BD NEWS

NEWSLETTER FOR BEHÇET'S DISEASE

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A Dedicated Student of BD Passes Away

Prof. Tsuyoshi Sakane (b. May 29, 1942) died on October 28, 2000, after a brief course of heart problems.

Prof. Sakane finished medical school in Kyoto, Japan. Between 1976 -1979 he was a research fellow at NIH (Bethesda, USA). Between 1979 -1991 he worked in Department of Internal Medicine in Shimane Medical University. Since 1991 he has been the Chief Professor of The Departments of Immunology and Medicine, Institute of Medical Science and Division of Rheumatic Diseases, Collagen Disease and Allergic Diseases at St. Marianna University School of Medicine in Kawasaki Japan.

Prof. Sakane contributed immensely to our current understanding of the aberrant immune mechanisms in RA, SLE and Behçet's disease. He and his collaborators published many seminal research articles on the B and T cell dysfunction in Behçet's disease. The neutrophil hyperractivity in the HLA B51 transgenic mice model was also described in his lab. Prof. Sakane was the Chairman of the Behçet's Disease Research Committee of Japan between 1990-1996.

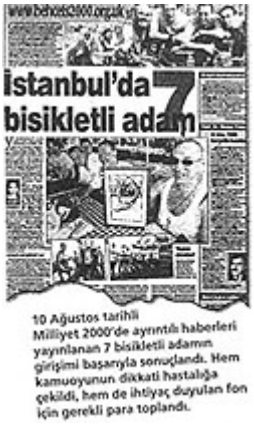
Prof. Sakane had a very sharp wit and those who knew him on a more personal level were also privileged to share his explosive, yet delightful sense of humour.

He is survived by his wife, a daughter and two sons.

Convenors for the BD Study

Seven British Cyclists Visit Istanbul

*By Vivien HAWKER (UK)**


İstanbul'da 7 bisikletli adam

10 Ağustos tarihli Milliyet 2000'de ayrıntılı haberleri yayınlanan 7 bisikletli adamın girişimi başarıyla sonuçlandı. Hem kamuoyunun dikkati hastalığa çekildi, hem de ihtiyaç duyulan fon için gerekli para toplandı.

On August 9th 2000, 7 men arrived at the Cerrahpasa Behçet's Disease Research Unit, Istanbul, having cycled 1850 kms, over 2 mountain ranges, through 5 countries and in just 12 days! Their symbolic destination-the place where Hulusi Behçet put his name to the disease. It was a miracle that these men made it! They weren't young and 10 months previously weren't fit but they were my family and friends and committed to doing something positive that would make a difference.

During the morning we exchanged gifts. We gave a photograph of the Circle of Life statue which stands in the entrance to the Hammersmith Hospital donated by my consultant, Prof Haskard and we received two photographs; one of Behçet on holiday in Nice, 1934 and the other of a handwritten prescription, which I have since presented to the Behçet's Syndrome Society at their AGM.

Prof. Hasan Yazici and his colleagues gave freely of their time and expertise and much information was shared both formally through presentations and informally during the tour of the unit and the evening celebrations.

There was a definite buzz of being where the action is. This is a center of excellence devoted to the research and treatment of Behçet's sufferers and because of the

Groups

As was discussed during the Council meeting in Seoul last spring The Executive Committee of ISBD has recently asked the following individuals to be the convenors for a series of Study Groups. The study groups are expected at long term to coordinate the research programme into Behçet's Disease on an international basis.

S.H. Assaad-Khalil - Drug trials including collaborative trials;
A. Silman - Epidemiology;
H. Direskeneli - Basic research;
S. Ohno - Eye research;
D. Bang - Dermatology research;
A. Chamberlain - Outcome measures;
I. Kone-Paut - BD in the pediatric age;
S. Lee - Physician training

BD NEWS

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higher prevalence of the disease in Turkey, they have the resources (sufferers) to carry out research studies and drugs trials. It was interesting also to discuss the differences in the Health Services and in particular, the impact on the disease process, of a self-referral system, which promoted early diagnosis.

That evening we dined together at the Dedeman Hotel (courtesy of a Behçet's patient), which we all enjoyed very much and I was particularly appreciative of the opportunity to talk with specialist doctors and find out what advances are being made in the research for treatment and cure. I was also offered private consultations by several members of the team and gratefully accepted; the results of which may be of personal benefit to me.

The purpose of the marathon ride was to raise awareness and knowledge of Behçet's Disease and to raise money to commission the making of a professional teaching video targeted at student doctors and GP's on refresher courses.

These objectives have been achieved. As a result of the venture, Behçet's Disease has had radio, newspaper and TV coverage nationally and internationally, in 7 countries. We have had an audience of 4 million people. We will be handing over approximately £ 7500 to the Behçet's Syndrome Society with whom we will work to produce the video.

On behalf of Behçet's sufferers in this country I would like to take this opportunity to thank the physicians of the Cerrahpasa BD team for their generosity, time and participation in assisting us achieve such a worthwhile goal.

* Ms. Vivien Hawker suffers from BD

Use of interferon-α in Behçet`s Disease

By Ina KÖTTER & Nicole STÜBIGER (Germany)

Although there has been some improvement in the prognosis of ocular BD with the standard regimens (steroids, colchicine, cyclosporin A, azathioprine, cytotoxic agents, pentoxyphilline, benzathin penicillin, thalidomide), there still is a great risk of significant loss of vision in case of ocular involvement with retinal vasculitis irrespective of the kind of immunosuppresive or cytotoxic regimen used. The combination immunosuppressive regimens and the cytotoxic agents bear the longterm risk of secondary neoplasia. Thus, there still is a need to further improve the therapy of BD by instituting new therapeutic agents.

Interferon is a cytokine that was discovered more than 40 years ago by Isaacs and Lindenmann, who observed that virus-infected cell cultures produced a protein that rendered cells resistant to infection by many viruses. Interferon-α belongs to the so-called type-1-interferons and can be produced by virtually all somatic cells after viral infection. By inducing the release of intracellular enzymes such as 2`5`-oligoadenylate synthetase and double-stranded RNA-dependent protein kinase, it causes degradation of viral messenger RNA and inhibits protein synthesis. IFN-α additionnally has various immunomodulatory effects: increased expression of major histocompatibility complex antigens, increased natural killer and cytotixic T cell activity, shift of the T-cell response towards a TH1-type and many more. It also has antiproliferative and antiangiogenetic properties. There are two different human recombinant α-IFN`s in use for the treatment of viral hepatitis and myeloproliferative syndromes, as well as for certain solid tumours and lymphomas (IFN-α2a and IFN-α2b). They differ in one amino acid only and there probably is no great difference in their efficacy for the abovementioned disorders.

Interferon-α (2a) was instituted in 1986 in the treatment for BD by Tsambaos et al. from Patras in Greece. The rationale for using it was the possible viral etiology of BD and the antiviral properties of IFN-α. This group treated three patients with BD, one of whom had ocular involvement. The dosage was relatively high (9-12 Mill iU i.m./day) and the treatment period short (11-16 days). Anyhow, all symptoms (mucocutaneous, fever, thrombophlebitis and arthritis) remitted, except the ocular disease. Later on, 19 small studies and case reports appeared in the literature. Up to now, considering the latest abstracts from the 9th International Conference on Behçet`s Disease held in Seoul in May 2000, a total of 315 patients have been treated with IFN-α2a or α2b for BD, 40 of whom primarily had ocular involvement (mostly posterior uveitis with retinal vasculitis).

The results in all these studies and case reports from 17 different groups and 7 countries are very promising, although it is difficult to compare them, because different inclusion criteria, treatment regimens and outcome measures were used.

IFN-α clearly is effective for mucocutaneous lesions and arthritis, with a tendency towards lower efficacy for oral aphthae than for the other manifestations. As far as ocular manifestations are concerned, the first case reports on patients with refractory severe ocular BD who were successfully treated with IFN-α appeared in 1993 and 1994. In the 4 cases reported, the patients had retinal vasculitis and received IFN-α in addition to their (ineffective) immunosuppressive agents. All patients achieved complete remission of ocular inflammation.

After a pilot study with 7 patients, our group has treated 52 patients with severe ocular BD (posterior uveitis with retinal vasculitis) with IFN-α2a alone (maximum steroids 10 mg prednisolone) (3-6 Mill iU s.c. daily at the beginning, maintenance dosage 3 x 3 Mill iU / week, after 6-12 months tapering until discontinuation) from 1994 until now. The mean observation period is 26 months. Median BD activity score and posterior uveitis score fell from 7,3 to 3,7 (not significant) and from 3,7 to 0,4 ($p<0,0001$) respectively. Mean visual acuity significantly rose from 0,5 to 0,8 ($p<0,005$). 90% of the patients were responder. Time to response was 3,7 weeks for the posterior uveitis score (reduction of at least 50%). IFN could be discontinued after a mean treatment duration of 13,4 months in 36% of the patients without relapse of ocular disease for a mean period of 13,2 months. A recent, randomised controlled study on IFN-α2b plus colchicine plus benzathine penicillin versus colchicine plus benzathine penicillin alone that appeared in The Lancet (Demiroglu H et al, Lancet 355: 605-609, 2000), unfortunately had to be retracted from publication by the editor, due to fraud.

The side effects of IFN-α described in BD patients roughly are the same known from patients with hepatitis C or chronic myelogenous leukemia (flu-like syndrome in the first 2 weeks, reddening at the site of injection, itching, alopecia, depression, leukopenia, thyroiditis, exacerbation of psoriasis, occurrence of autoantibodies and anti-interferon-antibodies). Other side effects, mimicking BD symptoms, as retinal infiltrates (described in hepatitis C) and pathergy phenomenon (described in CML) have not occurred in the BD patients treated with IFN-α by now. To the contrary, pathergy phenomenon disappeared under IFN, as did retinal infiltrates due to vasculitis (own observations).

In conclusion, IFN-α is a promising agent in the treatment especially of severe ocular BD, where the results of the immunosuppressive regimens still are unsatisfactory. The dosage necessary to achieve optimal results probably is 3-6 Mill iU daily for 4-8 weeks, maintenance dosage 3 Mill iU 3x/week, with a treatment duration of at least 6 months before discontinuation of the drug. We would like to underline that in our hands it is not possible to discontinue azathioprine or cyclosporin A in severe ocular BD without relapse or even rebound phenomena - thus, IFN in this respect may be superior to the standard immunosuppressants. The time to response also seems to be shorter than with immunosuppressants. The mechanism of action of IFN-α in BD is still unclear and should be examined in further trials. A controlled randomised crossover study of IFN versus CSA should urgently be performed in order to be able to clearly determine the significance of IFN in the treatment of BD.

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Familial Aggregation and Genetic Susceptibility to Behçet's Disease

By Ahmet GÜL (Turkey)

The aetiology of Behçet's disease is unknown. However, family studies indicate a strong genetic background for Behçet's disease with a complex inheritance model. The majority of patients with Behçet's disease are sporadic cases with asymptomatic parents. However, clustering of Behçet's disease in some families has long been observed. A positive family history was noted among 2-3% of the Japanese and 8-34% of the Turkish and Middle Eastern patients with Behçet's disease. Description of familial aggregation with the prevalence of familial cases in a group of patients open to many biases, and recurrence risk in relatives, especially in siblings (λs) is the preferred way to document the familial aggregation.

We aimed to investigate the sibling recurrence risk ratio (λs) in Behçet's disease for the estimation of the magnitude of genetic factors in the disease pathogenesis. The λs is defined as the ratio of risk of being affected among the siblings of patients and risk of being affected in the general population. A significant deviation from unity suggests familial aggregation, and it is a good way of quantifying the genetic effects without knowing the exact mode of inheritance of the disease studied.

We interviewed 170 consecutive unrelated patients with a detailed questionnaire, and ascertained their family trees as well as Behçet's disease related manifestations in their relatives. Then, to avoid an ascertainment bias, we selected the immediately older sibling, or if an older sibling was not available, the immediately younger sibling of the index cases for further evaluation. We contacted 166 siblings by telephone, and all 29 subjects with recurrent oral ulcers were invited for further examination. Seven of them were diagnosed as Behçet's disease fulfilling the International Study Group criteria. Sibling recurrence rate for Behçet's disease was found to be 4.2%, which gives a λs value of 11.4-52.5 by using the figures from the previous studies on the point prevalence of Behçet's disease in Turkey (8-37/10,000).

This considerably high λs value indicates a strong evidence for a hereditary background in Behçet's disease, and warrants more detailed molecular genetic studies for the identification of susceptibility loci.

Association of HLA-B51 with Behçet's disease is regarded as being the strongest evidence of genetic contribution described to date. This strong association has been confirmed in different ethnic groups, but genetic linkage of this region to Behçet's disease has not yet been documented. We have recently analyzed 12 multicase Behçet's disease families to ascertain whether there is genetic linkage between HLA-B and Behçet's disease using the transmission disequilibrium test (TDT) since it is a test for linkage in the presence of association and not sensitive to a stratified population. We used 5 polymorphic microsatellite markers (DQCAR, TNFd, TNFa, TNFb and MICA5) within the major histocompatibility complex (MHC) region as well as serologically determined HLA-B and HLA-A antigens for the analysis. Extended TDT and a Monte Carlo simulation with 1,000 replicates revealed evidence of linkage to Behçet's disease only for HLA-B. Chi-squared statistics of the individual alleles revealed a positive result only for HLA-B51.

We also estimated the contribution of HLA-B (λHLA-B) to the overall genetic susceptibility to Behçet's disease using identity by descent (IBD) sharing of HLA-B alleles in these families. Using the proportion of affected pairs sharing zero HLA-B alleles, we calculated λHLA-B to be 1.6, and hence the contribution of HLA-B to the overall genetic susceptibility to BD was estimated to be 12-

19% with an assumption of a multiplicative interaction between disease susceptibility loci.

The contribution of the HLA-B locus to the overall genetic susceptibility to BD is relatively small, and further studies are needed to map other susceptibility genes for Behçet's disease using either a whole-genome-screening or a candidate gene approaches.

A novel susceptibility gene?

We have currently been investigating 28 multicase families of Behçet's disease, and our preliminary results of non-parametric linkage analysis in these families have revealed a novel susceptibility locus for Behçet's disease in a region about 17 cM to HLA-B locus (6p22-p23). This novel telomeric locus for Behçet's disease might be in linkage disequilibrium with HLA-B51, or alternatively there might be 2 loci for Behçet's disease on the 6p acting together. We hope that identification of this novel susceptibility gene could help to understand the pathogenesis of Behçet's disease further.

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A Report on the First International Convention for Patients with Silk Road Disease (Behçet's Disease)

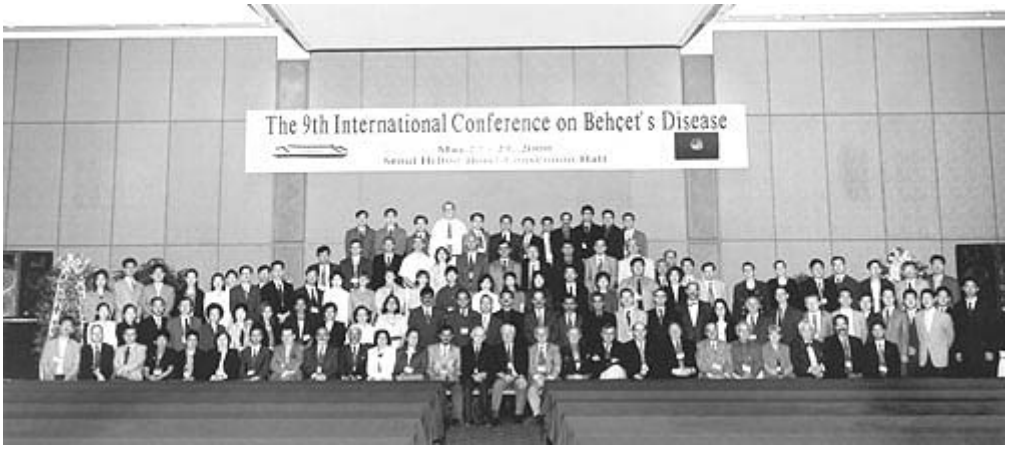
By Shigeaki OHNO (Japan)

The First International Convention for Patients with Silk Road Disease (Behçet's Disease) was held at Shonan Village Center, Japan, from May 19 - 22, 2000. Professor Ohno, Yokohama City University, was the President and Dr Nishida the Secretary General. In total, 314 physicians and patients gathered from 18 different countries. 43 participants were from foreign countries. A "Declaration of Yokohama 2000" was released to commemorate the First Convention. In particular, May 20 was decide to be the "International Behçet's Disease Day". We are very much grateful to all participants, volunteers and companies who have generously supported the First Convention. We sincerely hope that this support will be further continued for the future success of the convention for the patients suffering from this difficult disease.

The Second Convention for the Patients with Behçet's Disease will be held on June 27-29, 2002, together with the 10th International Conference on Behçet's Disease in Berlin, Germany, Professor Zouboluis will be the president of this conference.

The 9th International Conference on Behçet's Disease, Seoul, Korea, May 27-29, 2000 and the Official Foundation of the International Society for Behçet's Disease (ISBD)

By Dongsik BANG (Korea)



The 9th International Conference on Behçet's Disease (ICBD) was held for three days from May 27 to 29, 2000, in Seoul, Korea. The first ICBD to open in the Far East Asian region was the Tokyo conference in 1981. The Seoul conference was the second ICBD to be held in this region. It has been 19 years since the Tokyo conference.

Although Korea, the host country, is geographically located at a far distance from Europe, America, the Middle East, and the Mediterranean region, more than 250 participants from 23 countries were in attendance. A total of 175 (100 poster presentations, 72 oral presentations, 3 plenary lectures) papers were presented along with active discussions.

On May 27, the opening day of the conference, Professor Sungnack Lee, the president of the 9th ICBD, Dr. Je G. Chi, the president of the Korean Medical Association, and Mr. Halil Dag, the Turkish ambassador in Korea, gave their congratulatory addresses. The 9th ICBD was organized by Professor Sungnack Lee as the President of the Organizing Committee and Professor Dongsik Bang as the Secretariat General, with the assistance of the Department of Dermatology of Yonsei University, Yonsei University Behçet's Disease Specialty Clinic, and Ajou University Behçet's Disease Specialty Clinic Teams.

The congress was supported and sponsored by the Korean Dermatological Association, the Korean Rheumatism Association, the Korean Ophthalmologic Society, the Korean Academy of Medical Sciences, the Korean Medical Association, and the Korean Study Group for Behçet's Disease.

As the first day plenary lecturer, Dr. T. Lehner gave his lecture entitled, "Immunopathogenesis of Behçet's Disease". On the second day, Dr. S. Ohno gave his plenary lecture entitled, "Molecular Genetics of Behçet's Disease", and Dr. J.W. Yoon's "Molecular Pathogenic Mechanisms of A Cell-Specific Autoimmune Disease (Type 1 Diabetes)" was presented on the last day of the conference.

The oral presentations were divided into twelve sessions, which included Epidemiology, Diagnosis and Assessment of Disease Activity, Immunology, Genetics, Endothelium, Mucocutaneous manifestations, Neurologic and Vascular manifestations, Gastrointestinal manifestations, Ocular manifestations, Rheumatologic manifestations, and Management.

There were visible advancements in the fields of Immunology and Molecular Genetics. Also, future possibilities of gene therapy in Behçet's disease were shown.

The most meaningful event to occur during the conference was the official foundation of the International Society for Behçet's Disease, after having held conferences without a formal society since 1964. During the congress, all representatives of the former International Study Group on Behçet's Disease held an election to choose the president, vice president, honorary president, and council members of the newly formed society. Dr. C. Barnes was elected as President, Dr. S. Lee as Vice-President, Dr. H. Yazici as President-Elect/Secretary, and Dr. D. Haskard as Treasurer. Professor Dilsen, Ehrlich, Lehner, and Dr. O'Duffy were nominated as Lifetime Honorary Presidents of ISBD. The 2-year membership fee of the new society is US$100. I believe and hope that the new ISBD will contribute much to the future academic advancement of Behçet's disease and in the promotion of mutual friendship between its members.

On the last day of the 9th ICBD, Dr. T. Nishida from Japan and his father, Mr. N. Nishida, gave their presentation entitled, "The first international convention for patients with Silk Road Disease (Behçet's Disease)," as the representative of all Behçet's disease patients. The presentation showed the results of the International Convention for Patients with Behçet's Disease, which was held on May 19-22, 2000, in Japan. The convention was hosted by Dr. S. Ohno, and it was a meaningful time to realize that doctors and patients should work hard together to win over the disease.

The welcome and farewell parties provided the participants with opportunities to have greater understanding and appreciation of the tradition and the culture of Korea. The 9th ICBD was officially closed with the promise to meet at the 10th ICBD in Berlin in 2002.

9th ICBD Secretary General
Dongsik Bang, MD, PhD

Next International Conference on BD

10th International Conference on Behçet's Disease; June 27 - 29, 2002; University Medical

Center Benjamin Franklin; Berlin; under the auspices of the International Society of Behçet's Disease (ISBD); and supported by the Deutsches Register Morbus Adamantiades-Behçet-Verein i.G.; President: Prof. Dr. Ch. C. Zouboulis; Scientific Secretariat: Department of Dermatology University Medical Center Benjamin Franklin, The Free University of Berlin, Fabeckstrasse 60 - 62,14195 Berlin, Germany, Fax: 49-30-84456908; e-mail: zoubbere@zedat.fu-berlin.de; Organization: RKM Konferenzmanagement Theklastrasse 12, 12205 Berlin; Fax: 49-30-77190441, E-mail: RKMCR@aol.com. Early registration fee (before February 28, 2002): 420 DM; Late registration fee (from March 1, 2002) and on site registration: 550 DM. There is a 50 DM discount in the registration fee (both for early and late) for the members of ISBD.

The 2nd International Convention for Patients with Silk Road Disease (Behçet's Disease); June 27 - 29, 2002 University Medical Center Benjamin Franklin, Berlin;

Secretariat: Department of Dermatology University Medical Center Benjamin Franklin; The Free University of Berlin; Fabeckstrasse 60 - 62; 14195 Berlin; Germany; Fax: 49-30-84456908; e-mail: zoubbere@zedat.fu- berlin.de; Organization: RKM Konferenzmanagement; Theklastrasse 12; 12205 Berlin;Fax: 49-30-77190441; E-mail: RKMCR@aol.com Early registration fee (before February 28, 2002): 350 DM; Late registration fee (from March 1, 2002) and on site registration: 450 DM