Letter from ENETS Chairman

If you are reading this newsletter now, you are likely one of nearly 270 medical professionals who have taken an active interest in neuroendocrine tumor disease – how best to diagnose it and how best to treat it. When the European Neuroendocrine Tumor Society, or ENETS, was formed last year, the founding members knew there was increasing interest in the study of the illness. From the 19th century until the 1960s, scientists steadily observed the composition and behavior of neuroendocrine cells. And the complexity of neuroendocrine tumor disease has since intrigued researchers worldwide. In this sense then, it should come as no surprise that the European Neuroendocrine Tumor Society, ENETS, has — since its founding in March 2004 — doubled its membership and attracted the attention of the pharmaceutical industry.

This was quite evident at our 2nd Annual Educational Conference that was held in Cracow, Poland, in April, 2005. With 400 participants, representing 40 countries, it was our biggest gathering ever. Evaluation surveys afterward were very positive and the ENETS Coordinating Office received dozens of new membership applications. One participant was impressed enough to return to his country and get to work on establishing a national neuroendocrine tumor society. So, word continues to spread about ENETS and on behalf of the founding members, I am pleased and optimistic that the next few years look just as promising.

In this issue of the ENETS Newsletter, you will find an overview of the Cracow conference. The lectures presented there will soon be put onto CDs and, upon request, sent to those interested. Please check out the ENETS website, www.neuroendocrine.net, for when the CDs will be available.

Also inside is an interview I gave with regard to the ENETS Guidelines for the Diagnosis and Treatment of Neuroendocrine Gastrointestinal Tumours. Finally, be sure to mark your calendars: ENETS is already planning its next annual conference, to be held in Prague, 22–24 March, 2006. I look forward to seeing you there.

Bertram Wiedenmann, MD
Chairman ENETS
2nd Annual ENETS Educational Conference for the Diagnosis and Treatment of Neuroendocrine Tumors
Who, What, When and Why
20–22 April, 2005, Cracow, Poland

Judging by the dozens of feedback forms ENETS has received from those who attended the ENETS conference, there was something for just about everyone in the stunning theater house in one of Europe’s most beautiful cities.

‘Excellent lectures …’ writes a researcher from Austria. The assembly of experts ‘was fantastic’ says another from Portugal, and one anonymous participant comments on the ‘excellent venue and social program’.

About 400 researchers from 40 countries attended the annual conference of the European Neuroendocrine Tumor Society in Cracow, Poland, in April 2005. The meeting was held in the dazzling Slowacki Theater and most of the lectures had an interactive format, whereby participants could vote on different treatments for neuroendocrine tumor (NET) disease. Scores were then projected on a screen and possible answers discussed. The conference was made possible by a generous, unrestricted educational grant from Novartis.

The chance to meet both familiar and new researchers and clinicians, to glimpse at the soon-to-be published ENETS Guidelines for the Treatment of Neuroendocrine Gastrointestinal Tumours, to update clinical knowledge, and naturally, to see Cracow, ‘the jewel of Poland’, as the city is called, as well as the impressive Wieliczka Salt Mine – where the conference’s gala dinner was held – all rated high on the participants’ lists.

The conference opened on the afternoon of 20 April 2005 with a welcome and introduction from Bertram Wiedenmann of Berlin, current chairman of ENETS. He spoke of the founding of ENETS in 2004 and how the Society has grown to about 270 members. He also extended thanks to the Polish co-organizers and welcomed all guests to Cracow. Finally, he alluded to the aim of the conference: hands-on approaches to update clinical knowledge, and naturally, to see Cracow, a bit.

The second day started with the session, ‘NET of Pancreas’. Barbro Eriksson of Uppsala, Sweden, and Rudolf Hyrdel of Bratislava, Slovakia, chaired the session. Prof. Eriksson, who co-authored the ENETS Guidelines, presented the guidelines on NET of the pancreas, including epidemiology and clinicopathological staging, biochemistry and stimulatory tests, histopathology and therapeutic options. Massimo Falconi from Verona, Italy, presented his ‘Non-Functioning NET of the Pancreas,’ focusing on the diagnosis and therapy of localized and surgically resectable pancreatic NET. Dermot O’Toole of Clichy, France, followed by presenting a typical case of a non-functioning NET of the pancreas with metastatic disease, demonstrating the benefit of intelligently coordinated surgical interventions. This presentation was followed by the singer of the Obligato Orchestra and the singers Krytyyna Tyburowska and Jan Zakrzewski. A welcome reception in the theater’s foyer allowed participants to meet and mingle, as well as head out to explore Cracow a bit.

In his presentation of NET of the duodenum, Dermot O’Toole eloquently demonstrated the typical case of a non-functioning NET of the pancreas, including epidemiology and clinicopathological staging, biochemistry and stimulatory tests, histopathology and therapeutic options. Massimo Falconi from Verona, Italy, presented his ‘Non-Functioning NET of the Pancreas,’ focusing on the diagnosis and therapy of localized and surgically resectable pancreatic NET. Dermot O’Toole of Clichy, France, followed by presenting a typical case of a non-functioning NET of the pancreas with metastatic disease, demonstrating the benefit of intelligently coordinated surgical interventions. This presentation was followed by

Guido Rindi of Parma, Italy, followed with a case of benign NET of the stomach, focusing on the diagnostic procedures and prognosis of patients with benign NET.

Beata Kos-Kudla of Zabrze, Poland, then spoke about the various aspects of patients with malignant NET of the stomach. In his presentation of NET of the duodenum, Robert T. Jensen from Bethesda, Md., USA, eloquently demonstrated the typical case of gastrinoma, involving the audience intensely in a discussion of diagnostic procedures, therapy and prognosis.

Britt Skogsdal of Uppsala, Sweden, spoke on genetics in general and hereditary syndromes of NETs, i.e. MEN-1 syndrome and Von-Hippel-Lindau disease in particular. Her lecture was followed by a concert in the theater, by the Obligato Orchestra and the singers Krytyyna Tyburowska and Jan Zakrzewski. A welcome reception in the theater’s foyer allowed participants to meet and mingle, as well as head out to explore Cracow a bit.

The second day started with the session, ‘NET of Pancreas’. Barbro Eriksson of Uppsala, Sweden, and Rudolf Hyrdel of Bratislava, Slovakia, chaired the session. Prof. Eriksson, who co-authored the ENETS Guidelines, presented the guidelines on NET of the pancreas, including epidemiology and clinicopathological staging, biochemistry and stimulatory tests, histopathology and therapeutic options. Massimo Falconi from Verona, Italy, presented his ‘Non-Functioning NET of the Pancreas,’ focusing on the diagnosis and therapy of localized and surgically resectable pancreatic NET. Dermot O’Toole of Clichy, France, followed by presenting a typical case of a non-functioning NET of the pancreas with metastatic disease, demonstrating the benefit of intelligently coordinated surgical interventions. This presentation was followed by

Robert Jensen, of Bethesda, Md., USA, Kjell Öberg and Barbro Eriksson, both of Uppsala, Sweden, all presented at the conference. During one of the breaks, they swap experiences and a joke or two.
Reza Kianmanesh of Warsaw, Poland, discussed a case of gastrinoma in the context of sporadic MEN-1 syndrome. She also presented the management of associated pituitary and parathyroid disease. Valdis Pirags of Riga, Latvia, then looked at a rare case of hypoglycemia in a patient with a metastatic tumor. He discussed the findings of diagnostic procedures and lessons to be learned from the case of a non-endocrine tumor presenting with a paraneoplastic hypoglycemia syndrome which mimicked insulinoma.

Roza Kramanchoch of Clichy, France, followed with his state-of-the-art lecture on ‘Surgical Treatment of Extensive Liver Disease’. He outlined strategies and results of liver surgery in metastatic NET disease, giving a comprehensive overview, which was well received by the audience.

This year’s conference, like the one in Budapest in March 2004, included the Society’s recognition of a researcher who has contributed a lifetime of service to the study of NET research. This year’s Life Achievement Award was given to Prof. Werner Creutzfeldt of Goettingen, Germany. His former student, Burghard Góke of Munich, Germany, spoke of his mentor’s scientific prowess and highlighted how he felt accepted and encouraged by Werner Creutzfeldt even though his (Góke’s) hair was long and he dressed like a hippie. His impressive contributions, including more than 500 publications in the field of NETs, were also briefly summarized. This highlighted Prof. Creutzfeldt’s deep involvement and dedication to the world of neuroendocrinology.

Bertram Wiedenmann also spoke warmly of his colleague, the late Prof. Stefan Rosewicz of Berlin, Germany, who died of a heart attack in May 2004 and who was revered for his scientific legacy and promise. Rosewicz was also a well-recognized presenter at the 2004 ENETS conference.

Session 3, ‘NET of the Small Intestine and Appendix’, was chaired by Hakan Ahliman of Gothenburg, Sweden, and Ursula Plöckinger of Berlin, Germany, both authors of the ENETS Guidelines. They presented an overview of the diagnostics and the surgical and medical treatment strategies of NET. Goran Åkerström of Uppsala, Sweden, presented a case of non-functioning NET of the ileum with local disease and nicely outlined the appropriate surgical approach. Kjell Öberg, also of Uppsala, Sweden, then spoke about functioning NET of the ileum with metastatic disease, focusing on the successful treatment of a female patient who had suffered from a metastatic mid-gut NET with carcinoid syndrome for 20 years. Robert Sutton of Liverpool, UK, then presented a case of NET of the appendix, a situation routinely experienced in the field. He also mentioned the continuing discussion over the extent of surgical therapy and the potential outcomes and influence, thereby illustrating aspects also considered in the ENETS Guidelines.

Session 4, ‘NET of the Colorectum’ included the presentation of the guidelines by Martyn Caplin of London, UK, and Günter Krejs of Graz, Austria. Martyn Caplin, who contributed to the corresponding chapter on the ENETS Guidelines, presented a brief and comprehensive outline of the diagnostic and therapeutic algorithms. Emmanuel Mitry of Boulogne, France, presented the first case, a metastatic NET of the colon, in which he included surgical observations, pathology, disease progression, and cytoreductive surgery. He was followed by Gianfranco Delle Fave of Rome, Italy, who presented a typical case of NET of the rectum, providing a practical approach to these patients. Eric Van Cutsem of Leuven, Belgium, presented a poorly differentiated neuroendocrine carcinoma of the rectum and discussed the established treatment strategies as well as future possible options in treating colorectal adenocarcinomas and, in so doing, launched an intense discussion with the audience.

Next on the agenda was the ENETS’ annual General Assembly. Bertram Wiedenmann summarized the events of the last year including the establishment of the ENETS Coordinating Office and ENETS as an official scientific society. He highlighted the 1st International Patient Day for NET patients, held in November 2004 in Berlin, and the coordination of the ENETS Guidelines, as well as plans for the future to establish task forces. The ENETS treasurer, Ursula Plöckinger, then gave an overview of the Society’s income and expenditures. Future conferences and activities of the society were also discussed.

The high point for many conference attendees, however, was a tour of the Wieliczka Salt Mine, just outside Cracow. With dozens of chapels and magnificent salt sculptures, the mine, which reaches 327 meters below ground, fascinated all the visitors who flowed into the mine’s great ‘Warszawa Chamber’ for the conference’s gala dinner, replete with orchestra, light displays and even a brief history of Cracow, provided by Bertram Wiedenmann.

The conference’s last day included a state-of-the-art lecture by Larry Kvols of Tampa, Fl., USA, on ‘Current and Future Use of Somatostatin Analogues in Metastatic Neuroendocrine Disease’. Session 5, ‘Treatment Options in Systemic Disease and Unknown Primary’ was then chaired by Eugene Woltering of New Orleans, La., USA, and Eric Van Cutsem. Frédéric Maire of Clichy, France, spoke on a NET of unknown primary, metastatic to the liver. Her patient, in whom an extrapancreatic tumor manifestation was not detectable at any time, received a liver transplant enabling a pathologic evaluation of the diffusely diseased organ, showing multiple intrahepatic NET manifestations. Ursula Plöckinger followed with a case of NET of the ileum, metastatic to the liver and the bones. She highlighted the diagnostic procedures, therapeutic strategies and options in this interesting and complex case showing bone involvement which is often missed during clinical examinations. The final case presentation, given by Ashley Grossman of London, UK, was on ectopic hormone secretion dealing with various aspects, including diagnostic difficulties of paraneoplastic ectopic hormone syndromes. The final lecture of the conference was a state-of-the-art lecture on ‘Targeted Radiotherapy’, given by Eric Krenning of Rotterdam, the Netherlands. His lecture focused on the exciting new developments and first data from clinical trials with radioactively labeled somatostatin analogues, not only for diagnostic purposes but also for treatment of metastasized NETs. His data on efficacy and safety, as well as clinical outcomes, and were perceived as encouraging.

The conference was concluded by Bertram Wiedenmann and Wouter de Herder of Rotterdam, the Netherlands, the president-elect of ENETS. They presented the preliminary program for the next annual conference which will be held in Prague in 2006. This conference is planned to include not only updates on evidence-based diagnostic and therapeutic strategies, but also new developments in basic science.

Elizabeth Zach and Ulrich-Frank Pape

ENETS Newsletter

As a result of generous grants from IPSEN and Novartis, the 3rd Annual Conference of the European Neuroendocrine Tumor Society will be held in Prague, Czech Republic, on September 20-22, 2005. The conference will feature international leaders in neuroendocrine tumor biology, diagnosis, and therapy. For more information, please visit the website at www.neuroendocrine.net where the deadline will be posted. Online registration will tentatively begin September 2005. The website will be updated on a regular basis. The conference site and accommodations will be at the Prague Hilton Hotel. The conference will be supported by generous grants from IPSEN and Novartis.
The Most Comprehensive NET Guidelines Worldwide

Diagnostic and treatment planning for patients with neuroendocrine tumours (NETs) is a challenge for physicians in terms of their experience and willingness toward interdisciplinary cooperation. The ENETS Guidelines for the Diagnosis and Treatment of Neuroendocrine Gastrointestinal Tumours, published in April 2005 in the journal Neuroendocrinology, presents both the current practice-related state of NET research, as well as expert consensus. In this interview, which was conducted by Dr. Thomas Heim in Cracow during the ENETS conference in April 2005 and which was originally published in German in a post-conference newsletter by Novartis Oncology in Germany, Prof. Bertram Wiedemann, ENETS’s first chairman and co-organizer of the Cracow conference, discusses the Guidelines and the opportunity to improve early detection.

‘Up to now, NET guidelines have been mainly based on expert opinions.’

Guidelines for the treatment of gastrointestinal tumors – developed by an expert body in the framework of ENETS – were published in April 2005. Last year, a consensus report regarding the NET management of the gastroenteropancreatic system, in which you also participated as an author, was published (Öberg et al: Consensus report on the use of somatostatin analogs for the management of neuroendocrine tumors of the gastroenteropancreatic system. Ann Oncol 2004;15:966–973). What is new about the current version in comparison to last year’s?

The new consensus report should be considered as a supplement. The 2004 report focused heavily on treatment with somatostatin analogues. The current consensus report considers the overall range of diagnosis and various treatment modalities in a comprehensive manner. And, in addition, we have a multidisciplinary consensus panel.

How long did this take to prepare?

The first steps had already been taken in 1995. However, only the creation of an expert organization made the performance of a continuous guideline procedure possible. I think we can proudly claim to have developed the most comprehensive NET management guidelines worldwide.

Are there any recent landmark studies that influenced your recommendations?

Due to the rarity of neuroendocrine tumors, the data are very limited. We could only rely on four or five studies which, in a strict sense, comply with the prerequisites of evidence-based medicine.

This means that Guidelines in this field are mainly based on small, non-controlled studies and expert opinions.

That’s correct. This is one of the reasons why it is so important that the experts involved continue their cooperation in order to start generating such recommendations.

How can these Guidelines help the individual physician treating NET patients?

The physician will find a current summary of the available data, for example, sensitivity and specificity of individual diagnostic procedures. In addition, based on the current literature we tried to show in practice the sequence of individual diagnostic and therapeutic steps.

How can these guidelines help physicians avoid mistakes in the treatment of NET patients?

This conference made it clear how varied the opinions and, ultimately, therapy decisions of many physicians are and how these opinions can deviate from what NET experts consider a long-existing consensus. For example, the different types of gastric NETs need a differentiated prognosis and, as a consequence, surgical treatment. I was surprised that some colleagues are still of the opinion that patients with absolutely benign tumors should undergo vast surgery, although such procedure is completely unnecessary. In other cases, the respective necessary measures are not taken, although clear curative chances exist. In this context, the recommendations as to diagnostic procedures are extremely decisive.

What role does histological diagnosis play in NET management?

Mistakes in therapy planning are often based on an insufficient histological NET diagnosis. This means false-positive or false-negative results or inexact assessment of the tumor stage. As a consequence, patients are often treated in excess or less than they really need to be for many years. On the other hand, the field of NET diagnosis demands high expertise of the pathologist, and, on the other hand, target-oriented imaging.

According to these guidelines, what is the importance of tumor markers in NET screening?

We considered a quite larger scope than the reality of economics in medicine would permit. In the past, especially with regard to the use of inexact targeted tumor markers, waste of financial means was frequent. Under current cost-value pressures, we are obliged to limit our activities to what is absolutely necessary. Of course, it is not easy to reach generally accepted recommendations as the discussion participants belong to completely different health systems which rely on completely different financial means. One of the important milestones is the knowledge that chromogranin A constitutes a valuable parameter in development observation, however, provided that the same assay method is used.

And with respect to screening?

It is absolutely useless. Even the use of 5-HIAA only makes sense in patients with large metastatic tumors that, in addition, frequently present a carcinoid syndrome.

Do you think that the frequency with which tumor markers are used in Europe is too high or too low?

Assessing the situation is difficult but NET registry data from can provide the necessary support. I presume that, in general, tumor markers are used in excess. The problem is the frequent use of incorrect markers. For example, in some NET patients tumor markers such as NSE and Ca19-9 are applied. These markers are relevant in dedifferentiated adenocarcinomas or small-cell carcinomas, respectively. In the case of well-differentiated NET, they are of no importance.

‘Due to wrong or undifferentiated diagnosis, patients are often treated in excess or get less than they really need for many years.’

The example you selected from the field of surgical therapy could also be applied to other therapy modalities, such as radiotherapy, chemotherapy, and biological therapy: Only physicians with sufficient NET experience within their medical discipline are able to treat these patients accordingly. Since it often happens that decisions between various methods are necessary or a combination of different methods is taken into consideration, the only possible way seems to be the interdisciplinary discussion. Is this the key solution for optimizing management?

In fact, interdisciplinary cooperation is, on the one hand, a prerequisite. However, another important point is experience. During the Cracow conference it has become increasingly clear to me that individual centers treating a minimum number of NET patients are able to work out the issue in a much more consistent manner and therefore are able to present better therapy results than any institution with little or no experience. In principle, this is applicable to all medical disciplines. Nevertheless, the experiences of individual centers show certain differences. Let’s take imaging as an example: Some centers dispose of more experience in MRT; others in endosonography. The orientation of some gastroenterologists is more endoscopic/endosonographic. Others, in their function as endocrinologists, put their major focus on hormone tests.

I suppose in such cases the combination of different approaches is not always easy since people have the tendency to think that their own method, in which they possess a lot of experience, is the best one. The aim is to use ENETS as a real and unique channel. It can only be achieved by rigorous discussion and by clarifying many of the still existing controversies. But this is another problem with rare diseases. The planning of a prospective study requires both seeing the patient on an individual basis and agreeing on a standardized procedure, according to which patient results are categorized and thus summarized in different study branches.