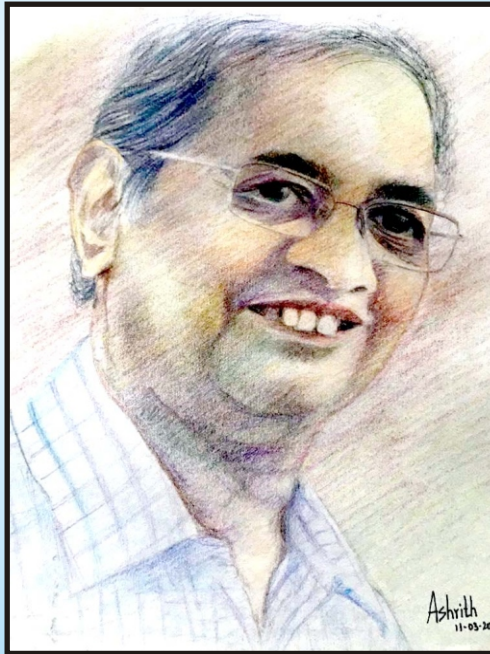


Dr. V. KUMARASWAMI
1950 - 2016

A many-splendoured personality...



PREFACE

**Dr. V Kumaraswami, MD, MNAMS, PhD, FRCP
(1950 -2016)**

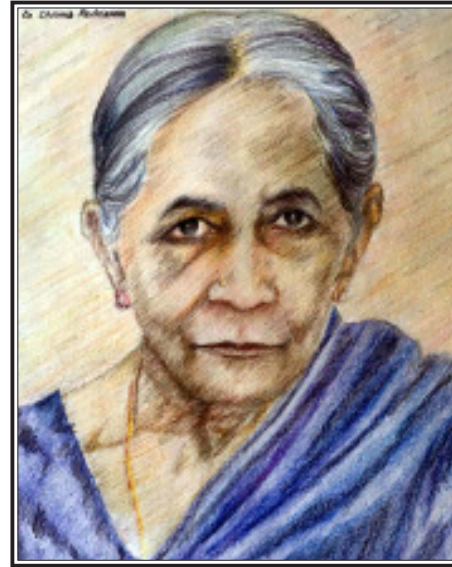
Dr. V Kumaraswami, former Director -in-charge of the National Institute for Research in Tuberculosis and the National Institute of Epidemiology was an internationally acclaimed scientist in the field of lymphatic filariasis. His pioneering research work marked a significant contribution for the global control of this disease. Apart from his scientific research contribution Dr. Kumaraswami mentored many young scientists in their budding research careers. He was a warm and compassionate human being whose presence touched many lives. It's difficult to believe that it is already two years and more since Dr. V Kumaraswami passed away along with his wife and mother in a tragic road traffic accident in March 2016. On the occasion of the second endowment lecture for Dr. Kumarswami to be delivered by Dr. Eric Ottesen, Director, Neglected Tropical Diseases Support Center of the Global Task Force, USA, and an internationally reputed specialist in the field of lymphatic filariasis, the NIRT would like to honour

Dr. Kumaraswami's memory with a commemorative booklet carrying the many eulogies paid to him by a wide spectrum of people who came into contact with him during his career, with a list of his published scientific abstracts.

- Dr. Srikanth Tripathy, MD

Director -in-charge

National Institute for Research in Tuberculosis
Indian Council of Medical Research



Dr. V. Kumaraswami's wife Lakshmi and Mother Kamalamma who passed away in the tragic road accident on 4 March 2016 along with Dr. Kumaraswami

The portraits of Dr. Kumaraswami on the cover and of his wife and mother above were drawn by Mr. Ashrith, Dr. Kumaraswami's nephew

The sketches that figure in this booklet are from the sketchbook of Dr. Kumaraswami, and made available to us by his daughter Mrs. Manjusha. Dr. Kumaraswami was an avid amateur artist.

Prof. K.V. Thiruvengadam, B.Sc., M.D., D.Sc., (Hon.), FRCP (EDIN),

FELLOW
NATIONAL ACADEMY OF MEDICAL SCIENCES
INTERNATIONAL COLLEGE OF CHEST PHYSICIANS
COLLEGE OF ALLERGY & IMMUNOLOGY

MASTER TEACHER AWARD BY THE INDIAN COLLEGE OF PHYSICIANS (2012)
DR. B. C. ROY AWARDEE FOR AN EMINENT MEDICAL TEACHER (1977)
AWARDED PADMASHRI BY THE PRESIDENT OF INDIA (1981)

FORMERLY PROFESSOR & HEAD OF DEPT. OF MEDICINE,
MADRAS MEDICAL COLLEGE AND
PHYSICIAN, GOVT. GENERAL HOSPITAL, CHENNAI
HONORARY PHYSICIAN TO THE PRESIDENT OF INDIA
REGD. No. 11041

FORMERLY EMERITUS FELLOW AND REGENT FOR INDIA,
INTERNATIONAL ACADEMY OF CHEST PHYSICIANS OF ACCP
HON. CONSULTANT PHYSICIAN
ICMR TUBERCULOSIS RESEARCH CENTRE,
KALYANI MISSION HOSPITAL

83, (Old No. 41) G.N. CHETTY ROAD, CHENNAI - 600 017, PHONE : 2815 4949, 2815 2287.

Dr.V.Kumaraswami

Dr. V Kumaraswami has been an outstanding personality in the field of research and treatment policies – field of Tuberculosis , filariasis , Asthma and tropical Eosinophilia etc. In the course of his work in Tuberculosis Research Centre , he has held the position of Director in Charge .

He was a high calibre scientific researcher ; He was appointed to WHO and other International organisations in the fields of Filariasis , some of the neglected Tropical diseases and Tuberculosis .

Dr. Kumaraswami was a very efficient researcher ; perfectionist , modest and helpful to colleagues – without reserve or expectation of any return

Though small in stature , Dr. Kumaraswamy was a great and lovable human being . To my knowledge , there was no one who disliked him .

His academic excellence is evidenced by the awards he won in the medical college and later in his professional career .

K.V. Thiruvengadam

Vasanthapuram Kumaraswami, the ajatashatru (one who has no enemies) is no more. A tragic accident on Chennai- Bengaluru highway put an end to a life of service, compassion, caring and dedication on March 4, 2016. Also killed in the car crash were his wife Lakshmi and mother Kamala.

Second eldest of seven children, born to Shri Balasubramanian, an eminent lawyer, and Shrimati Kamala in Kavali in Andhra Pradesh, Kumaraswami studied in Madras Christian College High School in Chennai. Stanley Medical College was his alma mater from where he graduated as a young doctor in 1975 and also obtained MD in general medicine. He earned the membership of the National Academy of Medical Sciences in 1979. In 1994, Kumaraswami was awarded Ph.D. degree from University of Madras, and conferred the Fellow of the Royal College of Physicians in 2009. Kumaraswami was fortunate to have had Dr. K V Thiruvengadam, an eminent physician and Professor of Medicine as his guide and mentor, from whom he imbibed methodical patient-centric approach, strict adherence to medical ethics and willingness to share knowledge ad lib, all of which he practiced throughout his life. He had been selected as an ICMR Talent Scholar soon after graduation. He was crime de la creme. He joined Tuberculosis Research Centre (TRC), Chennai (later

renamed National Institute for Research in Tuberculosis, NIRT) of the ICMR in 1978. Dr. S P Tripathy, the then Director of TRC assigned him to work on pulmonary eosinophilia and lymphatic filariasis.

In the following years the studies on lymphatic filariasis (LF) were expanded from Tamil Nadu to other endemic areas, including Kerala and Odisha. Kumaraswami and Dr Eric Ottesen of National Institute of Health, USA, worked as a team and their combined efforts resulted in several collaborative studies in the three States. Their efforts met with spectacular success in epidemiology, immunology and chemotherapy and provided the basis for filariasis control in India. Dr Tripathy, who later became Director General of the ICMR remembers that, “country owes a lot to Kumaraswami in helping in the elimination of the bulk of filariasis and elephantiasis problem”.

Kumaraswami was roped in by the WHO/TDR (Special Programme for Research and Training in Tropical Diseases) to help in filariasis. He contributed to the founding of the Global Programme to Eliminate Filariasis. He provided the drive behind much of what went on in global research agenda on filariasis. He implemented a number of studies in India and other endemic countries through the WHO/TDR.

VK, as he was affectionately called, was among the first in the world to evaluate the impact of ivermectin on LF. As one of the stalwart advocates for the Global Programme, he convinced policymakers to initiate and expand the nascent mass drug administration programme in India and the entire South-East Asia Region. VK had a special skill of transforming technical and policy information into precise messages that everybody could understand. He had a good business sense for getting things done. He seemed to know all the right people. On his death the WHO posted on its website, "His death is an irreparable loss to the entire global neglected tropical diseases community". He guided scores of young professionals to undertake filariasis research and, with the help of colleagues, planned and implemented path breaking research studies on treatment, pathology and morbidity management of LF.

VK had a tremendous sense of humour, and once made a scientific presentation at the Journal club of the TRC supported with charts and tables, of a new viral disease, which he called HIV-3. It was only much later that the audience realized that it was April Fool's day. Able to see the funny side in any serious situation and often this facet helped him to deal with difficult situations with wisdom and equanimity. Never lost his

cool in the most trying of circumstances and provided exemplary leadership in the last few years of service with the ICMR when he shouldered the onerous responsibilities of Director-in-Charge of two of the largest ICMR institutes at Chennai, the NIRT and the National Institute of Epidemiology simultaneously. Dr Soumya Swaminathan, current Director-General, ICMR and Secretary, Department of Health Research, has been a colleague of Kumaraswami since 1992 at TRC, remembers him as "one of the most brilliant people I have met, with a sharp, analytical mind and a keen sense of enquiry. This was complemented by a wonderful sense of humour and deep humility and grace - a truly unique combination of traits".

Following his voluntary retirement from the ICMR, he divided his time between his children and grandchildren (who got most of it) and LF, shuttling between the USA, and India. VK remained active in the cause to which he has been devoted for well over four decades: the hope of getting the world rid of lymphatic filariasis. He continued working tirelessly dedicating two years of service to The Task Force for Global Health, Atlanta, USA, as Associate Director International Programmes. He also helped NTD (Neglected Tropical Diseases) Programmes, at RTI, RT Envision Washington DC. Condoling his death a spokesperson of the

organization said that “Every so often the world is touched by individuals whose technical brilliance is matched by a genuine affection for people and a commitment to service; whose personal success is accompanied by a quiet humility and unassuming charity; whose patience and dedication inspires those around them. Dr Kumaraswami was just such a man, and our community is the lesser for his passing”. No matter where he worked, he left an indelible mark.

Who can forget his frankness, his cordiality, his honesty, the absence of all disguise. Till his death VK remained the same -a simple, sincere person, and an affectionate and unconditional friend. Dr Eric Ottesen with whom he had ‘shared’ 40 years of his life, remembers him through his long career with ICMR, and via all the work he did on filarial diseases with WHO and so many other international programmes targeting neglected diseases and the neglected populations suffering from them. Anguished at his death Eric, now Director of Global Task Force’s Neglected Tropical Diseases Support Centre writes, “What he taught - or ‘shared with’ - me over the years about caring for patients, caring for colleagues, undertaking challenges, exercising leadership, displaying trust, maintaining tranquillity and - dare I say it? - still beating the system (without the system’s ever feeling beaten!) is all part of

his wisdom that / treasure and that I know is equally recognized and treasured by all who had the good fortune to know and work with him”.

Though short in height, he was towering in impact. His presence in the room was felt. Remaining steadfast in his quiet perseverance while preserving tranquility and trust in those around him. A constant companion of VK was a book. A voracious reader he could read several books simultaneously. A little known fact about VK is that he used to paint -an artist of exceptional merit, a hobby that he had hoped to spend considerable time on after retirement. He was also technologically gifted and computer savvy. He was the first to introduce computers at TRC (as early as the 1980s) when computers were still a rare commodity. The introduction of new technology always excited him.

He was the ultimate family man, a devoted husband to his dear wife Lakshmi, and caring son to his mother Kamala. His daughter Manjusha and son Sameer are settled in the USA. In the last few years 382 INDIAN J MED RES, MARCH 2016 his professional commitment was rivalled only by his attachments to his grandchildren. They were the centre of Kumaraswami’s universe. He doted on them.

He often talked of his hopes of eliminating filariasis from the world within his lifetime. While that dream may not have been realized, Kumaraswami has left a legacy that all those involved in LF elimination will long remember. His optimism was contagious. We all will miss his passion his intellect, his guidance, and of course his smile.

- Lalit Kant* & M S Jawahar**

*Former Head, Division of ECD, ICMR

** Former Scientist 'G', NIRT, ICMR

IJMR March 2016

It's a great privilege to be able to share my thoughts today with such an incredible group of people – not just because you are outstanding individuals and highly influential leaders (which you are!), but because you are a very special group of truly compassionate individuals brought together in sadness around the loss of our dear friend Dr. V. Kumaraswami who lived a life of service, compassion, caring and dedication which he learned from many of you and which he shared so generously with all of us. My sincerest condolences go out to his children, his brothers and their families.

Kumaraswami shared 40 years of his life with me – from before he had his own family, before the marriage to his wonderful, sadly-deceased wife Lakshmi, even

before he completed his graduate program at Stanley. What he taught – or 'shared with' – me over the years about caring for patients, caring for colleagues, undertaking challenges, exercising leadership, displaying trust, maintaining tranquility and – dare I say it? – still beating the system (without the system's ever feeling beaten!) is all part of his wisdom that I treasure and that I know is recognized and shared by so many in this room today.

In the years of his 'post-presidency' (as we in the U.S. would say) – those years after he retired from being director-in-charge at NIRT and NIE for the Indian Council on Medical Research – many more people had the opportunity to meet and work with Kumaraswami for the first time. And what never ceased to amaze me was that the specialness we all understand from our years of sharing life with him was recognized and appreciated almost immediately by everyone who interacted with him – on projects that usually targeted the many dimensions of LF and other NTDs for WHO, for NIH, for RTI, for USAID (and for GOI!) – sometimes carried out at our Task Force for Global Health in Atlanta, sometimes from Manju's home in Connecticut, sometimes from Chennai, from Washington, Delhi, Seattle.

Kumaraswami's expertise was everyone's "all-purpose tool," no matter where he was:

- ❖ Need help with the NTD program in Indonesia?
 - Call Kumaraswami!
- ❖ Have need for teaching or training?
 - Call Kumaraswami!
- ❖ Need to organize a clinical research project?
 - Call Kumaraswami!
- ❖ Need the right speaker for a meeting (on anything)?
 - Call Kumaraswami!
- ❖ Need someone to write a scientific paper, a technical manual, an advocacy piece?
 - Call Kumaraswami!
- ❖ Need to work effectively and appropriately in India?
 - Call Kumaraswami!

There was nothing that he would not do – with a positivity, cheerfulness and selflessness that humbled us all. How did the 'outside,' new acquaintances feel about 'VK' [since many could not easily pronounce his name]? No surprise at all: Just as we do! The comment from one junior colleague upon hearing of his death sums up so many people's feelings:

"He was an incredible human being—such a kind, and gentle soul. I loved working with him. He was such

a great teacher, with a remarkable ability to convey information in a simple, understandable and respectful way."

Simple, understandable, respectful – what a teacher! What a legacy for us to carry forward!

Let me add just one final comment. Kumaraswami and I first saw the movie Star Wars together in Madras in 1978, so I feel it's appropriate to use an allusion to it today. In these 'post-presidency' years of his I would often need to describe Kumaraswami to people to explain how he would be just the right consultant to handle our problem with.....whatever it was..... So, you can imagine that after all the superlatives I used, when these people would first meet him, they expected to see someone like Hans Solo stride in. Instead, what did they get? They got Yoda!diminutive in size but enormous in impact – wise beyond reason, a calm, patient, capable Grand Master who was the trainer of so many of us who today have gathered to express our appreciation for the time we had with him and our sadness.

- Eric Ottesen
Director NTD - SC
Global Task Force
Atlanta, USA.

It is with great anguish that I narrate my association with my beloved ex-colleague, the late Dr. Kumaraswami. Unlike most doctors, including myself, who end up in a research career by accident, for Dr. Kumaraswami a research career was a matter of preferred choice. He was a highly intelligent medical graduate, and to be picked up as an ICMR Talent Scholar through an all-India, competitive examination was very easy for him. With ICMR funding he completed the M.D Medicine course at the Madras Medical College under the guidance of the renowned Professor of Medicine, Dr. K V Thiruvengadam. As director of TRC I had the good fortune to recruit him as a research scientist soon after he completed the M.D course. I knew I had before me a highly intelligent and capable scientist. I allocated him to the project on Tropical Pulmonary Eosinophilia and Filariasis in collaboration with Dr. Frank Neva and Dr. Eric Ottesen of National Institutes of Health, USA. In retrospect I could see that it was a wise decision because it allowed the talented scientist to provide undivided attention to a single area of research. He was highly productive in the chosen area and was outstandingly successful.

His initial success in research on filariasis and Tropical Pulmonary Eosinophilia was a matter of envy for others, who started questioning the relevance of filariasis research in a tuberculosis institute. This would

inevitably have resulted in an untimely termination of the project but for the providential visit of the then Union Health Secretary, Shri Pimputkar, who was probably the only Union Health Secretary to have visited the TRC. The critics of the filariasis studies had ensured that the Scientific Advisory Board of the council to have recommended the termination of the filariasis project because of its irrelevance to tuberculosis. Shri Pimputkar went around the institute and familiarised himself with the Centre's achievements, including the studies on filariasis. At the meeting of The Council's Governing Board in Delhi, when the minutes of the Scientific Advisory Board came up for approval, Shri Pimputkar picked up the recommendation of the SAB regarding the closing down of the Filariasis project at TRC, and on his suggestion the Governing Body rejected the recommendation of the SAB and went on record to say that the commendable work on filariasis must be continued. This provided an impetus for the continuing of filariasis research at TRC. With the Governing Body's blessings, Dr. Kumaraswami received unhindered scope for expanding his activities in filariasis research. The studies which were confined to Tamil Nadu were expanded to other areas which were endemic for filariasis, including Kerala and Orissa. Dr. Kumaraswami and Dr. Ottesen worked as a team and their combined

efforts resulted in several collaborative studies in the three states. Their efforts met with spectacular success in epidemiology, immunology and chemotherapy and provided the basis for filariasis control in India. The country owes a lot to Dr. Kumaraswani in helping in the elimination of the bulk of the filariasis and elephantiasis problem. His studies on Filariasis did not end in India- he worked in collaboration with Dr. Ottesen in studies on filariasis in countries outside India.

His filariasis studies in TRC and other parts of India received considerable funding from the National Institutes of Health, USA for staff, equipment and consumables. I have no hesitation in stating that the equipments provided by these studies were responsible for starting an Immunology Department in the TRC. There was no immunology department at the then TRC. The immunological investigations for filariasis provided a base for establishing the immunology department at TRC.

Although the bulk of his research was in filariasis, he was equally involved in Tuberculosis research at the TRC and provided considerable support- both scientific and administrative to the then Director of TRC, Dr. P R Narayanan and also assumed charge of TRC for about two years before his retirement from ICMR service. Throughout he discharged his responsibilities admirably.

Dr.Kumaraswami was highly intelligent, well-informed and contributed significantly in discussion of scientific subjects. My association with him was of mutual respect. I received the fullest cooperation from him as a colleague and have fond memories of my association with him. His sudden demise had put an end to what could have been as productive a life as before. His sudden departure leaves a void in the scientific circle. More importantly his son and daughter have been deprived of two generations. May god give them the strength and courage to face the future ahead.

- Dr. S.P Tripathy

Former Director General,
Indian Council of Medical Research
Former Director, Tuberculosis Research Centre



CITY SKYLINE, PEN AND INK

I first came in to contact with Kumarawami in mid 1970s when he, as an ICMR Talent Scheme scholar, attended a basic course in statistics that I conducted, and which was attended by other luminaries such as Dr. Katoch, our former DG. I recall that his steady and systematic approach impressed me very much at the time, and this opinion was fortified by subsequent contact with him as a research scientist. I soon realized he was a voracious reader and therefore up to date and knowledgeable on nonmedical issues also. Benjamin Disraeli once said that the most successful man in life is the man who has the best information. Kumaraswami was far in advance of his times in the use of new gadgets, and was, for instance, the first to use Apple and Macintosh computers in his routine work at the TRC. His slides and presentations were always crisp, and his poker-faced humour was simply delightful. He was a great team man and was always more comfortable working with Committees than projecting his image as a scientist.

But it is the humane side of Kumaraswami that I admired more, especially his concern for individuals, whether patients, colleagues or friends, cutting across age, gender and social class. Not at all surprising as he is out and out a KVT product. I am sure there will be a plethora of adjectives and superlatives about his personal traits from other speakers. So, I won't

attempt too much myself, especially as my vocabulary is neither expansive nor flowery. It is said that when newspaper correspondents approached Winston Churchill at the height of the Second World War and asked him for his opinion on Adolf Hitler, and were expecting a bombastic blast of foul words, he simply mused for a minute and said "Hitler is a BAAAAD man". In the same style, I would like to describe Kumaraswami as a GOOOD Man, who left us far too soon. He had no enemies and could therefore be called 'Ajatashatru'. But considering that he was regarded as a friend by everybody, it would be more appropriate to label him as 'JaganMitra' (my thanks to Dr. Tripathy who came up with this word). To be brief, Kumaraswami was personally effective, never produced adverse reactions and was universally acceptable – I wish we could have a treatment regimen like him (effective, nontoxic, acceptable) for MDR TB!

It is often said that 'Behind every successful man, there is a woman'. In this case, I am sure it was his wife, Lakshmi. She was a bubbly character who was as pretty as she was vivacious, certainly more adventurous than he, and who steadfastly stood by him throughout, and nursed his ambitions. She had a penchant for buying 'new' things and was fond of displaying these with impish glee when I visited them. Noting the circumstances of

her demise, I wonder if, despite being a devout Hindu, she took a Christian-like wedding vow of 'to love, honour and cherish you, and follow you wherever you go, till death do us part'. If so, it is no surprise that she went all the way with him.

A tribute is also due to Kumaraswami's mother, the 'Rajmata' who shaped the lives of her children, all of whom are professionally successful and one of whom (Ravi) is here in the audience. It is significant that she lived throughout in the same house as Kumaraswami and Lakshmi – is it any wonder then that she died with them?

Summing up, we need to offer a big 'Thank You' to Kumaraswami for enlivening science and enlightening lives. And commiserations to the entire family for their unparalleled triple loss. I pray that God gives all of them the strength to cope with this catastrophe, and that the two children, Manju and Sameer will be inspired by Kumaraswami's high ideals and benevolent philosophy.

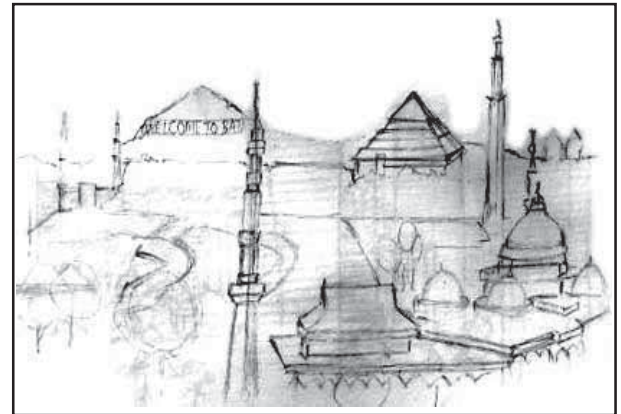
- Dr. S Radhakrishna

Former Director
Institute of Research in Medical Statistics
Indian Council of Medical Research

In the sudden and tragic demise of Dr.Kumaraswamy, we have all lost a very good friend and colleague. A gentleman to the core he always listened with admirable respect and patience to counter arguments in discussions of research proposals. This quality extended to the interactions with colleagues and staff when he was director in-charge of both the NIRT and NIE, endearing him to all.

I pray the lord to grant the departed soul eternal peace.

- Prof.K. Ramachandran



SKYLINE (MAYBE BATAM, INDONESIA)

The Neglected Tropical Diseases Support Center is profoundly saddened by the loss of Dr. V Kumaraswami, his wife Lakshmi and his mother Kamala on March 4, 2016. Dr. Kumaraswami's passing is a blow not only to the field that benefited from his boundless expertise, but to all who were touched by his remarkable kindness and spirit of service.

Dr. Kumaraswami was a physician and director in charge of two institutes of the Indian Council of Medical Research (ICMR): the National Institute for Research in Tuberculosis and the National Institute of Epidemiology. He was integral to the founding of the Global Programme to Eliminate Lymphatic Filariasis, making crucial research advancements on the disease's pathology. A stalwart advocate for lymphatic filariasis elimination efforts, Dr. Kumaraswami continued working tirelessly following his retirement from ICMR, dedicating two years of service to The Task Force for Global Health.

He was an unfailing advisor on a wide range of topics, including training, programmatic success and clinical research. His professional influence was rivaled only by the personal effect he had on everyone fortunate enough to meet him. Though diminutive in size, he was enormous in impact - remaining steadfast in his quiet perseverance while preserving tranquility and trust in those around him. The field of neglected tropical

disease research is poorer for having lost him, but richer for having had him, even if for too short a time.

- Neglected Tropical Disease Support Centre

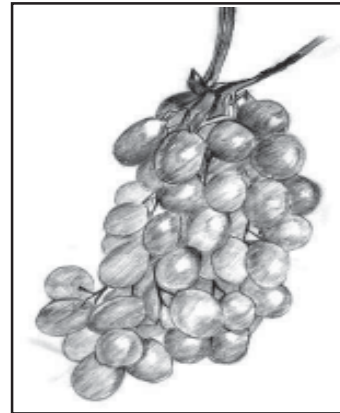
The task Force for Global Health
Georgia, USA

His death is an irreparable loss to the entire global neglected tropical diseases community.

-The World Health Organization

Dr. Kumaraswami's presence in the room was felt; a quiet giant in the NTD field and a savvy scientist who really helped groom so many future generations and alleviate the suffering of many more. His sincere smile, wisdom and mentorship will sorely be missed.

- USAID



STILL LIFE

Every so often the world is touched by individuals whose technical brilliance is matched by a genuine affection for people and a commitment to service; whose personal success is accompanied by a quiet humility and unassuming charity; whose patience and dedication inspires those around them. Dr. Kumaraswami was just such a man, and our community is the lesser for his passing.

- RTI ENVISION

The US Agency for International Development (USAID) for Neglected Tropical Diseases (NTD) family expresses our deepest condolences at the news of the passing of Dr. V Kumaraswami, his wife, and mother this weekend in Vellore, India. Dr. Kumaraswami influenced so much and meant a lot to so many in the NTD community, from the young students he mentored to leading researchers in the global NTD arena. He no doubt made a huge impact on the poorest and most vulnerable populations, particularly those suffering from lymphatic filariasis. Throughout his career at the Indian Council of Medical Research and later with the Task Force for Global Health, Dr. Kumaraswami -11 VK" to those who knew him best - was a champion for NTDs, and his calm, somber, yet razor sharp presence will be deeply missed. We join with the global NTD family in mourning this tragic loss.

Dr. Kumaraswami's presence in the room was felt; a quiet giant in the NTD field and a savvy scientist who really helped groom so many future generations and alleviate the suffering of many more. His sincere smile, wisdom.

- US Agency for International Development (USAID) Neglected Tropical Diseases

On March 2nd 2016 I had a long chat with Kumaraswami at the wedding of his nephew in Bangalore. I left the next day to my place and on the morning of March 4th around 11 AM I called him while he was travelling towards Chennai with his mother and wife. I was requesting him to join our medical college batch whatsapp group and he promised to join in as soon as he would reach Chennai. In another hour I heard about the accident and in a matter of seconds I permanently lost a friend who I was closely associated with for the past 55 yrs.

Kumaraswami Vasanthapuram who for us was KUMARA was my senior by a year in school and my neighbor too. We went to school together, played cricket together, went to college together, did combined study together and shared hundreds of jokes and anecdotes.

When we both were in the role of directors of our respective institutions we used to meet in Delhi in some meetings. While the meetings would go on we would

sit in the back rows like in college days and Kumara will be cracking jokes on the others in the meeting. Though we were in our 60's, those moments made me feel like I was back in college. For all his fun loving nature, he was brilliant with a tremendous grasp of immunology and his knowledge of filariasis was unique, A disease which not many have found interesting despite its public health importance.

In 1971 just before we were to face the Pharmacology examinations Kumaraswami had a gastric bleed caused by aspirin and he was admitted in the hospital. We used to take turns to sit by his bedside and read the textbooks and help him prepare for the examination while he was in hospital. The greatest surprise was when the results were announced and he had scored higher than any of us. Such was his ability to imbibe knowledge. Just before the examination he used to pick up a novel and relax while we would be desperately trying to read our text books. He was good at drawing and painting and showed me some of his new drawings just two days before he passed away. Every moment I had spent with him was filled with laughter and wit. I am sure everyone who had an opportunity to work or spend time with him would also have similar sentiments. Kindness, patience particularly with kids was an amazing ability he had, Within seconds he will make a howling kid, smile. I

should consider it my good fortune to have known Kumaraswami for almost 5 decades.

- Dr. B Sesikeran

Former Director, National Institute of Nutrition
Indian Council of Medical Research, Hyderabad

Einstein said “the difference between stupidity and genius is that genius has its limits”. For those of us fortunate to be in a study group with Kumara, we thought his genius had no limits. His knowledge of the limbic system or the Peutz-Jegher syndrome in those days was beyond mere mortals like us. Kumara had a sharp eye and a keen wit making observations of the human condition with intelligence and imagination. He dedicated his life not to amassing wealth but to expand knowledge.

I was fortunate to have him as my friend

- Dr. S. Anand, MD

NYU School of Medicine, New York, USA

Dr. Kumaraswami was my class mate and during those MBBS days, although I did not get much chance to interact with him as we were separated into different batches based on alphabetical order, I did not fail to notice that he was one bright young man and admired his dignified bearing and behavior at all times. When I did my M.D. I met him frequently, and he helped me a lot including with my dissertation. I got to really

understand his full potential and strength in academics. I saw him on and off after I moved away to the U.S. when he visited here, or in Chennai when I visited. I am proud to have been one of his friends and mourn the loss of this dear soul whose remarkable life should not have ended so soon and in this manner.

I pray that his children, Sameer and Manju will be able to bear and heal from this tragedy with time and wish the family well.

- **Vasantha Iyengar**

Pathologist, retired from Kaiser Permanente
Rockville, MD, USA



GARUDA

Kumara, as we all knew Kumaraswami has undoubtedly left an everlasting impression on all his friends and colleagues. My contact with him was from our 2nd year of Medicine in Stanley Medical College, Madras. He was very witty and had an excellent sense of humour. These two qualities and his demeanor often reminded me of the brilliant R K Laxman.

Kumara was outstanding in his academics and we all felt proud when he was selected for ICMR. I was fortunate to have had interaction with him during my house surgeoncy in Professor KVT's unit and it was a great learning experience for me. Unfortunately after that I left for England and lost direct contact with him but was always happy to hear about his progress. His choice of research for less fanciful topics like Filariasis etc speaks volumes about his care for the less privileged. The Medical fraternity in India and all his friends will miss Kumara for a multitude of reasons but he will always remain in our hearts and memories.

- **Dr E.B.S.Ramanathan**, MS FRCS FRCOrth MChorth
Senior Consultant, Orthopedics & Sports Medicine
Muscat Private Hospital, Muscat, Oman
Secretary General, Asian Federation of Sports Medicine
Visiting Professor, Tamilnadu MGR Medical University

Kumaraswami was a dear and sincere friend of mine for more than 40 years I got to know him well during my house surgeon days at Stanley Medical College. He was always there to help me when needed especially during stressful call duty days. He would cheer me up with his unique wit and sense of humor along with the words of wisdom he frequently conveyed. I appreciate the many books and music cassettes he gave to me knowing that I would enjoy them greatly.

Kumaraswami and I continued to stay in touch after I left India and came to the USA. I met him each time I visited Chennai and we were able to speak often including during his visits to the US. He kept me abreast of his research in L.F. and updated me on his family and children.

I am very grateful to have had Kumaraswami as a friend for many years. He lived his life with empathy and selflessness that touched those around him. I believe that he recognized that every interaction he had was a chance to positively impact others. That is a rare quality that many of us witnessed first hand and appreciated tremendously.

- Dr. Udhaya Krishnan
Lancaster, California, USA



KRISHNA, ABSTRACT

My friendship with Kumaraswami started on the night that we returned from one of those picnics during second year. We realized we were both 'goltis' and that cemented it. We also found out that we loved to read and my source for books was non-existent but he seemed to find all kinds of books for me to read. Then Mohan happened in my life and there was a big race between both of them to get me books to read!!

During our clinicals, Kumaraswami would meet me after our ward rounds in the mornings. And exchange meaningless but funny stuff. Boy, he had gift with

words. There were also days when he helped me with understanding clinical medicine!

In the mid 70s, of course we went our separate ways until the 80s when we got back together on our infrequent India trips.

There is that famous recommendation letter he wrote me which jumpstarted my medical career!!! We kept in touch through phone calls whenever he visited the US and exchanged information about our children. He was bubbling with joy when he talked about his son and daughter and later his grandchildren. The last occasion I talked to him was in 2011 when he was at the CDC on his freelance work and I invited him for my daughter Neela's wedding .

I regret that I did not get to see him much more and cannot get over it. But I am glad and thankful for the time I had with him and feel blessed. My friendship with Kumara was not based on scholarship but real affection for each other and I miss it so much.

- **Dr. L Meenakshi Mohanram**

Atlanta, USA

I have known Kumara since high school as we lived in the same street. I have never seen him mad even

during local cricket matches. It was always fun to visit his house. The whole family was very nice. He was a genius with a great sense of humour. He can always explain very complicated subject and make it look simple. He will be missed very much,

- **Dr. L Rajendran**

Buffalo, USA

Dr V Kumaraswami ("Kumara" to most of us who knew him well) was a very special person. Deeply sincere and honest in every aspect of his being, there was, at all times, a single, unchanging persona that he projected over the fifty years that I knew him. Always willing to help (particularly so with young people who were starting out in their careers) you could count on his vast reserves of knowledge and his world wide circle of friends and well wishers when he agreed to take part in any project or cause. And, there were many; his name was almost always the earliest to come up. At a time in our early career days, when it was the norm for most of us to think of glamorous, clinical specialities, Kumara chose to stick with a career as a researcher in a very essential but low profile field: filariasis. The record will show the extent to which he excelled in this chosen endeavour. He was a delight to be around: a keen, self deprecating sense of humour; a wide and hugely well

informed world view; a gift for art, drawing and illustration; all made him an outstanding conversationalist, speaker and teacher.

In the words of the Great Bard of Avon:

“His life was gentle, and the elements
So mix’d in him that Nature might stand up
And say to all the world ‘This was a man!’

Kumara was special. I miss him dearly.

- **Dr. Arjun Rajagopal,**

Former Chief of Staff
Sundaram Medical Foundation
Chennai

I would just like to remember Dr.Kumaraswami as an energetic, always-willing to help person who has helped so many of us with his advice about science, careers and life in general. Even though he was such an accomplished researcher, clinician and Filariasis expert, I remember him mostly for being a kind and easily approachable human being. He will be missed by all. Just relieved thinking that he is in a better place now.

- **Dr. Sunil Kurian**

Staff Scientist
Dept. of Molecular & Experimental Medicine,
The Scripps Research Institute,
La Jolla, California, USA

I associated with him during my 13 years of research on lymphatic filariasis, when I was in RMRC-Bhubaneswar. He was LF research coordinator at WHO/TDR and helped us a lot in completing those projects successfully.

- **Dr. Bontha V Babu**

Head, Division of Health Systems Research
Indian Council of Medical Research



THE BRIDGE OF SIGHS, VENICE

I am greatly saddened by this news. I remember Dr Kumaraswami not only as a wonderful researcher who put India on the world map on NTD research, but a gentle, simple, kind human. He encouraged me to pursue my doctoral training in the US, and was kind enough to write letters of reference. His support and encouragement mattered a lot to me, and I mourn his passing.

- Prof.MadhukarPai, MD, PhD

Canada Research Chair in Epidemiology & Global Health
Director, McGill Global Health Programs
Associate Director, McGill International TB Centre
McGill University, Montreal, Canada

I have known Dr. V Kumarswamy for nearly one and half decades. As the director of NIMS, we have shared space in many meetings. I was indeed shocked and saddened to hear the news about the tragic incident that resulted in his and his family member's untimely death. I always remember him as an eminent scientist and enthusiastic administrator who not only has left his imprints by the work he carried out in his duration as the director-in-charge of NIRT and NIE but also personally touched the life of several of us. His friendly personality is admired always. I remember him taking out time to personally show me new building and facility of the institute. Though he will be missed in person, I hope the wisdom and warmth

that he shared with all of us will always fill our lives and keep us motivated to be wonderful human beings. I send my deepest condolence to the scientific community and family members and pray Almighty to bestow strength to all us to wade through this hard time.

- Dr. Arvind Pandey

Director, National Institute of Medical Statistics
Indian Council of Medical Research

It was very sad to hear of Dr. Kumaraswami's demise. I started my research career with him in filariasis research. He was a wonderful scientist to work with. I do remember a lot of occasions when we went for blood collection drives at night as microfilariae are seen at night. I knew his family well. It was a shock that these three wonderful people were taken away abruptly. I pray to god that their souls rest in peace.

- Dr.Ramesh Paranjape

Former Director, National AIDS Research Institute, Pune

Government Hospital of Thoracic Medicine
Tambaram Sanatorium and the members serving here mourn the tragic demise of Dr. and Mrs. Kumaraswami. We wish to record our deep sense of appreciation and gratitude to Dr. V Kumaraswami, a noble scholar,

humble Teacher, honest researcher, kind and courteous in His approach, and a warm humourous Friend, who has helped a lot many of us individually and the Institution of Tambaram as a whole by guiding us in the path of Research and caring TB patients with the kindness of a Mother, responsibility of a Father and fondness of a true friend. May their souls rest in peace.

- **Dr. R. Sridhar**

Superintendent, GHTM Tambaram

It was a pleasure to be introduced with Dr. Kumarswami at Regional Medical Research Centre, Bhubaneswar during 1991. He was instrumental in my working in Filariasis, after that the WHO meeting was held at RMRC. He instigated the scientific spirit, to work in Filariasis. This led me to select the Ph.D Topic during those days.

He was a true YOGI in Science, as I know him. Very Clear in his concept, pin point way of writing and crystal clear way of presentation. He was instrumental, in my association with The Lymphology Society of India, along with Dr. S K Kar. As Organising Secretary, I had the opportunity to conduct the LymphoCon-9 & 10 at RMRC, Bhubaneswar during 2010 & 2013. During those days he helped me a lot, in many ways in conducting these two conferences. As a Life Member he used to

coordinate all the old members and patch-up the differences among the members and bring all the members in one platform.

There are many incidences in ICMR, NVBDCP meetings and at RMRC interaction with him was a pleasure. There are many points in my memory lane. In short I will call Dr Kumaraswami as a GOOD TEACHER & a TRUE Friend. I Pray Lord Jagarnatha for a Peace abode for him”

- **Dr. Amarendra Mahapatra**

Central Public Information Officer,
Regional Medical Research Centre ,
Indian Council of Medical Research



MADRAS - WATER COLOUR

I had met Dr. Kumaraswami at NIRT in relation to a visit made for HIV vaccine trial. I fondly remember his smiling and welcoming stance at the seat of the director in charge NIRT. At any place he would remember and acknowledge the presence of juniors he had met in the past, even briefly. I feel deep gratitude for having known Dr. Kumaraswami. May his soul rest in peace! Deep condolences to the bereaving family who are bearing a great loss

- **Dr. Seema Sahay**

National AIDS Research Institute, Pune

It is very hurting to learn that Dr. V Kumaraswami, Ex. Director-in-Charge, NIRT and Ex. Director-in-Charge, NIE, his wife and mother passed away on Friday, 4th March 2016 in a tragic road accident. My deepest sympathies are with his family on this tragic incident. I wish to extend my heartfelt condolences on the bereavement caused by the untimely death of Dr. V Kumaraswami, his wife and mother. I pray for their souls to rest in peace and for their family members to regain strength from this .

- **Dr. R S Sharma**

Head, Scientist - G & Sr. Deputy Director General
Division of Reproductive Biology & Maternal Health
Indian Council of Medical Research

Though I had known Kumaraswami sir for quite a long time, only recently I got an opportunity to associate closely with him. I had gone to Delhi on Feb 21st to attend a DNDi-ICMR Clinical Experts Meeting on Lymphatic Filariasis. He was travelling in the same flight as me. Beginning from there, he kept me company. We discussed about my research projects and he gave me some really valuable advice and encouraged me to strive hard and never give up. He even introduced me to the WHO scientists who were his acquaintances and made sure that I spoke to them. Within the short period of my association with him, I have understood that he is a respectable and down to earth person. His magnanimity of mind impressed me very much. His beautiful enumeration of the complicated pathogenesis of lymphatic filariasis is still ringing in my ears!

It was indeed an honour to spend time with such a great soul and his untimely demise brings immense grief and sorrow to me. Though he is no more, his memory will live on and on among the numerous people he has inspired. May his soul rest in peace.

- **Dr. Nisha Mathew**

Scientist -E/Deputy Director
Vector Control Research Centre, Puduchery
Indian Council of Medical Research

Almighty God you snatched away abruptly from us a humane person violently thoughI do not have the wisdom to question you.....divine are your ways.

I am personally saddened to hear the untimely demise of Dr V. Kumaraswami, who was a fatherly figure for me. He was an extraordinarily humane person. My association with him dates back to 1990s when I was a pursuing my master's degree in Medical Entomology at the Vector Control Research Centre (ICMR), Puducherry. At that time I was referred to him for treating my tuberculosis condition. His clinico-immunology acumen and treatment thereof put me to track. Subsequently, Dr Kumaraswami adjudicated my PhD thesis and officiated as examiner for the public viva-voce presentation. Thereafter, he had mentored me right through my professional career until a few months back, when I spoke to him that we have launched the distribution of DEC fortified salt to the community at risk in the remotely located Nancowry islands. He extended his best wishes for the initiative and told me that he looked forward to hearing about the results. A tribute to his personality, would ideally be to achieve the desired goal of eliminating the lone foci of sub-periodic filariasis from the country.

Dr. Kumaraswami championed the Indian cause of LF elimination in the international arena. A brilliant human being, who relentlessly pursued authenticity in TB and LF research. There are many in the scientific fraternity who will mourn deeply his passing as his was a life of service, love, compassion and excellence. The vacuum left by him cannot be filled up that easily, because there cannot be another Dr. Kumaraswami. My fond memories with him, his kind words of wisdom would enable me to drive further in accomplishing goals in life.

We pray to the almighty GOD to provide the internal strength to his family for bearing the loss. May his ATMA rest in peace.

- Dr A. N. Shriram

Regional Medical Research Centre
Indian Council of Medical Research
Port Blair, Andaman Nicobar Islands

ICMR and our country lost a great scientist under tragic circumstances. All that we can do is to pray for the family and hope that his legacy in research is carried forward. The initiative from your side is appropriate and the small way that all of us can pay homage.

- Subarna Roy

Indian Council of Medical Research , New Delhi

It's very shocking and tragic to know the untimely death of Dr. V Kumaswami, Former Director-in-Charge, NIRT& NIE. I had very short personal interaction with him and that was quite inspiring. His scientific contribution and acumen are well known to the medical fraternity. This is indeed a great loss for the whole scientific community, family and friends. We will keep him missing. May the departed soul rest in peace. My deepest condolences

- **Dr Rajni Kant**

Indian Council of Medical Research
New Delhi



COORG

It is indeed very palpating to listen unexpected demise of our beloved Dr. Kumarswami along with his wife and mother. It is too tough to blur the image of his smiling face. More than decades ago, during the year 1992-94, when I was Technical Assistant, Dr. Kumarswami used to visit our Institute along with Dr. R Prabhakar, Director of our Institute . It was our first ever experience to conduct an extensive, well-planned, multi-disciplinary study collating demographic, sociological, clinical and serological information of nearly 10,000 populations of Kala-azar endemic area under his guidance.

Personally as an active participant in that study, I cannot forget his beckon that strengthened my proficiency and potentiality for community-based epidemiological studies. Usually unintended contribution of anyone is of no much importance in one's life, but when we flash back at a particular point of time it really make a sense. At this moment, I feel that what I am today has a correlation with indirect inculcation of passion to me towards field-based studies by Dr.Kumarswamy.

May the almighty give peace and calm to departed souls of Dr.Kumarswami, his wife and mother. I pray God to give strength to rest of his family members to get rid of this distress.

- **Rakesh Bihari Verma**

Rajendra Memorial Research Institute of Medical Sciences
Agamkuan

It is indeed a sad news for everybody who love science. Though I do not have much interactions with him, I met him on number of occasions. His gentle nature, helping hand cannot be forgotten. I pray god to place his soul in peace.

- **Dr R. Hari Kumar**

Scientist 'E', National Institute of Nutrition, Hyderabad
Indian Council of Medical Research

Dr. Kumarasami was a pleasant person and friendly with everyone. There were 2 or 3 occasions when I approached him because of a medical problem and he immediately contacted the appropriate specialist and made an appointment for me. Very sorry to hear about his tragic demise. Sorry I am unable to attend the memorial meeting as I am on a holiday tour of Singapore and Malaysia. May his soul rest in peace.

- **P R Somasundaram**

Former Senior Deputy Director (Statistics)
Tuberculosis Research Centre, Chennai

I am a former staff of NIRT (formerly TRC). After my retirement, I was appointed as a Sr. Consultant by WHO to supervise the repeat National tuberculin survey (ARTI) conducted in India during 2009-10. During this period, I was allotted a room in TRC and using the same laptop used in the Model DOTS project during my service in TRC. There was some kind of pressure from a section of the staff asking me to return the laptop. But Dr. V Kumaraswami, then officer-in-charge of TRC permitted me to continuously use the laptop knowing the importance of the project, my seniority and experience in epidemiology of TB. This was a reward to me and I will never forget the kind of support and the motivation extended to me during my service in TRC and afterwards. I, also, had an opportunity to work with him in a project on filariasis, analyze and publish the data. He was an expert in TB, HIV, Immunology and Filariasis with commendable contributions. He was sincere, dedicated and hardworking and his untiring efforts rendered in these fields made him famous in India and abroad. Apart from all these he was a jovial and smiling personality. This sense of humour was an additional qualification apart from his professional career.

It was a great tragedy that all the four travelled in the car passed away in the accident. It is a great loss to

TRC as well as to the entire staff including those retired and also to his children. We are unable to explain the reasons for the tragedy but fate. It should not have happened to him and his dearest ones.

Let us pray to the Almighty for his and others soul to rest in peace.

- **Dr. P. G. Gopi,**
Aminjikarai, Chennai



Coorgi Woman and Child

It is really heart breaking news for me. I want to share following lines in his memory. It's is a great loss to the filariasis research in the world. My association with him is quite memorable, as a guide as well as a co-researcher. His comprehension and understanding in filariasis research & development is unmatched and will remain as source & force of motivation to the present and future researcher in the area. His contribution to the GPELF in the globe and India will remain as a landmark for all. We the research group from RMRC, Bhubaneswar and especially myself will never forget his inspiration, advice and selfless help he has provided at any moment and any situation. Giving him a call or sending him an e-mail was always giving a relaxation because there was no need to remind him for the response, which must be benefiting to the queries. I pray god for giving a high place in the spiritual world.

- **Dr. Bhagirathi Dwibedi**

Scientist-D
Regional Medical Research Centre, Bhubaneswar
Indian Council of Medical Research

Dr. V Kumaraswami, a renowned clinical researcher and even greater mentor, was a guiding light in my professional career. I first met him in 1994, when I served as a Senior Research Fellow, fresh out of medical school and thrown into the unknown world of clinical research. He took great care in guiding and

advising me on my career choices and it indeed it was his introduction to my Ph.D mentor, Dr T V Rajan, that served as a stepping stone to my research career. It was perhaps my good fortune that I ended working in the same field as him - clinical and basic parasitology and therefore our collaborations only grew from strength to strength. When I had the opportunity to return to NIRT (then TRC) under the umbrella of the ICER program, it was his pragmatic guidance that again was the shining light in my early days as an independent researcher. I was saddened to hear about his retirement but still excited to meet him and work with him in the field of filarial infections. It was with great shock and sorrow that I received the news of his passing one cold morning in Denver, CO, where I was attending a meeting. It is with profound grief that I write this memory of him. It is said that time heals all wounds but may his memory shine in our minds forever. He will certainly be missed and we may never see his like again.

- **Dr. S. SubashBabu, MBBS,Ph.D**

Scientific Director
NIH-ICER-NIRT, Chennai

We are deeply grieving and lamenting as you are, on the untimely departure of our beloved mentor, teacher and guide.

So many hats... so many titles... so many words... yet we are speechless...

We are shocked and angered at the unfairness and the meaninglessness that took him and his family from us. Unfortunately we must accept the ruthless hands of death, acknowledge our loss and the loss that his passing brings.

We all owe to Dr. Kumaraswami as we are not whom we are without him. He has shaped our view on science, intellect, work, life and many other things. As students, it is our duty to let you know about 'our Dr. VK' as we know him.

We all have a kaleidoscope of memories that defined Dr. VK and that will always be borne in our heart. Around him, we always felt the deeper and loving intelligence of him guiding and protecting us. He had a gentle-breeze like presence around us and we all looked up at him as our Hero, who was poised, intelligent yet grounded.

He was the first to introduce us to the internet world in early 2000s. He taught us about Firefox and Opera

browsers. He showed us how to connect computers to projectors. Almost all the thesis of early PhD students of TRC and the manuscripts have been corrected by him. He has shared music albums with us and we knew that he liked V S Narasimhan's violin and Hariprasad Chaurasia's flute. If you walk into his office in late afternoons, you could hear classical instrumentals being played in the background. He always ate little and mostly curd rice. His lunch box was small but the lunch box he brought for students was always big. We all at some point have tasted the delicious food that his wife Mrs. Lakshmi had prepared and sent for us. He was a voracious reader who read and discussed about various books. One of his recent favorite authors was Haruki Murakami. He always wanted to read Ponniyin Selvan but was waiting for a good English translation.

His love for students was enormous. He always made sure we were safe and often enquiring about our family and our recent hometown visits. His affectionate way of calling us as 'sir' or 'Madam' is echoing in our ears. He ALWAYS had time for students. To give you an example, we had a tradition among early Ph.D students like Radha, Aravindhan, Ramalingam, Uma, Selva and others to celebrate our birthdays in the immunology office room. Almost every time, one or the other student will be held in their labs by their PIs on a

discussion and the rest of us would be waiting for that one student. Dr. VK would walk out of his room, would scan us and ask, "Where is ... Is he in a discussion?". Then he would walk straight to the lab and tell the PI that he wants to grab the student for a minute for a question and the rest you can assume...

He possessed unparalleled scientific and clinical knowledge. He always discussed about the various hypotheses and the clinical observations with the students. He was the first to teach us how to perform a 'Pubmed' search. He guided most of us even after graduating from TRC to choose our careers and apply for jobs. He kept in close contact with us, enriching our lives, guiding our decisions and blessing our lives until yesterday.

He was such a lovely family man who loved his wife, mom and children. He always referred to his wife jokingly as 'senior research fellow'. He was a proud grandfather of two grand-daughters.

It is with much sadness today we realized that we have lost our 'go-to' person, a great mentor, a brilliant teacher, a wonderful human being and his wife who knew nothing but love and their affection for us. Most of us are scrolling back and forth his emails, his voice

messages, his pictures and wishing for the unfortunate event to be undone...

He was there when we needed help in science,
He was there when we wanted clinical advices,
He was there when we needed the wisdom to navigate us in life,
He was there when we needed to choose our careers,
He was there when we wanted to share our family stories, AND
He WILL be there when we do the same...

- **Dr. Prabha, PhD, MPH**

National Institutes of Health, USA



COORG

My heart felt message to my ever respected Mentor, Supervisor and Guide in my research activities as a research scholar working under him I got trained by him in Laboratory Medicine and Clinical Field Work. He will step by step increase your knowledge to the expectation of international standards and train you to be the first to trace the path where our future research scholars can Travel that path and globally mankind should be protected. I learnt from him personally so many things but to mention few 1) Discipline 2) Punctuality 3) Truthfulness 4) Keeping the Commitment 5) Discussing with your senior and junior colleagues and taking into account their suggestions 6) Finally presenting to his teachers and world authorities in that field take their corrections and suggestions and then only he will accept that was the gold standard he made in his department whatever work our students are doing in our research institute he will meticulously follow that work will attain excellence in results.

As his research scholar I would have the ability to see only tip of sir he takes energy from Sun God and Moon God and he has lighted all our research scholars in our prestigious institute and our sir was blessed to be guided by Prof. K V Thiuvengadam from 3rd year Medical student, final year MBBS student! MD student research

scholar under him and till date he will take appointment with his Mentor Teacher and present his scientific discussions for his valuable suggestions comments and further follow up. Prof. K V Thiruvengadam sir will always give his valuable time to him at any part of the day or night . My tears in my eyes my heart is accelerating my mind was trained by sir for the past three decades and it says all his students will be aligned like laser technology speed and give our global village the wisdom he has inoculated in our brain and mind.

To conclude only God can console all of us

- **Dr. S Rajasekaran**, MBBS, DCP, DMRD

My acquaintance with Dr. Kumaraswami started in 1975 - nearly 40 years ago. He was an SRO at the TRC then - he along with Dr. Vijayasekaran and Dr. Jamal were working on Lymphatic Filariasis. They were collecting microfilaraemic blood and sending them to Eric Ottesen in the United States. Later on, though he was in Tuberculosis research, he distinguished himself as one of the leaders of filarial research. Since VCRC was also working on Lymphatic Filariasis naturally we came close to each other, personally as well as scientifically. When I organized an International Seminar on Filarial Research in 1989 at VCRC, VK was the resource person. A document published at that time, can still be

considered an important guideline for Research on Filariasis. Dr. VK was a born scientist, therefore it is no surprise that he is loved and respected by everyone who know him. But he possessed certain unique qualities, rarely found in many, and that makes him very distinguished. He was very humane when dealing with others, and was very helpful in every way. I had the good fortune in getting the advice of Dr VK on many matters, and he used to peer review several publications of mine published in FRONTLINE in recent years. He used to say that my articles are incisive, but said such writings are necessary to stimulate thinking. Very recently, we have been in touch re ZIKA virus, which is in the news recently, and on which I am writing another article, and I will miss his critical advice.

He was a good friend, a renowned scientist and a very good human being. I will miss him. May his soul rest in peace.

- **Padmashree Prof. Dr. P K Rajagopalan**

MSc, PhD, MPH (Calif), Dip Acar (Maryland),
CIBiol (London), FRSB (London)

Fellow of the Royal Society of Tropical Medicine, (London)

Former Director, Vector Control Research Centre

Indian Council of Medical Research

I had the privilege and opportunity to work with Dr. VK during my PhD days and stood to gain immensely from my interactions. He came across as a down to earth, jovial, charismatic leader with a profound influence on my life at TRC. He was meticulous, scientifically rigorous and tech savvy way ahead of his peers. He thought us to believe in ourselves and dream big in discovering new ideas to the benefit of needy patients.

We had a memorable time with him and Dr. PR Narayanan in our small studio apartment in Bronx during 2002 and spent a day touring New York City. We were blown away by his child-like enthusiasm and eagerness to learn more about new places and people he came across.

He was and will be deeply engraved in our memories as a humble human being, friend and charismatic leader. May his soul rest in peace.

- **Dr.Vasan Sambandamurthy, PhD**
Bangalore

All of us are still in a state of shock and disbelief at the sudden stroke of a fate, so cruel, that it not only snuffed out the life of our friend Dr. Kumaraswami, but also those of two very precious women in his life, in one catastrophic moment. Words will not suffice to express

my profound sense of grief at the passing away of Dr. Kumaraswami, Lakshmi and Kamalamma. We keep seeking reasons, when we know, all too well, that there are no answers for some questions in life.

What can I say about someone whom I've known for more than three decades and never expected to be writing a eulogy for. He was a colleague, friend and mentor all rolled in one. When I came back to TRC after a hiatus of four years I started working in his Ivermectin trial and he was the one who took care of my project extensions until I finally got a permanent post in 1990. I used to wonder if I would even be extended and many a time he would take the trouble to personally come over to our section and say "don't worry, you will be getting your extension letter soon." He had a way with words and most of it transferred into action. He has helped me so much- not only in my career but even in planning my daughter's wedding! His granddaughter was the apple of his eye and he would show me pictures of the little one and beam with happiness.

The last time I met him was in the summer of 2015 when my husband and I visited him at his house. Lakshmi and Dr. VK were preparing for their trip to the USA and I remember Lakshmi telling me "this time I have told doctor (VK) that he should spend time with us and not

go away anywhere on work” They were going abroad to spend time with their son and daughter and I’m sure in retrospect the children would cherish those days with their parents.

My heart goes out to the family specially Manju and Sameer who lost both parents and their grandmother all at once. My prayers for the departed souls and for those they left behind for strength to carry on.

- **Meenalochani Dilip**

National Institute for Research in Tuberculosis, Chennai
Indian Council of Medical Research



KRISHNA

Dr. V. Kumarasamy, as all of us know him is an eminent personality, a walking encyclopaedia, administrative wizard and a great problem solver on top of everything a down to earth person with a lot of sense for humour.

It was a great honour to be associated with Dr. VK as we fondly call him, since my ph.D days as a student in his immunology division in then TRC and to have the opportunity of his continued mentorship during my postdoctoral days abroad and after taking up my present position as Head of the Division of Bacteriology back at NIRT. Whether it was introducing me to google scholar during my student days or calling me over the phone during my first postdoctoral position in Paris to make sure that I was safe and comfortable or promptly providing his testimonial for getting my green card in US, or giving his touch of mentorship and encouraging me to join in NIRT, when I told him about the offer I received for my present position, He had mentored and guided me at various instances in my life for which I am greatly indebted to him and have no words to express the same.

Dr. VK as we all know is a very dynamic and cheerful person and he spreads his magical enthusiasm and goodwill where ever he goes. It is always a great

delight to hear his bright and cheerful voice greeting us in his own favourite way of using 'Sir and Madam's' and leaving us with the feeling that we were his great VIPS and that he is here for us.

He is a very thoughtful person and as I already mentioned a great problem solver. When anybody approaches him with his or her great issues, they are always given the needed guidance and help and he does this with so much ease and confidence that it lightens the burden on the other person, but he silently does his own background work to provide the necessary help and support to solve their problem.

An incident that I should relate here regarding his crystal clear memory. This was in 1995, when I was the student, he had a brief meeting with my father for the first time and during the course of their discussion it was brought to light that Dr. VK's father Mr. Balasubramaniam was my father's professor in Madras Law College. This was a very brief incidence. Recently, about two months ago, I met Dr. Ravi who is here with us, in a meeting at Delhi where Dr. Ravi mentioned to me that he is Dr. VK's brother and on the next day meeting, Dr. Ravi came back to me saying that he had a chat with his brother over the phone and that Dr. VK

had actually remembered about meeting my Dad earlier and mentioned the aforementioned conversation regarding his father and my father. Imagine, this was after 20 years. Such was his memory power and this also reflects the fondness he had for the people he knows.

I can go on and on about the numerous incidences where he had touched the hearts of many in his own unassuming way but for want of time.

It came as a rude shock to me as it would have been to others, to hear the very sad news on 4th of March and that was only less than about 16 hrs after speaking to Dr. VK. And his call on the 3rd of March was to help a student for guidance. I could still hear his voice in my ears and is still unbelievable to me that he is with us no more. I still keep fretting over the fact that I had wished him only Good night that evening but he why he gives all of us an unexpected goodbye along with his beloved wife, Madam Lakshmi and his loving mother - probably to lessen their suffering of missing him in this world - a very thoughtful person as always.

With his loss, NIRT has lost one of its very eminent scientists and the world has lost its key contributor on Lymphatic filariasis.

We understand that it is an irreparable loss to his loving children and his near and dear ones, to lose the three beloved family members, a loss that no amount of comforting words could replace.

- **Dr. Uma Devi R., PhD**

Head, Department of Immunology
National Institute for Research in Tuberculosis, Chennai

I fall short of words to describe what I feel about Dr V Kumaraswami, who was my mentor in the field of ethics committees. I had known him since 2009 when he joined the YRG CARE IRB, and when he became the Co Chair of the IRB a year later, and then the Chair after a few years, I had the opportunity to interact with him very frequently. I was always in awe of his depth of knowledge in all fields, and his simplicity and sense of humor put me at ease. He motivated me to do my best in the field, and was instrumental in my joining the ethics committee of MDRF, which gave me much exposure. His passing away was a major shock to me, and while it took me a very long time to recover, not a day goes by without my thinking of him and his guidance. We miss him very much....

- **Dr. S. Swarnalakshmi, Ph.D**

IRB Manager
YR Gaitonde Center for AIDS Research and Education (YRG CARE)

Dr. V. Kumaraswami.....shortly 'VK' @ TRC
an 'Information Bureau'
a 'Solution Finder' or a 'Problem Solver'
an 'Adviser' to anything
a 'keen Observer' of everyone around him.

"Knowledge is Power"

- ❖ Yes he is the man of power with knowledge on all subjects;
- ❖ an active member of British Council Library;
- ❖ and he is the man @ TRC... extensively utilized the British Council Library along with institutional membership, he had personal membership also;
- ❖ I used to see him... frequently...with number of books he used to carries from BCL;
- ❖ I do not know how many books he read at British Council...!and I don't know how many hours he used to spend for reading the books every day...!
- ❖ His family only has to answer!

A letter to Dr. VK.....

if we hear something about us.....,

by our children..,

by our grand-children..,

by our brothers / sisters..,

by our friends..,

by our colleagues..,

by our boss.....

in front of the lovable audience

that would certainly be such a wonderful moment...

Can't be forgettable in our life time;

But this occasion happened.....as like,

how the Government of India gives

Bharat Ratna, Padma Vibhushan, Padma Bhushan, etc.,

awards to the recipients... in most of the occasions...

after the they passed away!

It is supposed to be happened at the time of your Retirement Function...

if I tell, in your language.....

yes Sir.....you missed...Sir!

- R Rathinasabapati

Senior Library and Information Officer, NIRT



One of the most distinguishing features of Dr. Kumaraswami's personality was his sense of humour. He could see the funny side of any situation. This was a paper that he and I published in the Journal of Irreproducible Research in August 2010.

- Dr. M S Jawahar

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Do Females Influence Male Success? A Case Control Study

M. S. Jawahar & V. Kumaraswami, Tuberculosis Research Centre, Chennai, India

It is commonly believed that 'behind every successful man there is a woman' (Groucho Marx et al. circa 1938). However, this widely held theory has never been subjected to scientific scrutiny. A search in the literature for studies examining the soundness of this theory (PubMed, Google) yielded nil results. In our pursuit of evidence-based medicine we attempted to validate and scientifically examine this influential statement. We therefore decided to test the hypothesis 'behind every successful man there is a woman' using a case control study format.

The "cases" for this study were "successful men" defined as males 21 to 60 years of age living in self-owned independent houses or apartments, owning a chauffeur-driven self-owned car of at least 1000 cc engine capacity, and earning an annual income of Indian Rs. 5,00,000. Eunuchs and transvestites and those residing in dwellings owned by the spouse and those driving cars presented as dowry were not eligible. The "controls" were age-matched males living in the study area who did not fulfill the criteria for "successful men".

The study was carried out in Chennai, South India, where traditionally, male machismo and male subversion cohabit successfully. Data were collected for demographic variables, educational status, annual income, marital status and nature, type and duration of relationships with females (mother, stepmother, grandmother, step-grandmother, sister, step-sister, cousin sister, niece, wife, fiancée, female friend, domestic help, stenographer, secretary, sales girl, call girl, mistress). Each case and control was also asked to identify the most influential female member in his "success".

Data were elicited using a structured questionnaire after extensive local validation and pilot testing. Cases and controls were interviewed in private by male and female social workers. Information was recorded in interviews lasting a maximum of one hour to avoid exhaustion due to stressful answers.

Informed consent was obtained from all participants. No financial inducement was offered for participation in the study. Data were analysed using EpiInfo 6.04D software. Adjusted odds ratio (AOR) with 95% confidence interval (95%CI) was calculated for the comparison of the variables between cases and controls. Univariate and multivariate analyses were carried out to explore the influence of the various categories of female interrelationships for cases and controls.

Results: A total of 2567 cases and 10250 controls were enrolled (case:control ratio 1:4). Univariate analysis showed that there was no statistically significant difference between the numbers of the various categories of women who had a major influence on the cases and controls (AOR 1.23; 95% CI 0.76 – 2.01). Multivariate analysis showed that after adjusting for the duration of the relationship, cases (successful men) had a larger number of mistresses compared to controls (AOR 2.33; 95%CI 1.55 – 3.28).

The results of this study have shown for the first time that **the commonly held view that there is a woman behind every successful man is fallacious. We found that there were equal numbers of women behind unsuccessful men.** Apart from a small subgroup of successful men who had more mistresses behind them compared to the controls, this theory was not proved. We are aware that feminist scholars (Greer et al.) will interpret the results of the sub-group analysis as vindication of their claim that women are responsible for the success of men. On the other hand, we would like to point out that these men achieved their success despite the pressures of the conflicting interests of spouses and mistresses.

The significance of the findings of this study cannot be overemphasized. Throughout history, countless men have been persuaded to take a wife in the belief that this was the path to success. By laying to rest one of the longest-held myths, we feel that we have made a significant contribution to human welfare.

PUBLICATIONS OF DR. V. KUMARASWAMI

1. Hussain R, Hamilton RG, **Kumaraswami V**, Adkinson NF Jr, Ottesen EA. IgE responses in human filariasis. 1. Quantitation of filaria-specific IgE. J Immunol 1981;127:1623-1629.

Abstract: We have developed a noncompetitive solid phase radioimmunoassay to quantitate human IgE antibodies against soluble adult antigens of *Brugia malayi* (B.m.), a filarial parasite, in sera of patients with various forms of clinical filariasis in Madras, India. A single reference serum was shown to contain 23 micrograms/ml of B.m.-specific IgE by depletion analysis and was used as a standard serum throughout the study. The levels of specific IgE ranged in the patients sera from 2 to 23,000 ng/ml. When these individuals were divided into clinical groups, the individuals with tropical pulmonary eosinophilia had the highest levels (mean = 8630 ng/ml) and were significantly higher than all the other groups (p less than 0.001). The lowest levels were seen in patients with circulating microfilariae (mean = 30.5 ng/ml). Patients exhibiting lymphatic obstruction (i.e., chronic pathology group) had levels slightly higher than microfilaremics (mean = 68 ng/ml) but were not significantly different (p less than 0.1). Surprisingly, individuals living in endemic areas but who had no clinical signs of filariasis also showed appreciable levels of B.m.-specific IgE (mean = 55 ng/ml). The B.m.-specific IgE represented 0.1 to 48% of the total IgE. High percentages of specific IgE may be responsible for evoking allergic symptomatology in patients with tropical pulmonary eosinophilia.

2. Ottesen EA, **Kumaraswami V**, Paranjape R, Poindexter RW, Tripathy SP. Naturally occurring blocking antibodies modulate immediate hypersensitivity responses in human filariasis. J Immunol 1981;127:2014-2020.

Abstract: Although the basophils and mast cells of patients with chronic helminth infection are sensitized with specific IgE antibody and frequently exposed to parasite antigens *in vivo*, these rarely manifest allergic reactions to their parasites. To investigate the regulatory mechanisms limiting immediate hypersensitivity responsiveness in such patients, we used the *in vitro* antigen-induced histamine- release (HR) reaction of human basophils as a correlate of *in vivo* allergic responses. For 13 patients with bancroftian filariasis HR responses were elicited by graded doses of microfilarial antigen in the absence of serum or in the presence of normal human serum, autologous serum, or serum from other infected patients.

In all instances, sera from patients with filariasis contained a factor that specifically inhibited HR to parasite antigen. Normal sera had no such inhibitory effect, but sera from other filariasis patients inhibited as effectively as autologous serum. This HR blocking factor was heat stable (56°C x 2 hr) and nondialyzable. Its parasite antigen specificity was demonstrated by its inability to block the HR of patient cells triggered by anti-IgE anti-body and its lack of inhibitory effect on the Hr response of ragweed-sensitized cells reacted with ragweed antigen E. Fractionation of the sera by staphylococcus protein A-Sepharose chromatography showed that the blocking factor was an IgG antibody whose activity could be removed by specific immunoabsorption with filarial antigen. The levels of

blocking antibody in the sera of these patients were high, comparable to those reported for atopic patients on immunotherapy regimens. These findings demonstrate that IgG blocking antibodies directed against parasite allergens are a regular component of the immune response to chronic filarial infection and suggest their potential role in vivo for specifically modulating allergic responsiveness to parasite antigens.

3. Spry CJ, **Kumaraswami V**. Tropical Eosinophilia. Seminars in Hematology 1982; 19:107-115.
4. Thiruvengadam KV, Kesavan CR, Ahmed B, **Kumaraswami V**. Bronchial reactivity in allergic rhinitis. Lung India 1982;1:1-3.

Abstract: Bronchial sensitivity test was done on a total of 50 allergic rhinitis patients with a view to assess the bronchial reactivity in subjects with allergic rhinitis. It was found that the bronchial tree in 31 (62%) of 50 allergic rhinitis patients was hyper-reactive to the specific allergen though they had not yet developed overt bronchial asthma, Bronchial challenge with histamine produced a positive response more often in patients with allergic rhinitis than in normal healthy individuals. A positive response to bronchial challenge was more likely when history, endermal test and nasal provocation tests were all positive to begin with. Longterm follow up of this group of allergic rhinitis patients may indicate whether they are prone to develop bronchial asthma later.

5. Alagappan V, Harinaraya CV, **Kumaraswami V**, Thiruvengadam KV. Some aspects of filarial disease. Ind Med Gaz 1983;CXVII:55-58.
6. Raja A, **Kumaraswami V**, Narayanan PR, Tripathy SP, Thiruvengadam KV. Cell-mediated immunity in chyluria. Indian J Med Res 1983;77:443-446.
7. Weil GJ, Hussain R, **Kumaraswami V**, Tripathy SP, Phillips KS, Ottesen EA. Prenatal allergic sensitization to helminth antigens in offspring of parasite-infected mothers. J Clin Invest 1983;71:1124-1129.

Abstract: Total and filaria-specific immunoglobulin E (IgE) levels were studied in cord blood from infants born in Madras, India, where filariasis and intestinal helminth infections are highly endemic. Increased total IgE levels were observed in 82% of 57 cord sera tested (geometric mean 12.6 ng/ml; range 1-1,900 ng/ml). Thirty three of these sera also contained IgE antibodies specific for filarial antigens as determined by solid-phase radioimmunoassay. Comparison of ratios of filaria-specific IgE to total IgE in paired maternal and cord sera suggested that cord blood IgE was derived from the fetus in most cases and not from transplacental antibody

transfer. Our results suggest that prenatal allergic sensitization to helminth parasites occurs in the tropics. Such sensitization may contribute to the heterogeneity in host immune response and disease expression noted in filariasis and other helminth infection.

8. Durairaj A, Gurumurthy V, Subramanian JR, Jayaseelan, Kannan S, Kumaraswami V, Thiruvengadam KV. Evaluation of ribavirine in acute viral hepatitis. *J Assoc Physicians India*. 1984;32(9):789-791.
9. **Kumaraswami V**, Narayanan PR. Eosinophils and the lung in tropical pulmonary eosinophilia. *Lung India* 1985;111:25-26.
10. Paranjape RS, **Kumaraswami V**, Prabhakar R, Narayanan PR. Increased serum levels of antifilarial (IgA) antibodies in patients with tropical pulmonary eosinophilia. *Lung India* 1985;111:27-29.

Abstract: Tropical Pulmonary Eosinophilia (TPE) is diagnosed on the basis of high peripheral eosinophilia associated with clinical symptoms and signs. Elevated levels of total and antifilarial immunoglobulins is one of the characteristic features of TPE. Ten clinically diagnosed TPE patients and ten controls were compared for their anti-filarial and anti-ascaris antibody levels of classes IgG, IgM and IgA. While, IgG antibodies exhibited considerable cross reactivity between Ascaris and Filarial antigens, IgM antibodies showed nonspecific binding to filarial antigens. However, IgA antibodies were found to discriminate between TPE and control sera better than IgG and IgM antibodies.

11. Paranjape RS, **Kumaraswami V**, Prabhakar R, Subramanian S, Narayanan PR. Anti-filarial IgG antibodies in patients with bancroftian filariasis and tropical pulmonary eosinophilia. *Indian J Exp Biol* 1985;23:676-678.

Abstract: Anti-filarial (anti-B. malayi adult as well as anti-B. malayi microfilarial) IgG antibody levels were measured by enzyme linked immunosorbent assay (ELISA) in asymptomatic microfilaria carriers, acute, chronic and tropical pulmonary eosinophilia (TPE) patients, endemic and non-endemic controls. Controls from endemic areas had higher antibody titres compared with controls from non-endemic areas. The antibody response in different groups of filariasis patients was not stage specific. There were no association between clinical disease and antibody levels except in TPE. Though TPE patients had very high antibody levels, a proportion of them had low levels suggesting heterogeneity in TPE population.

12. Raghavan U, Ahamed B, Narayanan S, **Kumaraswami V**, Thiruvengadam KV. Urticaria-some observations. *Aspects of Allergy and Applied Immunol* 1985;XVIII:81-90.

Abstract: Urticaria has been known from antiquity. The disorder was known to the Arabs as essera and it has found a place in the writings of Cesium (circa 30 BC - 45 AD). Although the condition was recognised as an entity, its cause was a mystery to the physicians of those times. It was initially thought to be a manifestation of idiosyncrasy and later believed to be a form of neuroses. However, now the pathophysiological basis of urticaria is well understood. The development of antihistamine group of drugs, paved the way for the management of urticaria.

13. Narayanan PR, Vanamala CR, Alamelu R, **Kumaraswamy V**, Tripathy SP, Prabhakar R. Reduced lymphocyte response to mitogens in patients with Bancroftian filariasis. *Trans R Soc Trop Med Hyg* 1986;80:78-84.

Abstract: Peripheral blood lymphocytes from patients with acute and chronic *Wuchereria bancrofti* infections responded poorly to concanavalin A, phytohaemagglutinin and pokeweed mitogen when cultured in heat-inactivated pooled normal serum. The lymphocyte response to mitogens in carriers of microfilariae (mf) were normal. The suppression of transformation to mitogens was not reversible by the removal of plastic adherent cells. Incubation with mitogens and the adult filarial worm antigen (BmA) did not alter the mitogen response either in control subjects or in filarial patients. The possible mechanism of immunosuppression is discussed.

14. Nutman TB, **Kumaraswami V**, Ottesen E. Parasite-specific energy in human filariasis. Insights after analysis of parasite antigen-driven lymphokine production. *J Clin Invest* 1987;79:1516-1523.

Abstract: The antigen-specific immune unresponsiveness seen in bancroftian filariasis was studied by examining lymphokine production in peripheral blood mononuclear cells (PBMC) or PBMC sub-population from 10 patients with asymptomatic microfilaremia, 13 patients with elephantiasis and 6 normal North Americans. In each group of patients, the kinetics of the lymphokine response and the response to mitogens and non-parasite antigens did not differ significantly. In marked contrast, when antigen induced

lymphokine production was examined, most patients with microfilaremia were unable to produce either interleukin-2 (IL-2) or γ -interferon (i.e., were nonresponders), and the few who could (hyporesponders, generally with quite low microfilaremia levels) did so at levels significantly less than those of patients with elephantiasis, all of whom showed strong responses to parasite antigen. Removal of neither adherent cells or T8 + cells affected the parasite-specific energy seen in those with microfilaremia, suggesting a state of T cell tolerance to the parasite in patients with this most common clinical manifestations of bancroftian filariasis.

15. Nutman TB, **Kumaraswami V**, Pao L, Narayanan PR, Ottesen EA. An analysis of *in vitro* B cell immune responsiveness in human lymphatic filariasis. *J Immunol* 1987; 138:3954-3959.

Abstract: The immunoregulatory mechanisms involved in B-cell function in patients with varying clinical manifestation of bancroftian filariasis were examined by studying the ability of peripheral blood mononuclear cells (PBMC) or PBMC subpopulations from patients with elephantiasis, asymptomatic microfilaremia (MF), and acute tropical pulmonary eosinophilia (TPE) to produce polyclonal and parasite-specific antibody *in vitro*, both spontaneously and in response to a mitogen (PWM) and to parasite antigen.

When the spontaneous or mitogen-driven polyclonal responses were examined, all groups produced significant amounts of IgM and IgG; those with TPE produced

extremely high levels. However, when in vitro parasite antigen-specific responses were examined, those with MF were unable to produce filaria-specific antibody either spontaneously or in response to PWM or parasite antigen; in contrast, patients with chronic lymphatic obstruction or TPE produced large quantities. Removal of neither adherent cells nor T8 + T cells affected the parasite-specific B-cell anergy seen in those with MF. This absent or severely diminished capacity to produce antibody on parasite antigenic stimulation in patients with MF is likely responsible for the low levels of parasite-specific antibody seen in this most common clinical manifestation of bancroftian filariasis. Its inability to be reversed by the removal of “suppressor elements” suggests a state of B-cell unresponsiveness to the parasite.

16. Pinkston P, Vijayan VK, Nutman TB, Rom WN, O'Donnell KM, Corelius MJ, **Kumaraswami V**, Ferrans VJ, Takemura T, Yenokida G. et al. *J Clin Invest.* 1987;80(1): 216-225.

Abstract: Although acute tropical pulmonary eosinophilia (TPE) is well recognized as a manifestation of filarial infection, the processes that mediate the abnormalities of the lung in TPE are unknown. To evaluate the hypothesis that the derangements of the lower respiratory tract in this disorder are mediated by inflammatory cells in the local milieu, we utilized bronchoalveolar lavage to evaluate affected individuals before and after therapy. Inflammatory cells recovered from the lower respiratory tract of individuals with acute, untreated TPE (n = 8) revealed a striking eosinophilic alveolitis, with marked elevations in both the proportion of eosinophils (TPE 54 +/- 5%; normal 2 +/- 5%; P less than 0.001) and the

concentration of eosinophils in the recovered epithelial lining fluid (ELF) (TPE 63 +/-20 X 10(3)/microliter; normal 0.3 +/- 0.1 X 10(3)/microliter; P less than 0.01). Importantly, when individuals (n = 5) with acute TPE were treated with diethylcarbamazine (DEC), there was a marked decrease of the lung eosinophils and concomitant increase in lung function. These observations are consistent with the concept that at least some of the abnormalities found in the lung in acute TPE are mediated by an eosinophil-dominated inflammatory process in the lower respiratory tract.

17. **Kumaraswami V**, Ottesen EA, Vijayasekaran V, Devi SU, Swaminathan M, Aziz MA, Sarma GR, Prabhakar R, Tripathy SP. Ivermectin for the treatment of *Wuchereria bancrofti* filariasis. Efficacy and adverse reactions. *JAMA* 1988;259:3150-3153.

Abstract: Ivermectin treatment was evaluated for efficacy and side effects in 40 patients in South India, who had microfilaremia and bancroftian filariasis. Ivermectin was administered once orally at four dose levels (range, 25 to 200 ug/kg), and at each it was found to be completely effective in clearing blood microfilariae within five to 12 days. In most patients, microfilariae reappeared by three months; by six months the levels averaged 14% to 32% of pretreatment values in the four study groups, and all groups showed equivalent efficacy. Detailed monitoring identified some side effects in almost all patients; usually fever, headache, light-headedness, myalgia, sore throat, or cough that occurred most prominently 18 to 36 hours after treatment. These were most frequent and severe in patients with the greatest

microfilaremia, but only when treated with the two higher doses of ivermectin (100 and 200 ug/kg). The low-dose (25 ug/kg) ivermectin group, despite equivalent efficacy in parasite killing, had clinical reaction scores that were minimal and that were not correlated with parasitemia. Since efficacy and side effects of ivermectin therapy compare favourably with those reported for treatment with the standard antifilarial drug diethylcarbamazine citrate, the major advantage of single-oral-dose administration makes ivermectin the best candidate to replace diethylcarbamazine as the treatment of choice for bancroftian filariasis.

18. Freedman DO, Nutman TB, Jamal S, **Kumaraswami V**, Ottesen EA. Selective up-regulation of endothelial cell class I MHC expression by cytokines from patients with lymphatic filariasis. *J Immunol* 1989;142:653-656.

Abstract: Local host immune responses to the lymphatic-dwelling filarial parasite *Wuchereria bancrofti* are important in the pathogenesis of the lymphangitis that leads to filarial elephantiasis. That the lymphatic endothelial cells may be important in this inflammatory process was shown by the ability of supernatants generated from filarial Ag-driven PBMC of individuals with filarial elephantiasis caused by *W. bancrofti* infection to up-regulate class I MHC expression on human umbilical vein endothelial cells when compared to unstimulated control supernatants from the same individual (relative fluorescence intensity = $159\% \pm 13.5$; $p < 0.001$). In contrast, individuals with the same filarial infection but manifesting no lymphatic disease were unable to generate, in response to filarial Ag the cytokines

required for this activation (relative fluorescence intensity = $93\% \pm 2.6$). Supernatants induced by a non-filarial Ag (purified protein derivative) were able to effect class I MHC up-regulation in both patient groups. The same filarial Ag-driven supernatants did not cause detectable class II MHC staining on human umbilical vein endothelial cells. These results suggest a likely role for parasite Ag-driven, cytokine-mediated endothelial cell activation in the pathogenesis of lymphatic inflammatory/obstructive filarial disease.

19. Lai RB, **Kumaraswami V**, Krishnan N, Nutman TB, Ottesen EA. Lymphocyte subpopulations in Bancroftian filariasis: activated (DR⁺) CD8⁺ T cells in patients with chronic lymphatic obstruction. *Clin Exp Immunol* 1989;77:77-82.

Abstract: To examine the relationship between lymphocyte phenotypes and states of activation in patients with Bancroftian filariasis, dual colour flow cytometry and concurrent *in vitro* cell culture were performed on normal individuals (NV; n=15), and on patients with either asymptomatic microfilariemia (MF; n=12) or elephantiasis (CP; n=11). In contrast to findings by others in a population with Brugian filariasis, the percentages of total B lymphocytes (CD 19), T lymphocytes (CD8) in both patient groups were found to be within the range defined by clinically normal individuals. Furthermore, there were no differences among the groups in the expression of the IL-2 receptors (CD25) on T cells. There was, however, a significantly greater proportion ($p < 0.01$) of 'activated' cytotoxic suppressor lymphocytes (defined by co-expression of CD8 and HLA-DR) in patients with elephantiasis ($16.4 \pm 8.6\%$) than in the MF

(8.9±2.6%) or NV (8.3±2.9%) groups. Further, when the expression of this activation antigen was examined in parallel with *in vitro* mitogen responsiveness, an inverse correlation between the percentage of (CD8 + HLA-DR + lymphocytes and pokeweed mitogen-induced proliferation was seen ($r=-0.54$; $p < 0.001$). These data provide further definition of the immunoregulatory abnormalities seen in human filarial infections and suggest that activated CD8 + T lymphocytes may be involved in the pathogenesis of the chronic obstructed lymphatic form of this disease.

20. Nutman T, Vijayan VK, Pinkston P, **Kumaraswami V**, Steel C, Crystal RG, Ottesen EA. Tropical pulmonary eosinophilia: analysis of antifilarial antibody localized to the lung. *J Infect Dis* 1989;160:1042-1050.

Abstract: Acute tropical pulmonary eosinophilia (TPE) is characterized by wheezing, pulmonary infiltrates, marked peripheral blood eosinophilia, and very high serum levels of filaria-specific antibodies. To evaluate the amount and character of the filaria-specific antibodies in the lungs in this disorder, bronchoalveolar lavage was carried out in individuals with acute TPE, in normal subjects, and in patients with elephantiasis or asthma. Striking elevation of total IgE were found in the lower respiratory tract epithelial lining fluid (ELF) of patients with TPE along with high levels of filarial-specific IgG, IgM, and IgE. When patients with acute TPE were treated with diethylcarbamazine and evaluated again 6-14 days later, there was marked reduction in ELF parasite-specific IgG and IgE, which paralleled a rapid clinical response. Immunoblot comparison of the antigen

recognition patterns of ELF and serum antibodies demonstrated a general similarity in parasite antigens recognized, but the lung IgE and IgG antibodies appeared to recognize only a certain subset of the parasite antigens recognized by serum antibodies. Thus, a profound antibody response to filarial infection is found in the lungs of patients with TPE, suggesting that these filaria-specific antibodies play an important role in the pathogenesis of this disorder.

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22. Ottesen EA, Vijayasekaran V, **Kumaraswami V**, Pillai SVP, Sadanandam A, Frederick S, Prabhakar R, Tripathy SP. A controlled trial of ivermectin and diethylcarbamazine in lymphatic filariasis. *N Engl J Med* 1990;322:1113-1116.

Abstract: Ivermectin is a new antifilarial drug that can be given in a single oral dose. To compare the efficacy and side effects of ivermectin with those of diethylcarbamazine, the standard antifilarial treatment, we conducted a randomized, double-blind trial in 40 South Indian men with lymphatic filariasis caused by *Wuchereria bancrofti*. Patients were randomly assigned to one of three treatments; a single low dose of ivermectin (mean+ SE), 21.3+ 0.7 mg per kilogram of body weight; n=13) followed by placebo for 12 days; a single high dose of ivermectin (mean, 126.2+3.7 mg per kilogram; n=13) followed by placebo for 12 days; or diethylcarbamazine for 13 days (6 mg per kilogram per day for 12 days preceded by 3 mg per kilogram for 1 day; n=14). Eleven patients were initially assigned to

receive placebo and after five days were reassigned to one of the three treatment groups.

23. Sarma GR, Immanuel C, Ramachandran G, Krishnamurthy PV, **Kumaraswami V**, Prabhakar R. Adrenocortical function in patients with pulmonary tuberculosis. *Tubercle*. 1990;71(4):277-282.

Abstract: Adrenocortical function was studied in patients with pulmonary tuberculosis and the findings compared with those in healthy subjects. Plasma Cortisol levels in newly diagnosed patients were appreciably higher than in the healthy subjects (P less than 0.001). A normal (positive) response to ACTH (tetracosactrin) stimulation was observed in 35 (97%) of 36 healthy subjects, 15 (56%) of 27 newly diagnosed patients with tuberculosis and 5 (42%) of 12 chronic cases (i.e. those who had had the disease for more than 3 years); the difference between the healthy subjects and the two groups of tuberculosis patients was highly significant (P less than 0.001). Dexamethasone caused an appreciable decrease in the plasma Cortisol levels of tuberculosis patients. Considering the diurnal variation of Cortisol secretion, there was a steady decline in the Cortisol levels between 08:00 and 20:00 in the healthy subjects ($P = 0.02$); in the tuberculosis patients, however, there was a decrease up to 16:00 followed by a significant increase ($P = 0.05$), and the mean value at 20:00 was similar to that at 08:00.

24. Rom WN, Vijayan VK, Cornelius MK, **Kumaraswami V**, Prabhakar R, Ottesen EA, Crystal RG. Persistent lower respiratory tract inflammation associated with

interstitial lung disease in patients with tropical pulmonary eosinophilia following conventional treatment with diethylcarbamazine. *Am Rev Respir Dis*. 1990; 142(5): 1088-1092.

Abstract: Tropical pulmonary eosinophilia (TPE) presents as an acute syndrome with dyspnea, fluffy infiltrates, and rounded opacities on the chest radiograph, reduced lung function, marked eosinophilia in the blood and lower respiratory tract, and high titers of specific IgE and IgG antifilarial antibodies. The standard therapy for TPE is a 3-wk course of diethylcarbamazine (DEC) following which there is almost always a marked improvement in all parameters. However, clinical observations suggest that the disease can persist despite DEC therapy and lead to chronic dyspnea with restrictive lung impairment. To evaluate the concept that DEC therapy is not completely "curative" for TPE, but rather leaves most individuals with a mild, chronic form of TPE defined by persistent inflammation of the lower respiratory tract, we evaluated 23 individuals an average of 12 +/- 2 months following a standard 3-wk course of diethylcarbamazine for acute TPE. In the majority there were mild, persistent symptoms referable to the lung, chest X-ray abnormalities, blood eosinophilia, and elevated serum IgE and filarial specific IgG. On the average, lung function was consistent with the presence of chronic, mild interstitial lung disease. When the inflammatory cells from the lower respiratory tract were examined, there was a persistent eosinophilic alveolitis (TPE/post-DEC 1769 +/- 376 eosinophils/microliters epithelial lining fluid; normal subjects 256 +/- 38, p less than 0.02). Evaluation of the lower respiratory tract inflammatory

cells recovered from the TPE/post-DEC-treated individuals demonstrated spontaneous release of exaggerated amounts of O2- and H2O2 compared to normal subjects (p less than 0.05, both comparisons).

25. Lai RB, **Kumaraswami V**, Steel C, Nutman TB. Phosphocholine-containing antigens of *Brugia malayi* nonspecifically suppress lymphocyte function. *Am J Trop Med Hyg.* 1990;42(1):56-64.

Abstract: The immunosuppressive effect of *Brugia malayi* antigen (BmA) on phytohemagglutinin (PHA) driven T cell proliferation was evaluated in patients with filariasis (n = 14) and compared to control individuals (n = 12). When peripheral blood lymphocytes were co-cultured with BmA and PHA, BmA markedly suppressed the T cell proliferative response to PHA in both filarial patients and control individuals in a dose-dependent manner. The suppression resulted neither from any direct toxicity of BmA nor from nonspecific absorption of the PHA mitogenic activity by BmA. The major suppressive component appears to be phosphocholine (PC), an immunodominant molecule present in abundance on filarial parasites and on circulating filarial antigen. Both purified PC as well as PC-containing antigens affinity purified from BmA were capable of suppressing the proliferative responses of co-cultured autologous lymphocytes to PHA. The suppressive activity was not abolished by mitomycin-C treatment and was greater in patients with filariasis than in normal controls, suggesting that levels of PC-containing antigens determines the magnitude of the suppressive effect of PC-antigen. Further, as induction of the suppressive activity was completely abrogated

when antigen pre-treated cells were T cell-depleted, the suppressive effect appears to be mediated primarily by T cells.

26. Immanuel C, Sarma GR, Krishnamurthy PV, Ramachandran G, **Kumaraswami V**. Salivary Cortisol in the assessment of adrenocortical function in patients with pulmonary tuberculosis. *Indian J Med Res* 1992;95:1-7.

Abstract: Adrenocortical function was assessed on the basis of changes in salivary Cortisol in patients with pulmonary tuberculosis and the findings compared with those in healthy subjects. A method of direct radioimmunoassay of salivary Cortisol was standardized and the sensitivity was 0.8 nmol/1. Cortisol levels in saliva were significantly higher in the patients than in the healthy subjects (p < 0.001). The diurnal rhythm of Cortisol secretion was distributed in the patients with a significant increase in salivary Cortisol beyond 1800 h. While dexamethasone caused an appreciable suppression (87%), stimulation with ACTH (tetracosactrin) resulted in a marked increase in salivary Cortisol, the increase being significantly higher in the healthy subjects than in the patients (p < 0.001). Attempts to classify subjects as positive or negative responders to tetracosactrin based on increases in salivary Cortisol in relation to 'plasma Cortisol' changes were however not successful, as the agreement between the two methods ranged from 73 to 80 per cent with various criteria used.

27. Mohan V, **Kumaraswami V**, Viswanathan M. Immunology of Diabetes. J Assoc Physicians India 1992;40:461-464.

Abstract: The field of immunology is closely linked to diabetes mellitus in several ways. Basically the subject of immunology and diabetes may be considered under four headings:

- i) Immunology and the etiology of diabetes
- ii) Animal models in studies on immunology of diabetes
- iii) Immunology and the complications of diabetes
- iv) Immunology and the treatment of diabetes.

28. King CL, **Kumaraswami V**, Poindexter RW, Kumari S, Jayaraman K, Ailing DW, Ottessen EA, Nutman TB. Immunologic tolerance in lymphatic filariasis. Diminished parasite-specific T and B lymphocyte precursor frequency in the microfilaremic state. J ClinInvest.1992;89(5):1403-1410. “

Abstract: To explore the mechanisms of antigen-specific immune unresponsiveness seen in microfilaremic patients with bancroftian filariasis, T and B cell precursor frequency analysis was performed using PBMC from individuals with either asymptomatic microfilaremia (MF, n = 7) or chronic lymphatic obstruction (CP, n = 20). Highly purified CD3+ cells were partially reconstituted with adherent cells and their proliferative response to parasite antigens determined in cultures of T cells by limiting dilution analysis. A filter immunoplaque assay also assessed the frequency of both total and parasite-specific Ig-producing B cells. While the lymphocyte proliferation to mitogens and to a nonparasite antigen (Streptolysin-O, [SLO]) were similar in all groups of patients, the frequency of parasite-specific CD3+ T cells

was significantly lower (geometric mean [GM], 1/3,757) in MF patients when compared to that in CP patients (GM 1/1,513; P less than 0.001). Similarly, the proportion of lymphocytes producing parasite-specific IgE or IgG was significantly lower in MF patients (IgE mean, 0.2%; IgG mean, 0.33%) compared with CP patients (IgE mean, 3.2%; IgG mean, 1.76%; P less than 0.05 for both comparisons). These observations imply that low numbers of parasite-specific T and B lymphocytes may be partially responsible for the severely diminished capacity of lymphocytes from patients with MF to produce parasite-specific antibody and to proliferate to parasite antigen *in vitro*. Such differences in parasite-specific lymphocyte responses suggest that tolerance by clonal anergy may be a critical mechanism for maintaining the microfilaremic state.

29. Shenoy RK, **Kumaraswami V**, Raj an K, Thankom S, Jalajakumari. Ivermectin for the treatment of periodic Malayan filariasis: a study of efficacy and side effects following a single oral dose and retreatment at six months. Ann Trop Med Parasitol. 1992;86(3):271-278.

Abstract: Ivermectin, a new antifilarial drug and currently the drug of choice for the treatment of onchocerciasis, has been shown to be effective in bancroftian filariasis. We report here, for the first time, the efficacy and safety of the drug in the treatment of filariasis caused by periodic *Brugia malayi*. Sixty male, asymptomatic microfilaraemics of Alleppey district, Kerala, South India, received single oral doses of ivermectin in a double blind study. Four dosages were used: 20, 50, 100 and 200 micrograms kg-1 body weight. Clearance of

microfilariae, which was not complete, began as early as 12 hours post-treatment and was maximal at the end of one month. Microfilaria levels began to rise thereafter and reached 20-50% of pretreatment levels at six months. The two higher doses (100 and 200 micrograms kg⁻¹) were more effective in suppressing microfilaraemia at six months ($P < 0.05$). After six months, 32 patients were retreated using the same dose of ivermectin that they had received initially. The pattern of clearance was essentially similar to that seen during the first treatment phase and microfilaria levels were 10-35% of pretreatment levels at the end of the next six months. Twenty-eight individuals who were not retreated at six months continued to have increasing levels of microfilariae, reaching 60% of pretreatment levels at the end of the next six months. Side effects (such as fever, headache, myalgia), which were mild to moderate, were seen in most patients and were unrelated to the dose ($P > 0.05$) or pretreatment levels of microfilariae.

30. Kar SK, Patnaik S, **Kumaraswami V**, Murty RSN. Side reactions following ivermectin therapy in high density bancroftian microfilaraemics. *Acta Tropica* 1993;55:21-31.

Abstract: Side reactions following ivermectin treatment were evaluated in sixty males with high density bancroftian microfilaremia (GM 1388 ml). Following a single oral dose of ivermectin of different strengths (20, 50, 100 or 200 mg/kg), microfilariae clearance and side reactions were monitored in a double blind fashion. Microfilaria levels fell rapidly after ivermectin administration in

all dosage groups and 98% of pretreatment microfilariae was cleared after 12 h of treatment. The rate of microfilaria (mf) clearance was slower with 20 ug/kg than with the highest dose (200 mg/kg) administered. Forty six patients (77%) became amicrofilaraemic within 2 weeks of treatment. Side reactions were noted in 97% of cases. The most common reactions were fever, headache, weakness, myalgia and cough which appeared by 12 h and subsided by 72 h following treatment. The frequency and intensity of side reactions were related to pretreatment mf densities and were independent of the dose administered. Unusual side reactions were noted in a few patients with high density microfilaraemia. These included intense cough, shortness of breath, blood tinged mucoid expectoration associated with patchy pneumonitis of the lung. Itchy rashes, lymphatic nodules and raised alkaline phosphatase level were also observed in some patients. These side reactions were transient, self limiting and were not serious enough to warrant any treatment. These exaggerated unusual reactions were possibly due to allergic response of the susceptible host to rapid killing of large number of microfilarae.

31. Kar SK, Patnaik S, Mania J, **Kumaraswami V**. Ivermectin in the treatment of bancroftian filarial infection in Orissa, India. *Southeast Asian J Trop Med Public Health* 1993;24:80-86.

Abstract: Ivermectin treatment was evaluated for its efficacy and side reactions in sixty patients of Orissa with bancroftian filarial infection and microfilaremia. Ivermectin was administered as a single oral dose at

four dosage levels (20, 50, 100 and 200 mg/kg), and both microfilarial clearance and associated side reactions were monitored in a double blind fashion. Blood microfilariae were cleared in all patients at all dosages within 1 to 14 days. In most patients microfilariae reappeared by third month. The microfilaria appearance by third and sixth month averaged 12.2 to 44 per cent of pretreatment values in the four study groups. Side reactions were encountered in almost all patients, the commonest being fever, headache, weakness, myalgia and cough which occurred most prominently 12 to 72 hours after treatment. Side reactions were more frequent and severe in patients with high microfilaria counts. Clinical reaction scores for each group were independent of the dose administered. The 200 mg dose group showed significantly more rapid microfilariae clearance and its delayed reappearance as compared with the other dosage groups and without inducing significantly greater clinical reaction scores.

32. King CL, Mahanty S, **Kumaraswami V**, Abrams JS, Regunathan J, Jayaraman K, Ottesen EA, Nutman TB. Cytokine control of parasite-specific anergy in human lymphatic filariasis. Preferential induction of a regulatory T helper type 2 lymphocyte subset. *J Clin Invest* 1993;92:1667-1673.

Abstract: The immunological mechanisms involved in maintenance of an asymptomatic microfilaremic state (MF) in patients with lymphatic filariasis remain undefined. MF patients have impaired filarial antigen (Ag)-specific lymphocyte proliferation and decreased frequencies (Fo) of Ag-

specific T cells, and yet elevated serum IgE and antifilarial IgG4. To investigate the mechanism of Ag-specific anergy in MF patients in contrast to amicrofilaremic individuals with chronic lymphatic obstruction (CP), the Fo of Ag-specific lymphocytes from peripheral blood mononuclear cells secreting either IL-4 or IFN- γ were assessed by filter spot enzyme-linked immunosorbent assay, and IL-10 and transforming growth factor- β (TGF- β) mRNA transcript levels were assessed by a semiquantitative reverse transcriptase polymerase chain reaction technique. The Fo of filaria-specific IL-4 secreting lymphocytes were equivalent in both MF (geometric mean(GM) = 1:11,700) and CP (GM = 1:29,300, $p=0.08$), whereas the Fo of IFN- γ -secreting lymphocytes were lower in MF (GM = 1:39,300) than in CP (GM = 1:4,200, $p < 0.01$). When the ratio of IL-4/IFN- γ (T helper type 2 (Th2/TH1)-secreting cells) was examined, MF subjects showed a predominant Th2 response (8:1) compared with a Th1 response in CP individuals (1:4). mRNA transcript levels of IL-10 were also significantly elevated in MF compared with CP individuals ($P < 0.01$). Further, IL-10 and TGF- β were shown to have a role in modulating the Ag-specific anergy among MF subjects, in that neutralizing anti-IL-10 or anti-TGF- β significantly enhanced lymphocyte proliferation response (by 220-1,300%) to filarial Ags in MF individuals. These findings demonstrate that MF subjects respond to parasite antigen by producing a set of suppressive cytokines that may facilitate persistence of the parasite within humans while producing little clinical disease.

33. Limaye AP, Ottesen EA, **Kumaraswami V**, Abrams JS, Regunathan J, Vijayasekaran V, Jayaraman K, Nutman TB.

Kinetics of serum and cellular interleukin-5 in posttreatment eosinophilia of patients with lymphatic filariasis. *J Infect Dis* 1993;167:1396-1400.

Abstract: Peripheral blood eosinophil counts and serum levels and *in vitro* production of eosinophilopoietic cytokines were assessed before and at frequent intervals after diethylcarbamazine treatment of Bancroftian filariasis. Eosinophil counts peaked at day 7 after the start of treatment ($3.59\% \pm 118\%$ of pretreatment levels) and declined to pretreatment levels by day 17. Serum interleukin-5 (IL-5), undetectable in 14 of 15 patients before treatment, rose sharply but transiently, with peak levels-1 ($32 = 7$ pg/mL) 2 days after diethylcarbamazine treatment. Granulocyte-macrophage colony stimulating factor and IL-3 were not detectable in serum at any time. *In vitro* mitogen-induced IL-5 levels decreased significantly in 7 of 9 patients 3 days after treatment when serum IL-5 was at near-peak levels. By day 10 IL-5 values increased in 8 of 9 patients compared with treatment values ($P < 0.02$). These data define the temporal relation between serum IL-5 levels and the subsequent development of eosinophilia and suggest that lymphocytes are the source of IL-5.

34. Mahanty S, King CL, Kumaraswami V, Regunathan J, Maya A, Jayaraman K, Abrams JS, Ottesen EA, Nutman TB. IL-4- and IL-5-secreting lymphocyte populations are preferentially stimulated by parasite-derived antigens in human tissue, invasive nematode infections. *J Immunol* 1993;151:3704-3711.

Abstract: Helminth infections in humans and animals are associated with strong T helper 2 (Th2) responses.

To determine whether parasite-derived Ag preferentially expand a Th2-like cell population, a filter immunoplaque assay was used to enumerate the frequencies (F o) of PBMC and CD4 + -enriched PBMC from individuals with helminth infections secreting selected cytokines in response to parasite derived (PAG) and nonparasite antigens (NP Ag). In 20 individuals with lymphatic filariasis, frequency analysis of PBMC secreting IL-4 and IFN- g indicated that the F o of PAG-specific IL-4 secreting cells (geometric mean F o (GM): 1/12, 100) was 57-fold higher than the corresponding F o of NPAg-reactive cells (GM: 1/692,000; $p < 0.02$). In marked contrast, the F o of IFN-g-secreting cells responding to Pag (GM: 1/2,700) did not differ from those of cells specific for NPAg (GM: 1/3,400; $p = 0.83$). In another group of helminth infected individuals, the F o of highly enriched CD4 + cells secreting IL-4 and IL-5 in response to Pag (GMs: 1/2,600 and 1/5,600 CD4 + cells, respectively) were also found to be significantly higher than those specific for NPAg (GMs: 1/291,000 and 1/303,000 CD4 + ; $p < 0.05$ and $p < 0.01$, respectively), whereas the corresponding F o of IFN- g -and granulocyte-macrophage-CSF-secreting cells were equivalent for PAG and NPag. Furthermore, the proportion of PAG-specific IL-4 and IL-5 secreting CD4 + cells relative to all cells secreting the given cytokine were approximately 29-fold higher than the proportion of NP Ag-specific cells secreting these cytokines. Again, the corresponding proportions of Ag-specific IFN-g-and GM-CSF-secreting CD4 + cells were equivalent for PAG and NPag. Thus, in this *ex vivo* system, a circulating population of IL-4 and IL-5 secreting (Th2-like) cells has been shown to exist

in humans; PAg appears to expand these cells preferentially.

35. Shenoy RK, **Kumaraswami V**, Raj an K, Thankom S, Jalajakumari. A comparative study of the efficacy and tolerability of single and split doses of ivermectin and diethylcarbamazine in periodic brugian filariasis. *Ann Trop Med Parasitol* 1993;8:459-467.

Abstract: The use of ivermectin in lymphatic filariasis (both bancroftian and brugian) has been recently explored in several studies. We report in this paper, for the first time, a direct comparison of the efficacy and tolerability of single doses of ivermectin and diethylcarbamazine (DEC) in brugian filariasis. We also present our findings on the use of split doses of ivermectin and DEC on microfilaraemia levels and the occurrence of adverse reactions. Fifty male, asymptomatic microfilaraemics drawn from the Alleppey District, Kerala, India, were allocated one of the following five treatment regimens in a double blind randomized study. (1) single oral 6 mg/kg dose of DEC; (2) single oral 6 mg/kg dose of DEC preceded by 1 mg/kg DEC primer; (3) single oral 220 mg/kg dose of ivermectin; (4) single oral 200 mg/kg dose of ivermectin preceded by a 20 mg/kg ivermectin primer; or (5) a single oral 400 mg/kg dose of ivermectin preceded by a 20 mg/kg ivermectin primer. The kinetics of microfilaria clearance differed in the two (DEC/ivermectin) groups in the first month post-treatment. At the end of 1 year there were no differences in the microfilaria levels in the two DEC-tested groups and the 420 mg/kg ivermectin group. The safety of the 400 mg/kg dose of ivermectin was established in this study

which has shown that, currently, this dose would be the best choice for brugian filariasis. Patients in the ivermectin groups had significantly lower adverse reaction scores than patients who had received DEC. There was no advantage in splitting the dose of either DEC or ivermectin, either in terms of efficacy or tolerability. Lymphadenitis, lymphangitis or scrotal reactions, which were reported in previous studies to be indicative of a macrofilaricidal effect of anti-filarial drugs, were not observed in the present study. The ability of single doses of either ivermectin or DEC to achieve prolonged suppression of microfilaraemia (upto 1 year), as demonstrated in the present study, should be helpful in the design of better control strategies for lymphatic filariasis.

36. Witte MH, Jamal S, Williams WH, Witte CL, **Kumaraswami V**, McNeill GC, Case TC, Panicker TM. Lymphatic abnormalities in human filariasis as depicted by lymphangioscintigraphy. *Arch Intern Med.* 1993; 153(6):737-744.

Background: Investigation into filarial lymphedema has been hampered by the lack of a simple, safe, and easily repeated test to image the peripheral lymphatic system. Recent refinements in radionuclide lymphangio scintigraphy have established this noninvasive technique as the initial procedure of choice for visualizing lymphatics. Accordingly, we applied lymphangioscintigraphy to patients with filariasis and, for purposes of interpretation, compared the findings with those in patients with non-filarial lymphedema.

Methods: Thirty-three patients with classic symptoms or signs consistent with acute or chronic filariasis underwent lymphangioscintigraphy, and the findings were compared with those in five patients without lymphatic dysfunction and in 50 other patients with primary or secondary lymphedema without exposure to filariasis.

Results: As in patients with nonfilarial lymphedema, scintigraphic abnormalities in the 33 patients with filariasis included delayed or absent tracer transport of the radiotracer (25 patients), tortuous and bizarre deep lymphatics (seven patients), dermal diffusion (15 patients), retrograde tracer flow (six patients), and faint or absent regional nodal visualization (14 patients). Even in patients with long-standing filarial lymphedema, peripheral trunks were often visualized (at least in part), and regional nodes and more central lymphatics sometimes filled after light exercise. In some of the latter patients, however, discrete lymphatic trunks were not detected.

Conclusion: Lymphangioscintigraphy is a simple, safe, reliable, noninvasive method with which to examine the peripheral lymphatic system, including truncal and nodal abnormalities, in endemic populations with occult and overt lymphatic filariasis.

37. Shenoy RK, Sandhya K, Suma TK, **Kumaraswami V.** A preliminary study of filariasis related acute adenolymphangitis with special reference to precipitating factors and treatment modalities. *Southeast Asian J Trop Med Public Health* 1995;26:301-305.

Abstract: Episodic adenolymphangitis (ADL) is one of the important clinical manifestations of lymphatic filariasis. Recurrent ADLs contribute to the progress of the disease and also have important socioeconomic implications since they cause significant loss of mandays. The present study was conducted in order to identify the precipitating factors responsible for ADL attacks and also to examine the different modalities of treatment. Sixty five individuals with filariasis related ADL attacks, who are residents of Alleppey district (endemic for Brugia malayi) were studied. All efforts were taken to identify the precipitating factors for ADLs in these individuals. They were hospitalized for a period of five days or more. All of them received symptomatic antipyretic/anti-inflammatory therapy and tropical antibiotic/antifungal treatment of the affected limbs. They were then randomly allocated to one of the following four regimens: group I -symptomatic alone; group II - symptomatic plus antibiotics; group III - symptomatic followed by diethylcarbamazine citrate (DEC) and group IV - symptomatic plus antibiotic followed by DEC. Patients in groups III and IV received DEC every three months upto one year. There was a significant relationship between the number of ADL attacks and the grade of edema. Presence of focus of infection in the affected limb could be identified in 28 of the 65 patients. In the majority of patients (48) response to treatment was rapid (resolution in less than five days). Neither antibiotics nor DEC (given at intervals of three months) appeared to alter the frequency of ADL attacks. On the other hand, simple hygienic measures combined with good foot care and local antibiotic/antifungal cream application (where

required), were effective in reducing the number of ADL attacks.

38. Burri H, Loutan L, **Kumaraswami V**, Vijayasekaran V. Skin changes in chronic lymphatic filariasis. *Trans R Soc Trop Med Hyg* 1996;90:671-674.

Abstract: Seventeen men and 31 women with unilateral lower limb lymphoedema attributed to chronic lymphatic filariasis were examined in the filarial out-patient clinic of the Government General Hospital, Madras, India. Skin changes such as skin fold thickening, hyperkeratosis, hypo- or hyper-trichosis, pachydermia, pigmentary changes, chronic ulceration, epidermal and sub-epidermal nodules, and clinical intertrigo were observed and compared between the different lymphoedema grades. These lesions are not specific to chronic lymphatic filariasis, and have been described in other conditions displaying lymphostasis. They are thought to be favoured by secondary infections, which should be dealt with appropriately to prevent the progression of the disease and the onset of elephantiasis.

39. Mahanty S, Luke HE, **Kumaraswami V**, Narayanan PR, Vijayshekar V, Nutman TB. Stage-specific induction of cytokines regulates the immune response in lymphatic filariasis. *Exp Parasitol* 1996;84:282-290.

Abstract: Parasite stage-specific T cell responses were studied in Indians with lymphatic filariasis manifesting as elephantiasis (CP, n = 11) and asymptomatic microfilaremia (MF, n = 8), using antigens derived from the microfilarial, adult male only,

and mixed adult male and female worms. Proliferative responses to microfilarial and mixed (male-female adult worm) antigens in MF individuals were markedly impaired compared to corresponding responses in individuals with CP. In contrast, T cell proliferative responses to adult male-derived antigens were not statistically different between the two groups. Analysis of antigen-driven cytokine secretion by peripheral blood mononuclear cells from MF and CP individuals revealed significantly lower IL-2 and IFN-gamma production by MF in response to microfilarial and mixed antigens (but not to adult male antigen) compared to CP individuals. No differences were observed between MF and CP in parasite antigen-driven IL-4 or IL-5 production. Spontaneous and parasite-specific IL-10 secretion was also measured to determine if cytokine cross-regulation of Th1 responses may be a mechanism underlying the observed Th1 suppression. Spontaneous and microfilarial antigen-driven IL-10 was found to be significantly higher in MF than in CP individuals. These data indicate that MF individuals exhibit preferentially impaired Th1-type responses to microfilarial antigens and that microfilarial-induced IL-10 may be critical in the downregulation of specific Th1 responses.

40. Mahanty S, Mollis SN, Ravichandran M, Abrams JS, **Kumaraswami V**, Jayaraman K, Ottesen EA, Nutman TB. High levels of spontaneous and parasite antigen-driven interleukin-10 production are associated with antigen-specific hyporesponsiveness in human lymphatic filariasis. *J Infect Dis* 1996;173:769-773.

Abstract: To determine whether counterregulation by interleukin (IL)-10 plays a role in the generation or maintenance of the antigen-specific hyporesponsiveness seen in asymptomatic microfilaremic (MF) patients, parasite antigen (PAg)- and nonparasite antigen (NPAg)-driven IL-10 production by peripheral blood mononuclear cells (PBMC) was studied in 10 MF patients and in 11 patients with chronic lymphatic pathology (CP). PBMC from MF patients spontaneously secreted 10-fold more IL-10 than did PBMC from patients with CP. PAg also induced significantly more IL-10 production by PBMC from CP patients. There was a negative correlation between PAg driven IL-10 production by PBMC and PAg-specific T cell proliferation in the MF group. IL-10 secretion by plastic adherent cells from MF persons was higher in response to PAg than NPAg, whereas IL-6 and tumor necrosis factor- α secretion were equivalent for PAg and NPAg, suggesting that PAg preferentially induces IL-10 secretion in these cells. Thus, PAg-induced IL-10 likely plays an important role in down-regulating antigen-specific proliferative responses in MF patients.

41. Ravichandran M, Mahanty S, **Kumaraswami V**, Nutman TB, Jayaraman K. Elevated IL-10 mRNA expression and downregulation of Th1-type cytokines in microfilaraemic individuals with *Wuchereria bancrofti* infection. *Parasite Immunol* 1997;19:69-77.

Abstract: To understand the molecular basis of parasite-specific anergy in human lymphatic filariasis caused by the nematode *Wuchereria bancrofti*, parasite antigen-dependent cellular proliferation and cytokine gene expression were investigated. By reverse transcriptase polymerase chain

reaction (RT-PCR), the levels of cytokine mRNA were determined in the peripheral blood mononuclear cells (PBMCs) of different clinical groups of filariasis patients. This includes individuals with circulating microfilariae (MF) patients with chronic lymphatic obstruction (CP), and exposed but uninfected individuals (EN). Those with CP exhibited both a Th2 and a Th1 parasite antigen-driven response. In PBMCs from those with MF, there was a marked downregulation of cellular response to parasite antigens, with lowered expression of Th1-specific cytokines (IFN γ - and IL-2) and this was paralleled by increased IL-10 expression. The EN individuals had a purely Th-1 type pattern with absence of IL-4 and IL-5 expression. Further, the mRNA expression of the costimulatory surface marker, CD80 (B7-1), was not associated with either disease status or IL-10 expression. There was a significant negative correlation between IL-10 mRNA expression and PBMC proliferation in the MF individuals, thus indicating the possible role of IL-10 in antigen-specific hyporesponsiveness.

42. Suma TK, Shenoy RK, Varghese J, Kuttikkal VV, **Kumaraswami V**. Estimation of ASO titer as an indicator of streptococcal infection precipitating acute adenolymphangitis in brugian lymphatic filariasis. *Southeast Asian J Trop Med Public Health* 1997;28:826-830.

Abstract: Recurrent episodes of acute adenolymphangitis (ADL) are important clinical manifestations of lymphatic filariasis which contribute significantly to the progression of lymphedema. It is increasingly being recognised that secondary bacterial

infections play an important role in the etiology of ADL. We examined the role of streptococcal infection as a precipitating factor of ADL in brugian filariasis, by determining the anti-streptolysin O (ASO) titers and by isolating the causative organism wherever possible. The study population consisted of 30 patients with filariasis related ADL (Group A), 30 patients with chronic filarial edema (Group B) and 60 age and sex matched healthy adults (Group C). ASO titer was estimated by the latex agglutination method at the time of entry into the study, at the 15th day and at 3, 6 and 12 months. ASO titers were persistently elevated in 90% of patients in Group A and a portal of entry for bacterial infection was deleted in all of these patients. In Group B only six patients had persistently elevated ASO titers. These patients had grade III lymphedema and three of them had monilial infections in the affected limb. In the control group none had persistently elevated ASO titers. The elevated ASO titers and the detection of a site of entry for bacteria in patients with ADL supports a streptococcal etiology for this condition.

43. Suresh S, **Kumaraswami V**, Suresh I, Rajesh K, Suguna G, Vijayasekaran V, Ruckmani A, Rajamanickam MG. Ultrasonographic diagnosis of subclinical filariasis. *J Ultrasound Med* 1997;16:45-49.

Abstract: Asymptomatic persons with lymphatic filariasis may harbor microfilariae in the circulation, and despite the lack of symptoms, these patients may have occult pathologic lesions and renal abnormalities. Earlier investigators have shown that it is possible to detect live adult filarial worms and dilation of lymphatic channels with

ultrasonography. It is also possible to assess response to therapy. Using sonography, we detected twirling motions in dilated lymph channels and characteristic sonographic findings associated with presence of adult filariae. On follow-up examination we also found evidence of loss of worm activity after chemotherapy.

44. Zimmerman PA, Buckler-White A, Alkhatib G, Spalding T, Kubofcik J, Combadiere C, Weissman D, Cohen O, Rubber! A, Lam G, Vaccarezza M, Kennedy PE, **Kumaraswami V**, Gorgi JV, Detels R, Hunter J, Chopek M, Berger EA, Fauci AS, Nutman TB, Murphy PM. Inherited resistance to HIV-1 conferred by an inactivating mutation in CC chemokine receptor 5: studies in populations with contrasting clinical phenotypes, defined racial background, and quantified risk. *Mol Med* 1997;3:23-36.

Background: CC chemokine receptor 5 (CCR5) is a cell entry cofactor for macrophage-tropic isolates of human immunodeficiency virus-1 (HIV-1). Recently, an inactive CCR5 allele (designated here as CCR5-2) was identified that confers resistance to HIV-1 infection in homozygotes and slows the rate of progression to AIDS in heterozygotes. The reports conflict on the effect of heterozygous CCR5-2 on HIV-1 susceptibility, and race and risk levels have not yet been fully analyzed. Here we report our independent identification of CCR5-2 and test its effects on HIV-1 pathogenesis in individuals with contrasting clinical outcomes, defined race, and quantified risk.

Materials and Methods: Mutant CCR5 alleles were sought by directed heteroduplex analysis of genomic DNA from

random blood donors. Genotypic frequencies were then determined in (1) random blood donors from North America, Asia, and Africa; (2) HIV-1+ individuals; and (3) highly exposed-seronegative homosexuals with quantified risk.

Results: CCR5-2 was the only mutant allele found. It was common in Caucasians, less common in other North American racial groups, and not detected in West Africans or Tamil Indians. Homozygous CCR5-2 frequencies differed reciprocally in highly exposed-seronegative (4.5%, n = 111) and HIV-1-seropositive (0%, n = 614) Caucasians relative to Caucasian random blood donors (0.8%, n = 387). This difference was highly significant ($p < 0.0001$). By contrast, heterozygous CCR5-2 frequencies did not differ significantly in the same three groups (21.6, 22.6, and 21.7%, respectively). A 55% increase in the frequency of heterozygous CCR5-2 was observed in both of two cohorts of Caucasian homosexual male, long-term nonprogressors compared with other HIV-1+ Caucasian homosexuals ($p = 0.006$) and compared with Caucasian random blood donors. Moreover, Kaplan-Meier estimates indicated that CCR5-2 heterozygous seroconvertors had a 52.6% lower risk of developing AIDS than homozygous wild-type seroconvertors.

Conclusions: The data suggest that homozygous CCR5-2 is an HIV-1 resistance factor in Caucasians with complete penetrance, and that heterozygous CCR5-2 slows the rate of disease progression in infected Caucasian homosexuals. Since the majority (approximately 96%) of highly exposed-seronegative individuals tested are not homozygous for CCR5-2, other resistance factors must exist. Since CCR5-2 homozygotes have no obvious clinical problems,

CCR5 may be a good target for the development of novel antiretroviral therapy.

45. Mahanty S, Ravichandran M, Raman U, Jayaraman K, **Kumaraswami V**, Nutman TB. Regulation of parasite-antigen driven immune responses by interleukin-10 (IL-10) and IL-12 in lymphatic filariasis. *Infect Immun*. 1997;65(5): 1742-1747.

Abstract: We investigated the mechanisms by which interleukin-10 (IL-10) regulates antigen-specific hyporesponsiveness in asymptomatic microfilaremic (MF) individuals. Peripheral blood mononuclear cells from MF individuals (n = 11) were stimulated in vitro with *Brugia malayi* antigen (BMA) or mycobacterial purified protein derivative (PPD) in the presence of neutralizing anti-IL-10 or isotype control monoclonal antibodies. As expected, BMA stimulated little or no gamma interferon (IFN-gamma) secretion in MF individuals, whereas PPD stimulated IFN-gamma in all but one. Neutralization of endogenous BMA-driven IL-10 secretion led to augmentation of IFN-gamma in seven of nine MF individuals (1.5- to 10-fold) and did so in a BMA-specific manner (PPD-driven IFN-gamma was augmented in only two of eight MF individuals and only 1.5- to 2-fold), indicating that IL-10 downregulates type 1 responses in these individuals. Type 2 responses (IL-5 secretion) were unaffected by the IL-10 blockade. To assess whether IL-12 could reverse the type 1 downregulation observed, the effect of recombinant human IL-12 (rhIL-12) on BMA-driven IL-5 and IFN-gamma production was also evaluated. rhIL-12 augmented both BMA- and PPD-driven IFN-gamma

production 5- to 10-fold in six of nine MF individuals. These data demonstrate that IL-10 downregulates BMA-driven type 1 responses and that IL-12 can overcome downregulation of Th1 responses associated with MF but does so in a non-antigen-specific manner.

46. Shenoy R, George LM, John A, Suma TK, **Kumaraswami V**. Treatment of microfilaraemia in asymptomatic brugian filariasis: the efficacy and safety of the combination of single doses of ivermectin and diethylcarbamazine. *Ann Trop Med Parasitol* 1998;92:579-585.

Abstract: Although combinations of ivermectin and diethylcarbamazine (DEC) have been shown to be superior to either drug alone in the suppression of bancroftian microfilariae, their efficacy against infections with *Brugia malayi* has never been investigated. The present, open trial is the first on the efficacy and safety of a combination of single doses of ivermectin and DEC when used against microfilaraemias of brugian filariasis. Twenty-one, asymptomatic but microfilaraemic (109-6934 microfilariae/ml blood, with a median of 841/ml) men, aged 18-48 years, each received oral doses of ivermectin (400 micrograms/kg) and DEC (6 mg/kg) as a single treatment. Twelve hours post-treatment, 96.5%-100% of the microfilariae in each subject had been cleared and 12 of the subjects were amicrofilaraemic. A further reduction in microfilarial counts was evident 1 month post-treatment (mean clearance = 99.0%) and the counts continued to fall at least until the last follow-up, at 1 year post-treatment, when the mean clearance was 99.9% and 13 (68.4%) of the 19 subjects then investigated were

amicrofilaraemic. All subjects experienced adverse reactions of one form or another, lasting for up to 48 h post-treatment; these included fever, myalgia, headache, and lethargy. Postural hypotension was recorded in two subjects and dilated, inflamed lymphatic channels were seen in another two. The combination of ivermectin and DEC demonstrated a microfilaricidal effect superior to that of either drug used alone, both in the initial rapid clearance of microfilariae and in sustaining the effect for 1 year. This finding has important implications for the control of lymphatic filariasis.

47. Shenoy RK, Suma TK, Raj an K, **Kumaraswami V**. Prevention of acute adenolymphangitis in brugian filariasis: comparison of the efficacy of ivermectin and diethylcarbamazine, each combined with local treatment of the affected limb. *Ann Trop Med Parasitol* 1998;92:587-594.

Abstract: Acute attacks of adenolymphangitis (ADL) not only force patients with lymphatic filariasis to seek medical attention but also hasten the progression of filarial oedema. Patients with filariasis-associated ADL are currently treated with repeated courses of the antifilarial drug diethylcarbamazine (DEC), with or without antibiotics and anti-inflammatory agents. In this double-blind, placebo-controlled study, the efficacy of local treatment of the affected limb combined with repeated doses of ivermectin or DEC, in preventing the occurrence of ADL in *Brugia malayi* lymphatic filariasis, was examined. Overall, 120 patients who had each had at least two ADL attacks in the previous year were each admitted to the study at

the time of an ongoing episode of ADL. The patients were randomly allocated to receive 12, monthly treatments of ivermectin (400 micrograms/kg), DEC (10 mg/kg) or placebo, in addition to local care of the affected limbs. There was a significant reduction in the frequency of ADL attacks in each of the three groups during the 2-year study period ($P < 0.001$ for each comparison). Most importantly, there were no significant differences in frequency of attacks between the three groups, either at the end of the treatment phase or at the end of the post-treatment phase ($P > 0.15$ for each comparison), suggesting that foot care combined with appropriate use of local antibiotics or antifungals is adequate to reduce the number of ADL attacks. The implications of these observations for planning morbidity control in lymphatic filariasis are discussed.

48. Shenoy RK, Varghese J, Kuttikkal VV, **Kumaraswam V**. The efficacy, tolerability and safety of diethylcarbamazine-fortified salt in the treatment of the microfilaraemias of brugian filariasis: an open, hospital-based study. *Ann Trop Med Parasitol* 1998;92:285-293.

Abstract: Cooking salt fortified with diethylcarbamazine (DEC) has been successfully used to control lymphatic filariasis in several parts of the world. The kinetics and efficacy of DEC-fortified salt in clearing microfilaraemias of *Brugia malayi* and the salt's tolerability and safety are examined in this study. Twenty individuals with *B. malayi* microfilaraemias (pre-treatment levels of 108-6358 microfilariae/ml; median = 309/ml) consumed DEC-fortified salt (0.2%, w/w) with their food for 1 year,

initially in hospital (for 1 week) and later at home. The mean daily intake of DEC was 21.4 mg (range = 9.0-39.4 mg). Even on the first day of consuming the salt, there was a decrease in the microfilarial levels of 14 patients and a sharp increase in six patients. Microfilarial levels tended to fluctuate thereafter but there was a progressive, general decline. At the end of the study year, eight patients were amicrofilaraemic and microfilarial clearance was >95% in 58% of the patients. Eight patients did not develop any adverse reactions. Lymph-node tenderness and enlargement were seen in eight patients (40%), and dilated, inflamed lymphatic channels standing out as cords ('string sign') were seen in another five patients. These reactions were transient and did not require any specific treatment. The DEC-fortified salt was well accepted by the study population. The DEC content of fortified salt and the duration of its use for the control of brugian filariasis need to be re-examined. Health education should include messages that mild, self-limiting, adverse reactions are likely to occur even with the use of such salt.

49. Gopinath R, Hanna LE, **Kumaraswami V**, Pillai SV, Kavitha V, Vijayasekaran V, Rajasekharan A, Nutman TB. Long-term persistence of cellular hypo responsiveness to filarial antigens after clearance of microfilaremia. *Am J Trop Med Hyg* 1999;60:848-853.

Abstract: The persistence of parasite-specific cellular hypo-responsiveness after clearance of blood microfilariae (mf) was studied in 18 individuals who had been treated with a single dose of ivermectin, diethylcarbamazine,

or a combination 2-3 years previously and who had initially cleared their parasitemia. At recruitment into the present study, 50% were again mf+ and 50% remained mf-. There were no significant differences between the mf+ and mf- groups in the amount of interferon-gamma (IFN-gamma) produced by peripheral blood mononuclear cells in response to adult or microfilarial antigens, although IFN-gamma production in response to purified protein derivative was greater in the mf+ group (geometric mean [gm] = 3,791 pg/ml; P = 0.02) than in the mf- group (gm = 600 pg/ml). These data suggest that although microfilaremic individuals may temporarily regain the ability to produce IFN-gamma to parasite antigens post-treatment, they subsequently revert to a state of hyporesponsiveness to mf-containing antigens that appears to be independent of the recurrence of microfilaremia and the response to nonparasite antigens.

50. Gurumurthy P, Ramachandran G, Vijayalakshmi S, Kumar AK, Venkatesan P, Chandrasekaran V, Vijasekaran V, **Kumaraswami V**, Prabhakar R. Bioavailability of rifampicin, isoniazid and pyrazinamide in a triple drug formulation: comparison of plasma and urine kinetics. *Int J Tuberc Lung Dis* 1999;3:119-125.

Setting: The present study assesses bioavailability indices for rifampicin, isoniazid and pyrazinamide when administered to healthy volunteers separately or in a fixed triple-drug formulation, Rifater 125 SCT.

Objective: To compare the pharmacokinetics of rifampicin, isoniazid and pyrazinamide based on their

blood concentrations up to 12 hours with the proportions of the doses of the drugs and their metabolites excreted in urine up to 12 hours, and to assess the bioavailability indices for the free and fixed triple drug formulations.

Design: An open cross-over study was conducted in 18 healthy volunteers with normal hepatic and renal functions to whom the drug combinations were administered in free and fixed dose formulations a week apart, to the same subjects.

Results: Concentrations of the three drugs/metabolites were assessed in blood and urine. The results indicated the absence of negative pharmacokinetic interactions between the drugs when administered in both the free and the new fixed triple drug formulation.

Conclusion: Human bioavailability studies provide direct straightforward information, particularly when studying compounds such as rifampicin and other major anti-tuberculosis drugs. The results of the present study indicate that the pharmacokinetic properties of rifampicin, isoniazid and pyrazinamide as assessed after individual and combined administration do not change when combined in a single pharmaceutical preparation. The bioavailability indices calculated based on plasma concentrations and urinary levels for all three drugs compared well.

Keywords: anti-tuberculosis drugs; bioavailability; urine; plasma

51. Olszewski WL, Jamal S, Manokaran G, Pani S, **Kumaraswami V**, Kubicka U, Lukomska B, Tripathi FM, Swoboda E, Meisel-Mikolajczyk F, Stelmach E, Zaleska M. Bacteriological studies of blood, tissue fluid, lymph and lymph nodes in patients with acute

dermatolymphangiadenitis (DLA) in course of 'filarial' lymphedema. *Acta Tropica* 1999;73:217-224.

Abstract: Filarial lymphedema is complicated by frequent episodes of dermatolymphangiadenitis (DLA). Severe systemic symptoms during attacks of DLA resemble those of septicemia. The question we asked was whether bacterial isolates can be found in the peripheral blood of patients during the episodes of DLA. Out of 100 patients referred to us with 'filarial' lymphedema 14 displayed acute and five subacute symptoms of DLA. All were on admission blood microfilariae negative but had a positive test in the past. Blood bacterial isolates were found in nine cases, four acute (21%) and five subacute (26%). In 10 acute cases blood cultures were found negative. Six blood isolates belonged to Bacilli, four to Cocci and one was Sarcina. To identify the sites of origin of bacterial dissemination, swabs taken from the calf skin biopsy wounds and tissue fluid, lymph and lymph node specimens were cultured. Swabs from the calf skin biopsy wound contained isolates in nine (47%) cases. They were Bacilli in nine, Cocci in three, Acinetobacter and Erwinia in two cases. Tissue fluid was collected from 10 patients and contained Bacilli in four (40%) and Staphylococci in three (30%). Lymph was drained in four patients and contained isolates in all samples (100%). They were Staphylococcus epidermis, xylosus and aureus, Acinetobacter, Bacillus subtilis and Sarcina. Three lymph nodes were biopsied and contained Staphylococcus chromogenes, xylosus, Enterococcus and Bacillus cereus. In six cases the same phenotypically defined species of bacteria were found in blood and limb tissues or fluids. In the 'control' group

of patients with lymphedema without acute or subacute changes all blood cultures were negative. Interestingly, swabs from biopsy wound of these patients contained isolates in 80%, tissue fluid in 68%, lymph in 70% and lymph nodes in 58% of cases. In healthy controls, tissue fluid did not contain bacteria, and lymph isolates were found only in 12% of cases. This study demonstrates that patients with acute episodes of DLA reveal bacteremia in a high percentage of cases. Diversity of blood and tissue bacterial isolates in these patients points to a breakdown of the skin immune barrier in lymphedema and subsequently indiscriminate bacterial colonization of deep tissues and spread to an blood circulation.

52. Shenoy RK, **Kumaraswami V**, Suma TK, Raj an K, Radhakuttyamma G. A double-blind, placebo-controlled study of the efficacy of oral pencillin, diethylcarbazine or local treatment of the affected limb in preventing acute adenolymphangitis in lymphoedema caused by brugian filariasis. *Ann Trop Med Parasitol* 1999;93(4):367-377.

Abstract: Acute attacks of adenolymphangitis (ADL) contribute significantly to the morbidity seen in cases of filarial lymphoedema. Such cases are now being treated with multiple courses of the antifilarial drug diethylcarbazine (DEC), either alone or in combination with antibiotics or anti-inflammatory drugs, based on anecdotal experience. In this, the first double-blind, placebo-controlled study, 150 patients with lymphoedema caused by brugian filariasis, each

of whom recalled two or more ADL attacks in the previous year, were enrolled on a comprehensive foot-care programme. Each was also randomly allocated to one of the following five daily regimens (30 patients/regimen) for 1 year: 800 mg oral penicillin; 1 mg DEC/kg; 800 mg oral penicillin plus 1 mg DEC/kg; local antibiotics; or placebo. Each patient was followed up for another year. For each regimen group (including the placebo group), the number of ADL attacks in the treatment year was significantly less than that in the year prior to treatment ($P < 0.001$). Although, in all but the placebo group, there was a slight increase in the number of episodes in the follow-up year compared with the treatment year, the increase was only significant in the two groups given penicillin. Of all the treatments tested therefore, foot care seems to play the most important role in the prevention of ADL attacks. Additional benefit may accrue from local or systemic antibiotic use in those with high grades of oedema, but antiliberals have no place in the prevention of ADL attacks in an individual patient. These observations should help in the rational management and prevention of ADL attacks in filarial lymphoedema, so that the progression of the disease may be halted and morbidity reduced.

53. Shenoy RK, Dalia S, John A, Suma TK, **Kumaraswami V**. Treatment of the microfilaraemia of asymptomatic brugian filariasis with single doses of ivermectin, diethylcarbamazine or albendazole, in various combinations. *Ann Trop Med Parasitol* 1999;93:643-651.

Abstract: Several new chemotherapeutic tools are now available for the control of lymphatic filariasis. Combinations of single doses of antifilarial drugs are generally superior to single drugs. The efficacy and safety of albendazole in combination with diethylcarbamazine (DEC) or ivermectin, for the treatment of *Brugia malayi* infection, were investigated, for the first time, in an open, hospital-based study. Fifty-one asymptomatic microfilaraemics (with 108-4034 microfilariae/ml; median = 531) of both sexes and aged 14-70 years were randomly allocated to receive single-dose treatments of ivermectin (200 micrograms/kg) with diethylcarbamazine (DEC; 6 mg/kg), ivermectin (200 micrograms/kg) with albendazole (400 mg), DEC (6 mg/kg) with albendazole (400 mg), or albendazole (400 mg) alone. Albendazole alone had no effect on the microfilarial levels at the 1-year follow-up but both groups given DEC had significantly lower microfilaraemias ($P < 0.015$ and $P < 0.02$) than that given ivermectin with albendazole. Overall, 47%-64% of those given DEC but only 14% of those given ivermectin with albendazole appeared to be amicrofilaraemic 1 year post-treatment. The adverse reactions seen in the study were mild, transient and qualitatively similar to those seen earlier with ivermectin and DEC. The combination of DEC and albendazole, both well tested drugs, offers a new option for countries such as India where there is no onchocerciasis or loiasis and where ivermectin may not be immediately available. The direct and indirect effects of albendazole on intestinal helminths would be additional benefits.

54. Gopinath R, Hanna LE, **Kumaraswami V**, Perumal V, Kavitha V, Vijayasekaran V, Nutman TB. Perturbations in Eosinophil Homeostasis following Treatment of Lymphatic Filariasis. *Infect Immun* 2000;68:93-99.
- Abstract:** Treatment of patients with patent *Wuchereria bancrofti* infection results in an acute clinical reaction and peripheral eosinophilia. To investigate the dynamics of the eosinophil response, changes in eosinophil activation and degranulation and plasma levels of eosinophil-active chemokines and cytokines were studied in 15 microfilaremic individuals in south India by sequential blood sampling before and after administration of 300 mg of diethylcarbamazine (DEC). Clinical symptoms occurred within 24 h. Plasma interleukin-5 (IL-5) and RANTES levels peaked 1 to 2 days posttreatment, preceding a peak peripheral eosinophil count at day 4. Major basic protein secretion from eosinophils paralleled IL-5 secretion, while levels of eosinophil-derived neurotoxin peaked at day 13 after treatment. Expression of the activation markers HLA-DR and CD25 on eosinophils rose markedly immediately after treatment, while expression of VLA-4 and alpha4beta7 showed an early peak within 24 h and a second peak at day 13. Thus, the posttreatment reactions seen in filarial infections can be divided into an early phase with killing of microfilariae, clinical symptomatology, increases in plasma IL-5 and RANTES levels, and eosinophil activation and degranulation and a later phase with expression of surface integrins on eosinophils, recruitment of eosinophils from the bone marrow to tissues, and clearance of parasite antigen.
55. Narayanan S, Parandaman V, Rehman F, Srinivasan C, Gomathy D, **Kumaraswami V**, Paramasivan CN, Ramanathan VD, Narayanan PR. Comparative evaluation of PCR using IS6110 and a new target in the detection of tuberculous lymphadenitis. *Curr Sci* 2000;78:1367-1370.
- Abstract:** We evaluated TRC4 primers using polymerase chain (PCR) which amplify a new target sequence from *Mycobacterium tuberculosis* genome to diagnose tuberculous lymphadenitis and compared the results with PCR using the widely used IS6110 primers. The PCR results were also compared with conventional methods like smear, culture and histopathology. The sensitivity of PCR using both probes is higher than the conventional methods. Out of 101 samples analysed (49 fresh and 52 fixed specimens), PCR using IS6110 and TRC4 primers was positive in 64 and 70 samples, respectively, whereas results with culture and histopathology methods were positive only in 49 and 58 samples, respectively. The problem of false negativity of IS6110 due to the absence of IS6110 copy in 4 *M. tuberculosis* isolates was overcome by using TRC4 primers. The results indicate that with improvement in PCR techniques, PCR using both probes, IS6110 and TRC4 can be a rapid and sensitive adjunct to conventional techniques in the diagnosis of tuberculous lymphadenitis.
56. Shenoy RK, John A, Babu BS, Suma TK, **Kumaraswami V**. Two-year follow-up of the microfilaraemia of asymptomatic brugian filariasis, after treatment with two, annual, single doses of ivermectin, diethylcarbamazine and albendazole, in various combinations. *Ann Trop Med Parasitol* 2000;94:607-614.

Abstract: Repeated, single, oral doses of combinations of ivermectin, diethylcarbamazine (DEC) or albendazole are recognized as important tools for parasite control in lymphatic filariasis. In order to assess the effects of re-treatment using these combinations in *Brugia malayi* infections, 40 asymptomatic microfilaraemics were re-treated at the end of the first year, with an additional, single, dose of the combination they had previously received.

They were then followed-up for another year. The subjects, of both sexes and aged 14-70 years, each received a two-drug combination: ivermectin (200 micrograms/kg) with DEC (6 mg/kg); ivermectin (200 micrograms/kg) with albendazole (400 mg); or DEC (6 mg/kg) with albendazole (400 mg). The kinetics of microfilarial clearance were similar to that seen during the first treatment, the members of the two groups given DEC having less intense microfilaraemias, 1 year after the re-treatment, than those given ivermectin with albendazole ($P < 0.001$ for each comparison). At this time, the two DEC groups also had a higher proportion of amicrofilaraemic individuals (22 of 26) than the ivermectin + albendazole group (three of nine). There were fewer adverse reactions in all the groups after re-treatment than seen after the first treatment. In countries such as India, where there is no co-endemicity of onchocerciasis or loiasis, the options for control programmes in areas where brugian filariasis is endemic are DEC alone or DEC in combination with ivermectin or albendazole. Where there is no access to ivermectin, transmission control must be based on DEC alone or in combination with albendazole.

57. Shenoy RK, John A, Hameed S, Suma TK, Kumaraswami V. Apparent failure of ultrasonography to detect adult worms of *Brugia malayi*. *Ann Trop Med Parasitol*.2000;94(1):77-82.

Abstract: Adult worms of *Wuchereria bancrofti*, or rather their characteristic movements (the 'filarial dance'), can now be detected in the scrotal lymphatics of microfilaraemic males, using ultrasonography. This ability has been used to delineate the lymphatic pathology of bancroftian filariasis, guide the surgical removal of the adult worms and, most importantly, assess the macrofilaricidal effects of antifilarial drugs. In the present study, the first report of the use of ultrasonography in brugian filariasis, 22 men (aged 18-62 years) with 60-2972 (median = 370) *Brugia malayi* microfilariae/ml blood were subjected to ultrasonography using a linear, 7.5-MHz probe. In addition, four other men (aged 19-35 years), with *W. bancrofti* microfilaraemia [28-524 (median = 234) microfilariae/ml], were similarly examined. Adult worms were not detectable in any of the patients with *B. malayi* parasitaemia but were detected in the scrotal lymphatics of two of the four individuals with *W. bancrofti* infection. The reasons for the failure to detect adult *B. malayi* and the limitations of ultrasound as a screening tool are examined. The results highlight the differences between the two species that cause most lymphatic filariasis and the need for rapid development of tools that can be used for the control of brugian lymphatic filariasis.

58. Choi EH, Zimmerman PA, Foster CB, Zhu S, Kumaraswami V, Nutman TB, Chanock SJ. Genetic polymorphisms in molecules of innate immunity and susceptibility to infection with *Wuchereria bancrofti* in south India. *Genes Immun* 2001;2:248-253.

Abstract: A pilot study was conducted to determine if host genetic factors influence susceptibility and outcomes in human filariasis. Using the candidate gene approach, a well-characterized population in South India was studied using common polymorphisms in six genes (CHIT1, MPO, NRAMP, CYBA, NCF2, and MBL2). A total of 216 individuals from South India were genotyped; 67 normal (N), 63 asymptomatic microfilaria positive (MF+), 50 with chronic lymphatic dysfunction/elephantiasis (CP), and 36 tropical pulmonary eosinophilia (TPE). An association was observed between the HH variant CHIT1 genotype, which correlates with decreased activity and levels of chitotriosidase and susceptibility to filarial infection (MF+ and CP; $P = 0.013$). The heterozygosity of CHIT1 gene was over-represented in the normal individuals ($P = 0.034$). The XX genotype of the promoter region in MBL2 was associated with susceptibility to filariasis ($P = 0.0093$). Since analysis for MBL-sufficient vs insufficient haplotypes was not informative, it is possible the MBL2 promoter association results from linkage disequilibrium with neighboring loci. We have identified two polymorphisms, CHIT1 and MBL2 that are associated with susceptibility to human filarial infection, findings that merit further follow-up in a larger study.

Keywords: filariasis; polymorphism; chitotriosidase; mannose-binding lectin; innate immunity

59. Nutman TB, Kumaraswami V. Regulation of the immune response in lymphatic filariasis: perspectives on acute and chronic infection with *Wuchereria bancrofti* in south India. *Parasite Immunol* 2001;23:389-399.

Abstract: Delineating the immune responses in lymphatic filariasis has been complicated not only by the rapidly expanding knowledge of new immunological mediators and effectors, but also by new methodologies (in particular, circulating filarial antigen detection) for defining and categorizing filarial-infected individuals. By using assays for circulating antigen in the sera collected as part of the many immunological studies performed on individuals in a *Wuchereria bancrofti* -endemic region of South India, we have attempted to explore the influence of patency on the antigen-driven proliferative and cytokine responses seen in peripheral blood mononuclear cells of individuals with varying clinical manifestations of lymphatic filarial infection. Moreover, we have provided perspectives on the differences between acute and chronic infection with *W. bancrofti* and suggested mechanisms that may underly the modulation of the immune response as patency occurs.

Keywords: lymphatic filariasis, *Wuchereria bancrofti*, tolerance, circulating filarial antigen, cytokine, tropical pulmonary eosinophilia

60. Rahmah N, Lim BH, Anuar AK, Shenoy RK, Kumaraswami V, Hakim SL, Chotechuang P, Kanjanopas K, Ramachandran CP. A recombinant antigen-based IgG4 ELISA for the specific and sensitive detection of *Brugia malayi* infection. *Trans R Soc Trop Med Hyg* 2001;95:280-284.

Abstract: An IgG4 ELISA based on a novel recombinant antigen was evaluated for detection of *Brugia malayi* infection, using 2487 sera from various institutions: 2031 samples from Universiti Sains Malaysia, 276 blinded sera from 2 other institutions in Malaysia, 140 blinded sera from India and 40 blinded sera from Thailand. These sera were from various groups of individuals, i.e. microfilaraemics, chronic patients, endemic normals, non-endemic normals and individuals with other parasitic and bacterial infections. Based on a cut-off optical density reading of 0.300, the IgG4 ELISA demonstrated specificity rates of 95.6-100%, sensitivity rates of 96-100%, positive predictive values of 75-100% and negative predictive values of 98.9-100%. These evaluation studies demonstrated the high specificity and sensitivity of this test for the detection of active *B. malayi* infection. Thus, the IgG4 ELISA would be very useful as a tool in diagnosis and in elimination programmes for brugian filariasis.

Keywords: filariasis, *Brugia malayi*, diagnosis, IgG4, recombinant antigen, ELISA, evaluation, Malaysia, India, Thailand

61. Rahmah N, Taniawati S, Shenoy RK, Lim BH, **Kumaraswami V**, Anuar AK, Hakim SL, Hayati MIN, Chan BT, Suharni M, Ramachandran CP. Specificity and sensitivity of a rapid dipstick test (*Brugia Rapid*) in the detection of *Brugia malayi* infection. *Trans R Soc Trop Med Hyg* 2001;95:601-604.

Abstract: A total of 753 serum samples from 6 institutions in 3 countries (Malaysia, Indonesia and India) were

used to evaluate an immunochromatographic rapid dipstick test, *Brugia Rapid*, for diagnosis of *Brugia malayi* infection. The samples comprised sera from 207 microfilaria-positive individuals and 546 individuals from filarial non-endemic areas. The latter consisted of 70 individuals with soil-transmitted helminth infections, 68 with other helminth infections, 238 with protozoan infections, 12 with bacterial and viral infections and 158 healthy individuals. The dipstick is prepared with a goat anti-mouse antibody control line and a *B. malayi* recombinant-antigen test line. First, the dipstick is dipped into a well containing diluted patient serum, thus allowing specific anti-filarial antibody in the serum to react with the recombinant antigen. Then the dipstick is placed into an adjacent well containing reconstituted anti-human IgG4-gold. After 10 min, development of 2 red-purple lines denotes a positive result and one line indicates a negative reaction. The overall results of the evaluation showed 97% sensitivity, 99% specificity, 97% positive predictive value and 99% negative predictive value. *Brugia Rapid* is thus a promising diagnostic tool for detection of *B. malayi* infection, and would be especially useful for the brugian filariasis elimination programme.

Keywords : filariasis, *Brugia malayi*, diagnosis, dipstick, rapid test, recombinant antigen, IgG4, evaluation, Malaysia, Indonesia, India

62. Remme JH, Bias E, Chitsulo L, Desjeux PM, Engers HD, Kanyok TP, Kengeya Kayondo JF, Kioy DW, **Kumaraswami V**, Lazdins JK, Nunn PP, Oduola A, Ridley RG, Toure YT, Zicker F, Morel CM. Strategic emphases for tropical

diseases research: a TDR perspective. Trends Parasitol 2002;18:421-426.

Abstract: Setting priorities for health research is a difficult task, especially for the neglected diseases of the poor. A new approach to priority setting for tropical diseases research has been adopted by the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (known as the TDR). Priorities are defined on the basis of a comprehensive analysis of research needs and research opportunities for each of the ten major tropical diseases in the TDR portfolio. The resulting strategic emphases matrix reflects the priorities for tropical diseases research from the perspective of the TDR. Its purpose is not to impose global research priorities, but we believe the results could be useful to other organizations.

Keywords: WHO/TDR; priority setting; health research; neglected disease; burden of disease; research funding

63. Remme JH, Bias E, Chitsulo L, Desjeux PM, Engers HD, Kanyok TP, Kengya Kayondo JF, Kioy DW, **Kumaraswami V**, Lazdins JK, Nunn PP, Oduola A, Ridley RG, Toure YT, Zicker F, Morel CM. Strategic emphases for tropical diseases research: a TDR perspective. Trends Parasitol 2002;10:435-440.

Abstract: Setting priorities for health research is a difficult task, especially for the neglected diseases of the poor. A new approach to priority setting for tropical diseases research has been adopted by the UNDP/World Bank/WHO Special Programme for Research and

Training in Tropical Diseases (known as the TDR). Priorities are defined on the basis of a comprehensive analysis of research needs and research opportunities for each of the ten major tropical diseases in the TDR portfolio. The resulting strategic emphases matrix reflects the priorities for tropical diseases research from the perspective of the TDR. Its purpose is not to impose global research priorities, but we believe the results could be useful to other organizations.

64. Selvaraj R, Gopal G, Raja A, **Kumaraswami V**. Pattern recognition technique in immunological antigenic tests to identify *Mycobacterium tuberculosis* infection. Tuberculosis 2002;82:261-266.

Abstract: The importance of a diagnostic test that is simple and quick to identify *Mycobacterium tuberculosis* infection needs no emphasis. The tuberculin skin test (TST - 1 TU RT23) is the diagnostic tool for identifying *M. tuberculosis* infection at present. The test reaction on the skin is measured after 48-72 h. It is observed that often multi-modes are seen, when the reactions are drawn as a graph and the bimodality is seen very feebly. Because of the difficulties in the administration of TST, several serological tests were developed over three decades, but none of the studies showed the desired results. One study to evaluate purified protein derivative (PPD) antigen resulted in a claim of 80% sensitivity and 4% false-positivity rate (14), while other researchers were not able to obtain similar results. In addition, several problems were encountered due to the non-availability of antigens, and data analyses from an ELISA-based diagnostic test showed considerable

overlap of distributions of optical density (OD) values among patients and healthy individuals (10). Classical statistical techniques cannot explain the cause of these overlaps. Hence, an attempt is made in this article to resolve these difficulties by the pattern recognition technique (PRT). The technique lies in splitting the data into clusters using a supervised algorithm. The data set is normally split into a training set, a test set and a validation set. The PRT gets “trained” through the training data set until the infected and uninfected groups of individuals are correctly classified. The training occurs based on an algorithm on the training set. On successful completion of the training, this technique is further tested and validated in the respective data sets.

65. Shenoy RK, Suma TK, John A, Arun SR, **Kumaraswami V**, Fleckenstein LL, Na-Bangchang K. The pharmacokinetics, safety and tolerability of the co-administration of diethylcarbamazine and albendazole. *Ann Trop Med Parasitol* 2002;96:603-614.

Abstract: The pharmacokinetics, safety and tolerability of single, oral doses of diethylcarbamazine (DEC) and albendazole, given alone or in combination, were investigated in a double-blind, randomized and placebo-controlled trial involving 42 amicrofilaraemic subjects living in an area of India where lymphatic filariasis is endemic. The subjects (34 males and eight females, aged 18-52 years and weighing 46-66.5 kg) were randomly allocated to one of the three drug groups. Fourteen were given just DEC (6 mg/kg), another 14 were given just albendazole

(400 mg) and the remaining 14 were given both DEC (6 mg/kg) and albendazole (400 mg). Blood samples for pharmacokinetic study were collected at specified intervals before and after drug administration. Plasma concentrations of DEC and albendazole/ albendazole sulphoxide were estimated using gas chromatography and HPLC, respectively. The safety and tolerability of the treatments were evaluated through clinical and laboratory assessments.

Both the DEC and albendazole were well tolerated when given alone or in combination, no adverse events being observed. In all three treatment groups, the drugs were rapidly absorbed from the gastro-intestinal tract although there was marked inter-individual variation. The pharmacokinetics of DEC, albendazole and albendazole sulphoxide were similar, whether each drug was given alone or in combination. These results indicate that there is no adverse pharmacokinetic or pharmacodynamic reason why DEC and albendazole should not be co-administered to control lymphatic filariasis.

66. Suma TK, Shenoy RK, **Kumaraswami V**. Efficacy and sustainability of a footcare programme in preventing acute attacks of adenolymphangitis in Brugian filariasis. *Trop Med Int Health* 2002;7:763-766.

Abstract: Lymphatic filariasis is associated with considerable disability related to the intensity and frequency of acute adenolymphangitis (ADL) attacks. The global programme for elimination of lymphatic filariasis emphasizes the need to combine transmission control with alleviation of disability.

Footcare aimed at the prevention of secondary bacterial infections is the mainstay of disability alleviation programmes. We evaluated the efficacy and sustainability of an unsupervised, personal footcare programme by examining and interviewing 127 patients who had previously participated in a trial that assessed the efficacy of diethylcarbamazine, penicillin and footcare in the prevention of ADL. During the trial period these patients had been educated in footcare and were supervised. During the unsupervised period, which lasted 1 year or longer, 47 patients developed no ADL and ADL occurred less frequently in 72.5%. Most patients were practicing footcare as originally advised, unsupervised and without cost, which proves that such a programme is sustainable and effective.

Keywords: Brugian filariasis, acute adenolymphangitis, footcare programme, disability, socio-economic

67. O'Bryan L, Pinkston P, **Kumaraswami V**, Vijayan V, Yenokida G, Rosenberg HF, Crystal R, Ottesen EA, Nutman TB. Localized eosinophil degranulation mediates disease in tropical pulmonary eosinophilia. *Infect Immun* 2003;71:1337-1342.

Abstract: To explore the mechanism underlying the eosinophil-mediated inflammation of tropical pulmonary eosinophilia (TPE), bronchoalveolar lavage (BAL) fluid, serum and supernatants from pulmonary and blood leukocytes (WBC) from patients with acute TPE (n =6) were compared with those obtained from healthy uninfected individuals (n =4) and from patients

with asthma (n =4) or elephantiasis (n =5). Although there were no significant differences in the levels of interleukin-4 (IL-4), IL-5, IL-13, eotaxin, granulocyte-macrophage colony-stimulating factor, RANTES, or eosinophil cationic protein, there was a marked increase in eosinophil-derived neurotoxin (EDN) both systemically and in the lungs of individuals with TPE compared to each of the control group (P<0.02). Moreover, there was a compartmentalization of this response, with EDN levels being higher in the BAL fluid than in the serum (P<0.02). Supernatants from WBC from either whole blood or BAL cells were examined for chemokines, cytokines, eosinophil degranulation products, and arachidonic acid metabolites. Of the many mediators examined - particularly those associated with eosinophil trafficking - only EDN (in BAL fluid and WBC) and MIP-1 a (in WBC) levels were higher for TPE patients than for the non-TPE control groups (P<0.02). These data suggest it is the eosinophilic granular protein EDN, an RNase capable of damaging the lung epithelium, that plays the most important role in the pathogenesis of TPE.

68. Shenoy RK, Suma TK, **Kumaraswami V**. A qualitative study on the feasibility and benefits of foot hygiene measures practiced by patients with brugian filariasis. *J Commun Dis* 2003;35:9-16.

Abstract: Disability alleviation is an important component of 'Global Programme for Elimination of Lymphatic Filariasis'. In *Brugia malayi* infection the disability is largely due to acute attacks of

adenolymphangitis (ADL), which frequently prevent patients from attending their normal activities, causing much suffering and economic loss. The foot care programme has been shown to reduce the frequency and severity of these episodes. In the present study we used semi-structured interviews to evaluate the impact of the foot care in 127 patients with brugian filariasis. They were previously trained in this procedure and were advised to practice it regularly, unsupervised. All except one could recollect the various components of foot hygiene and were practicing it regularly. They were aware of the factors causing ADL attacks and were able to avoid them. Majority (95.2%) expressed their happiness with the relief provided by foot care, which prevented or reduced the ADL episodes. The motivation was such that they transmitted this knowledge to others suffering in the community and even physically helped them to carry out foot care. This study fully endorses the advocacy of foot care programme as an easy to carry out, effective, sustainable and economically feasible procedure to prevent acute ADL attacks.

Keywords: Brugian filariasis, Acute adenolymphangitis, Lymphoedema, Disability, Foot care

69. Suma TK, Shenoy RK, **Kumaraswami V.** A qualitative study of the perceptions, practices and socio-psychological suffering related to chronic brugian filariasis in Kerala, southern India. *Ann Trop Med Parasitol* 2003;97:839-845.

Abstract: Lymphatic filariasis is a major health problem in many parts of the tropical world. Although the disease itself is rarely fatal, the disability caused by the swollen extremities, the acute attacks of adenolymphangitis and the consequent sufferings of those affected are considerable. The economic burden imposed by lymphatic filariasis is not fully quantified and information on the social and psychological problems caused by the disease is scanty. Semi-structured interviews were therefore used, in southern India, to assess the perceptions, practices and socio-psychological problems of 127 patients with brugian filariasis. The patients were aware of the causative factors and the precautions to be taken to prevent progression of the disease. However, depression and loss of job opportunities were common in the study population. Patients also complained that the disease eroded their standing in the community and diminished their prospects of marriage. Awareness of these factors will be of help in planning suitable disability-management packages, including the rehabilitation of those who find it difficult to carry on with their existing jobs because of the severity of their disease.

70. Bradley MH, **Kumaraswami V.** Global Program to Eliminate Lymphatic filariasis. Essential tools -Drugs and Clinical drug trials. *Am J Trop Med Hyg* 2004;71:7-11.
71. **Kumaraswami V.** Lymphologists and the Global programme to eliminate lymphatic filariasis. *Indian J Lymphol* 2004;2:1.

72. Babu S, Blauvelt CP, **Kumaraswami V**, Nutman TB. Chemokine receptors of T cells and of B cells in lymphatic filarial infection: a role for CCR9 in pathogenesis. *J Infect Dis* 2005;191:1018-1026.

Abstract: We examined the expression of chemokine receptors on the surfaces of T cells and B cells from 27 individuals either with lymphatic filarial disease (lymphedema), with the asymptomatic or subclinical form of filarial infection, or without filarial infection. Individuals with lymphedema exhibited increased percentages of CCR9-expressing T cells and CCR9-expressing B cells and decreased percentages of both CXCR1-and-CXCR3-expressing T cells and CXCR1-and-CXCR3-expressing B cells, compared with asymptomatic or uninfected individuals. A significant correlation was found between the grade of lymphedema and the percentage of CCR9-expressing T cells and CCR9-expressing B cells. The percentages of CCR9-expressing T cells and CCR9-expressing B cells from patients with lymphedema was significantly up-regulated in response to live, infective-stage larvae of *Brugia malayi* but not to microfilariae of this parasite. Finally, individuals with lymphedema had significantly higher concentrations of interleukin-8, macrophage inflammatory protein (MIP)-I a , MIP-1 b , monocyte chemotactic protein 1, thymus-and-activation-regulated chemokine, and interferon-inducible protein 10 in their serum than did uninfected individuals. These results suggest that chemokine receptors (particularly CCR9) are involved in the pathogenesis of lymphatic filarial disease and that trafficking of particular cellular subsets may influence clinical outcome.

73. Babu S, Blauvelt CP, **Kumaraswami V**, Nutman TB. Diminished expression and function of TLR in lymphatic filariasis: a novel mechanism of immune dysregulation. *J Immunol* 2005;175:1170-1176.

Abstract: Lymphatic filariasis is a disease characterized by immune dysregulation involving APC and T cell populations. To assess the contribution of TLR in mediating this dysregulation, we examined the expression of TLR 1, TLR2, TLR4, and TLR9 on B cells and monocytes of filaria-infected and uninfected individuals. Baseline expression of TLR was significantly lower in B cells but not in monocytes of the filaria-infected group compared with the uninfected group. Upon stimulation with filarial Ag, a diminished up-regulation of TLR was observed in both B cells and monocytes of infected individuals. Finally, stimulation of B cells and monocytes with TLR ligands resulted in decreased B cell and monocyte activation/cytokine production, indicating a state of immune tolerance. This dysregulation is associated with diminished CD4 + T cell production of IFN- g and IL-5. The diminished expression and function of TLR is thus a likely consequence of chronic Ag stimulation and could serve as a novel mechanism underlying the dysfunctional immune response in filariasis.

74. Babu S, **Kumaraswami V**, Nutman TB. Transcriptional control of impaired Th1 responses in patent lymphatic filariasis by T-box expressed in T cells and suppressor of cytokine signaling genes. *Infect Immun* 2005;73:3394-3401.

Abstract: T-bet (T-box expressed in T cells) and GATA-3 are transcription factors that play a critical role in the development of Th1 and Th2 cells, as do genes of the SOCS (suppressor of cytokine signaling) family, albeit indirectly. Another transcription factor, Foxp3, is a master regulator of natural regulatory T cells (Tregs). To identify the role of these factors in impaired Th1 responses of patent filarial infection, analysis of cytokine, SOCS, and transcription factor mRNA expression was performed on purified T cells of filaria-infected individuals ($n = 6$) and uninfected controls ($n = 6$). As expected (and in contrast to cells of uninfected individuals), there was a significant depression of gamma interferon (IFN- γ) and a concomitant increase in interleukin-4 (IL-4), IL-5, and IL-10 mRNA expression following stimulation with parasite antigen (BmA) but not with a polyclonal T-cell (anti-CD3) stimulus. T-bet (but not GATA-3) was expressed at significantly lower levels in cells of filaria-infected individuals in response to BmA compared with those from the uninfected group, accounting, at least partially, for the diminished IFN- γ expression. Second, we found no significant differences in expression of Foxp3 between the two groups, although induction of Foxp3 expression correlated with induced expression levels of IL-10, implicating Tregs in the IL-10 expression seen. Finally, parasite-specific T-cell expression of SOCS-1, SOCS-5, and SOCS-7 was significantly diminished among infected patients; in contrast, expression of SOCS-3 increased. Our data therefore indicate that the impaired Th1 responses observed in patent lymphatic filariasis are associated with decreased expression of

T-bet, SOCS-1, SOCS-5, and SOCS-7 and increased expression of SOCS-3 in T cells.

75. Gyapong JO, Kumaraswami V, Biswas G, Ottesen EA. Treatment strategies underpinning the global programme to eliminate lymphatic filariasis. *Expert Op in Pharmacother* 2005;6:179-200.

Abstract: Lymphatic filariasis (LF) is a disease targeted for elimination. The global strategy is a once-yearly, single-dose, two-drug regimen utilized by communities at risk for LF, with the goal of reaching 80% population coverage yearly, for at least 5 years, in order to interrupt transmission of LF. Where onchocerciasis is co-endemic, the regimen is ivermectin 200 - 400 mg/kg plus albendazole 400 mg; elsewhere, the regimen should be diethylcarbamazine 6 mg/kg plus albendazole 400 mg. This paper reviews in detail the evidence for the efficacy and safety of these two-drug regimens underpinning the global strategy and makes recommendations for future developments in chemotherapy for LF, focusing on unresolved issues. These include optimal frequency, duration and end point of treatment, tools for monitoring successful therapy and means for detecting the potential development of resistance to any of the three antifilarial drugs on which the Global Programme to Eliminate LF depends.

Keywords: albendazole, combination treatment, diethylcarbamazine, ivermectin, lymphatic filariasis.

76. Kim YJ, Kumaraswami V, Choi E, Mu J, Follmann DA, Zimmerman P, Nutman TB. Genetic polymorphisms of

eosinophil-derived neurotoxin and eosinophil cationic protein in tropical pulmonary eosinophilia. *Am J Trop Med Hyg* 2005;73:125-130.

Abstract: Because eosinophil-derived neurotoxin (EDN) and eosinophil cationic protein (ECP) are critical in the pathogenesis of tropical pulmonary eosinophilia (TPE), we analyzed genetic polymorphisms of both in 181 individuals from southern India with varying clinical manifestations of *Wuchereria bancrofti* infection (including 26 with TPE). Using haplotype frequency analysis, we identified four known (of nine) and two novel haplotypes for EDN (1, 2, 7, 8, 10, and 11). For ECP, five (of seven known) haplotypes (1– 5) were identified. Although we found no significant association between frequencies of EDN and ECP polymorphisms and TPE development, we observed a unique pattern of EDN and ECP polymorphism distribution among this population. Genotype TT at locus 1088 of ECP in one TPE patient was not observed in any other clinical group. Although the EDN and ECP polymorphisms appear unlikely to be associated with the development of TPE, further analyses will be more definitive.

77. Pani SP, **Kumaraswami V**, Das LK. Epidemiology of lymphatic filariasis with special reference to urogenital-manifestations. *Indian J Urol* 2005:44-49.

Abstract: Lymphatic filariasis (LF) is currently endemic in as many as 80 countries round the globe, particularly in the tropics and sub-tropics. *Wuchereria bancrofti* as a causative organism accounts for over 90% of the global burden. India contributes about 40% of the total global burden and accounts

for about 50% of the people at the risk of infection. In India, states like Andhra Pradesh, Bihar, Gujarat, Kerala, Maharashtra, Orissa, Tamil Nadu, Uttar Pradesh and West Bengal contribute to about 95% of total burden. *W. bancrofti* is the predominant species accounting for about 98% of the national burden, widely distributed in 17 states and six union territories. Diethylcarbamazine (DEC) is an effective drug acting on the parasite (without report of resistance in past five decades) and mass annual single dose community drug administration with selective vector control could result in effective elimination of infection by interruption of transmission. The WHO has called for targeting filariasis elimination by 2020. India is the largest LF endemic country and has targeted the elimination of LF by 2015.

Keywords: Epidemiology; Lymphatic filariasis; Urogenital filariasis

78. Babu S, Blauvelt CP, **Kumaraswami V**, Nutman TB. Regulatory networks induced by live parasites impair both Th1 and Th2 pathways in patent lymphatic filariasis: implications for parasite persistence. *J Immunol* 2006;176:3248-3256.

Abstract: Patent lymphatic filariasis is characterized by a profound down-regulation of immune responses with both parasite Ag-specific tolerance and bystander suppression. Although this down-regulation is confined to the Th1 arm of the immune system in response to parasite Ag, we hypothesized a more generalized suppression in response to live parasites. Indeed,

when we examined the cytokine profile of a cohort of filaria-infected ($n = 10$) and uninfected ($n = 10$) individuals in response to live infective-stage larvae or microfilariae of *Brugia malayi*, we found significant impairment of both Th1 and Th2 cytokines characterized by diminished production of IFN- γ , TNF- α , IL-4, IL-5, and IL-10 in infected patients. The molecular basis of this impaired Th1/Th2 response was examined, and we identified three major networks of immunoregulation and tolerance. First, impaired induction of T-bet and *GATA5* mRNA underlies the Th1/Th2 deficiency in infected individuals. Second, regulatory networks, as evidenced by significantly increased expression of *Foxp3* (natural regulatory T cell marker) and regulatory effectors such as TGF- β , CTLA-4, PD-1, ICOS, and indoleamine 2,3-dioxygenase play an important role in immunosuppression. Third, the compromise of effector T cell function is mediated by the enhanced induction of anergy-inducing factors *cbl-b* , *c-cbl* (*cbl* is abbreviation for Casitas B lymphoma), *Itch* , and *Nedd4* . Indeed, blocking CTLA-4 or neutralizing TGF- β restored the ability to mount Th1/Th2 responses to live parasites and reversed the induction of anergy-inducing factors. Hence, we conclude that a profound impairment of live parasite-specific Th1 and Th2 immune responses occurs in lymphatic filariasis that is governed at the transcriptional level by a complex interplay of inhibitory mediators.

79. Babu S, Blauvelt CP, **Kumaraswami V**, Nutman TB. Cutting edge: Diminished T cell TLR expression and function modulates the immune response in human filarial infection. *J Immunol* 2006;176:3885-3889.

Abstract: Patent lymphatic filariasis is characterized by profound Ag-specific T cell hyporesponsiveness with impaired IFN- γ and IL-2 production. Because T cells have been shown to express a number of TLR and to respond to TLR ligands, we hypothesized that diminished T cell TLR function could partially account for the T cell hyporesponsiveness in filariasis. T cells expressed TLR1, TLR2, TLR4, and TLR9, and the baseline expression of TLR 1, TLR2, and TLR4, but not TLR9 was significantly lower in T cells of the filarial -infected individuals compared with the uninfected individuals (both endemic and nonendemic). TLR function was significantly diminished in the T cells of filarial-infected individuals based on decreased T cell activation/cytokine production in response to TLR ligands. Thus, diminished expression and function of T cell TLR is a novel mechanism underlying T cell immune tolerance in lymphatic filariasis.

80. Gopi PG, Subramani R, Santha T, Kumaran PP, **Kumaraswami V**, Narayanan PR. Relationship of ARTI to incidence and prevalence of tuberculosis in a district of south India. *Int J Tuberc Lung Dis* 2006;10:115-117.

Summary: Objective: To validate the currently used empirical relationship between annual risk of tuberculous infection (ARTI) and incidence and prevalence of smear-positive cases.

Setting: Two disease surveys to estimate the prevalence and incidence of tuberculosis (TB) among adults in Tiruvallur district, south India, and a tuberculin survey to estimate the ARTI among children.

Results: The incidence of TB was estimated to be 82 and prevalence 210 per 100 000 population and ARTI 1.6%. We estimated that 1% ARTI corresponded to 51 new and 131 prevalent cases.

Conclusion: The currently used empirical relationship between ARTI and incidence can be used by programme managers as an effective monitoring tool.

Keywords: survey; incidence; prevalence; ARTI

81. Hemanthkumar AK, Ramachandran G, Kumar P, **Kumaraswami V**, Swaminathan S. Can urine lamivudine be used to monitor antiretroviral treatment adherence? *eJIAS* 2006;8:53-62.

Abstract: Patient adherence to treatment is an important factor in the effectiveness of antiretroviral regimens. Adherence to treatment could be monitored by estimation of antiretroviral drugs in biological fluids. We aimed to obtain information on the quantity and duration of excretion of lamivudine in urine following oral administration of a single dose of 300 mg and to assess its suitability for adherence monitoring purposes. Spot urine samples were collected before dosing and at 4, 8, 12, 24, 28, 32, 48, 72, and 96 hours post dosing from 10 healthy subjects, and lamivudine was estimated by high-pressure liquid chromatography (HPLC). Lamivudine values were expressed as a ratio of urine creatinine. About 91% of the ingested drug was excreted by 24 hours, and the concentration thereafter in urine was very negligible. A lamivudine value of 0.035 mg/mg creatinine or less at 48 hours is suggestive of a missed dose in the last 24 hours. The study findings showed that estimation of urine lamivudine in spot specimens could be useful in monitoring patient adherence to

antiretroviral treatment. However, this needs to be confirmed on a larger sample size and among patients on once-daily and twice-daily treatment regimens.

82. Lipner EM, Gopi PG, Subramani R, Kolappan C, Sadacharam K, Kumaran P, Prevots DR, Narayanan PR, Nutman TB, **Kumaraswami V**. Coincident filarial, intestinal helminth, and mycobacterial infection: helminths fail to influence tuberculin reactivity, but BCG influences hookworm prevalence. *Am J Trop Med Hyg* 2006;74:841-847.

Abstract: The prevalence of helminth and tuberculosis infections is high in South India, whereas Bacille-Calmette-Guerin (BCG) vaccine efficacy is low. Our aim was to determine whether concurrent helminth infection alters the ability to mount a delayed-type hypersensitivity response to tuberculin. In a cross-sectional study in southern India, individuals 6-65 years of age were screened for intestinal helminths, circulating filarial antigenemia, tuberculin reactivity, active tuberculosis, and history of BCG vaccination; 54% were purified protein derivative (PPD) positive, 32% had intestinal helminth infection, 9% were circulating filarial antigen positive, and 0.5% had culture-confirmed active tuberculosis. Only age and BCG vaccination were significantly associated with PPD reactivity; however, BCG vaccination was associated with a lower prevalence of hookworm infection relative to those without prior BCG vaccination. Neither intestinal helminth infection nor filarial infection was associated with diminished frequencies of PPD positivity. Our findings suggest that preceding helminth infection does not

influence significantly the delayed-type hypersensitivity response to tuberculin.

83. Ramachandran G, Hemanthkumar AK, Rajasekaran S, Padmapriyadarsini C, Narendran G, Sukumar B, Sathishnarayan S, Raja K, **Kumaraswami V**, Swaminathan S. Increasing nevirapine dose can overcome reduced bioavailability due to rifampicin coadministration. *J Acquir Immune Defic Syndr* 2006;42:36-41.

Summary: We studied the effect of rifampicin on steady-state pharmacokinetics of nevirapine and the impact of increasing the dose of nevirapine on its peak (C max) and trough (C min) levels in 13 HIV-infected patients on regular antiretroviral treatment with nevirapine-containing regimens (200 mg twice daily). A baseline pharmacokinetic study was conducted and repeated after 1 week of daily rifampicin (450/600 mg). The study was repeated in 7 of 8 patients who had subtherapeutic C min nevirapine levels after increasing nevirapine dose to 300 mg twice daily. Liver function was monitored. Rifampicin caused significant reductions in C max (42%), C min (53%), and exposure (46%) of nevirapine ($P < .01$). The C min of nevirapine fell below the therapeutic range of 3 mg/mL in 8 of 13 patients. An increase of nevirapine to 300 mg twice daily raised C min to therapeutic range in all 7 patients without exceeding the toxic level of 12 mg/mL. There were no clinical or laboratory adverse events. Our findings suggest that decreased bioavailability of nevirapine because of rifampicin coadministration could be overcome by increasing the dose of nevirapine from 200 to 300 mg twice daily without short-term adverse events. Further studies to evaluate the long-term safety of higher dose of nevirapine are required.

Keywords: HIV-TB, pharmacokinetic drug interactions, nevirapine, rifampicin

84. Ramachandran G, Kumar AK, **Kumaraswami V**, Swaminathan S. A simple and rapid liquid chromatography method for simultaneous determination of zidovudine and nevirapine in plasma. *J Chromatogr B Analyt Technol Biomed Life Sci* 2006;843:339-344.

Abstract: We describe a simple, fast, isocratic, reversed-phase high performance liquid chromatographic method for simultaneous determination of plasma zidovudine and nevirapine with UV detection at 260 nm. The method involves liquid-liquid extraction with ethyl acetate and using 3-isobutyl 1-methyl xanthine as internal standard. The system requires a C 18 column (150mm x 4.6mm I.D.) and a mobile phase composed of potassium dihydrogen phosphate (15 mM; pH 7.5) and acetonitrile in the ratio of 80:20 (v/v). The assay was linear from 0.025 to 10.0 mg/ml for zidovudine and 0.05 to 10.0 mg/ml for nevirapine. The intra- and inter-day variations were less than 10% for both the drugs. The method was specific and sensitive enough to allow quantification of zidovudine and nevirapine in concentrations observed clinically. The average recoveries of zidovudine and nevirapine from plasma were 95 and 94%, respectively. The method was applied to a pharmacokinetic study in HIV-infected patients who were receiving antiretroviral treatment with zidovudine and nevirapine containing regimens. The method spans the blood concentration range of clinical interest. Due to its simplicity, the assay can be used for pharmacokinetic

studies and therapeutic drug monitoring in patients taking a combination treatment of zidovudine and nevirapine.

Keywords: Zidovudine; Nevirapine; Plasma; HPLC

85. Ramachandran G, Kumar AK, Swaminathan S, Venkatesan P, **Kumaraswami V**, Greenblatt DJ. Simple and rapid liquid chromatography method for determination of efavirenz in plasma. *J Chromatogr B Analyt Technol Biomed Life Sci* 2006;835:131-135.

Abstract: A simple and rapid high performance liquid chromatographic method for determination of efavirenz in human plasma was developed. The method involved extraction of sample with ethyl acetate and analysis using a reversed-phase C 18 column (150mm) with UV detection. The assay was linear from 0.0625 to 10.0 µg/ml. The method was specific for efavirenz estimation and the drug was stable in plasma up to one month at -20 °C. The average recovery of efavirenz from plasma was 101%. Due to its simplicity, the assay can be used for pharmacokinetic studies and therapeutic drug monitoring of efavirenz.

Keywords: Efavirenz; Plasma; HPLC

86. Shenoy RK, Suma TK, **Kumaraswami V**, Padma S, Rahman N, Abhilash G, Ramesh C. Doppler ultrasonography reveals adult-worm nests in the lymph vessels of children with brugian filariasis. *Ann Trop Med Parasitol*.2007; 101:173-180.

Abstract: Although ultrasonography has allowed 'nests' of live adult worms and dilated lymphatics to be detected in the early stages of infection with *Wuchereria bancrofti*, previous attempts to locate such adult-worm nests in brugian filariasis have been unsuccessful. In this study, the successful location of live adult *Brugia malayi* parasites, in the lymphatics of the axilla, thigh, epitrochlear region and/or popliteal fossa of children aged 3-15 years, is described for the first time. The 'filarial dance sign' (FDS), which indicates the presence of live adult worms, was observed in six children with microfilaraemia and in eight children who, though amicrofilaraemic, either had experienced an episode of lymphoedema (one) or were only positive for antifilarial IgG 4 antibodies (seven). In bancroftian infection, the adult-worm nests have mostly been seen in asymptomatic but microfilaraemic subjects.

The suspected worm nests, 18 in the 14 children, were all confirmed using colour-power and pulse-wave Doppler examinations. The worm nests were distinctly smaller and the wriggling movements were less rapid and less conspicuous than those seen in bancroftian filariasis. The importance of these findings in the management and control of lymphatic filariasis is discussed.

87. Shenoy RK, Suma TK, **Kumaraswami V**, Rahman N, Dhananjayan G, Padma S, Abhilash G, Ramesh C. Preliminary findings from a cross-sectional study on lymphatic filariasis in children, in an area of India endemic for *Brugia malayi* infection. *Ann Trop Med Parasitol*.2007;101:205-213.

Abstract: As the more obvious clinical manifestations of the disease are very uncommon in children, lymphatic filariasis has been considered to be primarily a disease of adults. In many recent reports, however, there is evidence indicating not only that filarial infection is commonly acquired in childhood but also that many infected children already have irreversible damage to their lymphatics. The preliminary results of a cross-sectional study on the patterns of *Brugia*-attributable pathology in 7934 children (aged 3-15 years) who live in an area of India with endemic *B. malayi* infection confirm these trends. The children were screened for microfilaraemia, evidence of filarial disease, and the presence of antifilarial IgG^A antibodies. One hundred children who were microfilaraemic but asymptomatic (32), with filarial disease or an history of such disease or microfilaraemia (29) or amicrofilaraemic and asymptomatic but seropositive for antifilarial IgG^A (39) were investigated further. They were given detailed clinical examinations, their levels of microfilaraemia were evaluated (by counting microfilariae filtered out of blood samples), their lymphatics were explored by Doppler sonography, and their limbs were checked by lymphoscintigraphy. The 'filarial dance sign', which indicates the presence of live adult worms, was detected by sonography in 14 children (apparently the first time this sign has been observed in brugian filariasis). Lymphoscintigraphy revealed dilated lymphatic channels in the limbs of 80 of the children. At the end of the study, each of the 100 hospitalized children was treated with a single combined dose of diethylcarbamazine and albendazole; the aim is to

follow-up the treated children every 6 months for 3 years. Even these preliminary results have important implications for filariasis-control programmes and emphasise the need for disability-alleviation efforts among children as well as adults.

88. Ramachandran G, Hemanth Kumar AK, Sarala K, Padmapriyadarsini C, Anitha S, Tharani CB, **Kumaraswami V**, Swaminathan S. Urine levels of rifampicin & isoniazid in asymptomatic HIV-positive individuals. *Indian J Med Res.*2007; 125:763-766.

Background & Objectives: AIDS and its associated gastrointestinal complications may impair the absorption of anti-tuberculosis (TB) drugs. Impaired absorption of anti-TB drugs could lead to low drug exposure, which might contribute to acquired drug resistance and reduced effectiveness of anti-TB treatment. The aim of this study was to obtain information on the status of absorption of rifampicin (RMP) and isoniazid (INH) in asymptomatic HIV-positive individuals, who are less immunocompromised. The D-xylose absorption test was also carried out to assess the absorptive capacity of intestine.

Methods : The absorption of RMP, INH and D-xylose was studied in 15 asymptomatic HIV- positive individuals with CD4 cell counts > 350 cells/mm³ and 16 healthy volunteers, after oral administration of single doses of RMP (450 mg), INH (300 mg) and D-xylose (5 g). Urine was collected up to 8 h after drug administration. Percentage dose of the drugs and their metabolites and D-xylose excreted in urine were calculated.

Results: A significant reduction in the urinary excretion of INH and D-xylose in HIV-positive persons compared to healthy volunteers was observed. The per cent dose of RMP and its

metabolite, desacetyl RMP was also lower in HIV-positive persons compared to healthy volunteers, but this difference was not statistically significant.

Interpretation & conclusion: Decreased urinary excretion of D-xylose and INH are suggestive of intestinal malabsorption in HIV-positive individuals. HIV infection could cause malabsorption of anti-TB drugs even at an early stage of the disease. The clinical implications of these findings need to be confirmed in larger studies.

Keywords: Asymptomatic HIV infection - isoniazid - malabsorption - rifampicin

89. Ramachandran G, Hemanthkumar AK, Rajasekaran S, Padmapriyadarsini C, Narendran G, Anitha S, Subramanyam S, **Kumaraswami V**, Swaminathan S. Steady-state pharmacokinetics of Nevirapine in HIV-1 infected adults in India. *J Int Assoc Physicians AIDS Care.*2007;6:251-254.

Background and Objectives: A variety of demographic factors, sex, and degree of immunosuppression can influence antiretroviral drug concentrations. The authors studied the influence of immune status, sex, and body mass index (BMI) on the steady-state pharmacokinetics of nevirapine delivered as a fixed-dose combination in HIV-1-infected patients in India.

Methods: Twenty-six HIV-1-infected adult patients undergoing treatment with nevirapine-based highly active antiretroviral therapy regimens participated in the study. Pharmacokinetic variables were compared between patients divided based on CD4 cell counts, sex, and BMI.

Results: Patients with higher BMI had lower peak and trough concentration and exposure of nevirapine than those with lower BMI; none of the differences in the pharmacokinetic variables of nevirapine between the various patient groups was statistically significant.

Conclusions: Patients' immune status, sex, or BMI had no impact on the pharmacokinetics of nevirapine. Plasma nevirapine concentrations were maintained within the therapeutic range of the drug in the majority of the patients.

Keywords : pharmacokinetics; nevirapine; India: immune status sex; BMI

90. Ramachandran G, Hemanth Kumar AK, Sukumar B, **Kumaraswami V**, Swaminathan S. Single dose pharmacokinetics of Efavirenz in healthy Indian subjects. *S A ARC J Tuberc LungDis. HIV/AIDS.*2007;4:38-43.

Background & Objective: Access to antiretroviral therapy in India is improving. Efavirenz (EFV) is a commonly used non-nucleoside reverse transcriptase inhibitor used to treat HIV infection. No information is available on the pharmacokinetics of EFV in Indian subjects. The aim of this study was to obtain information on single dose pharmacokinetics of efavirenz (EFV) in healthy Indian subjects.

Methods: Sixteen adult healthy volunteers (8 males and 8 females) were administered a single oral tablet of 600 mg EFV after an overnight fast. Blood samples were collected at 1, 2, 3, 4, 5, 6, 10, 24 and 48 hours post dosing. Plasma EFV concentrations were estimated by HPLC, and certain pharmacokinetic variables were calculated.

Results: Plasma EFV concentrations were higher in females than males at all the time points, the differences being significant at 1 ($p < 0.001$) and 2 ($p = 0.05$) hours. Females had significantly higher peak concentration (C max) of EFV than males ($p = 0.05$) (3.11 & 1.90 $\mu\text{g/ml}$). The inter-individual variability in C max and AUC 0-48 were 42 and 45% respectively.

Conclusions: This study provides basic information on the pharmacokinetics of EFV in Indian subjects. Females had higher peak levels of EFV than males. Inter-subject variability was high. Further studies are necessary to describe the pharmacokinetic profile of EFV under steady state conditions in Indian patients on antiretroviral treatment.

Keywords: Efavirenz, HIV infection, pharmacokinetics, Indian subjects

91. Kolappan C, Subramani R, **Kumaraswami V**, Santha T, Narayanan PR. Excess mortality and risk factors for mortality among a cohort of TB patients from rural south India. *Int J Tuberc Lung Dis.*2008;12:81-86.

Objectives: To estimate the excess general mortality among tuberculosis (TB) patients in a rural area (Tiruvallur) and identify risk factors for TB-related mortality.

Setting: The study population consisted of all TB patients aged > 15 years who were registered under the Revised National Tuberculosis Control Programme (RNTCP) during the years 2000 to 2003 at Velliyur TB unit (TU) in south India.

Design: This is a retrospective cohort study of 3405 patients treated under the DOTS strategy, followed up from the date of start of treatment till the date of

interview (for the survivors) or the date of death (for those who died).

Results: There were 2710 (79.6%) survivors and 695 (20.4%) deaths. The excess general mortalities for the cohort, expressed as standardised mortality ratio (SMR), was 4.2 (95% CI 3.9—4.5). High SMR values were obtained for patients belonging to the 15-44 years age group (12.1), patients on Category II regimen (9.3), treatment failures (9.1) and defaulters (7.8). The adjusted hazards ratios (aHR) were high for patients aged 45-59 years (1.9), > 60 years (3.1) and with incomplete treatment due to default or failure (6.4).

Conclusion: TB is one of the main causes of mortality in the younger age group. Among TB patients, the major risk factors for mortality are old age (> 45 years) and incomplete treatment.

Keywords: tuberculosis; mortality; standardised mortality ratio; DOTS; risk factors

92. Shenoy RK, Suma TK, **Kumaraswami V**, Dhananjayan G, Rahmah N, Abhilash G, Ramesh C. Lymphoscintigraphic evidence of lymph vessel dilation in the limbs of children with *Brugia malayi* infection. *J Commun Dis.*2008;40:91-100.

Abstract: Lymphatic filariasis (LF) is targeted for global elimination by the year 2020. It was earlier believed that LF is mostly a disease of adults. Recent studies indicate that in endemic countries filarial infection starts mostly in childhood even though the disease manifestations occur much later in life. The initial damage to the lymph vessels where the adult worms are lodged is dilation,

thought to be irreversible even with treatment. Most of these studies relate to bancroftian filariasis. Studies that address this early pathology in brugian filariasis in humans are scarce. We report here for the first time, the lymphatic abnormalities seen on lymphoscintigraphy (LSG) in children with *Brugia malayi* filariasis. LSG was performed in 100 children aged between 3-15 years, who were enrolled in the study either because they were microfilaremic; had present or past filarial disease or were positive for antifilarial IgG4 antibodies. Inguinal and axillary lymph nodes were imaged in most children. Dilated lymph vessels were visualized in 80 children and this pathology was evenly distributed in all the three study groups. Lymph vessel dilation was seen even in three year old children. The implications of these findings for management of LF and control programmes are discussed.

Keywords: Lymphatic filariasis in children, *Brugia malayi* infection, Lympho-scintigraphy, Lymph vessel dilation

93. Ramachandran G, Hemanth Kumar AK, Venkatesan V, Anitha S, Tharani CB, **Kumaraswami V**, Swaminathan S. Single dose pharmacokinetics of lamivudine in healthy volunteers: comparison of blood and urine kinetics. SAARC J Tuber Lung Dis HIV/AIDS.2008;V:6-9.

Aims: To study single dose pharmacokinetics of lamivudine (3TC) in healthy subjects.

Methods: Twelve healthy subjects were administered 3TC (150 mg) followed by timed blood and urine collections up to 24 hours. Pharmacokinetic variables and percent dose of 3TC in urine were calculated.

Results: Plasma exposure and percent dose of 3TC in urine were highly correlated ($p < 0.001$; $r = 0.96$). 3TC concentration at 24 hours was undetectable in all study subjects.

Conclusions: Timed urine measurements could be used to study bioavailability of 3TC. Plasma 3TC measurements could be used to monitor adherence among HIV-infected patients on antiretroviral treatment.

Keywords: Lamivudine; plasma; urine; compliance to treatment

94. Shenoy RK, Suma TK, **Kumaraswami V**, Rahmah N, Dhananjayan G, Padma S. Antifilarial drugs, in the doses employed in mass drug administrations by the Global programme to eliminate lymphatic filariasis, reverse lymphatic pathology in children with *Brugia malayi* infection. Ann Trop Med Parasitol. 2009;103:235-247.

Abstract: Lymphatic filariasis is increasingly viewed as the result of an infection that is often acquired in childhood. The lymphatic pathology that occurs in the disease is generally believed to be irreversible. In a recent study in India, Doppler ultrasonography and lymphoscintigraphy were used to explore subclinical pathology in 100 children from an area endemic for *Brugia malayi* infection. All the children investigated showed some evidence of current or previous filarial infection. Some were microfilaraemic but asymptomatic, some were amicrofilaraemic but had filarial disease or a past history of microfilaraemia and/or filarial disease, and the rest, though amicrofilaraemic, asymptomatic and without any history

of microfilaraemia or filarial disease, were seropositive for antifilarial IgG 4 antibodies. All the children were treated every 6 months, with a single combined dose of diethylcarbamazine (6 mg/kg) and albendazole (400 mg), and followed up for 24 months. By the end of this period all but one of the children were amicrofilaraemic and the 'filarial dance sign' could not be detected in any of the 14 children who had initially been found positive for this sign. Although lymphoscintigraphy revealed lymph-node and lymph-vessel damage in 82% of the children at enrolment, in about 67% of the children this pathology was markedly reduced by the 24-month follow-up. These results indicate that the drug regimens used in the mass drug administrations run by the Global Programme to Eliminate Lymphatic Filariasis are capable of reversing subclinical lymphatic damage and can provide benefits other than interruption of transmission in endemic areas. The implications of these findings are presented and discussed.

95. Babu S, Bhat SQ, Pavan Kumar N, Lipira AB, Kumar S, Karthik C, **Kumaraswami V**, Nutman TB. Filarial lymphedema is characterized by antigen-specific Th1 and Th17 proinflammatory responses and a lack of regulatory T cells. *PLoS Negl Trop Dis.*2009;3: e420.

Background: Lymphatic filariasis can be associated with development of serious pathology in the form of lymphedema, hydrocele, and elephantiasis in a subset of infected patients.

Methods and Findings: To elucidate the role of CD4 + T cell subsets in the development of lymphatic pathology, we examined specific sets of cytokines in individuals

with filarial lymphedema in response to parasite antigen (BmA) and compared them with responses from asymptomatic infected individuals. We also examined expression patterns of Toll-like receptors (TLR1–10) and Nod-like receptors (Nodi, Nod2, and NALP3) in response to BmA. BmA induced significantly higher production of Th1-type cytokines—IFN- γ and TNF- α —in patients with lymphedema compared with asymptomatic individuals. Notably, expression of the Th17 family of cytokines—IL-17A, IL-17F, IL-21, and IL-23—was also significantly upregulated by BmA stimulation in lymphedema patients. In contrast, expression of Foxp3, GITR, TGF β , and CTLA-4, known to be expressed by regulatory T cells, was significantly impaired in patients with lymphedema. BmA also induced significantly higher expression of TLR2, 4, 7, and 9 as well Nodi and 2 mRNA in patients with lymphedema compared with asymptomatic controls.

Conclusion: Our findings implicate increased Th1/Th17 responses and decreased regulatory T cells as well as regulation of Toll- and Nod-like receptors in pathogenesis of filarial lymphedema.

96. Babu S, **Kumaraswami V**, Nutman TB. Alternatively activated and immunoregulatory monocytes in human filarial infections. *J Infect Dis.*2009; 199: 1827-1837.

Background: Monocytes/macrophages from filaria-infected animals exhibit an alternatively activated phenotype; however, very little is known about the alternative activation phenotype of monocytes in human filarial infection.

Methods: To elucidate the activation and cytokine profile of monocytes in human filarial infection, we examined

the expression patterns of genes encoding arginase, nitric oxide synthase 2, alternative activation markers, and cytokines in monocytes from individuals with asymptomatic filarial infection and individuals without filarial infection, ex vivo and in response to filarial antigen (*Brugia malayi* antigen [BmA]).

Results: Monocytes from patients with asymptomatic filarial infection exhibited significantly diminished expression of *NOS2* and significantly enhanced expression of *ARG1*. These changes were associated with significantly increased expression of the genes encoding resistin, mannose receptor C type 1 (MRC1), macrophage galactose type C lectin (MGL), and chemokine ligand 18 (CCL18). In response to BmA, purified monocytes from infected individuals also expressed significantly lower levels of interleukin (IL)-12 and IL-18 but, in contrast, expressed significantly higher levels of transforming growth factor β , IL-10, and suppressor of cytokine signaling 1 mRNA. Inhibition of arginase-1 resulted in significantly diminished expression of the genes encoding resistin, MRC1, MGL, and CCL18, as well as significantly enhanced expression of *NOS2* and the genes encoding IL-12 and IL-18.

Conclusion: Patent human filarial infection is associated with the presence of monocytes characterized by an alternatively activated immunoregulatory phenotype.

97. Shenoy RK, Rahmah N, Suma TK, **Kumaraswami V**, Thaslim AK, Gopu R. Relevance of anti BmRI IgG4 antibodies in children from an area endemic for *Brugia malayi* infection in Kerala, India. J Commun Dis.2009;41:63-70.

Abstract: Brugian filariasis prevalent mostly in South-East Asian countries including India contributes to a small but significant proportion of the socioeconomic burden due to lymphatic filariasis. Along with bancroftian filariasis, brugian filariasis has been targeted for elimination globally. The lack of a reliable daytime diagnostic test has been seen as an important barrier to the successful implementation and monitoring of elimination programmes in brugia endemic areas. We evaluated an anti- *BmRI-IgG4* antibody test namely, '*Brugia Rapid*' in a large study meant to understand the clinical and pathological manifestations of brugian filariasis in children. We found the test superior to traditional night blood screening for microfilaraemia. Although an antibody detection test, we found it to be a reliable indicator of brugian infection. Among the 100 children studied extensively, 94% of the microfilaraemics, 86% of those showing filarial dance sign indicating presence of, live adult worms and 78% having abnormal lymphatics on lymphoscinti-graphy were IgG4 positive. Coupled with its advantages like ease of use any time of the day, high sensitivity and specificity, this test may be the ideal tool to assist programme managers in their efforts to eliminate lymphatic filariasis where brugian infections are found.

keywords: Lymphatic filariasis in children, *Brugia malayi* infection, Anti- *BmRI* -IgG4 antibody, '*Brugia Rapid*' test

98. Babu S, Bhat SQ, Kumar NP, Jayantasri S, Rukmani S, Kumaran P, Gopi PG, Kolappan C, **Kumaraswami V**, Nutman T. Human type 1 and 17 responses in latent

tuberculosis are modulated by coincident filarial infection through cytotoxic T-lymphocyte antigen-4 and programmed death-1. *J Infect Dis.*2009; 200:288-298.

Abstract: *Mycobacterium tuberculosis* and filarial coinfection is highly prevalent, and the presence of a tissue-invasive helminth may modulate the predominant type 1 T helper (Th1; interferon [IFN]- γ -mediated) response needed to control *M. tuberculosis* infection. By analyzing the cellular responses to mycobacterial antigens in patients who had latent tuberculosis with or without filarial infection, we were able to demonstrate that filarial infection coincident with *M. tuberculosis* infection significantly diminishes *M. tuberculosis*-specific Th1 (interleukin [IL]-12 and IFN- γ) and type 17 T helper (Th17; IL-23 and IL-17) responses related to increased expression of cytotoxic T lymphocyte antigen (CTLA)-4 and programmed death (PD)-1. Blockade of CTLA-4 restored production of both IFN- γ and IL-17, whereas PD-1 blockade restored IFN- γ production only. Thus, coincident filarial infection exerted a profound inhibitory effect on protective mycobacteria-specific Th1 and Th17 responses in latent tuberculosis, suggesting a mechanism by which concomitant filarial (and other systemic helminth) infections predispose to the development of active tuberculosis in humans.

99. Babu S, Bhat SQ, Kumar NP, Anuradha R, Kumaran P, Gopi PG, Kolappan C, **Kumaraswami V**, Nutman TB. Attenuation of toll-like receptor expression and function in latent tuberculosis by coexistent filarial infection with restoration following antifilarial chemotherapy. *PLoS Negl Trop Dis.*2009;3:e489.

Abstract: *Mycobacterium tuberculosis* (Mtb) and filarial coinfection is highly prevalent, and the presence of filarial infections may regulate the Toll-like receptor (TLR)-dependent immune response needed to control Mtb infection. By analyzing the baseline and mycobacterial antigen-stimulated expression of TLR1, 2, 4, and 9 (in individuals with latent tuberculosis [TB] with or without filarial infection), we were able to demonstrate that filarial infection, coincident with Mtb, significantly diminishes both baseline and Mtb antigen-specific TLR2 and TLR9 expression. In addition, pro-inflammatory cytokine responses to TLR2 and 9 ligands are significantly diminished in filaria/TB-coinfected individuals. Definitive treatment of lymphatic filariasis significantly restores the pro-inflammatory cytokine responses in individuals with latent TB. Coincident filarial infection exerted a profound inhibitory effect on protective mycobacteria-specific TLR-mediated immune responses in latent tuberculosis and suggests a novel mechanism by which concomitant filarial infections predispose to the development of active tuberculosis in humans.

100. Hemanth Kumar AK, Ramachandran G, Rajasekaran S, Padmapriyadarsini C, Narendran G, Anitha S, Sudha S, **Kumaraswami V**, Swaminathan S. Pharmacokinetics of lamivudine and stavudine in generic fixed-dose combinations in HIV-1 infected adults in India. *Indian J Med Res.*2009; 130:451-457.

Background & objectives: Antiretroviral drug concentrations are important determinants of clinical response to a drug accounting for both toxicity and efficacy. Several factors such as age, ethnicity, body weight and patients' immune status may influence antiretroviral drug concentrations. The aim of

the study was to determine the influence of immunological status, sex and body mass index on the steady state pharmacokinetics of lamivudine (3TC) and stavudine (d4T) in HIV-infected adults, who were undergoing treatment with generic fixed dose combinations (FDC) of these drugs in India.

Methods: Twenty seven HIV-1 infected patients receiving antiretroviral treatment (ART) for at least two weeks at the Government ART clinic at Tambaram, Chennai, took part in the study. Serial blood samples were collected predosing and at different time points after drug administration. Plasma 3TC and d4T levels were estimated by HPLC.

Results: The patients' immune status, sex or body mass index had no impact on the pharmacokinetics of 3TC. In the case of d4T, peak concentration was significantly lower in patients with CD4 cell counts < 200 cells/ul than those with = 200 cells/ ul ($P < 0.05$), but were within the therapeutic range. The mean CD4 cell counts increased from 101 cells/ul at initiation of ART to 366 cells/ul at 12 months of treatment.

Interpretation & conclusions: Blood levels of 3TC and d4T drugs that are part of generic FDCs commonly used by HIV-infected individuals in India were within the therapeutic range and not influenced by nutritional or immune status. There was a significant improvement in CD4 cell counts over 12 months of treatment. Indian generic FDCs manufactured and used widely in the developing world provide effective concentrations of antiretro viral drugs.

Keywords: Generic FDCs - India - lamivudine - pharmacokinetics - stavudine

101. Nalini K, Ananthakrishnan R, Augustine S, Vijayalakshmi NK, Gopi PG, **Kumaraswami V**, Narayanan PR. Impact of advocacy on the tuberculosis management practices of private practitioners in Chennai City, India. *Int J Tuberc Lun Dis.*2009;13(I):112-118.

Background : Innovative schemes to ensure the participation of private practitioners (PPs) in the Revised National Tuberculosis Control Programme (RNTCP) are necessary to identify and treat all patients with tuberculosis (TB). We developed a novel public-private mix (PPM) model to encourage PPs to practise DOTS and participate in the RNTCP while retaining their patients.

Methods: The Resource Group for Education and Advocacy for Community Health (REACH) developed and implemented the programme in partnership with the Chennai local health authority and the Tuberculosis Research Centre, Chennai , India . PPs were sensitised to the RNTCP and DOTS through a one-to-one approach or group meetings, and were assisted in referring patients. Surveys were carried out at baseline and at the completion of the study to assess changes in attitudes and practices.

Results: Six hundred PPs underwent sensitisation about the RNTCP, after which the proportion of PPs adopting DOTS increased significantly ($P < 0.001$), and the majority (72.8%) used sputum testing for diagnosing TB. The proportion of PPs who used X-ray alone for diagnosis declined to 16.0% from a baseline of 45.4%.

Conclusions: This PPM model, which emphasizes sustained advocacy for DOTS and allows PPs to retain private patients, looks promising and needs to be tested at other sites.

Keywords: tuberculosis; public-private mix; nongovernmental organisations; DOTS; advocacy; RNTCP; India

102. Babu S, Bhat SQ, Kumar NP, **Kumaraswami V**, Nutman TB. Regulatory T cells modulate Th17 responses in patients with positive tuberculin skin test results. *J Infect Dis.*2010;201:20-31.

Background: The factors governing latency in tuberculosis are not well understood but appear to involve both the pathogen and the host. We have used tuberculin skin test (TST) positivity as a tool to study cytokine responses in latent tuberculosis.

Methods: To identify the host factors that are important in the maintenance of TST positivity, we examined mycobacteria-specific immune responses of TST-positive (latent tuberculosis) or TST-negative individuals in South India, where TST positivity can define tuberculosis latency.

Results: Although purified protein derivative-specific and *Mycobacterium tuberculosis* culture filtrate antigen-specific Th1 and Th2 cytokines were not statistically significantly different between the 2 groups, the Th17 cytokines (interleukin 17 and interleukin 23) were statistically significantly decreased in TST-positive individuals, compared with those in TST-negative individuals. This Th17 cytokine modulation was associated with statistically significantly increased expression of cytotoxic T lymphocyte antigen 4 (CTLA-4) and Foxp3. Although CTLA-4 blockade failed to restore full production of interleukin 17 and interleukin 23 in TST-positive individuals, depletion of regulatory T cells significantly increased production of these cytokines.

Conclusion: TST positivity is characterized by increased activity of regulatory T cells and a coincident downregulation of the Th17 response.

103. Aravindhavan V, Mohan V, Surendar J, Rao MM, Pavankumar N, Deepa M, Rajagopalan R, **Kumaraswami V**, Nutman TB, Babu S. Decreased prevalence of lymphatic filariasis among diabetic subjects associated with a diminished pro-inflammatory cytokine response (CURES 83). *PLoS Negl Trop Dis.*2010;4:e707.

Abstract: Epidemiological studies have shown an inverse correlation between the incidence of lymphatic filariasis (LF) and the incidence of allergies and autoimmunity. However, the interrelationship between LF and type-2 diabetes is not known and hence, a cross sectional study to assess the baseline prevalence and the correlates of sero-positivity of LF among diabetic subjects was carried out (n = 1416) as part of the CURES study. There was a significant decrease in the prevalence of LF among diabetic subjects (both newly diagnosed [5.7%] and those under treatment [4.3%]) compared to pre-diabetic subjects [9.1%] (p = 0.0095) and non-diabetic subjects [10.4%] (p = 0.0463). A significant decrease in filarial antigen load (p = 0.04) was also seen among diabetic subjects. Serum cytokine levels of the pro-inflammatory cytokines—IL-6 and GM-CSF— were significantly lower in diabetic subjects who were LF positive, compared to those who were LF negative. There were, however, no significant differences in the levels of anti-inflammatory cytokines—IL-10, IL-13 and TGF- β — between the two groups. Although a direct causal link has yet to be shown, there appears to be a striking inverse relationship between the prevalence of LF and diabetes, which is reflected by a diminished pro-inflammatory cytokine response in Asian Indians with diabetes and concomitant LF.

104. Aravindhan V, Mohan V, Surendar J, Rao MM, Ranjani H, **Kumaraswami V**, Nutman TB, Babu S. Decreased prevalence of lymphatic filariasis among subjects with type-1 diabetes. *Am J Trop Med Hyg.*2010;83:1336-1339.

Abstract: Several animal studies have shown a protective effect of helminth infections against type-1 diabetes mellitus (T1DM). However, epidemiologic studies demonstrating this protective relationship with T1DM are largely lacking, although an inverse correlation between the prevalence of lymphatic filariasis (LF) and prevalence of allergies and autoimmunity has been shown. A cross-sectional study was undertaken in southern India to assess the baseline prevalence of seropositivity of LF among persons with T1DM (n = 200) and normal glucose tolerant (NGT) persons (n = 562). The prevalence of LF was 0% among persons with T1DM and 2.6% among NGT persons ($P = 0.026$). The percentage of persons who were positive for filarial antigen-specific IgG4 (but not antigen-specific IgG) was also significantly lower in persons with T1DM (2%) compared with NGT persons (28%) ($P < 0.001$). Thus, there appears to be a striking inverse relationship between the prevalence of LF and T1DM in southern India.

105. Bennuru S, Maldarelli S, **Kumaraswami V**, Klion AD, Nutman TB. Elevated levels of plasma angiogenic factors are associated with human lymphatic filarial infections. *Am J Trop Med Hyg.*2010;83(4): 884-890.

Abstract: Lymphatic dilatation, dysfunction, and lymphangiogenesis are hallmarks of patent lymphatic filariasis, observed even in those with subclinical microfilaremia, through processes associated, in part, by vascular

endothelial growth factors (VEGFs). A panel of pro-angiogenic factors was measured in the plasma of subjects from filaria-endemic regions using multiplexed immunological assays. Compared with endemic normal control subjects, those with both subclinical microfilaremia, and those with longstanding lymphedema had significantly elevated levels of VEGF-A, VEGF-C, VEGF-D, and angiopoietins (Ang-I/Ang-2), with only levels of basic fibroblast growth factor (bFGF) and placental growth factor (P1GF) being elevated only if lymphedema was evident. Furthermore, levels of these factors 1-year posttreatment with doxycycline were similar to pretreatment levels suggesting a minimal role, if any, for *Wolbachia*. Our data support the concept that filarial infection *per se* is associated with elevated levels of most of the known pro-angiogenic factors, with only a few being associated with the serious pathologic consequences associated with *Wuchereria bancrofti* infection.

106. Shriram AN, Krishnamoorthy K, Saha BP, Roy A, **Kumaraswami V**, Shah WA, Jambulingam P, Vijayachari P. Diurnally subperiodic filariasis in India-prospects of elimination: precept to action? *Parasitol Res.*2011; 109:1-8.

Abstract: The elimination of lymphatic filariasis in the Andaman and Nicobar Islands provides unique opportunities and challenges at the same time. Since these islands are remote, are sparsely populated, and have poor transport networks, mass drug administration programs are likely to be difficult to implement. Diurnally subperiodic *Wuchereria*

bancrofti vectored by *Downsiomyia nivea* was considered for the scope of vector control options. Considering the bioecology of this mosquito, vector control including personal protection measures may not be feasible. However, since these islands are covered by separate administrative machinery which also plays an important role in regulating the food supply, the use of diethylcarbamazine (DEC)-fortified salt as a tool for the interruption of transmission is appealing. DEC-fortified salt has been successfully pilot tested in India and elsewhere, operationally used by China for eliminating lymphatic filariasis. Administration of DEC-fortified salt though simple, rapid, safe, and cost-effective, challenges are to be tackled for translating this precept into action by evolving operationally feasible strategy. Although the use of DEC-fortified salt is conceptually simple, it requires commitment of all sections of the society, an elaborate distribution mechanism that ensures the use of DEC-fortified salt only in the endemic communities, and a vigorous monitoring mechanism. Here, we examine the inbuilt administrative mechanisms to serve the tribal people, health infrastructure, and public distribution system and discuss the prospects of putting in place an operationally feasible strategy for its elimination.

107. Ray D, Harikrishna S, Immanuel C, Victor L, Sudha S, **Kumaraswami V**. Acquired alpha 1-antitrypsin deficiency in tropical pulmonary eosinophilia. Indian J Med Res.2011;134:79-82.

Background & objectives : Observation of an increased frequency of an intermediate deficiency of serum alpha 1-antitrypsin (al-AT) in patients with Tropical Pulmonary Eosinophilia (TPE) was earlier reported. Though the

possibility of existence of an acquired deficiency was suggested, without phenotyping a hereditary al-AT deficiency in TPE could not totally be ruled out. In this study, we have done Pi (Protease inhibitor) phenotyping to investigate the possibility of association of any heterozygous (or homozygous) al-AT deficiency in patients with TPE.

Methods : Serum al antitrypsin (al-AT) was measured in 103 patients (Group A) with TPE, 99 patients with pulmonary eosinophilia who had associated intestinal worm infestation (Group B) and 43 healthy volunteers who served as controls. In 19 al-AT deficient patients (9 of Group A and 10 of Group B), al-AT level was measured before and after treatment. In 58 patients with TPE and in 5 controls, phenotyping was done.

Results : Fifteen patients of Group A and 16 from Group B showed intermediate al-AT deficiency (150 mg % or less. None of the control subjects had al-AT deficiency (<200 mg%). After treatment with DEC and/or deworming, in 19 patients there was a significant ($P < 0.001$) rise in al-AT levels. Results of phenotyping showed that all had M1 or M2 allele and none had S or Z variant (either homozygous or heterozygous) thus ruling out any underlying genetic cause for the observed al-AT deficiency.

Interpretation & conclusions : The observed al-AT deficiency may be due to the chronic inflammation in TPE and associated oxidative stress. However, in such al-AT deficient patients with TPE and those with worm infested pulmonary eosinophilia, faecal al-AT concentration and faecal al-AT clearance should be routinely estimated to rule out the possibility of any intestinal protein loss.

Keywords: al; antitrypsin; acquired deficiency; tropical pulmonary eosinophilia

108. Senbagavalli P, Anuradha R, Ramanathan VD, **Kumaraswami V**, Nutman TB, Babu S. Heightened Measures of Immune Complex and Complement Function and Immune Complex-Mediated Granulocyte Activation in Human Lymphatic Filariasis. *Am J Trop Med Hyg.* 2011;85:89-96.

Abstract: The presence of circulating immune complexes (CICs) is a characteristic feature of human lymphatic filariasis. However, the role of CICs in modulating granulocyte function and complement functional activity in filarial infection is unknown. The levels of CICs in association with complement activation in clinically asymptomatic, filarial-infected patients (INF); filarial-infected patients with overt lymphatic pathologic changes (CPDT); and uninfected controls (EN) were examined. Significantly increased levels of CICs and enhanced functional efficiency of the classical and mannose binding lectin pathways of the complement system was observed in INF compared with CPDT and EN. Polyethylene glycol-precipitated CICs from INF and CPDT induced significantly increased granulocyte activation compared with those from EN, determined by the increased production of neutrophil granular proteins and a variety of pro-inflammatory cytokines. Thus, CIC-mediated enhanced granulocyte activation and modulation of complement function are important features of filarial infection and disease.

109. Sundaramurthi JC, Ramanandan P, Brindha S, Subashree CR, Prasad A, **Kumaraswami V**, Hanna LE. DDTRP - Database of drug targets for resistant pathogens. *Bioinformatics.* 2011; 7:98-101.

Abstract: Emergence of drug resistance is a major threat to public health. Many pathogens have developed resistance to most of the existing antibiotics, and multidrug-resistant and extensively drug resistant strains are extremely difficult to treat. This has resulted in an urgent need for novel drugs. We describe a database called 'Database of Drug Targets for Resistant Pathogens' (DDTRP). The database contains information on drugs with reported resistance, their respective targets, metabolic pathways involving these targets, and a list of potential alternate targets for seven pathogens. The database can be accessed freely at <http://bmi.icmr.org.in/DDTRP>.

Keywords : DDTRP; drug targets; resistant pathogens; database; drug discovery

110. Babu S, Anuradha R, Pavan Kumar N, George PJ, **Kumaraswami V**, Nutman TB. Filarial lymphatic pathology reflects augmented toll-like receptor-mediated, mitogen-activated protein kinase-mediated proinflammatory cytokine production. *Infect Immun.* 2011;79:4600-4608.

Abstract: Lymphatic filariasis can be associated with the development of serious pathology in the form of lymphedema, hydrocele, and elephantiasis in a subset of infected patients. Toll-like receptors (TLRs) are thought to play a major role in the development of filarial pathology. To elucidate the role of TLRs in the development of lymphatic pathology, we examined cytokine responses to different Toll ligands in patients

with chronic lymphatic pathology (CP), infected patients with subclinical pathology (INF), and uninfected, endemic-normal (EN) individuals. TLR2, -7, and -9 ligands induced significantly elevated production of Th1 and other proinflammatory cytokines in CP patients in comparison to both INF and EN patients. TLR adaptor expression was not significantly different among the groups; however, both TLR2 and TLR9 ligands induced significantly higher levels of phosphorylation of extracellular signal-regulated kinase 1/2 (ERK1/2) and p38 mitogen-activated protein (MAP) kinases (MAPK) as well as increased activation of NF- κ B in CP individuals. Pharmacologic inhibition of both ERK1/2 and p38 MAP kinase pathways resulted in significantly diminished production of proinflammatory cytokines in CP individuals. Our data, therefore, strongly suggest an important role for TLR2- and TLR9- mediated proinflammatory cytokine induction and activation of both the MAPK and NF- κ B pathways in the development of pathology in human lymphatic filariasis .

111. Kumar NP, Anuradha R, Suresh R, Ganesh R, Shankar J, **Kumaraswami V**, Nutman TB, Babu S. Suppressed type 1, type 2 and type 17 cytokine responses in active tuberculosis in children. *Clin Vaccine Immunol*.2011; 18:1856-1864.

Abstract: Type 1 cytokine responses are known to play an important role in immunity to tuberculosis (TB) in children, although little is known about other factors that might be important. In addition, children are more prone to developing extrapulmonary manifestations of TB than adults. To identify the immune responses

important both in control of infection and in extrapulmonary dissemination, we examined mycobacterium-specific cytokine responses of children with pulmonary TB (PTB) and extrapulmonary TB (ETB) and compared them with those of healthy control children (HC). No significant differences were found in the cytokine responses either with no stimulation or following mycobacterial-antigen (Ag) stimulation between children with PTB and ETB. On the other hand, children with active TB compared with HC showed markedly diminished production of type 1 (gamma interferon [IFN- γ] and tumor necrosis factor alpha [TNF- α]), 2 (interleukin 4 [IL-4] and IL-13), and 17 (IL-17A, IL-21, and IL-23)-associated cytokines with no stimulation and in response to mycobacterial antigens. This was not associated with significantly altered production of IL-10 or transforming growth factor β (TGF- β). Among children with ETB, those with neurologic involvement exhibited more significantly diminished Ag-driven IFN- γ and IL-17 production. Pediatric TB is characterized by diminished type 1, 2, and 17 cytokine responses, with the most profound diminution favoring development of neurologic TB, suggesting a crucial role for these cytokines in protection against pediatric tuberculosis.

112. Hassan S, Logambiga P, Raman AM, Subazini TK, **Kumaraswami V**, Hanna LE. MtbSD-A comprehensive structural database for Mycobacterium tuberculosis. *Tuberculosis*.2011 ;91:556-562.

Summary: The *Mycobacterium tuberculosis* Structural Database (MtbSD) (<http://bmi.icmr.org.in/mtbsd/MtbSD.php>) is a relational database for the study of protein

structures of *M. tuberculosis*. It currently holds information on description, reaction catalyzed and domains involved, active sites, structural homologues and similarities between bound and cognate ligands, for all the 857 protein structures that are available for *M. tb* proteins. The database will be a valuable resource for TB researchers to select the appropriate protein-ligand complex of a given protein for molecular modelling, docking, virtual screening and structure-based drug designing.

Keywords: *Mycobacterium tuberculosis*; Proteins; Ligands; Domains; Database

113. Anuradha R, George JP, Pavankumar N, **Kumaraswami V**, Nutman TB, Babu S. Altered circulating levels of matrix metalloproteinases and inhibitors associated with elevated type 2 cytokines in lymphatic filarial disease. *PLoS Negl Trop Dis.*2012;6:e1681.

Background: Infection with *Wuchereria bancrofti* can cause severe disease characterized by subcutaneous fibrosis and extracellular matrix remodeling. Matrix metalloproteinases (MMPs) are a family of enzymes governing extracellular remodeling by regulating cellular homeostasis, inflammation, and tissue reorganization, while tissue-inhibitors of metalloproteinases (TIMPs) are endogenous regulators of MMPs. Homeostatic as well as inflammation-induced balance between MMPs and TIMPs is considered critical in mediating tissue pathology.

Methods: To elucidate the role of MMPs and TIMPs in filarial pathology, we compared the plasma levels of a panel of MMPs, TIMPs, other pro-fibrotic factors, and

cytokines in individuals with chronic filarial pathology with (CP Ag+) or without (CP Ag -) active infection to those with clinically asymptomatic infections (INF) and in those without infection (endemic normal [EN]). Markers of pathogenesis were delineated based on comparisons between the two actively infected groups (CP Ag+compared to INF) and those without active infection (CP Ag - compared to EN).

Results and Conclusion: Our data reveal that an increase in circulating levels of MMPs and TIMPs is characteristic of the filarial disease process per se and not of active infection; however, filarial disease with active infection is specifically associated with increased ratios of MMP1/TIMP4 and MMP8/TIMP4 as well as with pro-fibrotic cytokines (IL-5, IL-13 and TGF p). Our data therefore suggest that while filarial lymphatic disease is characterized by a non-specific increase in plasma MMPs and TIMPs, the balance between MMPs and TIMPs is an important factor in regulating tissue pathology during active infection.

114. Anuradha R, George PJ, Pavan Kumar N, Fay MP, **Kumaraswami V**, Nutman TB, Babu S. Circulating microbial products and acute phase proteins as markers of pathogenesis in lymphatic filarial disease. *PLoS Pathog.*2012;8:e 1002749.

Abstract: Lymphatic filariasis can be associated with development of serious pathology in the form of lymphedema, hydrocele, and elephantiasis in a subset of infected patients. Dysregulated host inflammatory responses leading to systemic immune activation are thought to play a central role in filarial disease pathogenesis. We measured

the plasma levels of microbial translocation markers, acute phase proteins, and inflammatory cytokines in individuals with chronic filarial pathology with (CP Ag+) or without (CP Ag -) active infection; with clinically asymptomatic infections (INF); and in those without infection (endemic normal [EN]). Comparisons between the two actively infected groups (CP Ag+ compared to INF) and those without active infection (CP Ag - compared to EN) were used preliminarily to identify markers of pathogenesis. Thereafter, we tested for group effects among all the four groups using linear models on the log transformed responses of the markers. Our data suggest that circulating levels of microbial translocation products (lipopolysaccharide and LPS-binding protein), acute phase proteins (haptoglobin and serum amyloid protein-A), and inflammatory cytokines (IL-1 p, IL-12, and TNF- a) are associated with pathogenesis of disease in lymphatic filarial infection and implicate an important role for circulating microbial products and acute phase proteins.

115. Babu S, Anuradha R, Pavan Kumar N, Jovvian George P, **Kumaraswami V**, Nutman TB. Toll-like receptor-and filarial antigen-mediated, mitogen-activated protein Kinase- and NF-kB-dependent regulation of angiogenic growth factors in filarial lymphatic pathology. *Infect Immun* 2012;80(7):2509-2518.

Abstract: Filarial lymphatic pathology is of multifactorial origin, with inflammation, lymphangiogenesis, and innate immune responses all playing important roles. The role of Toll-like receptors (TLRs) in the development

of filarial pathology is well characterized. Similarly, the association of pathology with elevated levels of plasma angiogenic factors has also been documented. To examine the association between TLR function and the development of lymphangiogenesis in filarial infections, we examined TLR- and filarial antigen-induced expression and production of various angiogenic growth factors. We demonstrate that TLR ligands (specifically TLR2, -3, and -5 ligands) induce significantly increased expression/production of vascular endothelial growth factor A (VEGF-A) and angiopoietin-1 (Ang-1) in the peripheral blood mononuclear cells of individuals with lymphatic pathology (CP individuals) compared to that in cells of asymptomatic infected (**INF**) individuals. Similarly, filarial antigens induce significantly enhanced production of VEGF-C in CP compared with **INF** individuals. TLR2-mediated enhancement of angiogenic growth factor production in CP individuals was shown to be dependent on mitogen-activated protein kinase (MAPK) and **NF-kB** signaling, as pharmacologic inhibition of either extracellular signal-regulated kinase 1/2 (ERK1/2), p38 MAPK, or **NF-kB** signaling resulted in significantly diminished production of VEGF-A and Ang-1. Our data therefore strongly suggest an important association between TLR signaling and lymphangiogenesis in the development of pathology in human lymphatic filariasis.

116. Mehendale S, Thakar M, Sahay S, Kumar M, Shete A, Sathyamurthi P, Verma A, Kurle S, Shrotri A, Gilmour J, Goyal R, Dally L, Sayeed E, Zachariah D, Ackland J, Kochhar S, Cox JH, Excler JL, Kumaraswami V, Paranjape R, Ramanathan VD. Safety and immunogenicity of DNA and MVA HIV-1 subtype C vaccine prime-boost regimens:

A phase I randomised trial in HIV-uninfected Indian volunteers. *PLoS One*.2013; 8(2):e55831.

Study Design: A randomized, double-blind, placebo controlled phase I trial.

Methods: The trial was conducted in 32 HIV-uninfected healthy volunteers to assess the safety and immunogenicity of prime-boost vaccination regimens with either 2 doses of AD VAX, a DNA vaccine containing Chinese HIV-1 subtype C env gpl 60, gag, pol and nef/tat genes, as a prime and 2 doses of TBC-M4, a recombinant MVA encoding Indian HIV-1 subtype C env gpl 60, gag, RT, rev, tat, and nef genes, as a boost in Group A or 3 doses of TBC-M4 alone in Group B participants. Out of 16 participants in each group, 12 received vaccine candidates and 4 received placebos.

Results: Both vaccine regimens were found to be generally safe and well tolerated. The breadth of anti-HIV binding antibodies and the titres of anti-HIV neutralizing antibodies were significantly higher ($p < 0.05$) in Group B volunteers at 14 days post last vaccination. Neutralizing antibodies were detected mainly against Tier-1 subtype B and C viruses. HIV-specific IFN- γ ELISPOT responses were directed mostly to Env and Gag proteins. Although the IFN- γ ELISPOT responses were infrequent after AD VAX vaccinations, the response rate was significantly higher in group A after 1st and 2nd MVA doses as compared to the responses in group B volunteers. However, the priming effect was short lasting leading to no difference in the frequency, breadth and magnitude of IFN-% ELISPOT responses between the groups at 3, 6 and 9 months post-last vaccination.

Conclusions: Although DNA priming resulted in enhancement of immune responses after 1st MVA boosting, the overall DNA prime MVA boost was not found to be immunologically superior to homologous MVA boosting.

117. Senbagavalli P, Hilda JN, Ramanathan VD, Kumaraswami V, Nutman TB, Babu S. Immune complexes isolated from patients with pulmonary tuberculosis modulate the activation and function of normal granulocytes. *Clin Vaccine Immunol*.2012; 19(12): 1965-1971.

Abstract: Circulating immune complexes (ICs) are associated with the pathogenesis of several diseases. Very little is known about the effect of ICs on the host immune response in patients with tuberculosis (TB). The effects of ICs isolated from patients with TB in modulating the release of calcium, cytokines, and granular proteins were studied in normal granulocytes, as were their chemotactic, phagocytic, and oxidative burst processes. ICs from TB patients induced decreased production of cytokines and platelet activating factor (PAF) from normal granulocytes. ICs from TB patients also induced enhanced chemotaxis and phagocytosis but caused diminished oxidative burst. This was accompanied by an increased release in intracellular calcium. On the other hand, ICs from TB patients induced increased release of the granular proteins human neutrophil peptides 1 to 3 (HNP1-3). Thus, ICs from patients with TB exhibit a profound effect on granulocyte function with activation of certain effector mechanisms and dampening of others.

118. George PJ, Anuradha R, Kumar NP, Kumaraswami V, Nutman TB, Babu S. Evidence of microbial translocation associated with perturbations in T cell and antigen-presenting cell homeostasis in hookworm infections. *PLOS Negl Trop Dis*.2012;6(10):el830.

Background: Microbial translocation (MT) is the process by which microbes or microbial products translocate from the intestine to the systemic circulation. MT is a common cause of systemic immune activation in HIV infection and is associated with reduced frequencies of CD4(+) T cells; no data exist, however, on the role of MT in intestinal helminth infections.

Methods: We measured the plasma levels of MT markers, acute-phase proteins, and pro-and anti-inflammatory cytokines in individuals with or without hookworm infections. We also estimated the absolute counts of CD4(+) and CD8(+) T cells as well as the frequencies of memory T cell and dendritic cell subsets. Finally, we also measured the levels of all of these parameters in a subset of individuals following treatment of hookworm infection.

Results: Our data suggest that hookworm infection is characterized by increased levels of markers associated with MT but not acute-phase proteins nor pro-inflammatory cytokines. Hookworm infections were also associated with increased levels of the anti-inflammatory cytokine~IL-10, which was positively correlated with levels of lipopolysaccharide (LPS). In addition, MT was associated with decreased numbers of CD8(+) T cells and diminished frequencies of particular dendritic cell subsets. Antihelminthic

treatment of hookworm infection resulted in reversal of some of the hematologic and microbiologic alterations.

Conclusions: Our data provide compelling evidence for MT in a human intestinal helminth infection and its association with perturbations in the T cell and antigen-presenting cell compartments of the immune system. Our data also reveal that at least one dominant counter-regulatory mechanism i.e. increased IL-10 production might potentially protect against systemic immune activation in hookworm infections.

119. Pavan Kumar N, Anuradha R, Andrade BB, Suresh N, Ganesh R, Shankar J, Kumaraswami V, Nutman TB, Babu S. Circulating biomarkers of pulmonary and extra-pulmonary tuberculosis in children. *Clin Vaccine Immunol*.2013;20(5):704-711.

Abstract: Tuberculosis (TB) in children is not only more likely to cause more severe disease than that seen in adults, it is also more likely to be extrapulmonary. Moreover, pediatric TB is very difficult to diagnose and suffers from a lack of understanding of host biomarkers for monitoring the progression of disease. Hence, we sought to identify the expression patterns of a variety of biomarkers in the plasma of children with pulmonary TB (PTB) and extrapulmonary TB (ETB), as well as in healthy control (HC) children. Thus, we examined a variety of circulating markers reflecting tissue inflammation, oxidative stress, innate immune activation, fibrosis, and the cytokine response. Children with active TB, compared to HC children, showed markedly elevated plasma levels of matrix metalloproteinases and their endogenous inhibitors. In addition, children with active TB had

significantly elevated levels of C-reactive protein, a -2 macroglobulin, and haptoglobin, as well as hemoxygenase 1. Markers of innate immune activation (lipopolysaccharide [LPS] and lipopolysaccharide-binding protein [LBP]) were significantly lower in ETB than in PTB children. Although there were no significant differences between the two groups in their levels of cytokines (type 1 [gamma interferon (IFN- γ), tumor necrosis factor α (TNF- α), interleukin 2 (IL-2), and IL-12], type 2 [IL-4, IL-5, IL-13, and IL-33], and most type 17 [IL-17A, IL-22, IL-1 β , and IL-6] and type 1 interferons [IFN- γ and IFN- β]) or most of the cytokines associated with immune modulation (IL-10 and IL-20), pediatric TB was associated with elevated plasma transforming growth factor β (TGF- β), IL-21, and IL-23 levels. Thus, pediatric TB is characterized by elevated levels of a variety of biomarkers at homeostasis, suggesting that these responses may play a crucial role in disease pathogenesis.

120. Chatterjee S, Kolappan C, Subramani R, Gopi PG, Chandrasekaran V, Fay MP, Babu S, Kumaraswami V, Nutman TB. Incidence of active pulmonary tuberculosis in patients with coincident filarial and/or intestinal helminth infections followed longitudinally in south India. *PLoS One*.2014;9(4):e94603.

Background: Filarial (and other helminth) infections are known to modulate mycobacteria-specific pro-inflammatory cytokine responses necessary for maintaining latency in tuberculosis (TB). We sought to address whether helminth co-infection alters

progression to active pulmonary TB in a co-endemic area of South India.

Methods/Principal Findings: Incidence of active pulmonary TB was assessed in 5096 subjects from five villages among helminth-infected (hel +) and -uninfected (hel -) groups. Baseline stool examinations, circulating filarial antigen, and tuberculin skin testing (PPD) were performed along with chest radiographs, sputum microscopy, and culture. During three follow-up visits each 2.5 years, patients were assessed using PPD tests and questionnaires and—for those with potential symptoms of TB—sputum microscopy and culture. Of the 5096 subjects, 1923 were found to be hel + and 3173 were hel - . Follow up interval stool examination could not be performed. In each group, 21 developed active TB over the course of the study. After adjusting for sex, age, BCG vaccination status, and PPD positivity, no difference was seen in active TB incidence between hel + and hel - groups either at baseline (relative risk (RR) 1.60; 95% confidence interval (CI): 0.69, 3.71, $P=0.27$), or when followed prospectively (RR 1.24; 95% CI: 0.48, 3.18, $P=0.66$).

Conclusions/Significance: Our findings suggest that, despite the immunomodulatory effects of helminth infection, baseline co-morbid infection with these parasites had little effect on the clinical progression from latent to active pulmonary TB.

121. Shriram AN, Krishnamoorthy K, Sivan A, Saha BP, Kumaraswami V, Vijayachari P. Impact of MDA and the prospects of elimination of the lone focus of diurnally sub periodic lymphatic filariasis in Nicobar Islands, India. *Acta Trop*.2014; 133:93-97.

Abstract: Mass Drug Administration is being carried out in Andaman and Nicobar Islands, India since 2004. Cross-sectional microfilaria (Mf) survey was conducted in Nancowry group of islands, the lone foci of diurnally sub-periodic form of bancroftian filariasis in Nicobar district, to examine its eligibility for Transmission Assessment Survey (TAS). A total of 2561 individuals (coverage: 23.9%) were screened from five islands. The overall Mf prevalence was 3.28%. Except one island, all other islands recorded Mf prevalence >1%, ranging from 2.5% to 5.3%, indicating persistence of infection despite six annual rounds of MDA. Mf prevalence was age dependent and was higher among males, but not significantly different between genders. Age and gender specific analysis showed a significant reduction in all the age classes among females vis a vis pre-MDA prevalence while the reduction was significant only in 21-30 and 41-50 age classes in males. Exposure to day biting and forest dwelling *Downsiomyia nivea* can be attributed for the persistent infection besides non-compliance for MDA. Based on fits of modified negative binomial distribution, true prevalence of Mf carriers in the community was estimated to be 4.74%, which is markedly higher (about 24%) than the observed prevalence of 3.28%. Follow-up of cohorts showed evidence of continued persistence of infection and acquisition of new infections post six rounds of MDA. As the Mf prevalence was above >1% in four of the five islands, this area is not eligible for TAS, warranting continuation of MDA. Mass DEC fortified salt is suggested as an adjunct to hasten elimination of infection.

Keywords: Lymphatic filariasis; *Wuchereria bancrofti*; Sub periodic filariasis; Elimination India.