

Henry M. Wisniewski M.D. Ph.D.

After four decades of a very prominent research career, Professor Henry M. Wisniewski died on September 5, 1999 of illness at his home on Staten Island, New York. He was born in Luskowko, Poland on February 27, 1931. His father was a principal of a school and wrote poetry; his mother was a teacher (Fig. 1). His earliest school-age memories included the struggle to survive in a Catholic convent after his father was arrested by the Gestapo, incarcerated as a political dissident against the Third Reich, and extirpated from society. The interruption of early formal training did not diminish his enthusiasm and determination to learn.

Henry's professional career began with his academic training at the Gdansk Medical School in Poland where he was awarded a M.D. degree with Dean's Distinction in 1955 (Fig. 2). In 1954, he married Krystyna Wylon (Fig. 3) and together they had two children: Alexander, born in 1955, and Thomas in 1960, both of whom became physicians (Fig. 4).

As a medical student, because of the great shortage of physicians, he worked for over two years as a neurosurgeon, and later moved to the Department of Pathology, where in a few years time he became a board-certified pathologist (Fig. 5). In this department, he started research on extracts from the willow tree fungi, which turned out to be quite effective in the treatment of mice ascites tumors. Later, he worked on acridine compounds, which are used today in cancer therapies. His professor, Czarnocki, a famous pathologist, recognized his researcher potential and arranged his transfer to the Polish Academy of Sciences (PAS) in Warsaw to work with world-renowned Adam Opalski, who was Professor of Neurology and Neuropathology. Opalski was best known for "Opalski cells", which are found in the brain associated with hepatic encephalopathy. In Opalski's lab, Henry started to work on brain ischemia, brain hemorrhages, hydrocephalus and various forms of neurodegeneration to better define the pathogenesis of the brain dysfunction.

Subsequently he earned a Ph.D. degree in Neuropathology in 1960 and docent degree in 1965 (Fig. 6). During those days, scientists working in the Polish Academy of Sciences were a privileged group whom the government allowed to travel abroad for training

and research experience. This gave him the occasion to visit and work from several months to over one year in Bratislava, Czechoslovakia; Tbilisi, Georgia, and Moscow, as well as attend international neuroscience conferences in Western Europe.

In 1960, he received an invitation from George Olszewski in Toronto, Bunge Institute, Canada. Olszewski was a famous neuroanatomist/neuropathologist, who became the father of the Canadian Neuropathological Association. Henry worked for over one year on blood-brain barrier (BBB) permeability in Olszewski's laboratory and published several scientific papers with him. From Olszewski's laboratory (Fig. 7), Henry moved to Igor Klatzo's laboratory at the National Institutes of Health in Bethesda, where Henry worked on the BBB employing Klatzo's model of cortical cold lesion, as well as on the aluminum-induced model of neurofibrillary tangle (NFT) changes (Fig. 8). The latter was the result of a fortuitous observation. While reviewing old slides, Henry found cresyl violet- and hematoxylin- and eosin-stained sections of brain and spinal cord from diphtherotoxin or Holt's adjuvant (an aluminum based adjuvant), injected rabbits, which Dr. Klatzo had brought several years earlier from Dr. Russell's laboratory. Dr. Klatzo told Henry that he found in the spinal cord of some of these animals large vacuoles, that he had not seen before. At that time, Dr. Klatzo worked on experimental allergic encephalomyelitis (EAE), which was induced by subcutaneous injection of spinal cord suspension with tuberculin oil as an adjuvant. As he recalled, all of the animals developed EAE, with the exception of about five rabbits, which, instead of EAE, showed these neuronal vacuolar changes. Henry reviewed the experiment data written in a notebook and it turned out that the spinal cord emulsion for the injection had been prepared by a German technician, who injected the majority of the rabbits and kept notes about the behavior of the animals. According to the notes, only the rabbits injected intracerebrally with Holt's adjuvant (i.e. aluminum) developed seizures and had vacuolar changes. When Henry saw this, he knew that he had stepped onto something very interesting and therefore started to work on aluminum encephalopathies. Henry repeated the experiments and



Fig. 1. Henry (lower left), with his older sister, Jadzia (center), and younger brother, Leszek (lower right); above them, their mother and father. His relatives complete the photo, 1937.

found using silver stained sections, that the large vacuoles now appeared to be large aggregates of fibrillar material. These aggregates resembled the neurofibrillary tangles of Alzheimer's disease (AD), and therefore he believed that this represented a model of neurofibrillary degeneration. Bob Terry later repeated their experiments and, under the electron microscope, also found neurofibrillary aggregates instead of cytoplasmic vacuolation.

Because the Alzheimer neurofibrillary tangles, as well as senile plaques, are birefringent after Congo red staining in polarized light, Henry also stained the aluminum tangles with Congo red. However, using the routine crossed prisms for identification of the Alzheimer tangles, he could not see any birefringence in the aluminum-induced tangles. On the other hand, Klatzo told him that after Congo red stain, using crossed prisms with the addition of the Zeiss gypsum retardation plate, he could see intracytoplasmic birefringence in the aluminum-induced tangles. Utilization by Klatzo of the Zeiss gypsum retardation plate caused confusion

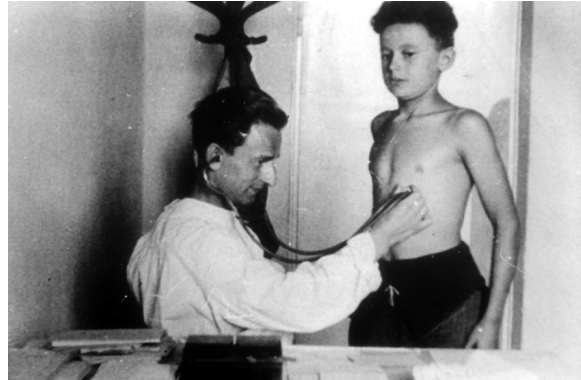


Fig. 2. Henry examining his patient, 1955.



Fig. 3. Henry and his wife, Krystyna, 1958.

later because its use was forgotten and the original work was cited to indicate that both the Alzheimer tangles and the aluminum induced tangles show birefringence after Congo red stain, which is not true. Later, Henry found that after thioflavin-S staining, only Alzheimer neurofibrillary tangles showed the characteristic fluorescence and the aluminum-induced neurofibrillary tangles were negative, as well as the species specificity of aluminum induced tangles (which occur only in rabbits, cats, guinea pigs and ferrets).

Over this period, Henry and Klatzo also introduced a new classification of brain edema, cytotoxic and vascular. From 1963–1966, he continued his research in PAS Warsaw, Poland, studying various processes of neurometabolic and neurodegenerative diseases. In 1966, Henry was appointed as a Research Fellow by Professor Robert Terry (Fig. 10) at the Albert Einstein College of Medicine (AECM) in New York. He ascended the academic ranks quickly to become a full Professor in 1969; he stayed at AECM until 1975. For the next



Fig. 4. Henry with his sons Thomas (left), and Alexander (far right), standing in front of their home on Nixon Avenue, Staten Island, New York, 1976.

30 years Henry became a very productive and creative Alzheimer researcher.

When Henry started his career as an electron microscopist with Robert Terry; there was considerable controversy about the ultrastructural morphology of the neurofibrillary tangles. Initially it was thought that Alzheimer neurofibrillary tangles may represent an accumulation of closely packed normal neurofilaments [61,62]. In 1963, Professor Mike Kidd (Fig. 11) published a paper in *Nature* [38], under the title "Paired helical filaments in electron microscopy of Alzheimer disease". In this article describing the morphology of the individual profiles of the tangles, he wrote, "At high magnification, the filaments composing the bundles were seen to be double helices". These consisted of two 100-A filaments 150A from center to center and completing one full turn in 600A. He concluded that "it is possible that they are neurofilaments occurring in vastly increased numbers and associated in pairs". This report prompted the reexamination of all diseases and conditions in which neuropathologists described the presence of neurons with neurofibrillary changes. Results of this study were published by H. Wisniewski, R.D. Terry and A. Hirano (Fig. 12) under the title "Neurofibrillary pathology" [108], which represented the introduction of this term. This paper distinguished between diseases and conditions in which neurofilaments accumulate and diseases in which the tangles are made of paired helical filaments (PHFs) or twisted tubules. For the first time, it was shown that PHFs accumulate in many unrelated conditions; however, irrespective of the disease, usually the same neurons were affected by neurofibrillary pathology.

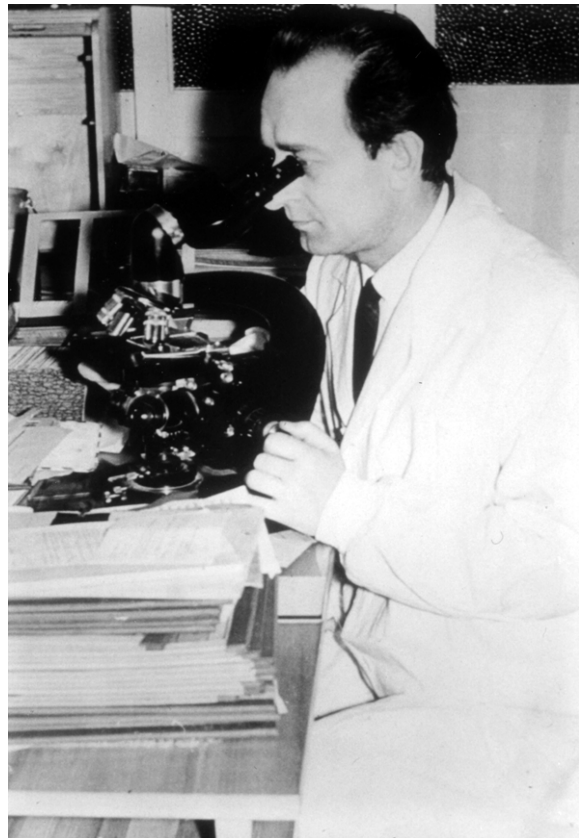


Fig. 5. Henry at the microscope in his lab, 1960.

In 1970 Michael Shelanski (Fig. 13) began work on the biochemistry of PHF, while Henry worked on the EM of the purified fractions. At the time, the subcellu-



Fig. 6. Henry performing experiments in his laboratory, 1965.

lar purification methods were not well developed, and there were great difficulties in getting pure fractions of PHFs. From the morphological studies of PHFs, Henry knew that as a result of bad fixation, all microtubules and part of the neurofilaments disappeared. However, the PHFs were very well preserved, almost like petrified wood. Hence, Henry told Mike to leave the brains at room temperature to rot for a few days to see how well the PHFs would do. To Henry's pleasant surprise this produced the cleanest fraction of PHFs; however, this work was not continued as Shelanski left AECM to work at NIH. Henry continued EM studies on PHF from tissue sections and published in 1976 a classic paper called "Neurofibrillary tangles of paired helical filaments" [95]. This publication solidified the use of the term PHF in the literature.

The first report on the biochemistry of PHFs was published in 1974 by Iqbal, Wisniewski, Shelanski, and others [34]. In this paper, a 50-kDa peptide was identified from isolated neurons with neurofibrillary tangles. Later Grundke-Iqbal et al. showed that antibodies to the 50-kDa PHF polypeptide label Alzheimer neurofib-

rillary tangles [26]. The same group of researchers also demonstrated that antiserum against normal human neurotubules purified by *in vitro* assembly precipitated both neurotubules and a 50-kDa peptide isolated from Alzheimer neurofibrillary tangles as well as labeling the tangles in sections of AD brains [27].

Also during this period, Henry worked with Drs. Cedric Raine and John Prineas (Fig. 14). They established the first analysis of bystander demyelination. Henry's studies were on the ultrastructure of demyelination [52,53,98]. Together with Barry Bloom this line of work led to the discovery of antibody-dependent cellular cytotoxicity as a major mechanism of inflammatory demyelination; these publications are citation classics in this topic [15,58,77,78].

In 1974–76 Henry moved to the Demyelinated Disease Unit, Newcastle upon Tyne, England, as the Director of the unit (Fig. 15). Work during this period, clearly pointed out that demyelinating antibodies are key players in the pathogenesis of chronic inflammatory demyelinating lesions, as well as emphasizing the structural diversity of the lesions in a seemingly simple and well defined experimental model of demyelination. After a decade of T-cell dominated research in the field of autoimmune encephalomyelitis and multiple sclerosis, there has now been a revival of these concepts in recent years. During this period fruitful collaborations began with Drs. Lassman and Bancher from Vienna (Fig. 16).

In 1976 Henry moved to the Office of Mental Retardation and Developmental Disabilities (OMRDD), New York State Institute for Basic Research in Developmental Disabilities (IBR) as the Director, where he stayed until his death. Under his auspices the IBR's reputation for scientific achievement increased greatly, making it a world class institution. His scientific contributions were eminent and covered nearly the entire spectrum of neuropathology and molecular neurobiology. He carried out pioneering studies on the ultrastructure of plaques, on tangles, on vessels affected by amyloid angiopathy, on plaque pathogenesis, and on the role of microglia, perivascular cells and myocytes in amyloid-formation, and he demonstrated aged monkeys and dogs to be models of Alzheimer amyloidosis. Collaborative work flourished with many researchers, who were recruited to the IBR, included Drs. Iqbal and Grundke-Iqbal, Robakis, Kotula, Mehta, Malik, Frackowiak, Wegiel, Merz, Rubenstein, Miller and Brown on the neuropathology, biochemistry and molecular biology of NFTs and amyloid, as well as those who worked on prion associated disease including Drs. Carp, Kascsak and others.

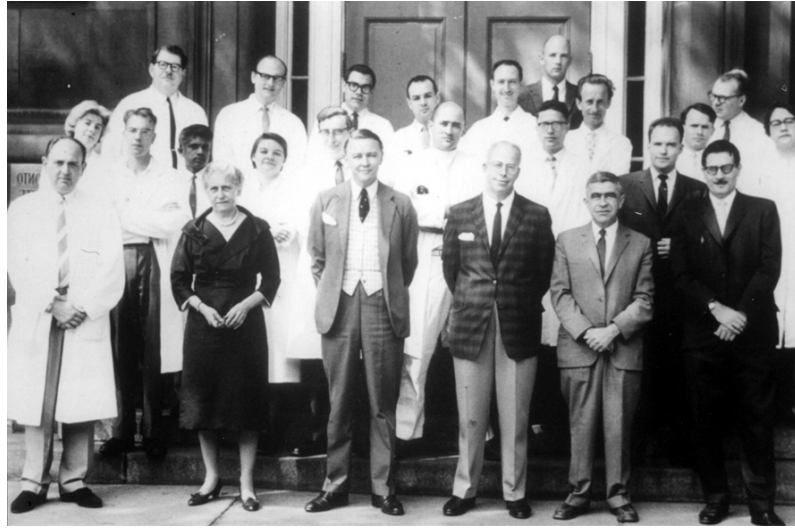


Fig. 7. Bunge Institute, Toronto, Dept. of Neuroanatomy/Neuropathology, Prof. Olszewski (second from right) and Henry (directly above him), 1961.



Fig. 8. Professor Klatzo and his staff at NIH, Bethesda, MD, with Henry (center, wearing dark suit) in 1962.

During his career Henry received some of the most coveted awards in the science community including the Weil Award of the American Association of Neuropathologists (1969); the Moore Award of the American Association of Neuropathologists (1972); the Career Scientist award of the Health Research Council of the City of New York (1969); the Association for the Help of Retarded Children (AHRC) Award; Member of Neurology Study Section B (NIH, 1978–82); New York City Branch Award (1984); President of the American Association of Neuropathologists (1984); Member of the Mental Retardation Research Commit-

tee (NIH, 1982–86); the Welfare League, Letchworth Village Chapter (AHRC) award (1985); the Benevolent Society for Retarded Children, Staten Island Chapter, Award (1986); Fellow of the American Association for the Advance of Science; Founding member of the International Alzheimer's Disease and Related Disorders Association (1988, see Fig. 17); named Neuropathologist of the Twentieth Century, X International Congress of Neuropathologists (1990); Foreign Member Polish Academy of Sciences (1991); Doctor of Science, Honoris Causa, Medical School of Gdansk, Poland (1991); Doctor of Science, Honoris Causa, College of Staten



Fig. 9. Henry arguing about experimental aluminum models with Peter Lampert, 1967.

Island (1992); Doctor of Science, Honoris Causa, Medical School of Poznan, Poland (1996); the Alfred Jurzyski Foundation Award in Neurobiology (1996); and the Lifetime Achievement Award from the American Neuropathology Society (1997, see Fig. 18). Henry has also been the recipient of numerous private fund, Alzheimer's Disease Association and National Institutes of Health grants.

1. Summary of the scientific contributions of Dr. Henry Wisniewski

1.1. Morphological studies of AD lesions

Henry's morphological studies include ultrastructural studies of plaques, neurofibrillary tangles (NFTs) and vessels affected by amyloid angiopathy. In a series of papers Henry provided a detailed description of the elements of senile plaques [64,65,106,107]. His classification of plaques as primitive, classical and burned-out plaques is still used today by Alzheimer researchers,

as well as the term recommended by him, neuritic plaques. This term is preferred by neuropathologists, because it underscores the presence of many abnormal nerve cell processes and terminals in the senile plaques. He also found that in contrast to the neuritic plaques in normal, aged individuals, the neuritic (senile) plaques in victims of AD contain many neurites with paired helical filaments (PHFs) [5]. Since this study, the presence of many PHF-positive plaques has been used by neuropathologists as an indicator that the specimens examined come from victims of AD. In other words, the presence of plaques with PHFs containing neurites helps differentiate between normal aging and AD.

Henry carried out extensive studies of the origin of neuritic (senile) plaques [76,86,94,95,104,111]. In these studies, he suggested that the accumulation of abnormal neurites does not lead to formation of amyloid. Instead the amyloid appears to be the precursor for the abnormal neurites. This line of reasoning was strongly supported by the extensive work Henry performed on Down's syndrome patients, where he found that amyloid deposit preceded NFT pathology by many years [37,43,57,102,103,124–126]. On the basis of this data, he concluded that amyloid deposits in AD start the process of neuropil pathology and not the other way around, as suggested by many neuropathologists and neuroscientists [76,86,104,111,128]. This provided essential groundwork for the amyloid cascade hypothesis. The formation of A β classical and primitive plaques in the numerous transgenic models, supports Henry's conclusion. These original studies showing that amyloid deposits initiate plaque formation and destroy tissue at the site of their deposition provided the underpinnings for the biochemical and molecular studies of amyloid β in AD.

1.2. Identification of non-neuronal cells in amyloid formation

Histochemical, immunocytochemical and 3-D reconstruction studies of classical neuritic plaques carried out by Henry and his associates revealed that microglia cells might be directly involved in the formation of amyloid deposits [22,67,94,110,112,119]. These findings, together with data from other laboratories showing involvement of the microglia in the immunological cascade of brain damage in AD, suggests the microglia cell to be of critical importance in the pathogenesis of AD brain pathology. Studies of the vessels affected by amyloid and dyschoric angiopathy allowed Henry and his associates to identify the smooth mus-



Fig. 10. Henry (front center, in dark suit) with Robert Terry (to the left of Henry in dark suit) and his staff at Albert Einstein College of Medicine, 1973.



Fig. 11. Henry (left, in white suit) with Mike Kidd during Alzheimer disease meeting, 1998.

cle cells (in small and larger vessels) and perivascular cells (in capillaries) as one source of $A\beta$, which forms amyloid deposits [23,84,113,114,120,122]. Taken together, their studies suggested that the amyloid deposits in AD can originate from several cells including microglia, perivascular cells and myocytes, with neurons being primarily associated with diffuse, non-fibrillar plaques [71,103,115–118,121]. These observations were of critical importance for the development of the current immunomodulating therapeutic strategies for AD, because they pointed out that inflammatory cells such as microglia have a significant role in amyloid formation and removal.

1.3. *Studies of PHF and neurofibrillary tangle (NFT) development*

Henry was also the first to confirm Kidd's model of the ultrastructure of PHFs by means of tilt-stage electron microscopy and X-ray images of scale models of a bifilar helix [95]. Furthermore, in 1984 [93], he showed that the protofilament of PHF, neurofilaments and microtubules, are very different and that accumulation of the latter structures in the form of tangles in aluminum-induced encephalopathy does not resemble the lesions seen in AD [108]. With Dr. C. Bancher, a



Fig. 12. Henry with Asao Hirano in Newcastle, England, 1974.

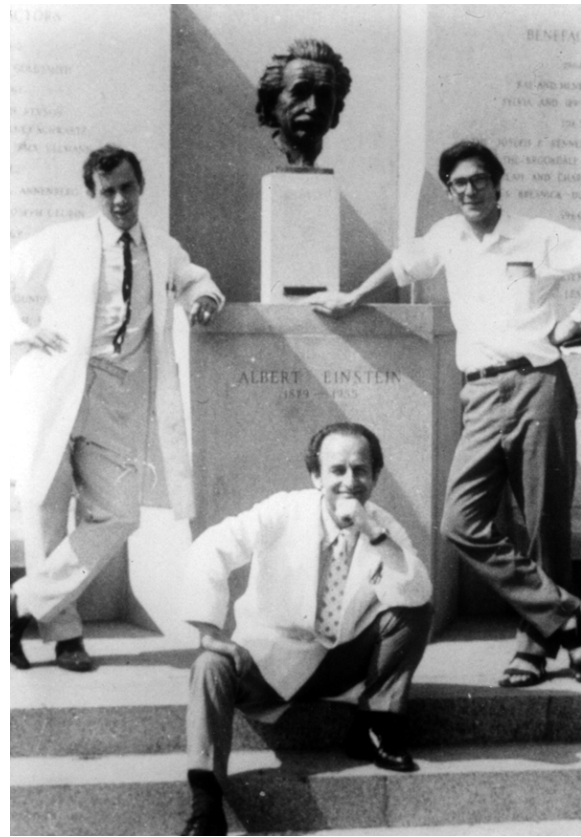


Fig. 14. Henry (sitting) with Cedric Raine (top, left) and John Prineas (top, right) at Albert Einstein College of Medicine, 1972.

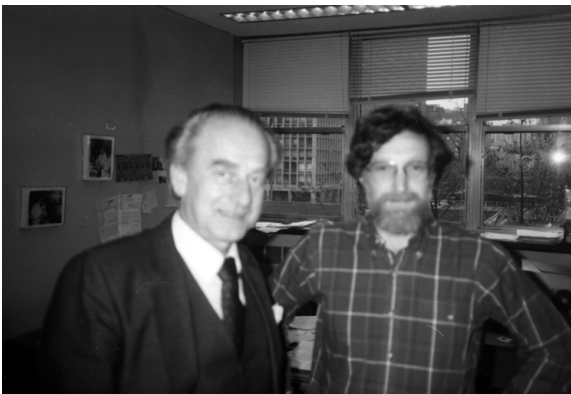


Fig. 13. Henry (left) with Mike Shelanski, 1973.

visiting scientist from Vienna, he studied the maturation of NFT formation [1–4]. These papers, as well as the study of the development of NFTs in subacute sclerosing panencephalitis [82] concluded that the formation of mature tangles is a slow process that may last for years. These observations are significant because they help explain the long pre-clinical and clinical course

of AD and suggest a large window of opportunity for treatment.

1.4. Demyelinating diseases and other degenerative conditions of the nervous system

Henry was also a major contributor to the development of the chronic relapsing models of demyelination in experimental animals [52,53,79,89,90,98]. His studies demonstrate that primary demyelination could be a result of specific sensitization [74], virus infection [99], or bystander cell-mediated reaction [78]; also that antibody dependent cell-mediated demyelination may play an important role in the pathogenesis of tissue damage, both in experimental allergic encephalomyelitis (EAE) and multiple sclerosis (MS) [15,44,58,75]. In 1970, his research on immune-mediated pathogenesis of demyelination in chronic relapsing EAE greatly influenced the introduction of immuno-suppressive therapy in MS. He was first to initiate the study that showed the therapeutic effect of Copolymer-1 in chronic re-



Fig. 15. Henry (in front, center left) with his team at Demyelinating Unit in Newcastle, England, 1974.

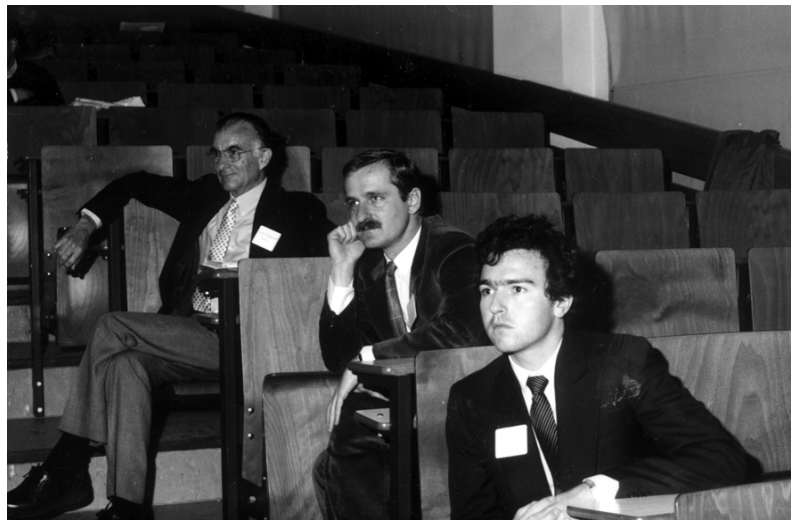


Fig. 16. Henry collaborated with Drs. Christian Bancher (foreground), Hans Lassman from Vienna (center), and his dear friend, Henry Webster from NIH (background), 1980.

lapsing EAE, which is the experimental counterpart of MS [36]. In his studies of viral encephalitis, he demonstrated the presence of viral antigen in the brain endothelium [80]. This study clarified one of the enigmas in the pathogenesis of inflammation in the brain as a result of systemic infection. Since the early 60s he has worked extensively on blood-brain-barrier permeability. This work started in Olszewski and Klatzo's laboratories in Toronto and at the National Institutes of Health [41,97] and is still continued today at the Insti-

tute. It was Klatzo and Henry who introduced the concept of vasogenic and cytotoxic brain edema, which is generally used by both researchers and clinicians [41, 59,66,91]. Henry also contributed to our knowledge of ultrastructural and biochemical pathology in Landry-Guillain-Barre [109] and Steele-Richardson-Olszewski syndromes [60], Pick disease [81], phenyl-ketonuria (PKU) [45-47,54], as well as hydrocephalus [72,73, 123] and aluminum and spindle inhibitors induced encephalomyelopathy [6,42,56,63,88,96,100,101,105].



Fig. 17. Henry (on far right) with the other two founders of International Alzheimer's Disease Congress (from left to right, Drs. Khalid Iqbal, Inge Grundke-Iqbal, Bengt Winblad, and Henry) 1990.



Fig. 18. Henry with his colleagues at American Association of Neuropathologists Meeting, 1997. Standing from left to right, Henry with Krystyna, John Trojanowski and Virginia Lee, Bernardino Ghetti, Donald Price, and Daniel Perl, Carl Leventhal from NIH. Seated, from left to right: and Nicholas Gonatas and Pierluigi Gambetti. In the background, far right side is E. Tessa Hedley Whyte.

1.5. Studies of animal models of AD neuropathology

It is well-known that the availability of experimental models or the existence of an animal counterpart of human disease is of great use in the development of diagnostic and treatment strategies for human ailments. It was Henry who first found the presence of

neuritic plaques in aged monkeys [85] and carried out ultrastructural studies of perivascular plaques in aged dogs [87]. His and his associates' recent studies of aged dogs showed the usefulness of these animals in studies of diffuse plaques, tau pathology, and amyloid angiopathy [69–71,127]. Searching for an animal model for neurofibrillary pathology, he found that spindle in-



Fig. 19. Henry with Krystyna enjoying a conversation in Polish with Pope John Paul at the International Conference on Down Syndrome organized by the Catholic University held in Rome, Italy, 1985.

hibitors (e.g., colchicine and vinblastine) cause disruption of microtubules and accumulate in 10 nm filaments in tangle form [56,101,105]. In collaboration with Igor Klatzo and Robert Terry, he found that in certain species aluminum induces formation of neurofibrillary tangles [42,88], made of 10-nm filaments [108]. This latter finding was one of the reasons that aluminum was thought to be involved in the etiology of AD. Even today, on the basis of epidemiological studies and observations that aluminum is found in some mature NFTs, some scientists believe that aluminum is a contributor to the pathology and dementia in AD.

1.6. Tissue culture cell model of beta-amyloidosis

Recently, with Janusz Frackowiak and Bozena Mazur-Kolecka he found that the amyloidogenic pathology of vascular smooth muscle cells can be transferred into cell culture. Cells cultured from brain blood vessels with amyloid angiopathy were found to produce abundant amyloid- β protein and produce both non-fibrillar and occasional fibrillar, thioflavin-S-positive deposits [21,48,83]. These were the first reports of the deposition of amyloid- β in culture conditions. This allowed the characterization of the cellular features involved in amyloidogenesis: altered processing of amyloid- β precursor protein, increased production of amyloid- β protein and symptoms of cell senescence. The deposition of amyloid-beta was also shown to be enhanced by apolipoprotein E4-known to be an AD risk factors, and to be modulated by body fluids and by regulatory cytokines [48]. This cell culture system repre-

sents a model in which potential therapeutic agents can be tested for their efficacy in preventing amyloidosis- β in AD.

1.7. Multidisciplinary studies at the Institute for Basic Research (IBR)

During the last 30 years, as Director of IBR, he had assembled a multidisciplinary team of scientists and created a climate in which such researchers such as I. Grundke-Iqbal and K. Iqbal have been able to flourish and build their own very successful research program on AD.

He has long realized the need for a multidisciplinary approach to study AD. From his days at the AECM in Terry's laboratory in the 60s, Henry had interacted closely with biochemists, molecular biologists, immunologists, neuroanatomists, brain imaging experts and clinicians (e.g., neurologists, psychologists and psychiatrists). The result of these studies were published in many papers by Henry and by neurochemists led by K. Iqbal and I. Grundke-Iqbal, which showed that tau is the major component of PHF [24–33,35]. Recognizing the importance of monoclonal antibodies in research and diagnosis of AD, he encouraged IBR scientists to initiate production of antibodies against the proteins involved in the pathogenesis of AD and prion dementias. The result of this research is the production by K.S. Kim and Henry of the most sensitive and specific antibodies for detecting human amyloid- β protein [39,40]. Two of these antibodies, 4G8, reactive to the 17–24 residue of A β , and 6E10, reactive to the 1–17 residue

to human A β are used extensively today by scientists throughout the world. IBR scientists also produced antibodies that detect Alzheimer-type NFTs (mAbs 525 and 3–39) and human-specific antibody for the detection of prion protein (PrP). The molecular biology team at the Institute, led by Nicholas Robakis and Henry, was one of the four laboratories to make the simultaneous, critical identification of the amyloid β precursor (APP) gene [55]. This gene encodes for the amyloid β precursor protein, which after proteolytic cleavage generates amyloid β . In 1989, with Institute immunologist Pankaj D. Mehta, Henry published data showing the presence of non-fibrillar soluble A β protein as well as soluble PHF antigens in the cerebrospinal fluid [49,92]. These findings are of great importance in the attempts to develop a laboratory diagnostic test for AD.

1.8. Collaborative studies with the New York University (NYU) Alzheimer Disease Center

Henry held the title of Adjunct Professor of Psychiatry at the NYU school of Medicine. In collaboration with the Mony de Leon, Henry participated in the early neuropathological validations of hippocampal atrophy as seen on post-mortem CAT scan and applied in vivo. These investigations led to the first reports of in vivo detected hippocampal atrophy in AD [16,18, 51] and subsequently to studies documenting the use of structural hippocampal imaging to predict future AD in preclinical or mild cognitive impairment cases [17,19, 20]. Later, the collaboration between Henry, Mony de Leon and Maciek Bobinski lead to the validation of the MRI based hippocampus volume [9] and the entorhinal cortex surface area [7] in AD. This highly productive collaboration, which later included Barry Reisberg and Steven Ferris, also produced many neuropathology reports that documented the importance of hippocampal formation pathology in the diagnosis and clinical staging of AD [8,10–14,50,68].

2. Summary

The findings of Henry Wisniewski have withstood the test of time; they set the stage for subsequent studies from many research groups and continue to have impact on current studies of AD. Henry authored or co-authored more than 700 scientific publications on a variety of topics relating to neuropathology. Moreover, Henry's enthusiasm for neuroscience and neuropathology was infectious, making it a pleasure to interact with

him. This joie de vivre attracted many scientists to join the field and to collaborate with him. His professional interests include developmental disabilities and dementia; neuronal fibrous protein pathology; demyelinating diseases; aging, Down syndrome, Alzheimer disease (AD); blood-brain barrier and topics relating to neurotoxicology. Many of his papers on AD, demyelinating diseases, and neurotoxicity remain the keystones for current research approaches.

Thomas Wisniewski MD
Associate Professor of Neurology
Pathology and Psychiatry
New York University School of Medicine
Dept. of Neurology and Pathology
Millhauser Laboratory, HN 419
550 First Avenue
New York, NY 10016, USA
Tel.: +1 212 263 7993
Fax: +1 212 263 7528

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