Reference: *Biol. Bull.* **168** (suppl.): 137–152. (June, 1985)

THE ZOOLOGICAL STATION AT NAPLES AND THE NEURON: PERSONALITIES AND ENCOUNTERS IN A UNIQUE INSTITUTION

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INTRODUCTION

When the young Dozent of Comparative Anatomy at the University of Jena, Dr. Anton Dohrn, became obsessed with the idea of building a Zoological Laboratory on the shores of the Mediterranean Sea at Naples, his enthusiasm was riding the crest of a wave of excitement that had spread throughout Europe and eventually reached the North American continent. It was the excitement generated by Darwin's new theory of evolution which was so infectious because it reinforced the new tendency towards a rational and mechanistic explanation of life phenomena that had already been in full development.

The science of Zoology had only recently been established. Only five years earlier, in 1865, Ernst Haeckel had been appointed professor of Zoology at the University of Jena on the recommendation of the great Karl Gegenbaur, then professor of Anatomy and Zoology at the same university, and was provided with a new Zoological Institute. This was the year in which Anton Dohrn received his Ph.D. degree at the University of Breslau under Eduard Adolf Grube (who had been appointed Professor of Zoology there in 1857). Dohrn had studied under Haeckel in 1862, after Haeckel had just become Extraordinarius of Comparative Anatomy in Gegenbaur's institute. In 1868, Dohrn became Privatdozent of Zoology in Jena, but later, in the same year we find him already in England and Scotland, and in 1869 at Messina in southern Italy, carrying out embryological studies on marine organisms. What a restless character he must have been: while a student, he changed universities five times! From the University of Königsberg he went to Bonn, then to Jena, moved to Berlin, and finally received his degree at Breslau. He was indeed a man of action: within a span of only three years after his return from Messina he had established the Zoological Station at Naples which opened its doors in 1873! It must be remembered, however, that at that time the Zoological Station was not yet the international institution it was to become. The Stazione Zoologica was built with Dohrn's private funds. Indeed, the contract with the city of Naples which granted him the right to use the land on which he had built his institute was signed, but two years later. All along it had been Dohrn's intention, however, to offer the services of his institute to scientists from all countries. To make this possible he sought, and obtained, on the recommendations of some of the most important scientists of his time, funds from scientific institutions and governments of many countries to whom he "rented" research facilities: the so-called "tables."

From the beginning Dohrn regarded Zoology as an experimental science and saw the main thrust in the development of morphology, embryology, and physiology. He seized the newly won status of zoology which he described so emphatically in his programmatic paper on "the present state of Zoology and the founding of zoological stations" which appeared in the *Preussische Jahrbücher* (vol. 30) in 1872:

> When thus Zoology with all its branches has acquired new stature and importance, it is not surprising that in zoological circles everyone labors with redoubled

> energy. As after a great victory the members of the victorious nation appear among the other nations with elated selfconfidence and are—albeit grudgingly—regarded by them with increased respect, so appear the Zoologists in the midst of the other scholars in the full consciousness that it is their science that has developed and brought to maturity the greatest concept of modern research, and that it is their task to nurse and extend it, and that the other sciences must receive it and must be fertilized and reformed by it.

In this important publication, Dohrn spelled out the new goals of Zoology: to study the basis of natural selection (*natürliche Züchtung*) and to investigate the evolutionary origins of animal adaptation to the environment. Dohrn envisions an ecologically oriented comparative physiology and emphasizes the need to explain organ functions on the basis of adaptation and evolutionary history. The foundation of zoological stations should provide the ideal places where such a science could be developed.

Dohrn saw, however, another important task in the foundation of marine stations: the opportunities they offer for the rising generation of zoologists. He wanted to provide promising young zoologists with the freedom to carry out research in the most conducive environment a zoologist can find, and to free them from financial worries for the time of their stay at the zoological station.

FRIDTJOF NANSEN: THE STRUCTURE OF THE NERVOUS SYSTEM

The motivation to encourage and support promising young zoologists must have prompted Dohrn to accept, in 1886, a young Norwegian zoologist by the name of Fridtjof Nansen as a guest of the Stazione Zoologica, at a time when neither Norway, nor any of the other Scandinavian countries had reached financial agreements with the Zoological Station. Nansen was keenly interested in a problem that engaged both physiologists and histologists in heated debates: the relationship between ganglion cells and nerve fibers, the nature of the nervous impulse and the cellular basis of the functioning of the brain. Nansen had been led to these questions through his investigation of a class of parasitic annelids, the myzostomids. When he studied the histology of their nervous system he found himself confronted with this fundamental issue and had to discover that the existing research literature could not help to resolve it. He felt impelled to carry out comparative studies.

Nansen has become famous not for his work in zoology, or neurohistology, but for his exploration of the arctic. With Sverdrup he crossed Greenland (two years after his stay at Naples), and from 1890 to 1896 he carried out his exploration of the north pole. As high commissioner of the League of Nations he introduced (in 1921) the famous Nansen-passport, and in 1922 he received the Nobel peace prize. His earlier accomplishments as a scientist and explorer have been recorded in a very readable biography by W. C. Broegger and Nordahl Rolfsen: "Fridtjof Nansen 1861–1893" (1896). This book contains a 22-page chapter entitled "In Naples" which describes, partly in Nansen's own words (quoted from his 1887 article in *Naturen*), the Zoological Station and the great impression Anton Dohrn made upon the receptive mind of the young Nansen.

Nansen, then Curator at the Museum of Natural History at Bergen, Norway, was only 25 years old when he came to Naples. He was dissatisfied with the prevalent histological techniques then available for the study of the structure of the nervous system. He was open-minded enough to recognize the great potential of the new staining method invented and developed by Camillo Golgi at Pavia. A born explorer, he immediately set out to travel to Pavia to get first-hand knowledge of the new method. In 1885 Nansen had won the Joachim Friele gold medal for

FIGURE 1. Fridtjof Nansen sent this portrait to Anton Dohrn. On its back he wrote the following dedication: "Dem Herrn Prof. Dr. A. Dohrn mit vorzüglicher Hochachtung zur freundlichen Erinnerung von Fridjof Nansen Bergen 3. April 1887" (Private archive of the Dohrn Family).

his work on that peculiar class of annelid worms, the Myzostoma (today known as Myzostomida). He accepted the medal in copper and used the value of the gold for his traveling expenses. After a short stay at Pavia he continued to Naples where he was assigned a working space in a large upstairs laboratory already occupied by five other scientists. The Zoological Station had already been open for a dozen years. Numerous countries supported it in exchange for the right to one or more "research tables" for their respective scientists. Norway at that time did not yet participate, and it was due to the generosity of the director of the Statione Zoologica that Nansen was given the opportunity to spend two months at this institution. Upon his return to Norway, Nansen published an article on the Zoological Station in the Norwegian popular science magazine *Naturen.* Excerpts can be found, in English translation, in Brögger and Rolfsen's Nansen Biography of 1896. Nansen's enthusiasm for Anton Dohrn's work and achievements can be gleaned from these quotations:

> The whole basement of the great building is fitted up as an aquarium for the general public; an aquarium which it would certainly be difficult to rival. This great room, with its many tanks, is soberly decorated, with a complete avoidance of all humbug [sic] or fantastic ornament, which would only serve to distract the attention from its essential purposes. It has a great attraction not only for the ordinary traveller, but for the scientific student as well. Down here he is able to pass hours in communion with nature, and face to face with the rarest of marine organisms, and in a comparatively brief time he may learn more of the life of the world than he could by long grubbing in volumes of printed wisdom, or rooting through the dead treasures of museums. He will contract the habit of using his eyes and of his powers of observation upon living nature, and learn to regard life as the essential object of research.
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> Acquaintance with the Station, for the majority of tourists, does not extend beyond this room. Far more important to science, however, are the laboratories situated in the upper stories of the building. Here naturalists from almost all European countries are at work, here they have everything they can possibly require for their studies. They can come to the Station, sit down at the work-table assigned to them, tell the Curator, Salvatore Lo Bianco, what particular animals they want, and presently the animals are brought alive to their very tables, where they can study them at leisure, with no need to stir from their places except for meals and sleep. Instruments, smaller tanks in which to keep the animals alive, and an excellent library, are all just at hand. This concentration of appliances is the novel and important feature of the institution. . . . If the workers are tired of the laboratory, they are free to go out in the vessels belonging to the Station, and watch the gathering in of fresh specimens. Beside several fishing boats, the Station owns two small steamers. . . . These steamers and boats are equipped for dredging, trawling, net-fishing, surface-fishing, and so forth. They are also supplied with diving apparatus, so that in this way, too, you can fetch up whatever you want.

What was it that Nansen wanted to accomplish at Naples; what actually did he accomplish? When his biographer W. C. Brögger inquired of Anton Dohrn what he remembered of Nansen's stay in his laboratory, Dohrn felt somewhat embarrassed that he could not be of much assistance; all he could recall was that Nansen was working "mainly on *Amphioxus* and on *Selachians,* making use of the new Golgi method." Dohrn recalled, however, that Nansen was "a smart dancer, who certainly did not disdain the company of lively ladies. I believe not to err when I report to you that a beautiful Scottswoman competed dangerously with his studies and presumably was the cause of his exchanging Naples for Rome earlier than he had originally intended."

In actual fact, Nansen had used his time very well indeed. Of course, the research he did at Naples was only a part of a wider ranging endeavor. He continued his comparative studies on the nervous system in Bergen where he also received from Naples more specimens of *Amphioxus,* "most excellently prepared in different ways by Salvatore Lo'Bianco." Already at Naples he had immersed himself in a thorough study of the research literature. It seems incredible that already in 1887, only one year after his return from Naples, where, after all, he had spent only two months, Nansen published a 214-page monograph with 11 plates, entitled *The Structure and Combination of the Histological Elements of the Central Nervous System.* Fully 80 pages of the monograph are devoted to the history of the subject. His literature list is respectable and amounts to no less than 21 pages. In this very illuminating account of the research of others and of his own, Nansen reaches conclusions about the general structure and function of nervous systems. Because he investigates ganglion cells mostly in invertebrates, and studies only the spinal ganglion cells of vertebrates, he assumes that ganglion cells have mainly a nutritive function. He correctly interprets the nature of what Franz Leydig had called the "*Punktsubstanz,*" and what later became to be known as the neuropil, as being composed of innumerable fine nerve branches. He also correctly interprets the course of nervous excitation during reflex actions. As to the connections between ganglion cells and nerve fibers he is somewhat ambiguous but favors the view that nerve fibers are outgrowths of ganglion cells.

It may seem surprising that Nansen does not once mention the work and ideas of Anton Dohrn on the subject, but Dohrn's research on the nature of nerve cells and ganglion cells had not yet advanced to the stage of publication, and the subject may never have come up in conversation between these two men. There was, however, an Hungarian neurohistologist working at the Zoological Station who certainly influenced greatly the thinking of Anton Dohrn, and who also was well acquainted with Fridtjof Nansen. He was Stephan von Apathy from Koloszvar. Apathy had developed a staining method involving gold-chloride, formic acid, methylene blue, and hematein, which permitted the demonstration of a "*Fibrillengitter:*" ganglion cells and nerve fibers were shown to contain fibrils. Apathy's preparations seemed to indicate that these fibrils formed a continuous network throughout the nervous system. The fibrils were seen to cross from one cell process to the next at their contact points. Apathy considered these fibrils to be the true conducting structures of the nervous system. Apathy was indeed an excellent histologist, and his superb preparations convinced and influenced many of the leading histologists, among them Wilhelm His, Franz Nissl, Max Bielschowsky, and Hans Held.

That it should have been possible to subscribe to the notion that the neurofibrils (to use a modern term) are the "conducting elements" of the nervous system is almost incredible when one remembers that electrophysiologists (Du Bois-Reymond, Hermann, Bernstein) had long before established the electrical nature of the nerve impulse: it would have been inconceivable to the biophysically trained physiologists that separate action currents can be conducted within a given nerve cell or even within a nerve process. Evidently, electrophysiology (today this would be called biophysics) was not taken that seriously by the histologists, and even a physiologist like Albrecht Bethe became so impressed by Apathy's results that he was willing to accept the hypothesis that the fibrils and not the nerve fibers are the true elements (or 'units' as we would say today) of the nervous system.

In their Nansen biography, Brögger and Rolfsen (1896) quote a letter evidently written to them by Apathy, who reminisces about the life he and others shared with

Nansen while they were at Naples. "One of these friends, a Hungarian scientist," they state,

> writes to us: 'He was the life of all our little festivities. Most of the students then working at the Station were in the habit of meeting at the Cafe Basta on the Corso Vittoriao Emmanuele; every evening at suppertime there was a little feast here, a musical gathering, light-hearted and refreshing in the highest degree. Nansen contributed greatly to the prevailing gaiety. It some times happened that we devotees of science became so enlivened with wine and music, that we proceeded to dance a quadrille; and on these occasions Nansen was Master of Ceremonies.
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> 'Once we chartered a carriage to drive to Castellamare and Sorrento by the famous coast road. On the way, another carriage with two ladies came up behind us. The ladies amused themselves by racing us and laughing at us as they shot past; whereupon Nansen sprang out of the carriage and ran by the side of the horse a long stretch of the way. Thus we overtook the ladies again, to the unbounded merriment of both parties.
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> 'In Sorrento Nansen met some Norwegian ladies. I was very tired and went to bed; but the Norwegian ladies wanted to get up a dance, and as there was a scarcity of partners, my presence was required. Nansen declined to give a moment's peace till I got up and dressed myself. Then he dragged me into the drawing-room, where we were greeted with loud applause by the ladies, who were quite alive to the situation.
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> 'At other times he would be quiet and absorbed, and would sit by the hour without uttering a word. I have seen him at the foot of Vesuvius, among the ruins of San Sebastiano, and on the melancholy lava-wastes. San Sebastiano was devasted by the eruption of 1874; nothing was left but a church. I have seen him sitting on a block of lava there by the church, hour after hour without stirring; he simply sat and gazed out into the distance. Time after time we others tried to make a start, and called to him—he never moved. Afterwards, on the way home, as he and I walked together, arm in arm, I tried to make him talk, but found him absolutely mute—there was not a word to be got out of him.'

ANTON DOHRN: THE NERVE FIBER

Before continuing with Stephan von Apathy and his impact through the Zoological Station at Naples, let me return once again to Anton Dohrn. With an immense effort, Dohrn occupied himself with his "Studien zur Urgeschichte des Wirbelthierkörpers" (Studies on the early history of the vertebrate body). As by a magnet he was drawn to the problem of the structure of the nervous system which he tried to resolve by studying lower vertebrates and their embryological development. It was a heroic effort of trying to understand the central nervous system of higher vertebrates on the basis of Haeckel's "biogenetic law," the notion that ontogeny recapitulates phylogeny and that any structure found in higher organisms must have its primitive counterpart in the earlier stages of evolution as represented in primitive animals. The question was, in Dohrn's words, "is the nerve fiber an outgrowth of the ganglion cell? or is it composed of numerous cells, the exponent of which can be regarded the Schwann nuclei?" Dohrn called the decision of this question "the foundation of our ideas about the nervous system." In the 16th of his "studies" he comes to the definite conclusion that the nerve fiber arises through the fusion of Schwann cells and that "the central ganglion cells have nothing to do with the beginning of the axis cylinder or the entire formation of the nerve fiber." Ganglion cell and nerve fiber are connected by contact, they are not genetically related. In his views, Dohrn finds himself supported by Apathy whom he quotes extensively.

Shortly after publication of his 16th "Studie" in 1891, Dohrn was plagued by doubts about the correctness of his interpretations. He rushed into print a retraction in the *Anatomischer Anzeiger* (vol. 7, p. 348). The famous Anatomist Albert Koelliker had announced a Lecture to be given at the Congress of Anatomists to be held in Munich with the ominous title "Ueber die Entwicklung der Elemente des Nervensystems, contra BEARD and DOHRN." Because of Dohrn's retraction, the actual lecture had the simpler title ". . . contra BEARD." Ten years later, Dohrn decided that he should not have retracted his views. His doubts, he said in his 20th "Studie," had been mainly "of subjective origin, and were due to a nervous depression caused by overwork, climatic and other influences, the like of which I unfortunately had to suffer repeatedly due to the abrasive work and the complicated conditions of life connected with my position as director of the Zoological Station" (p. 139, vol. 15 of the *Mitth. Zool. Stat. Neapel,* 1901).

It would be unfair to judge Anton Dohrn by his, by present standards, misguided endeavor to solve once and for all the enigma of the cellular relationship between ganglion cell and nerve fiber. Dohrn's vision was far more wide ranging, and truly important. He clearly saw the need to encourage the development of comparative physiology and biological chemistry, and he was able to generate interest in the enormous potential of a marine laboratory for the expansion of knowledge in this important area of experimental biology. Many of the important physiologists were attracted to the Zoological Station, among them Max Verworn, Sigmund Exner, Jaques Loeb, Willem v. Einthoven, and Jacob von Ueuxküll.

In 1906 Dohrn created, with newly acquired funds, departments for physiology and for physiological chemistry in the Zoological Station; he employed H. Burian and M. Henze as heads of these departments. Dohrn motivated Otto von Fürth to write the influential *Vergleichende chemische Physiologie niederer Tiere* (Jena, 1903), probably the first text of biological chemistry. There can be no doubt that it was due to the influence of Anton Dohrn and his Zoological Station that Winterstein was induced to publish the monumental *Handbuch der vergleichenden Physiologie* (published in eight volumes between 1911 and 1925, together no less than 9321 pages!): almost all of the authors had been working at the Zoological Station. Like this Station, the *Handbuch* was an international affair: the contributing authors hailed from eight different countries.

Already in the late 1890's, Hermann J. Jordan had been Dohrn's private assistant. Later, Jordan was to become one of the most influential comparative physiologists. On the recommendation of Jordan, T. H. Morgan appointed two of Jordan's pupils to important posts at the California Institute of Technology: C. A. G. Wiersma, and A. van Harreveld. The work of these great neurobiologists thus reflects the heritage of Anton Dohrn.

ALBRECHT BETHE: GANGLION CELL AND REFLEX

The neuron doctrine, enunciated by Wilhelm Waldeyer in his famous paper in the *Deutsche Medizinische Wochenschrift* of 1891, was welcomed by physiologists. But neurohistologists like Held, Nissl, and others, continued either to oppose it or to regard it with utmost caution. In 1896, Albrecht Bethe, a pupil of Goltz in Staßburg, later professor of Physiology at Frankfurt, came to Naples to study the nervous system of the shore crab, *Carcinus.* His goal was a complete histological and physiological description of the neurons in what he then considered to be a "simple nervous system." His encounter with Apathy forced him to completely revise his ideas about structure and function of nervous systems. In his important

book *Allgemeine Anatomie und Physiologie des Nervensystems,* published in 1903, Bethe writes that he had been skeptical at first of Apathy's papers:

> because of the aprioristic form in which they were written, and because of the peculiarity of the result which were suported either with no pictures at all, or with only schematic illustrations. My doubts disappeared rapidly, however, when Mr. von Apathy, on the occasion of our meeting at the Zoological Station at Naples in the Fall of 1896, had the kindness to show me his preparations. On the evening before this memorable day I had still told him that I considered what he had published outside of all possibilities, and that it must be due to self-deception when he thought that he could follow such fine fibrils individually for millimeters. What has been shown to me then, however, was of such convincing clarity, that I was forced, after some pretended objections, to relinquish my opposition. What happened to me was experienced by many others, and nobody of normal vision can elude the convincing impression of Apathy's preparations unless his eye is beclouded with envy or injured vanity.

As a consequence of his "conversion," Bethe looked at the nervous system as a syncytium. The ganglion cells were unnecessary to explain reflex actions, as he demonstrated by an experiment that henceforth would be known in the literature and in physiology texts as the "Bethe experiment." In Naples, working with *Carcinus,* Bethe did the following experiment: he removed the ganglion cells that surround the neuropil of the second antennae, severed the connections between this neuropil and the rest of the nervous system, and cut the esophageal commisures. He noted that the antennae still maintained their tonus and that they were held stiffly in their normal raised position. When mechanically stimulated the antennae were retracted, but afterwards were once again extended. From this experiment Bethe concluded that ganglion cells are either unnecessary for these reflexes to occur, or the reflex arcs do not go through the ganglion cells. As he was convinced now that it is the fibrils which serve as the connecting elements, he concluded that the "Primitivfibrillen" (the elementary fibrils of which the composite fibrils are composed) are the true conducting elements of the nervous system.

Bethe's experiment was widely quoted by those opposing the neuron doctrine. Indeed, Bethe himself declared "we must stop considering the neuron as a physiological unit and must admit that one and the same neuron is capable of many diverse actions, depending on which fibrillar tract is in operation."

The Zoological Station at Naples was indeed a cross-roads of the biological sciences. The meeting there between Apathy and Dohrn who became close friends, gave Dohrn the needed confidence that he was on the right track, that he had solved the riddle of the fundamental cellular nature of the vertebrate nervous system. Dohrn's work in turn gave affirmation, as did Apathy's work, to the many histologists (and physiologists) who opposed the neuron doctrine. The meeting of Apathy and Bethe led Bethe to completely reconsider his ideas about the structure and function of the nervous system. In 1893, Bethe had set out to completely describe the nervous system of what he considered to be a simple animal using neurohistological techniques as well as physiological experiments. He went to Naples with the express idea of "mapping the nervous system," of describing all its neurons and their interconnections—a task which has not been tried again until C. A. G. Wiersma began his pioneering studies of the central nervous system of crayfish in the late 1950's at the California Institute of Technology (see *Identified Neurons and Behavior of Arthropods,* edited by G. Hoyle, 1977). Bethe could have accomplished much of what neurobiologists started to do six decades later, had he not been discouraged by the histological findings of Apathy which he was able to confirm in

his own work on *Carcinus* carried out at Naples. It is touching to read the final passage of his third report on his *Carcinus* experiments which was published in 1998:

> When I began this work three years ago, I expected to advance with my knowledge of the anatomical structure of the Nervous system of *Carcinus* to a point where I could describe about all the nervous elements and their branches. After preliminary studies I considered their interconnections not to be too complicated, and I believed I should be able to clearly reveal the significance of each by physiological experiment. At that time it seemed that if this was achieved we would be very much closer to an understanding of the nervous system. The epochal work of Apathy has shaken this hope in its foundations.

It would now be necessary to discover the course of each single fibril—"and this is unthinkable. As I now overlook my whole work, I reach the sad conclusion that nothing has been gained from it for our factual knowledge. Were there not satisfaction in the search for knowledge, one would have to say in resignation: it is too difficult for us humans."

The "Bethe experiment" on *Carcinus* has been a stumbling block for the general acceptance of the neuron doctrine which holds that the axon is an outgrowth of a ganglion cell, that all nerve cells are ganglion cells (while Schwann cells like most other cells of the nervous system, are glia cells), and that each neuron is a separate unit which does not fuse anywhere with another cell, contacts being only in the nature of synapses. In 1909 the famous Otto Langendorff, writing in Nagel's authoritative *Handbuch der Physiologie des Menschen,* debates the Bethe experiment. He accepts Bethe's conclusions as valid for crustaceans but expresses the opinion that "reflexes of invertebrates are perhaps of a lower level," hence the neuron theory can still be valid for vertebrates. As late as 1927, another well known German physiologist, Emil Abderhalden, states in his textbook of Physiology (*Lehrbuch der Physiologie,* 1927, p. 115) that it is "an established fact" that the nervous system is constituted of cells which are interconnected by strands of fibrils. Bethe's experiment on *Carcinus* plays an important role in Abderhalden's arguments.

STEPHAN VON APATHY: NEUROFRIBRILS

In the history of neurohistology, Stephan von Apathy has been of great importance. The major breakthrough was the development of new staining methods while he was working at the Stazione Zoologica at Naples. For three years (1886–1889) Apathy occupied the Hungarian "research table" at Naples. Anton Dohrn assigned to him the task of writing a monograph on the *Hirudinea* for the now famous *Fauna und Flora des Golfes von Neapel.* Both men became close friends. Apathy based much of his later speculations on the fine-structure of the nervous system on whole-mount preparations of the gastrointestinal tract of the marine leech *Pantobdella muricata.* His publications, especially his paper "Das leitende Element des Nervensystems und seine topographischen Beziehungen zu den Zellen," published in 1897 in the Zoological Station's "house journal," the then prestigious *Mittheilungen aus der Zoologischen Station zu Neapel* (vol. 12), generated excitement and heated debate among neurohistologists.

In 1870, Apathy was appointed to the chair of Zoology at the University of Kolozsvar. He was 27 years old. A few years later he was also in charge of the chairs of histology and embryology (see the biography by A. Abraham, 1963). Kolozsvar is the Hungarian name of the former capital of Transylvania, an old Hungarian settlement which, mostly in the 13th century, received German settlers

and was named Klausenberg. It became part of the Austrian empire in 1691, and was claimed and occupied by Hungary in 1848. As Albrecht Bethe remembers in his obituary of Stephan von Apathy, who died in 1922, von Apathy returned unopened any letter addressed to him at "Klausenburg." His Hungarian nationalism was so strong that he refused to travel through Austria, an attitude which made it a matter of some complexity to reach the Zoological Station at Naples. Stimulated by the example of Anton Dohrn's accomplishments at Naples, Apathy instituted a "table system" at his institute and provided foreign scientists with laboratory space where they could carry out histological studies and get acquainted with his widely acclaimed techniques. Among his guests were Albrecht Bethe, Wilhelm Waldeyer, and a Dutch histologist, J. Boeke, who later became a famous neurohistologist and extended Apathy's studies to the mammalian autonomic nervous system. Boeke remained critical of the neuron theory and maintained that autonomic nerve fibers terminated in a terminal reticulum composed of (neuro)fibrils. Typical of his point of view is his paper of 1949 "The sympathetic end formation, its synaptology, the interstitial cells, the periterminal network, and its bearing on the neuron theory" (*Acta Anatomica* **8**: 18–61). Like Anton Dohrn, Apathy traveled widely to many European universities and became personally acquainted with the best scientists of his day. He put his whole effort into establishing a new "Zoological Station" at Koloszvar, and in 1909 his new Zoological Institute, one of the finest in all of Europe, was opened—complete with loggias and extensive facilities for the maintenance of freshwater and marine animals. As in Naples, the public facilities (the aquaria, museum, lecture rooms), were on the lower floor, the two upper floors contained the research laboratories, the administration, and the library.

How Apathy would have liked to show off his accomplishment to his friend Dohrn! Fate decided otherwise: on 3 October 1909, Apathy attended the funeral service for Anton Dohrn at Jena.

With the end of the first world war, the golden era of Apathy's institute and of his scientific career came to a sudden end. Apathy had become a politician but could not prevent the take-over of Transylvania by Rumania. When he was released from prison, he accepted a position at the Hungarian University at Szeged and tried once again to create a new zoological institute. He no longer had the strength; he died two years later.

J. C. Alexandrowicz: Stretch Receptor Neurons

Stephen von Apathy had survived Anton Dohrn by eleven years. In the meantime, the directorship of the Zoological Station at Naples had been transferred to Anton Dohrn's son Reinhard Dohrn, who, except for his years of exile during 1915–1924, conducted the affairs of the Zoological Station at Naples, guiding this prestigious and precious institution through the political turmoils of a nationalistic era and the so-difficult war and post-war years until he relinquished his leadership to his son Pietro Dohrn in 1954. (The accomplishments of Pietro Dohrn and the later history of the Zoological Station have been critically reviewed in leading articles in *Science,* 1969, and in *Nature,* 1983).

Reinhard Dohrn's diplomatic activities succeeded in 1924 to reach an agreement with Polish authorities to establish a Polish research table at the Stazione Zoologica. One of the faithful scientists using this table was J. C. Alexandrowicz, professor of ophthalmology, and from 1937 Undersecretary of State in the Polish Ministry of Education. Alexandrowicz's meticulous neuro-anatomical studies of crustaceans and cephalopods using methylene-blue staining techniques have earned him a sepcial

place in neurobiology. Perhaps his most important discovery, rivaled only by J. Z. Young's discovery of the giant axons of squid, are the stretch receptor organs of crustaceans. Although this discovery was made at Naples just before the second world war, it became known to the scientific world only several years after the end of the war: when the war started, Alexandrowicz became an officer of the Polish military medical corps. After the defeat of Poland when this country was divided up between Germany and the Soviet Union, Alexandrowicz was taken prisoner by the Russian army, and then was sent with the Polish expeditionary force, known as the Anders Army, to North Africa to help the British defeat the Germans. The contingent, in which he served as education officer, never saw action. When the war ended, Alexandrowicz was taken to England to become a farm laborer. It was Reinhard Dohrn who traced him with the aid of the Red Cross, and, through his connections with members of the Royal Society, initiated the establishment of a special professorship for Alexandrowicz at the Marine Laboratory at Plymouth. Alexandrowicz had lost all his valuable preparations. He now repeated his investigations and in 1952 began his series of publications on the structure and histology of crustacean stretch receptors that have become classics.

Alexandrowicz's investigations are the basis of important physiological work that was begun almost immediately after their publication and led to those discoveries (*e.g.,* Kuffler and Eyzaguirre, 1955) that have become the key to our understanding of how sensory neurons translate a stimulus into a series of nerve impulses, how they encode stimulus strength into an impulse frequency. Alexandrowicz described an efferent innervation of the stretch receptor neurons which was shown later to be purely inhibitory (Eyzaguirre and Kuffler, 1955). The crustacean stretch receptor preparation thus became an important tool in the investigation of inhibitory synaptic transmission. It was in these stretch receptor neurons that the first evidence was obtained that γ-aminobutyric acid (GABA) is the transmitter substance of inhibitory neurons, and that the transmitter action can be blocked by picrotoxin (Florey, 1953; Bazemore *et al.,* 1957). Indeed, it can be said without exaggeration that the stretch receptor neurons discovered by Alexandrowicz at the Zoological Station at Naples have been a cornerstone in the development of neurophysiology. To mention only two of the key findings: it was on stretch receptor preparations that the Japanese physiologist K. Uchizono showed for the first time that inhibitory nerve terminals are characterized by clear oval synaptic vesicles—in contrast to cholinergic terminals which always contain clear round vesicles. The work of the Swedish physiologist D. Ottoson on isolated stretch receptor neurons provided the first clear proof that the site of initiation of the nerve impulse is not the soma of the nerve cell, but the initial segment of its axon.

ERNST SCHARER: NEUROSECRETION

The Zoological Station has been instrumental in yet another important advance in the field of neurobiology: the discovery of what has become known as "neurosecretion," the elaboration and secretion of hormones by nerve cells. In 1928 Ernst Scharrer, then *Assistent* under Karl von Frisch at the Zoological Institute of the University of Munich, was granted the use of a research table at the Zoological Station at Naples. As he stated in a letter to Reinhard Dohrn, he wanted to fix the brain of many species of fish, and "if possible to investigate, with the aid of methylene blue staining, the innervation of the epiphysis." He discovered that certain neurons in the midbrain show evidence of secretion, confirming earlier findings of Carl Speidel (1919). With material from Naples, Scharrer continued his

studies on these "neuroglandular" cells of fishes and extended these studies to higher vertebrates where the same cell type was found. After he had married another pupil of von Frisch, Berta Scharrer, the inseparable couple continued to explore the comparative aspects of "neurosecretion," as the phenomenon was soon to be called: Berta Scharrer in invertebrates, Ernst Scharrer in vertebrates. Their association with Reinhard Dohrn and the Zoological Station became important not only for the development of this important field of neurobiology; the political situation in Germany made life intolerable for the Scharrers, and it was Reinhard Dohrn who helped with their emigration to the United States.

Already before the end of the second world war, in 1944, American scientists like R. E. Cooker (Chapel Hill), A. R. Moore (Oregon), and Ernst Scharrer, urged the president of the National Research Council (the precursor of the National Science Foundation) and Italian authorities to reopen the Statione Zoologica and to support the directorship of Reinhard Dohrn. Thanks to the untiring effort of Ernst Scharrer, who had moved from Ohio to the Department of Anatomy at Denver/Colordao, the National Research Council, as well as Columbia University (Wilson Fund), the American Association for University Women, and the American Society of Zoologists were persuaded to contribute funds in support of the Naples Zoological Station. In the summer of 1946, the president of the National Research Council, Ross Granville Harrison (whose activities at Woods Hole are discussed in other contributions of this Symposium) set up a Committee, chaired by Ernst Scharrer, to aid the Zoological Station at Naples. The Committee, which included as its members E. G. Conklin, Mrs. E. B. Harvey, R. G. Harrison, S. Hecht, L. H. Kleinholz, A. R. Moore, and H. H. Plough, met for the first time on 14 August 1946 at Woods Hole to decide on a program-in-aid to assist in the re-establishment of the Zoological Station at Naples as an international center of biological research. The program envisioned the establishment of additional American research tables, a fund-drive to improve and enlarge the library, and a shipment of food for the Mensa. Further plans concerned the modernization of the laboratory facilities and research equipment. The activities of this committee led to contributions by the Rockefeller Foundations and the UNESCO. The committee advised the Zoological Station in matters of library acquisitions and the purchase of research equipment. After 1950 the newly established National Science Foundation, the Lilly Endowment, Inc., and the Rockefeller Foundation increased the American engagement in the affairs of the Zoological Station enormously—but this is not the place to record the international ramifications of the Zoological Station and the history of the material support it has received from the international scientific community (which, after all, includes members of other nations that have made substantial contributions to the development of the Zoological Station). We return, therefore, to the topic of the role of the Zoological Station at Naples in the development of neurobiology.

On the initiative of Ernst Scharrer and Wolfgang Bargmann, the Zoological Station hosted, in 1953, the first International Symposium on Neurosecretion (this was the fourth international symposium held at the Zoological Station). This event has a special place in the history of biology because it was this symposium that established the concept that neurons produce hormones and that neurosecretion is an essential feature of the chemical control of animal development and function.

J. Z. Young: Giant Axons, Learning and Memory

It is impossible to review the relationship between the Zoological Station and the neuron without mentioning the research on the giant axons of squid, discovered

by J. Z. Young in 1936 when he worked at this institution. Since Prof. Young will review the history of this discovery in his lecture, it will be sufficient to restrict the discussion here to some further development of research made possible by the incredibly large size of the "giant synapses" between second- and third-order giant axons. In 1966 Berhard Katz and Riccardo Miledi from the University College in London came to the Stazione Zoologica to investigate the relationship between calcium and transmitter release. Their experiments have become classics; they prove that extracellular calcium is essential for transmitter release to occur and that calcium ions enter the nerve terminal when this becomes depolarized by the incoming presynaptic action potential.

The year-round availability of *Octopus* at Naples, and the recognition of the advanced development of the brain of these animals has prompted Y. Z. Young to embark, at the Statione Zoologica, on a study of learning and memory in these creatures. This was made possible by a large grant to the Stazione Zoologica for the establishment of a large "cephalopod facility" which, in its best days, included more than two hundred tanks in which as many octopuses could be individually housed and maintained. Together with several collaborators, especially Bryan Boycott, Martin Wells, and John Messenger, he mapped the neuronal circuits of the octopus brain and through ingenious training experiments he explored the learning ability of these animals. These studies led to new concepts of the neuronal mechanisms underlying memory. Several important monographs resulted from this research: M. J. Wells: *Brain and Behaviour in Cephalopods,* 1962; J. Z. Young: *A Model of the Brain,* 1964; J. Z. Young: *The Anatomy of the Nervous System of* Octopus vulgaris, 1971; and J. Y. Young: *Programs of the Brain,* 1978.

Conclusion

By providing research facilities near the sea where marine animals can be readily obtained and maintained, and, more importantly perhaps, by providing the intellectual atmosphere conducive to intensive research and stimulating interaction with other scientists, the Stazione Zoologica has permitted major advances in neurobiology to occur. As long as this institution was able to pursue the goals envisioned by its founder, Anton Dohrn, it was eminently successful. But such simple words cannot explain the impact the Zoological Station at Naples had on biologists all over the world. Intentionally I use the word 'biologists' and not the abstract form 'biology.' The Stazione Zoologica has been dominated by the spirit of its former directors, by the immense human dimension of its founder Anton Dohrn, by that great European, Reinhard Dohrn . . . all this has been attested to by so many public statements, that no further emphasis is needed. The most recent eulogies were presented (typically, in four languages) by dignitaries from many countries on the occasion of the celebration of the 100th birthday of Reinhard Dohrn on 13 March 1980 in the Vila Pignatelli in Naples (*Reinhard Dohrn 1880–1962,* edited by C. Groeben, 1983).

And yet, neither the location nor the personalities of the directors can explain the miracle of the "Naples experience" (to quote Maurice Wilkins) or the affection all those great scientists felt, and still feel, for the Zoological Station. Good research institutes can be found in many places in many countries, and the Statione Zoologica is certainly not among the best equipped laboratories—perhaps it never was! Nor has it been attractive because it harbored a local scientific genius at whose feet it was desirable to sit, in whose laboratory it was essential to learn methods unattainable anywhere else. The idea of an international home for an international science, nay, for the unfettered pursuit of the highest ideal of science, this original idea of Anton

Dohrn was so infectious, that, from the start, it caught the imagination of all those great minds who came in contact with it: Charles Darwin, Thomas Henry Huxley, Thomas Hunt Morgan, Edward Beecher Wilson, Hermann von Helmholtz, Emil Du-Bois Reymond, Filippo Botazzi, Silvestro Baglioni—and Fridjof Nansen, Stephan von Apathy, Albrecht Bethe, J. C. Alexandrowicz, Ernst Scharrer, J. Z. Young, but also of Benedetto Croce, Theodor Heuss, . . . the list is endless.

The Zoological Station became a place of the mind, an ideal jointly possessed and cherished by all those who experienced it. This is the reason why the organism of the Zoological Station was able to survive: not because it was itself strong enough to surmount all the adversities it encountered in its long history, but because it was revived from the outside on the strength of the idea carried by the community of all those who kept this idea alive and found ways to revitalize it both spiritually and materially. Science is not an abstraction but an immensely human activity. It is lived, not written, thus it needs a true home, not only a laboratory or an office. The Zoological Station at Naples has been such a home and has been, and is being regarded with that special kind of nostalgia accorded only to those special places in which the true spirit of man is recognized. Thomas Hunt Morgan called it a "holy city." Our present age would do well to live up to its tradition.

The brief histories given here are the stories of important scientists and of their important discoveries. But they are also memorials of great ideals, passions, and sacrifices, and they bear witness to the importance of a great dream which happened to come to life at Naples in the Zoological Station, the creation of that remarkable man, Anton Dohrn.

ACKNOWLEDGMENTS

The passages quoted from the writings of Anton Dohrn, Albrecht Bethe, and Ernst Scharrer, have been translated into English by myself. I am grateful to the librarian of the Stazione Zoologica, Walter Groeben, for making available to me the original sources of the scientific literature referred to. I am especially grateful to Christiane Groeben for providing access to the Dohrn Archives which she has so impressively filed and organized, and for providing copies of relevant documents and correspondence. I am indebted to Professor John Edwards of the University of Washington for introducing me to the Nansen biography of Brögger and Rolfsen (1896), and for lending me his copy of Fridjof Nansen's so important, and unjustly forgotten work *The Structure and Combination of the Histological Elements of the Central Nervous System* (1886). Much of the biographical and historical information on the history of the Zoological Station stems from the invaluable recent work by Karl Josef Partsch *Die Zoologische Station in Neapel, Modell internationaler Wissenschaftszusammenarbeit* which provides extensive documentation.

Important sources were the *Geschichte der Mikroskopie* edited by H. Freund and A. Berg (vols. 1 and 2, 1963, 1964), Alfred Kühn's important work *Anton Dohrn und die Zoologie seiner Zeit* (1950), Theodor Heuss' biography of Anton Dohrn (2nd edition, 1962), and the Festschrift *Reinhard Dohrn 1880–1962* edited by Christiane Groeben in collaboration with Antonie and Pietro Dohrn (1983).

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