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Perspectives in Neuropathology

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By
WEBB HAYMAKER

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It is most appropriate that the International Congress of Neuropathology — our fourth — should convene in Munich, for it is here that neuropathology obtained its birthright and it is here that our charter in neuropathology took form. Before entering this great auditorium you will have seen the impressive exhibit of the historical landmarks of German neuropathology prepared by Professor SCHOLZ and his Committee. Details are brought out in the brochure entitled *50 Jahre Neuropathologie in Deutschland (1885—1935)*, which is one of the important contributions to this Congress. I commend both exhibit and brochure to you, for in them you will find the story of that select coterie that included VON GUDDEN, EDINGER, WEIGERT, NISSL, ALZHEIMER, JAKOB, SPIELMEYER, BIELSCHOWSKY, OSKAR VOGT, and others. It is on the accomplishments of pioneers such as these that new developments to be reported in this Congress rest.

Among that celebrated group were two in particular whom I should like to give special mention because of their close attachment to Munich in the early days of neuropathology. They were VON GUDDEN and NISSL. It was in Munich some 90 years ago that VON GUDDEN began challenging the minds of his pupils — among them GANSER, NISSL, FOREL, VON MONAKOW and KRAEPELIN — to approach anatomical problems of the nervous system through experimental methods. In so doing, the VON GUDDEN school raised neuroanatomy in Europe to its modern level. This is all vividly brought out by Professor SPATZ in his recent article on VON GUDDEN in the *Münchner Medizinische Wochenschrift* (vol. 103, p. 1277, 1961).

NISSL, a man of no less stature, was a native of Old Bavaria and was possessed of a *Gemütlichkeit* — a zest for living life to the full — which characterizes the Bavarian populace. NISSL, who was one of VON GUDDEN'S most gifted pupils, began to make his presence felt here in Munich some 77 years ago when, as a medical student, he wrote an essay on pathological changes in the nerve cell *(Die pathologischen Veränderungen der Nervenzellen der Grosshirnrinde)*, which won him a prize. It was in this essay that NISSL introduced his method of selective staining of the basophilic structures of nerve cells. This classic writing as well as his studies on retrograde degeneration, and many others, have made him pre-eminent in the field of neuropathology.

While here in Munich you may wish to visit the laboratories where VON GUDDEN and NISSL once worked. VON GUDDEN first taught in the *Kreisirrenanstalt* in the

suburb known as München-Au, where he established a *Hirnanatomisches Laboratorium*. Were you to go out there you would find no trace of VON GUDDEN's laboratory, for the building is now occupied by a monastic order. All of his slide collection seems to have vanished. With NISSL you will have better luck, for he carried out his studies at the *Deutsche Forschungsanstalt für Psychiatrie, Max-Planck-Institut*, not far from where we are convening. There you will find what remains of the NISSL Collection, excepting that part of it which is here in the historical exhibit. The sections he once scanned are, in their faded brilliance, reminders of a rich source of our great heritage.

As you can see from your programs, we have a Congress of wide dimensions ahead of us, thanks to the choice exercised by the German National Committee, headed by Professor JACOB. There are so many probings into new fields of neurological science, around which strange vocabularies have arisen, that any one of us sitting through the sessions is bound to feel from time to time as though he were in the Tower of Babel.

This is the very point to which I should like to speak. We approach neuropathology with varied types of training and through numerous scientific disciplines. While this diversity of approach is all to the good, there is real danger that in the pursuit of specialities we may become fragmented like an astrocyte that has undergone clasmatodendrosis, and thus be diverted from the core of our subject. The maintenance of our vigor in the neurological sciences will continue to be dependent on the strength of neuropathology. This is the bond which holds us all together. This is why we are meeting together in the name of Neuropathology.

An obstacle to neuropathology in many parts of the world today is the lack of appreciation of neuropathology's value. Witness how some of our sister disciplines regard it! Psychiatrists living in lofty isolation make hardly any use of neuropathology, which may account for the state of suspended animation in which clinical psychiatry finds itself nowadays. Neurosurgeons use it, but often only for their own purposes; those who support only "piecemeal" diagnosis retard neuropathology more than they advance it. And all too many internists and neurophysiologists also think of neuropathology only as subsidiary to their own direct needs. Even investigators treat neuropathology all too lightly when they encourage younger men to enter highly specialized fields, such as electronmicroscopy, without adequate background in the structure of the normal or the diseased nervous system.

Another obstacle to neuropathology lies in the failure to realize neuropathology's scope. A good deal of the fault lies with those neuropathologists who, in cultivating too small a field, have neglected the precepts of that tradition born here in Germany and enriched by such masters as BONFIGLIO, MARINESCO, MINGAZZINI, OBERSTEINER, HENSCHEN, SCHAFFER, GLOBUS, HASSIN and GREENFIELD — a tradition perpetuated in the majestic HENKE-LUBARSCH, for which we shall always feel deeply indebted to Professor SCHOLZ.

The precepts of the past of which I speak and of which we should now again take stock are with respect to neuropathology's missions. They may be listed as 1. clinicopathological correlation, 2. clinicoanatomical correlation, and 3. research. Neuropathology's missions are, however, so broad that neuropathology cannot

be straitjacketed into a definition or compartmentalized in terms of one group of disciplines, or another. Let me illustrate: The forces that go to mold the cerebrum into lobes during phylogenetic or ontogenetic development and the factors concerned in the migration of nerve cells to their myriad ultimate positions are as relevant to neuropathology as they are to neuroanatomy, and the computer systems inherent in nerve-cell aggregates in strategic locations of the nervous system are no less significant to neuropathology than to neurophysiology.

Let us first consider *clinicopathological correlation* as a mission of neuropathology. One of the central themes of neuropathology has always been the exact description of the morphological changes in disease. Those who practice this art are perpetually challenged to interpret the most complex experiments of them all, those which nature has performed on that supremely organized and intricate structure, the human nervous system. Within the damaged nervous system the camouflage, in the form of myriad reactions, is such as to bury clues which even the most astute can often not unscramble. Of all our neurological sciences, neuropathology seems the most reluctant to give up its secrets. This was true even for the late GODWIN GREENFIELD, who, on looking through the microscope during the last month of his life, would remark: "This case has me stumped! I have never seen a lesion such as this before." Neuropathology is never "routine," for nature never repeats herself. In that sense, it is perpetually fresh, and thus has a quality not subject to the law of diminishing returns.

This aspect of our science is often called "diagnostic" neuropathology. An immediate reward consists in the extraction of plausible hypotheses as to causes and pathogenesis of disease. But "diagnostic" neuropathology loses its force when not correlated with clinical disciplines. Only when combined with clinical facts does neuropathology give disease a new dimension. Without neuropathology, clinical neurology and clinical psychiatry cannot be maintained at a high standard, neither in their obligation to diagnose disease nor to treat the patient, nor to teach.

A second mission of neuropathology is *clinicoanatomical correlation*. This branch of our science has had and will continue to have a major responsibility in the study of well established nervous diseases in order to provide the anatomical basis for behavior. The basic approach is that so effectively employed by CHARCOT and other neuropathologists of the nineteenth century and by the VOGTS and their pupils in more recent times.

A third mission of neuropathology is *research*. It is the scientific investigation of the causes and mechanisms of disease of the nervous system that neuropathology has in the past, at least, always taken a leading role. In its academic aspects, neuropathology consists in the scientific study of the causes and mechanisms of all those processes in the nervous system that disturb its normal function. To live up to his responsibility, the neuropathologist must not only provide the base from which specialists begin their work, but also give direction to research and be prepared to re-create diseases in animals and to study them under controlled conditions in the laboratory. Intending entrants into neuropathology will hesitate unless we in the neuropathological field indicate our willingness to keep abreast of the times. Neuropathology today is no longer the conventional neuropathology of yesterday. No unit can progress far that does not employ modern tools and techniques.

Among the specialized techniques of today in which the neuropathologist is uniquely equipped to play a leading role is electronmicroscopy, which has given us an entirely new dimension. It provides all the exhilaration of a newly-won freedom. Professor GRUNER describes electronmicroscopy as a field which brings sheer joy in that one can cast one's line anywhere in the unbridled sea of the nervous system knowing with certainty that a fish of surprising size will be there to swallow the hook. But these are sometimes strange fishes, whose very names find electronmicroscopists in disagreement. Some of these strange fishes may be the equivalent of the coelocanths, which will take us many years to understand. Studies in various quarters have suggested that electrolytes travel in some kind of intercellular space, but in what way we have yet to learn. All this is very complicated because some electronmicroscopists argue against the existence of even a potential space.

We approach molecular biology of the nervous system not only through the medium of the electronmicroscopy, but also through the application of enzymology. Here, again, is virgin territory awaiting the arrival of explorers, of which there are all too few. At our Symposium on hypoxemia in Baden bei Zürich last week, Dr. EVERSON PEARSE reminded us that our histological enzyme techniques to date are so primitive that only one-fourteenth of the enzymes known to exist can be demonstrated in tissue.

On the credit side of our ledger as far as neuropathology is concerned is the wide panorama of metabolic biochemical processes in diseased nervous system and the deep insight into dynamic pathological physiology of the nervous system which histochemistry has provided. An example is "Schilder's disease," which, for many years, was little more than a wastebasket of the demyelinative diseases, but now, with the aid of new techniques, we are able to define some of these diseases, and have a glimpse into their pathogenesis. I am referring, for instance, to the sudanophilic, Pelizaeus-Merzbacher, globoid-cell, and metachromatic types of demyelinative encephalopathy.

Immunopathology is now entrenched in the neurological field. Fluorescent antibodies set off into the brain can now seek out their appropriate antigens as a bloodhound after its quarry. Such indicators as fluorescein-labeled proteins and radioactive iodinated albumin now light up pathological processes as clearly as a city at night as seen from a plane.

Tissue culturists are dealing more and more with the nervous system. They see myelin develop, and then they dissolve it at will; they may yet be able to force open the unyielding door of multiple sclerosis. Techniques for the maintenance of cultures of neurons are sufficiently developed as to open a wide arena of opportunity for nutritional, pharmacological and electrophysiological studies. When utilizing tissue cultures of the nervous system the neurophysiologist can be sure that his delicate electrode is truly within a nerve cell and not in the expanded watery process of an adjacent astrocyte, a source of error against which the electronmicroscopis has warned the neurophysiologist with respect to the deductions he draws from stimulating the intact brain. Highly relevant also to neuropathology is cell biology. During the scientific sessions of this Congress, you will find that some who work at the cellular level will be according cell membranes unique virtues, others, devoted to the perikaryon, will be expounding on its role in memory

processes, others will be arguing that the dendrites are the really significant component when it comes to the functioning of nerve cells. This will be the way that issues will be sharpened in this particular field.

Silver methods, which have rescued us from the bond of the analin stain and the paraffin and celloidin block, have proved their importance not only to neurological research but also in "everyday" neuropathology. Such methods are essential in the differentiation of cell types. For example, with these methods, activated adventitial pericytes, on invading damaged brain, can be seen to throw out their thorny processes as they insinuate themselves into the confines of the intercellular space and become Hortega cells. We cannot establish a stable scientific economy in neuropathology unless we make more widespread use of this silver currency.

Now, each of us, whatever the scientific endeavor he may pursue has obligations to the whole field of science and medicine in our great enterprise of understanding, alleviating and preventing disease of the nervous system in every quarter of the globe. The neuropathologist is becoming more and more alive to these obligations. I am thinking, for example, of the illuminating contributions to our knowledge of the Landry — Guillain-Barré syndrome in the region surrounding the inland sea of Japan and Minamata disease in Kyushu. Studies of endemic disease in isolated communities have brought to light such disorders as myelopathy in Jamaica, familial amyotrophic lateral sclerosis and "Parkinson-dementia" among the Chamorro population in the Island of Guam, Kuru in the Eastern Highlands of New Guinea, and funicular myelopathy in tropical Africa. In the less Westernized and more impoverished countries we shall continue to find lathyrism and be able to study it. These diseases have posed knotty problems as to the relative importance of genetic and environmental factors, including smoldering infections, deficiency states, and undeclared toxic substances in the diet. A wealth of fascinating conditions probably still awaits discovery. I have not mentioned leprosy, which continues to be one of the world's greatest scourges; this is a field in which neuropathology is contributing too little.

Improved health has inevitably augmented the number of the aged, and thus the importance of a better understanding of the aging process in the brain and the control of cerebrovascular disease becomes obvious. In undertaking to study this problem the neuropathologist must not confine his studies to the cranial contents; he must study the extracranial vessels in the neck and vertebral canals and the cardiovascular system as a whole. In fact, he must equate all neurological disease with visceral alterations. He is no neuropathologist who has no solid background of morbid anatomy.

Since the second world war there has been a remarkable interest in international medicine, and in no field has this been more apparent than in neuropathology. In some countries, at least, the market for neuropathologists is excellent, and in such countries the stream of neuropathology, as it is presently expanding, is becoming irresistible. New opportunities in the form of fellowships and grants in neuropathology are constantly opening up. Conferences and symposia on neuropathological topics, too numerous to mention, are being held all over the world. New journals are springing up — the latest, the Acta Neuropathologica. Our own Congress now has representatives from 46 nations. Those that have joined us since

our previous Congress are Bulgaria, Ghana, Jamaica, Nigeria, Thailand and Venezuela, and to them I should like to extend a warm welcome. The World Federation of Neurology (WFN), which was only in the planning stage at the time of our IIIrd International Congress in Brussels in 1957, is now straddling the globe with the mission of instigating and coordinating research in the neurological sciences so that a closer cooperative relationship between nations can be brought to bear. The establishment of the International Brain Research Organization (IBRO), now taking on definite shape, has also responded to the mandate that basic neurological research be more effectively pursued on a world-wide basis. The presidents of these two organizations, Professor VAN BOGAERT and Professor JASPER have been conferring on the means of bringing about the most effective crossfertilization of these great international movements. The importance of their endeavors cannot be overestimated. We must pledge them our full support during this trying period of the development and growth of these organizations.

With so much to offer in the way of interest and responsibility in helping in the solution of the vast socio-economic problems imposed by neurological disease, it is perhaps surprising that in some countries — including some that are less impoverished — a dearth of entrants into the speciality of neuropathology exists. This undoubtedly has to do with the fact that little money is set aside from university, municipal and state budgets for the employment of neuropathologists. Departments of neuropathology tend to originate only in neurosurgical units or only as anlage of academic departments of pathology; all too seldom do they exist as individual units, and the academic accolade tends not to be bestowed on the neuropathologist. Municipalities do no more than pay lip service to the call for research into mental and neurological disease and the man who is prepared to devote his life to this cause is apt to find himself underpaid and working in an environment which lacks the stimulus of fellow workers.

The poor recruitment may, however, have its origin in other factors and it behooves us as established neuropathologists to look carefully into the training of new entrants into the speciality of neuropathology. Everyone of you in this august assembly who heads an institute or a great department has responsibility for neuropathology. In the U.S.A. the setting up of a Board in Neuropathology some years ago helped to indicate to the man in training the course of studies required of him. This, coupled with the establishment by universities of more chairs in neuropathology has improved the academic standing of the specialist and he is to be found now more often in the medical school where he has the stimulus of colleagues in the basic sciences, than in the non-teaching hospital.

In some countries, however, the would-be neuropathologist is not so well cared for and he tends to be a waif. He belongs to no school but has to find his own way and plot his own course. It can be argued, of course, that a too rapid prescription of studies may canalize the postgraduate student in a way that is undesirable in neuropathology. There is, however, a happy mean between a regular basic training in neuropathology and no training at all, and it is our duty to provide it.

Attitudes toward neuropathology as they exist today in many communities must be corrected, for the neuropathologist has too long been in the category of a second-class citizen. To remedy this situation it should be recognized that neuropathology can be effectively prosecuted only when the neuropathologist is provided

with the opportunity of carrying on neuropathological and neuroanatomical correlation and research. Only then will neuropathology flourish and attract the best minds. What is needed are 1. educational programs whereby the medical profession is made more fully aware of neuropathology as a medical science in its own right, 2. departments of neuropathology in more universities not only for the support of the clinical departments of neurology, neurosurgery and psychiatry, but also for training in the basic fundamentals of neuropathology, and 3. funds for fellowships and other training media in neuropathology and the provision of full-time academic positions with tenure for those who have been adequately trained.

When ARMANDO FERRARO convened together in Paris in 1951 a small number of neuropathologists representing as many countries, he did us a great service. Here was set into being our International Committee of Neuropathology which has been responsible for the planning of the present Congress as well as those held in 1951, 1955 and 1957. Our present International Committee would be derelict in its duty were it to sit through this Congress discussing academic problems and fail to give consideration to the critical situation in those whole continents where only a handful of neuropathologists exists. I hope that you will agree with me that the time is ripe for our International Committee to pursue a more active policy. While there are many forms of activity in which I am sure you would like to see us engaged as a world team, perhaps our greatest endeavor should be to encourage the further development of neuropathology in those nations where great need exists. I can promise you that this matter will be seriously considered at our meeting on Friday.

Our tradition is something of which we may well be proud, but let us convey more of our enthusiasm abroad in order to recruit new explorers. Regardless of the speciality each of us practices, there is an impelling force that motivates us all; it was expressed simply by that great Norwegian explorer and statesman, FRIDTJOF NANSEN: "The history of the human race is a continual struggle from darkness toward light . . . . Man wants to know, and when he ceases to do so, he is no longer man."

Summary

During the meeting of the IVth International Congress in Munich on 4—8 September, the status of neuropathology around the world was reviewed by the International Committee of Neuropathology, consisting of the Vice Presidents from 46 nations, with Professor JACOB (of Germany) the Secretary-General. The review indicated that neuropathology flourishes in relatively few world centres and that in numerous other geographical areas neuropathology exists merely as a diagnostic service or is, in other ways, subsidiary to clinical departments. In still other areas the neuropathologist belongs to no school, but, like a waif, has to plot his own course.

Such conditions exist even though it is universally recognized that strength in neuropathology is a prerequisite to continuing advance in the medical sciences. The solution to the problem in those areas of the world in which neuropathology has little stimulus will come when it is recognized that neuropathology is a medical sicence in its own right and can be effectively prosecuted and attract the best minds only when the neuropathologist is provided ample opportunity and is

accorded an academic status coequal with that of other major medical specialties. Among the neuropathologists' missions are (1) clinicopathological correlation, (2) clinicoanatomical correlation, and (3) basic research. These are the missions so effectively carried out years ago in Germany that established neuropathology as a major medical science.

The International Committee recognizes that in those countries expressing the desire for improvement in the status of neuropathology — whether through university or through governmental channels — the initial step in any ultimate solution is to have problems defined and needs ascertained. This survey is now underway. The Committee further recognizes that its primary concern should be in exploring ways and means whereby those desirous of entering a career in neuropathology can be adequately supported.

WEBB HAYMAKER, M. D.: Ames Research Center, NASA, Moffett Field, California.