The Bernhard Nocht Institute: 100 Years of Tropical Medicine in Hamburg

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The Bernhard Nocht Institute (BNI) is a four months younger and much smaller sibling of the Instituto Oswaldo Cruz. It was founded on 1 October 1900 as an Institut für Schiffs- und Tropenkrankheiten (Institute for Maritime and Tropical Diseases) and was later named after its founder and first director Bernhard Nocht. Today it is the Germany’s largest institution for research in tropical medicine. It is a government institution affiliated to the Federal Ministry of Health of Germany and the Department of Health of the State of Hamburg. As the center for research in tropical medicine in Germany the BNI is dedicated to research, training and patient care in the area of human infectious diseases, which are of particular relevance in the tropics. It is the primary mission of the BNI to develop means to the control of these diseases. Secondary missions are to provide expertise for regional and national authorities and to directly and indirectly improve the health care for national and regional citizens in regard to diseases of the tropics.

Key words: Bernhard Nocht Institute - tropical medicine - research

PAST

The roots of the Bernhard Nocht Institute (BNI) lie in the great cholera outbreak in Hamburg in 1892 during its fifth pandemic. Bernhard Nocht (1857-1945), a young Navy Doctor who had been trained at Robert Koch’s Institut in Berlin, came to Hamburg to help Koch to bring the epidemic under control. Because of his ability, it was subsequently offered him the position of a Harbour Doctor and he was appointed in 1893.

In this office Nocht saw the great and increasing number of sailors and travelers with tropical diseases entering Hamburg by ship. In the year 1900, for example, 500 ships with 15,000 persons arrived from overseas in the port of Hamburg. Tropical and other infections such as typhus, dysenteries or tuberculosis were commonly seen. For example, 11% of the travelers that arrived on sailing ships had malaria and 6% of travelers from steam ships.

From a previous visit to the tropics, Nocht had experience with tropical diseases and tried to persuade the authorities of the need to establish an Institute for research, training and therapy of tropical infections.

Although Robert Koch tried to bring such an Institute to Berlin at Nocht’s instigation, an Institut für Schiffs- und Tropenkrankheiten (Institute for Maritime and Tropical Diseases) was founded in Hamburg on 1 October 1900. Nocht was the first director, acting from 1900 to 1930. Within a short time he was able to gather a group of ambitious and able scientists. Fritz Schaudinn, who discovered Treponema pallidum, was the first head of the Department of Protozoology. After his sudden death in 1906, Stanislaus von Prowazek was his successor. Gustav Giemsa, the inventor of the famous Giemsa stain, started to work in 1900 as head of the Department of Chemistry. Friedrich Fülleborn, later Nocht’s successor as director, was the first head of the Department of Helminthology.

In 1914, the Institute had, besides the director, six scientists on its own payroll and four scientists were financed by the army or the colonial office. In this year the Institute moved into a new building that still today accommodates it. The costs of the building were 1,500,000 marks and of the interior 800,000 marks. The annual budget for research of the Institute in 1914 was 246,302 marks.

In the first decades of the BNI a number of major discoveries was made. Milestones were the discovery of Rickettsia prowazekii, the agent of epidemic typhus, by von Prowazek and da Rocha-Lima. Both von Prowazek and da Rocha-Lima got infected with the agent during their work and von Prowazek died in 1915. Da Rocha-Lima named the agent after his colleague and friend. He later described another louse-transmitted infectious
agent, *Rochalimea* (now *Bartonella* *quintana*), the causing agent of trench fever. Von Prowazek also described for the first time the infectious origin of trachoma (Halberstaedter & Prowazek 1909). As an animal model for the chemotherapy of malaria, the avian malaria was established and found suitable to test new derivatives of chinin such as plasmochin and atebrin. Using this model the protozoologist Eduard Reichenow and his coworkers described the extraerythrocytic development of plasmodial sporozoites as the missing link between the infective sporozoite and the infected erythrocyte (Reichenow & Mudrow 1943).

The helminthologist Hans Vogel discovered in 1931 the developmental cycle of *Opisthorchis felineus* (Vogel 1934) and described later in experiments lasting from 1938 to 1950, for the first time immunity against a trematode infection (Vogel & Minning 1953). In the 50’s, Vogel (1955) discovered *Echinococcus multilocularis* as a new species. More recent findings include the demonstration by Paul Racz and Klara Tenner-Racz together with Ashley Haase (Minneapolis) of a massive multiplication of HIV in the lymphnodes in the incubation period of Aids. Egbert Tannich was able in 1989 to separate *Entamoeba histolytica* and *E. dispar* (Tannich et al. 1989).

Nearly from its beginning the BNI had connections with the Instituto Oswaldo Cruz. Gustav Giemsa and Stanislaus von Prowazek stayed upon invitation by the Brazilian Government in 1908 in the Instituto Oswaldo Cruz (Fig. 3). In fact Giemsa was an author of the very first paper published by the *Memórias do Instituto Oswaldo Cruz* (Giemsa & Godoy 1909). In September 1909, Nocht appointed Henrique da Rocha-Lima, who had been previously Head of the Department of Pathology
at Instituto Oswaldo Cruz, as Head of a new Department of Pathology in his Institute. da Rocha-Lima stayed until December 1927 in Hamburg. Nocht himself came in 1929 to visit the Instituto Oswaldo Cruz. In 1977, the Department of Electron Microscopy of the Instituto Oswaldo Cruz was established jointly with the BNI. Fig. 4 shows the head of BNI’s Department of Protozoology, Prof. Heinz Mühlpfordt, demonstrating the use of the microscope to the President of Brazil Ernesto Geisel.

PRESENT

One hundred years later, the BNI is still the Germany’s largest research institute for tropical medicine. Research at the BNI is devoted to the characterization of host-pathogen-interactions in tropical infectious diseases. The research activities of the BNI concentrate on three areas: (1) cellular and molecular biology of infectious agents that cause tropical diseases; (2) the host response to such agents and its role in protection and pathology; (3) a disease oriented approach to pathogenesis and pathology. Accordingly BNI’s work focuses on infectious diseases caused by parasites and tropical viruses. Main topics of work are pathogenicity factors of parasites and cell biology of parasites, the analysis of the host-parasite-relationship including immunological defense mechanisms, and definition of genes causing susceptibility to certain tropical infections. In all these ventures special emphasis is put on two issues: relevance for disease prevention and control, and use of tropical infections as models for general issues in medicine and biology.

The BNI is a government institution affiliated to the Federal Ministry of Health of the Federal Republic of Germany and the Ministry of Health of the State of Hamburg and is financed jointly by the Federal Government and the States of the Federal Republic of Germany. The BNI has many cooperations and contacts with developing countries, most of them with countries in Africa but also with countries in South America and Asia. The Institute maintains a Cooperative Research Center in Kumasi, Ghana, mainly for research on onchocerciasis and malaria. The cooperative center is established according to a state agreement between the Republic of Ghana and the State of Hamburg, to establish longstanding contacts to scientists of the host country. Its hallmark is that each research project is carried out jointly by scientists from Hamburg and from Kumasi. Projects on Lassa fever and amoebiasis are presently pursued in Guinea and Vietnam, respectively.

Besides research, the BNI has many educational and service activities in the area of tropical medicine. Three members of the BNI hold full professorships at the University of Hamburg and are engaged in teaching. A three-month’s course on tropical medicine is held each year and is approved as an officially accredited diploma course by the American Society of Tropical Medicine and Hygiene. The BNI includes a Department of Clinical Medicine with 68 beds and an outpatient clinic where patients with tropical diseases are treated. The BNI performs specialized diagnostic tests for the detection of pathogens causing parasitic diseases. The Institute is equipped with the only true
Amoebiasis research is a major research program in which scientists from several sections work together. This program covers a variety of aspects concerning the biology and pathogenicity of *E. histolytica*. In 1989, the group of Egbert Tannich had first described that pathogenic and non-pathogenic amoebae could be distinguished by molecular genetic methods (Tannich et al. 1989). In fact, the two species *E. histolytica* and *E. dispar* are as distant in evolution as mice and rats. Subsequently, the molecules serving as pathogenicity factors have been determined (Bruchhaus et al. 1996, Tannich et al. 2000). T cells from putatively immune individuals proliferate to onchocercal antigens and produce IL-5 and IFN-γ in contrast to patients with generalized onchocerciasis. The defective response of the latter is due to production of the deactivating cytokines IL-10 and TGF-β. A T cell type resembling the Th3 or Tr1 regulatory T cells has been found in these patients. This T cell is specific for *O. volvulus* and its task may be a specific inhibition of T cell response by production of IL-10 and TGF at the same time scavenging IL-2 (Doetze et al. 2000).

The presence of endosymbiotic rickettsia-like bacteria of the genus *Wolbachia* in most filarial species has been known for more than 20 years. Achim Hoerauf et al. (1999) discovered in murine filariasis that these bacteria are susceptible to tetracycline antibiotics and that their depletion from the nematodes blocks worm development and abolishes fertility. They also demonstrated tetracycline to have no effect on the Wolbachia-free filaria *Acanthocheilonema vitaeae*, demonstrating that the antibiotic has no direct activity on nematodes. Then they conducted a tetracyclin treatment study on onchocerciasis patients in Ghana which showed that bacterial depletion can be achieved long-term and leads to a total and prolonged sterility of female
worms (Hoerauf et al. 2000). The efficacy thus surpasses that of ivermectin and may render an anti- 
*Wolbachia* therapy as a new option for the treatment of filariasis. A combination therapy of doxy-
cycline and ivermectin resulted in a significantly prolonged and enhanced microfilaridermia compared to sole ivermectin treatment (Hoerauf et al. unpublished). The finding that many of the patho-
genetic sequelae of onchocerciasis are due to reac-
tivity to *Wolbachia* antigen or LPS and not to *O. volvulus* itself (Brattig et al. 2000) has a bearing for the therapeutic interventions.

Aids research is also performed in a collabora-
tive effort of several departments. The distribution of HIV is studied in the lymphoid tissue of patients and the antibody response to major neutralizing epitopes of HIV and the cellular immune response are characterized. Recent data from the Department of Pathology showed that the oral mucosal route is a most efficient route of infection due to rapid in-
fected of oral mucosal-associated lymphoid tis-
sue in the simian immunodeficiency virus system (Stahl-Hennig et al. 1999, Zhang et al. 1999a). The quantification of HIV in the lymphoid tissue and the enumeration of productively infected cells showed that the unenlarged lymph nodes of HIV-
1-infected, asymptomatic patients with high CD4 T cell counts are sites for virus replication and CD4 T cell proliferation (Tenner-Racz et al. 1998). This is found also in late stages of the disease and has important implications for therapeutical strategies (van Ende et al. 1999, Zhang et al. 1999b).

Malaria research is another program with in-
stitute-wide cooperations. Ongoing projects char-
acterize the glutathione metabolism (Gilberger et 
al. 2000) and polyamine synthesis of *Plasmodium falci-parum*. These studies demonstrate that the plasmodicidal effect of an inhibitor of glutathion 
synthesis does not depend on its specificity towards 
its target enzyme in the parasite, but on the changed 
physiological needs for the metabolite GSH in the 
P. falciparum-infected RBCs. Therefore the deple-
tion of glutathione is proposed as a chemothera-
peutic strategy for malaria, and gamma-gluta-
mylcyesteine synthetase is proposed as a potential 
drug target (Luersen et al. 2000). *P. falciparum* in contrast to other organisms presents a unique bifi-
ctional ornithine decarboxylase plus S-
adenosylmethionine decarboxylase, an organiza-
tion which is possibly exploitable for the design of 
new antimalarial drugs (Muller et al. 2000).

Clinical studies on patients with severe malaria 
have supported the notion that the immune re-
sponse of T cells may not be beneficial but rather contribute to pathology (Schlotmann et al. 2000). However, NO may have a beneficial rather than a deleterious role in falciparum malaria (Chiwakata et al. 2000). Ongoing work also characterizes the 
repertoire of sporozoite gene expression in the 
mosquito and the proteomics of rhoptry proteins. 
A molecular genetic approach is presently used to 
identify genes involved in susceptibility for or re-
sistance to severe malaria as well as to other tropi-
cal infections such as onchocerciasis. This 
approach involves the scanning of the genome in 
families with defined manifestations of infectious 
diseases.

Besides these major areas of research, a vari-
ety of other agents and issues is investigated. These 
include the regulation of heat-shock protein expres-
sion in *Leishmania*. Novel heat shock proteins are 
identified, their role in infectivity is determined by 
genetic manipulation. Candidate target molecules 
are identified for chemotherapy of filariasis and 
malaria. Key enzymes involved in metabolism of 
glutathion and polyamines in filariae are charac-
terized and cloned. Parasite-specific peculiarities 
of such molecules are exploited as an approach for 
rational drug design. Oligogenic linkage and seg-
regation analysis is performed to identify loci in-
fluencing the intensity of infection with Schisto-
soma mansoni and *O. volvulus*. The epidemiology 
of filariasis and the occurrence in the vectors is stud-
ied. The immune response to *Trypanosoma cruzi* 
in patients with Chagas disease is studied. The role 
of different T cell subpopulations and the effect of 
infections on the behaviour of antigen-presenting 
cells by *T. cruzi* are studied. The immune response 
to an effector mechanisms against *T. cruzi* and the 
rodent filaria *Litomosoides sigmodontis* are ana-
lized in mice (Al-Qaoud et al. 2000). The immune 
mechanisms and possible targets for vaccination 
and therapy are studied in such model systems. 
Novel strategies of vaccination such as peptide-
loaded heat shock proteins (Breloer et al. 1999) 
may be promising in this respect.

The BNI is the only federal institute in the Fed-
eral Republic of Germany equipped with a maxi-
imum containment laboratory (BSL4) for work with 
hemorrhagic fever viruses. The Institute performs 
diagnostic tests for tropical virus infections and 
pursues research on epidemiology, virology and 
immunology of Lassavirus, Denguevirus and Han-
tavirus infections (ter Meulen et al. 2000). The 
recent imported cases of Lassa fever from West 
Africa have demonstrated the essential role of the 
BNI for the diagnosis and handling of such cases in 
Germany.

**OUTLOOK**

In the century of the existence of BNI, parts of 
tropical medicine have changed dramatically, mod-
ern techniques in molecular biology, immunology 
and genetics have changed the scientific look at a
parasite or a disease. In other parts, however, tropical medicine faces the same problems as decades ago. More and novel ones are to come. Overpopulation, migration, globalization, megacities, mass travel and rapid spread of infectious agents are paradigms of future problems. At the beginning of the second century of the existence of Instituto Oswaldo Cruz and Bernhard Nocht Institute their research on infectious diseases is needed as urgently as ever. Today our generation has a number of weapons against infectious agents at hand due to the research financed by previous generations. We owe it to the next generations not to cease in the permanent effort to combat these diseases.

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