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A brief history of the Hubrecht Laboratory

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A fertilised egg, a single cell developing into a complex organism containing millions of cells provides the fascinating puzzle which researchers in the Hubrecht Laboratory investigate at various disciplinary levels. The Hubrecht Laboratory is an independent institute, founded and controlled by the Royal Netherlands Academy of Science. Its mandate is to perform fundamental research with a multi-disciplinary approach, as is essential for understanding the enormously complex and intricate systems which integrate during the development of any organism. To elucidate these mechanisms, we need information from molecular biology, genetics, experimental embryology, and anatomy, to name but a few of the relevant disciplines. The intention for this institute has been to combine much of the necessary expertise under one roof with the idea of easy and productive exchange of ideas and discussion between different specialists.

If we look at the history of the Hubrecht Laboratory, we realise that its present structure is relatively recent. At the time of its foundation in 1916 it was neither as complex nor as specialised as it is now. The old institute was not at all suitable for experimental research, and could hardly have been called a laboratory in the present sense of the word.

We should therefore ask ourselves what the aim of the Hubrecht Laboratory was at the beginning of the century and how it evolved to its present state. Has the changing face of this laboratory reflected changes in the general approach to biological research over this period?

In order to answer these questions, we need to take a closer look at the particular circumstances under which the Hubrecht Laboratory was founded. Moreover, it is of importance to elaborate on the expectations of those who actually founded it, and on the ways in which both circumstances and expectations have changed with time.

We would argue that the role of the Royal Academy in the development of the Hubrecht Laboratory is of particular interest here. After all, it was the Academy which decided to grant the Hubrecht Laboratory the status of Academy institute, and thereby instituted features still present today. If the Hubrecht Laboratory had become, or was, a university department, one might doubt whether its unique multi-disciplinary organisation as described above, would have been established either as soon or as strongly as is now the case.

But before we can take a look at the foundation of the institute, we need to consider the man to whom it owes its name, the Dutch zoologist and university professor A.A.W. Hubrecht (1853-1915). For it was this man, and in particular his collection of embryological material, which prepared the ground for the issues at stake here.

Comparative embryology

It is no exaggeration to state that Hubrecht made the Dutch literally shiver with horror for the blasphemous implications of

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Fig. 1. Janskerkhof, Utrecht. *From a painting of 1670 showing the situation of the future "Hubrecht House" before its rebuilding.*

Fig. 2. The first "Hubrecht Laboratory", Janskerkhof.

Darwin's *Origin of Species*. Soon after he had read Darwin's evolutionary theory, Hubrecht revealed himself as a convinced protagonist, leaving no opportunity unexplored to demonstrate Darwin's credibility. With a passion probably unrivalled in the Netherlands, Hubrecht consequently devoted all of his academic life to convincing the world of the correctness of Darwin's evolutionary thesis.

"How little will you suspect how much the sponge with which you wash yourself in the morning resembled you, at that supreme moment in which both your lives started to exist", he exclaimed for example in one of the leading intellectual magazines of the Netherlands, *De Gids*[1] , in 1889. And at the end of an evening in which Hubrecht, armed with microtome, microscope and pencil, had gloriously demonstrated to the unbelieving audience the similarities between fish, lobster and sponge in their respective embryological states, one of the listeners sighed: "even Hildebrand would have been annoyed with the diligence with which the wonders of nature have been decoded tonight"[2] .

Apart from giving public lectures and writing articles for popular magazines, however, Hubrecht chose to study Darwin's thesis by collecting the material that in his eyes was most appropriate to investigate. Comparative embryology, according to Hubrecht, offered the most promising opportunities for investigation of particularly the theory of descent. For this reason he had already started, very early in his career, to travel around the world in order to obtain embryonic material, initially mostly of lower marine species but later also of the vertebrates.

Legendary anecdotes recall how deeply Hubrecht was devoted to this task. Famous, for example, is the story that Hubrecht offered twenty-five cents for every hedgehog brought to him, which, according to some, resulted in annihilation of the complete hedgehog population in the surroundings of Utrecht. Just as telling in this respect might be the detailed instructions Hubrecht gave to inhabitants of the Dutch East Indies in 1882, in which he not only tried to train them how to recognise and catch specimens of the rare mammals, Tarsius and Tree shrew, but also promised to reimburse all costs made.

At the age of fifty-seven, Hubrecht eventually asked the Minister of Internal Affairs for permission to retire from his educational tasks at the University, so as to be able to devote himself fully to the study of the embryological collection which he had been compiling from the time of his first visit to the Zoological Station in Naples in 1874. One year later, in 1911, the now Extraordinary Professor at the University of Utrecht founded the so-called *'Institut International d'Embryologie'*. Being an international, though very selective society of embryologists, the I.E.E. held regular meetings at which scientific results were presented and discussed[3] . An additional aim was to safeguard the Hubrecht Collection and make it available to the international scientific community. It was one of Hubrecht's hopes that other civilised nations would establish comparable *'Instituts'* and collections.

Yet contrary to Hubrecht's hopes, instead of investigating the descent of man, the civilised nations became involved in the Great War –much to the dismay of Hubrecht's partners in the *Institut International*, we should add. The effects of this War on the fate of the *Institut* were more profound than anybody could ever have imagined. Only three meetings of the board of the *Institut* had taken place when all plans that it might have had were smothered by the echo of the first shots in Sarajevo. The prospects of the *Institut* deteriorated still further with Hubrecht's death in 1915, and after the war had ended, the *Institut* was one of the many scientific victims of the intellectual mistrust that continued to disturb international scientific life well into the twenties.

One can easily imagine that without Hubrecht, without the *Institut International d'Embryologie*, and without the existence of natural successors who were prepared to take their place,

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[1] A.A.W. Hubrecht, 'Over erfelijkheid', *De Gids*, 1889, no.1, p.2.

[2] Nieuwe Rotterdamsche Courant, 29 November 1887. *Gemeente-archief Leiden*, inv. nr. 874.

[3] Initially membership of the I.E.E. was very selective, in accordance with the spirit of the times. However, the I.E.E. survives until today as the International Society of Developmental Biologists, which now numbers many hundreds of members.

[4] Nieuwe Rotterdamse Courant, 2 November 1915, *Universiteitsmuseum Utrecht.*

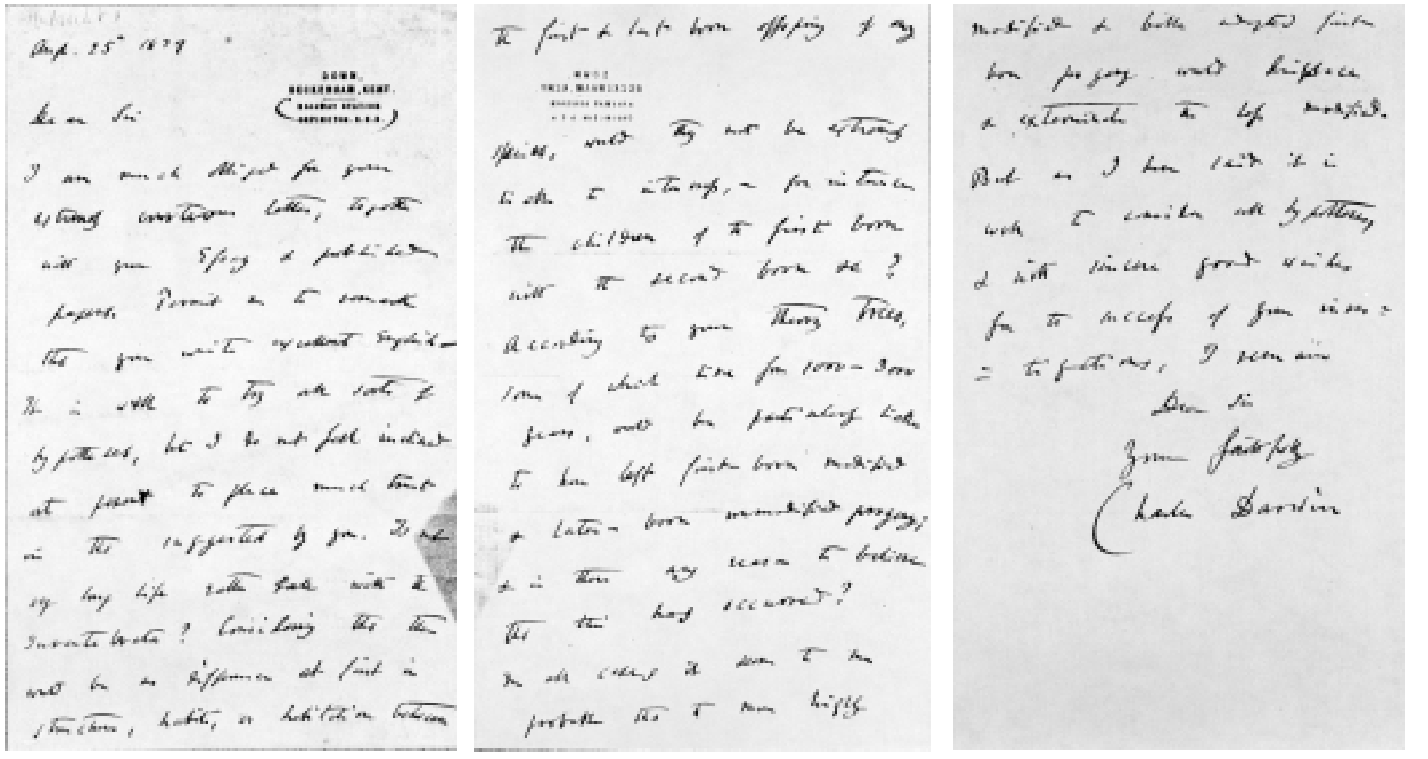

Fig. 3. Hubrecht and Darwin. *In September 1983, while Siegfried de Laat was clearing out some old papers from the bottom of a drawer in his new office, he came across the enclosed letter, written on 25 August 1879 to Ambrosius Hubrecht by Charles Darwin, from his home in Beckenham, Kent. Darwin was courteous, if less than enthusiastic about Hubrecht's new ideas.*

Hubrecht's heritage might simply have fallen into oblivion. However, Hubrecht's fellow Academy-members appeared quite aware of the danger, and after his death immediately jumped into action.

"An international Embryological Institute is of national interest", they wrote in one of the most prestigious Dutch newspapers in 1915. "Although such an institute primarily serves pure scientific purposes, we think nevertheless that a huge national interest is also at state here, and that the honour and the fame of the Netherlands with regard to the peaceful use of science make us responsible that Hubrecht's work not be lost. Let us therefore be sure that when the time comes (i.e. when the war is over), that we are ready to show to every foreigner, that we have done everything in our capacity, even in these turbulent times, to protect and promote science and civilisation."[4]

The most remarkable element in this plea to safeguard Hubrecht's Embryological collection is of course its stress on the national interest. It might strike the modern reader as a somewhat curious intermingling of scientific and political motives. The words

clearly express a sense of moral injustice that science might be threatened with contamination by political incentives. It was the 'peaceful area of pure science' that needed protection, but at the same time this 'pure area' served only national interests.

Yet, to the members of the Royal Academy at that time, no such dilemma existed. To them the notion of 'science' was intrinsically conceded with civilisation, with progress towards a better and more rational world, and with the trust that irrational things like wars would end naturally once the whole world was educated scientifically. To them the Netherlands, being a neutral country in a distorted world, simply had to live up to its duty and continue the scientific quest, irrespective of the temporary state of madness the world was living in. Dutch science, in short, was to serve as an example to the world; it was pure, civilised, enlightened, undistorted –no politics involved at all. The scientific enterprise was not intrinsically bound to places, times or politics, and neither was the Hubrecht collection. To the members of the Academy, Hubrecht's collection was therefore just one of the means that enabled them to continue their scientific quest within, and in the course of time and presumably also beyond, the national borders.

This so-called scientistic attitude also resonated in the choice the Academy made when it appointed a director to the refounded institute. For Daniel de Lange, the man the Academy appointed as the first director of the Hubrecht Laboratory –as it became called officially in 1916– was not only considered to be of outstanding scientific quality, but at the same time was a devout communist. Only the most resolute conviction that science and politics were two absolute and distinguished entities could have sustained the legitimacy of this appointment.

With Daniel de Lange as its director and the Royal Academy as its 'owner', the Hubrecht Laboratory was thus founded. After ample discussion, the Academy decided that its mission would remain more or less similar to that of the *Institut International*. So it would be De Lange's task to maintain and expand the Embryological collection, and to keep it accessible to the international community.

Fig. 4. Daniel de Lange, first director of the Hubrecht Laboratory. *Drawing by Jan Broers (1947).*

It is important to note that the Hubrecht Laboratory, in other words, was solely intended to serve scientific needs. It was not supposed to be a centre for experimental scientific research, but like a museum or a library, it was meant to provide the material necessary for research. And since by its very nature, the collection was suited for comparative embryological research only, the questions it was fit to answer were mainly of a phylogenetic and descriptive kind.

The consequences of this construction for the fate of both De Lange and the Hubrecht Laboratory are now easy to predict. Since Daniel de Lange's most important mission was to promote the Hubrecht Laboratory as an international centre for research, and since the Hubrecht Collection was suited for descriptive research only, the success of De Lange's efforts simply depended upon the extent to which the international community remained interested in the kind of descriptive research which the Hubrecht Collection was fit to answer.

De Lange became increasingly pessimistic in this regard. The number of scientists visiting the Laboratory, or asking for material, was steadily decreasing, he rightly observed at the beginning of the thirties. And this situation did not improve.

With the advantage of hindsight, it is not difficult to explain why. Embryological research in the United States and Germany for example, was moving in a completely different direction, and experimental research was beginning to yield promising results. The legitimacy of these new approaches to developmental biological research was further emphasised when in 1935 Hans Spemann was awarded a Nobel prize for his inquiries into the nature of the 'organizer'. Soon, new theories on the principles of neural induction started to arouse wild expectations, with speculations on the danger of what we would now call genetic engineering in their wake.

One should not forget, however, that the legitimacy of the practice of experimenting –in embryological research, at least– was fiercely contested, and not self-evident at all. This is not the place to analyse this dispute in detail, nor to trace its origins or content, as it is only of importance for this article to notice that whatever discussions embryological experiments evoked, the Hubrecht Laboratory did not participate in them. It persisted in its functions as described above. It was only after De Lange retired and the "young, talented and energetic" Pieter Nieuwkoop was appointed his successor, that the identity of the Hubrecht Laboratory started to change. To these changes we now turn.

Experimental embryology

In 1947, Dr. Chris P. Raven, Professor of zoology, animal geography and comparative anatomy at the University of Utrecht became director of the Hubrecht Laboratory, and his pupil Dr. Pieter Nieuwkoop was appointed deputy Director in charge of daily management. Raven had learned Spemann's experimental techniques from Prof. M.W. Woerdeman of Groningen University, who had learned them in turn from Spemann himself. Nieuwkoop's doctoral thesis, finished in difficult circumstances during the Second World War, made extensive use of these techniques.

Six years later it was considered that Nieuwkoop was ready to take over Raven's place, while Raven assumed the position of chairman of the so-called Embryological Committee –the board of the Hubrecht Foundation Fund.[5] Nieuwkoop remained in this position until his retirement in 1980. During the period of his directorship, the Hubrecht Laboratory underwent a complete metamorphosis, from a small service institute, with two employees, providing information only, to a multi-disciplinary research institute with more than fifty people on its pay-roll.

Fig. 5. The second Hubrecht Laboratory, de Uithof, Utrecht.

One runs the risk, however, of confusing the result of this metamorphosis with its course, if one presumes that it was inevitable. For, besides aiming to establish the necessary conditions for various sorts of scientific research, Nieuwkoop and Raven decided in 1947, for example, to consider the possibilities for re-establishing the Hubrecht Laboratory as "a true international centre for embryological research". Its main task was to "serve the needs of the present embryological community", they decided.

What the embryological community needed most, they stated, was not so much material from the Hubrecht collection, as information. Due to the intellectual isolation caused by the Second World War, the various embryological institutes in the world lacked coordination, they concluded, and were thereby in danger of performing the same investigations, which would be a waste of money, capacity and time.

Accordingly, several international projects were quickly initiated. The first of these was the Normal Table of *Xenopus laevis*, that is, a series of 66 developmental stages and their structural descriptions of an amphibian species that was beginning to be used widely in experimental studies. A young employee was sent out to South Africa, *Xenopus*' native country, to collect embryonic and larval material. This was then sent to ten co-workers in various countries, who were each responsible for a particular series of stages or organ system. The resulting book is still widely used today. A new edition was published in 1994.

The second project was the General Embryological Information Service; a journal devoted to ongoing, compared with completed, embryological studies, containing reports of descriptive, experimental and physiological investigations. Questionnaires were sent out each year to an increasing number of scientists all over the world and their ongoing projects were reported in an annual periodical, arranged geographically. The journal existed for many years.

For the third project Pieter Nieuwkoop made available his own, by then extensive collection of reprints for international reference use. This Collection was duly catalogued as to author and subject and was regularly extended over the years by asking authors to send their reprints. Titles were gleaned by selecting them from a variety of journals. Users could borrow reprints free of charge. Clearly, this Collection was also of great use to the scientists in the Laboratory itself.

Finally, the introduction of International Research Teams in 1954 was also intended to stimulate international cooperation. By inviting every two years a small group of advanced students from different countries to work together for half a year in the Hubrecht Laboratory, Nieuwkoop was aiming more at international communication than at the elucidation of new scientific facts. "Especially for the younger generations, who were unfamiliar with the free exchange of thought between researchers from completely different countries, with completely different characters, temperaments and nationalities, these activities of the Hubrecht Laboratory will be of huge importance", he wrote[6]. The International Research Teams were discontinued when a new director was appointed after Nieuwkoop's retirement.

The most striking element in these early considerations and the actions of Raven and Nieuwkoop is that they still considered the Hubrecht Laboratory as an institute designed to serve the scientific needs of others. They concluded that the division of labour that then existed had already been determined in 1916: that university laboratories were supposed to do embryological investigations, and that the Hubrecht Laboratory was there to administer and to sustain them. It was to be an international institute, in contrast with the University departments, which by the nature of their activities would almost necessarily be of a more local importance.

So, besides trying to exploit the research capacities of the Hubrecht collection, Nieuwkoop initially chose to invest in international communication and coordination and he did so with considerable success. "In those early days the atmosphere at the Laboratory was relaxed and friendly", some recall. "The staff members were the first in our country to call their director by his first name, although Nieuwkoop, perhaps understandably, re-

[5] The Foundation Hubrecht Fund was established in 1916, with capital supplied by the Hubrecht family, The proceeds of the capital were to pay for the budget of the newly established Hubrecht Laboratory, located in Hubrecht's former official residence next to the University Department of Zoology, in the centre of the town. The Hubrecht Fund was, and still is, administered by the Royal Academy. Much later, when the Laboratory was expanding, its budget became part of the Academy's annual budget and was therefore indirectly provided by the Department of Education and Science, as it is still today. The proceeds of the Hubrecht Fund were set aside for special projects.

[6] Preliminary plans for the activities of the future Hubrecht Laboratory as an international embryological institute, undated, present at the Hubrecht Laboratory in Correspondance 24 May 1945 - 10 August 1956.

Fig. 5. International Research Team, 1972.

tained a somewhat paternalistic attitude. Many long-standing friendships were established, particularly among members of the international research teams, and between them and the scientific staff. The latter uncomplainingly devoted much of their time to the international aims of the Laboratory rather than to their own research. All this was no doubt due to Pieter Nieuwkoop's inspiring influence."[7] At the beginning of the 1960's both the General Embryological Information Service and the International Research Teams were running so smoothly that Nieuwkoop considered the time had come to move to a building more suitable to do research.

Metamorphosis

Yet this movement marked the beginning of the metamorphosis mentioned before –a metamorphosis from a small institute designed to serve the needs of the international scientific community to a highly differentiated and specialised multi-disciplinary research institute of uncontested quality.

Since the new Hubrecht Laboratory was built in the outskirts of Utrecht, far away from 'the noise, the dust and the quiverings' of the city, and since it was equipped with many rooms for experimental research, it was ideally situated and suited to develop into a research institute. Within fifteen years the number of research departments increased from one to ten, such that each department, according to Nieuwkoop in 1977, "represented a well-defined part of the whole field of developmental biology". "The scientific aim of the institute is the study and experimental analysis of developmental processes as they express themselves at different levels (in particular the morphogenetic, cellular, genetic and molecular levels), whereby research at the different levels is integrated as much as possible."[8]

To emphasise the international character of the Laboratory, Nieuwkoop always tried to fill vacancies in the scientific staff by appointing specialists from abroad.

So, is this the end of the story? A new building and thus the birth of a Hubrecht Laboratory as we know it today?

No, this is only the beginning. The new building and the presence of ten different and completely autonomous research departments by the middle of the 1970's marked the beginning of a debate in which the question of research priorities, of authority, of position and, eventually, even of existence came to the fore, and which only recently resulted in the demarcation of the Hubrecht Laboratory as we know it today.

In order to understand the vehemence of this debate, we should step back for a moment from the Hubrecht Laboratory itself and consider the scientific landscape from which it emerged. In particular, we should consider the huge changes that occurred in this landscape after the Second World War and their consequences for scientific research –that of the Hubrecht Laboratory included.

For a long time, the performance of scientific research had been a matter of personal interest. Men like Hubrecht, De Lange and Nieuwkoop too, had been free to do the kind of research they thought interesting, valuable or necessary. Only the *output* of their research, i.e. their publications, was evaluated by the scientific, i.e. embryological, community.

With the foundation of a National Research Council in 1946, however, the *input* of scientific research became also a matter of discussion. The possibility of carrying out scientific projects financed by the Council depended after all on decisions which had to be taken before these projects could be put into practice. The implications of this practice of evaluating scientific work beforehand were profound –and to a large extent, we would argue, unintended.

In the first place, since 'quality' was required for projects to be funded, it entailed a debate about 'quality of research', and about the philosophy and criteria which would define that quality. In the second place, since only pure research was granted access to funding from the Council, it provoked discussions about the meaning of 'pure' research, as contrasted with 'applied' research –even in fields where no such distinction was ever considered possible, or appropriate. Thirdly, it forced researchers to formulate their aims and goals explicitly –thereby putting into question the enormous role of tacit knowledge in daily research practices. And finally, by asking researchers to reveal their plans, intentions and expectations on paper, the Council opened an avenue for scientists from different disciplines to discuss their various hitherto tacit assumptions, hypotheses, etc.

Although the Council was instituted as a means for Dutch science to 'catch up' the arrears it had suffered during the War, it also provided the experience and the instruments to steer the direction of scientific activities. These instruments were increas-

[7] Memories recalled by Dr. Job Faber.

[8] Jaarboeken (Annual Reports) KNAW, 1977.

ingly used in the 1970's –not to 'catch up arrears', but rather to respond to the growing request for 'socially relevant research'. Research policy, in other words, became a distinct responsibility for the Dutch government during the 1970's and its goal increasingly became that of debating the needs expressed by scientists and examining possibilities for fulfilling those formulated by society –a delicate matter, indeed.

For the Academy institutes too, the existence of a Research Council had important implications. Since they were excluded from the right to ask for funding, except when it was for projects that did not pertain to their core activities, they were obliged to initiate collaborations with university departments, in order to obtain extra funding from the Council.

Fig. 7. Construction of the new Hubrecht Laboratory, de Uithof, Utrecht 1999.

As long as the Hubrecht Laboratory adhered to its function as an institute designed solely to serve the needs of the international community, it could not identify with the new Research Council. But once it had moved to the new, purpose-built institute and had initiated research departments of its own, things started to change.

For one thing, some members of the newly installed departments supported the idea that cooperation with the universities was desirable and indispensable. For another, some felt that the different departments within the Hubrecht Laboratory should cooperate more extensively, rather than enjoy the pleasures of segregation and solitary intellectual freedom. At the same time, there were some who contested the scientific hierarchy implied by the pursuance of the various disciplines of anatomy, descriptive embryology, biophysics and molecular biology. And lastly, there was a changing political climate, in which the Dutch government was beginning to shift its attentions from the university departments to the so-called 'non-university institutes' and was requiring them to present a clearly demarcated, high quality research programme, whose core activities were sharply defined. These were the ingredients for the debate that characterised the genesis of the present Hubrecht Laboratory.

To the outsider, this debate might appear a somewhat philosophical contest about the possibility of combining a 'reductionist' and a 'holistic' approach to biological problems. Yet there was more at stake than the question of whether the department of molecular biology was to be part of the research programme of the Hubrecht Laboratory, or not. It was rather the question of how to formulate a research programme in which a key issue would be optimal cooperation between the various disciplines.

The formulation of such a research programme not only took time. It evoked highly emotional discussions and mutual distrust among the staff of the Hubrecht Laboratory. It provoked an unprecedented compartmentalisation which eventually led Nieuwkoop to retire in 1980, but eventually a successful research programme was formulated. In close cooperation with a so-called Reorganization Committee, appointed by the Royal Academy, the staff eventually reached agreement about a research programme which induced all disciplines present to cooperate in a quest to answer some basic questions in developmental biology. Instructive for the importance of this research programme may be the fact that Dr. S.W. de Laat was appointed as the new director of the Laboratory only after all members of the Laboratory had given their consent to this programme. Acceptance of it was therefore significant to the birth of the Hubrecht Laboratory as it is today: a multi-disciplinary institute, concentrating on pure research only, and internationally recognised for its high quality.

Concluding remarks

But what about the role of the Academy? At the beginning of this article we stated that the Academy invoked many of the characteristics still present in the Hubrecht Laboratory today and even claims that "if the Hubrecht Laboratory had become, or was, a university department, one might doubt whether its unique multidisciplinary organisation as described above would have been established both as soon and as strongly as it is now".

To some extent the answer has been given. In part, the identity of the Hubrecht Laboratory was shaped by the firm conviction of the Academy that serving the needs of pure science naturally equals serving the needs of civilisation, of rationality, of progress. This was the reason that the Academy instituted the Hubrecht Laboratory, when its very existence was endangered during the Great War.

Yet, these common ideals of science have changed during the last two decades. To many, pure science will no longer lead naturally to social benefit. Quite recently science policy makers have started to respond to this growing uneasiness about pure science by directing their attention towards the structure of the multi-disciplinary funding organisation.

The question nowadays is not only whether research is pure or applied, but whether it might be considered a valuable contribution to existing research programmes. Research is no longer

judged by its intrinsic qualities alone but also in relation to its social relevance.

The Hubrecht Laboratory enjoys a privileged position in this respect. Due to its non-university status, it was forced to construct and evaluate a research programme long before this became the modern policy makers ideal. This has proven to be a research programme with heuristic qualities. It therefore already meets most of the policy makers' requirements. Being an Academy institute nowadays equals being an institute fit to meet the demands put by science, society and contemporary politics.

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