The On-going Reorganization of the Bernhard Nocht Institute

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On the occasion of the 50th anniversary of the Institute of Tropical Medicine of Nagasaki University I bring you greetings from the Institute of Tropical Medicine in Hamburg and all good wishes for a glorious future. I personally wish to thank you for the honor of being invited to participate in this auspicious event. I greatly appreciate the privilege you accorded me.

Thinking about the theme of this symposium and what I might contribute to it, I decided to talk very concretely about the present situation and future endeavours of our institute in Hamburg rather than talking in generalities.

The Bernhard Nocht Institute (BNI) is in the process of a thorough reorganization which began in 1988, is still on-going and will continue for some time. The aim is to make it an institute of excellence in biomedical research in the field of tropical medicine. An important vehicle in achieving this goal is flexibility of mental attitude and flexibility in organizational structure of the institute every step of the way.

The BNI was founded in 1900 at the instigation of Robert Koch. Early members of the staff were Bernhard Nocht, Giemsa, Prowazek, Rocha-Lima, Schaudinn, Reichenow and Hans Vogel. Diseases then under investigation were malaria, rickettsial diseases, echinococcosis and schistosomiasis. A clinical division for in- and outpatients has been an integral part of the institute from the beginning. A three-months course in tropical medicine and parasitology for physicians was held annually and this tradition has been retained to this day.

In the 40 years prior to 1988 the productivity of the BNI steadily declined. To be sure the institute practiced tropical medicine in Hamburg and medicine in the tropics in Africa. However, the many small divisions were disjointed, shunned away from collaborating with each other and a common institute research program was sorely lacking. Tragic is that the BNI remained untouched by the biological revolution and the advent of recombinant gene technology in the 70s. One development stood out and this was the systematic elaboration of immune diagnostic tests for the detection of antibodies to parasites and of parasitic antigens in the serum of patients. Today most of the serological diagnostics for the detection of parasitic disease in the German Federal Republic is done at the BNI in Hamburg. Nevertheless, the institute would have slid inevitably into oblivion had the Science Council of the German Government not intervened. As a consequence of this government intervention a concept of reorientation and reorganization was devised in 1986 and adopted by the Senat of Hamburg in 1987. Reorganization began in January 1988 under my direction.

Reorganization has two major aspects: scientific reorientation and change of the struc-
tural organization of the institute. Intellectually and scientifically, emphasis is now being placed on disease-oriented basic research: work is being done on pathogenicity factors of infectious agents, T and B cell responses of the host, molecular disease mechanisms, parasite strategies of evading host defense, and rational vaccine development.

These research aims could only be tackled through the establishment of a section of Molecular Biology and through the introduction thereby of the technologies and concepts of molecular genetics, molecular immunology and protein chemistry. This was accomplished by assembling step-wise a sizable group of young scientists and instill in them the sense of virtual independence in their investigative endeavours. A significant number of them were retrieved from the United States where they were receiving advanced training at the time.

To my mind, an institute of tropical medicine should have the capability of tackling disease at the molecular level. Prerequisites are the mastering of DNA and RNA technology, protein sequencing, peptide synthesis, expression of recombinant proteins, computer aided structure analysis, transfection methodology and whatever more is required to solve a medical research problem.

For example, it ought to be possible to define those critical structures on the surface of a pathogen in terms of antigenic make-up, that render an organism vulnerable to an effective immune attack by the host and therefore susceptible to killing. Identification of such structures in molecular terms may pave the way to the development of vaccines.

The other aspect of institute reorganization is changing the structural organization. Following creation of the Section of Molecular Biology, the many small divisions of the earlier institute were consolidated and merged to two larger units, the Parasitology Section and the Medical Microbiology Section.

To lend stability to the institute, to endow it with scientific expertise and to safeguard training of young scientific talent, the BNI has available today three Research Professorships. They will be devoted to Molecular Biology, to Immunology and to Basic Clinical Research in Tropical Medicine.

The present structure of the BNI thus encompasses four units: The Molecular Biology Section, the Parasitology Section, the Medical Microbiology Section and the Clinical Division with 68 beds and an Outpatient Department.

As is to be expected, each section has its own specific research agenda. However, to rally the intellectual resources of the institute and to unify them in a common effort, two institute-wide Research Programs were initiated in 1988. Everyone who is willing and able to contribute may participate under the organizational supervision of a coordinator who is appointed by the director. In this fashion major personnel and financial resources of the institute have been invested in these two programs and in each a critical mass of intellectual talent could be attained to assure productivity and eventual success.

Two parasitic diseases were selected for these Institute Programs, amoebiasis and onchocerciasis, primarily because relatively little basic research had been done on them by 1988. From an immunological point of view they both are interesting and pose very different problems. *Entamoeba histolytica* is the most potent killer cell known. Any cell in its path, in-
cluding the cells of host defense, is killed before it has a chance to attack the invader. By contrast, *Onchocerca volvulus* is not grossly destructive to host tissues, but it succeeds to persist in the host for years evading elimination by the immune system.

Since its inception the Amoebiasis Program has made several significant contributions. For example, it is well known that of the 500 million individuals infected with *E. histolytica*, only 10% come down with invasive amoebiasis (colitis or extra intestinal abscesses). It was possible at the BNI to show that pathogenic and nonpathogenic isolates of *E. histolytica* are genetically distinct. Southern blots of their DNA degraded with restriction enzymes yield distinct patterns and this difference in DNA structure is absolutely conserved within the group of pathogenic and within that of non-pathogenic amoebae. They ought not be labeled with the same name. Medically this finding means, that 450 million people infected with non-pathogenic amoebae need not be treated because this organism will never become invasive.

Putative pathogenicity factors of pathogenic isolates have been cloned such as the adherence lectin with which amoebae attach to human cells, a cysteine proteinase which facilitates invasion of host tissue by digesting the extracellular matrix and the pore forming protein with which amoebae kill host cells. Recombinant proteins are now being tested in appropriate animal models as to whether they elicit protective immunity to *E. histolytica*.

The onchocerciasis program is much more involved and complex. Not only that the infectious larva and the adult worm are highly differentiated organisms, but the most important prerequisite for this study is access to patients. The BNI is fortunate to have owned in the rain forest of Liberia, West Africa, its own field station for more than 20 years. It is located in a hyperendemic area for onchocerciasis and many other parasitic diseases. Among this population, highly infested with *O. volvulus*, is a sprinkle of individuals that get infected but don't come down with the disease. It is our hypothesis that these individuals have developed protective immunity against the infectious larva and therefore have developed a mechanism of killing or otherwise eliminating it after it is inoculated into their skin by the blackfly. We want to find out by which acquired or innate immune mechanism the infectious larva can be killed, again with a view toward possible vaccine development.

For this purpose the infectious larva of *O. volvulus* has been produced in very large numbers by a very laborious process in West Africa. cDNA libraries have been constructed and T cells and sera of diseased and putative immune individuals have been secured. One protein of ~90 kDa has been identified that is recognized by the immune system of the putative immune individuals and not by that of diseased people. This protein is expressed by the infectious larva of *O. volvulus* as evidenced by the presence of mRNA encoding it. Antibody to the 90 kDa protein reacts with surface constituents of the infectious larva; and the question arises whether this antibody in putative immune individuals might be - at least in part - responsible for elimination of the infectious larva. Work is underway to check this hypothesis.

We have conducted an analysis of the MHC class II antigen subtypes in the Liberian population by gene technology. The variable DNA sequences of the DR, DQ and DP markers are amplified by PCR and the amplified segments are then typed by hybridization with syn-
thetic probes or they are sequenced. Comparing individuals afflicted with onchocerciasis with the group of putative immune individuals from the same endemic region, a highly significant difference was observed between them in the make-up of the DQA′ region. This observation supports the notion that the putative immune individuals constitute a distinct group and that susceptibility onchocerciasis has a genetic component.

The Institute Research Programs have attracted sufficient attention for the German Government to decide to support them with 13.5 million DM over the next 5 years. This support will undoubtedly enhance these programs but also it will release institute resources which may be used for the development of other areas. One of the disciplines most urgently to be developed at the BNI is Basic clinical Research. The situation has arisen at the BNI, where at the one end of the spectrum of activities very basic research work is being performed and at the other end physicians deliver routine patient care. There exist then two different cultures under the same roof, which do not speak the same language. Worse yet, the physician is too busy being a physician to learn from the basic scientist in the same institute or to do meaningful clinical research himself.

To bridge the gap between basic research and routine patient care, we have decided to assemble a group of physician-scientists who will conduct basic clinical research. These physician-scientists are expected to be board-certified internists, to have made scientific contributions and to be active in basic research. Without being burdened by routine patient care, they will have access to in- and out-patients at the institute's Clinical Division. They will also shoulder the major responsibility for field studies in the tropics. Among this group should eventually be one epidemiologist who has received advanced training abroad. With time the Basic Clinical Research Group could grow to become the fourth Section of the BNI. Without wanting to belabor it, this group of physician-scientists is expected to have an integrating impact on the diverse activities of the institute. It should now have become apparent, which course the Hamburg Institute of Tropical Medicine has chosen to take into its future. It is the only institute of its kind in Germany, a high-technology country.

The institute will not be involved in primary health care in the third world, it will not conduct health care delivery systems research in the tropics either.

I should mention that the Federal Republic of Germany greatly aides developing countries through the German Development Service and the Society for Technical Collaboration. These organizations maintain experts of all kinds in needy countries including physicians and nurses. For example, the Basic Health Care system of Benin in West Africa was established 25 years ago by the German Development Service and is still being operated by this organization because the local authorities are reluctant to take it over.

Of course, the institute must have a presence in tropical countries where the diseases are prevalent that are the subject of our research. Only 6 months after I had to close down our field station in Liberia because of the civil war, the institute opened up a provisional field station in Benin. Next year we will probably be in Guinea. These operations are carried out in collaboration with local universities and upon invitation by the country's ministry of health. They offer unique opportunities for transfer of know-how and technology.
In conclusion: it is our conviction that the Bernhard Nocht Institute can serve humanity best by performing disease oriented basic research. In this capacity the institute stands ready to join the global alliance in the fight against tropical diseases.