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Abbreviations:

AMPA:	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
CT:	computed tomography
EEG:	electroencephalogram
EMG:	electromyography
FDA:	Federal Drug Agency
GABA:	gamma-aminobutyric acid
ICU:	intensive care unit
MRI:	magnetic resonance imaging
NMDA:	N-methyl-D-aspartate
qEEG:	quantitative EEG
RSE:	refractory status epilepticus
SE:	status epilepticus

Summary

The history of epileptology in Basel may date back to the time of Paracelsus when he was professor of medicine at the University of Basel for less than two years (1527-1528) and where he wrote on etiologies, diagnosis and treatment of epilepsy. More than four centuries later (1952), the first electroencephalogram (EEG) was recorded in Basel. The section of EEG and epileptology at the University Hospital was established in the period of Giuseppe Scollo-Lavizzari (1968-1997) who wrote important publications in the field of EEG, epilepsy, neuropharmacology, sleep and coma. In parallel, the Basel pharmaceutical industry discovered milestone medications for the treatment of epilepsy, like the benzodiazepines, carbamazepine, oxcarbazepine, eslicarbazepine, and rufinamide. With this respect, people like Leo Henryk Sternbach (Roche), Hans Allgeier, Walter Schindler or Markus Schmutz (Ciba-Geigy/Novartis), made major contributions to improve antiepileptic drug therapy. The successors of G. Scollo Lavizzari in the field of epileptology, David Leppert (1998-2004) and Stephan Rüegg (from 2004 onwards), continued to work in the main fields of the section with additional emphasis to status epilepticus and autoimmune epilepsies. Since the advent of high-density array EEG machines and sophisticated software, a multicenter research group led by Peter Fuhr uses quantitative EEG for characterizing course and prognosis of chronic disorders of the CNS.

Epileptologie 2015; 32: 31 – 38

Key words: Pharmacotherapy, antiepileptic drugs, Basel, benzodiazepines, carbamazepine, status epilepticus, neurointensive care, quantitative EEG, chronic CNS disorders

Basler Beiträge zu Elektroenzephalographie und Epileptologie

Die Geschichte wissenschaftlicher Auseinandersetzung mit der Epilepsie kann in Basel vermutlich mindestens auf die Zeit von Paracelsus zurückgeführt werden, als er knapp zwei Jahre als Medizinprofessor angestellt war (1527-1528) und über die Ursachen, Diagnose und Behandlung der Epilepsie schrieb. Mehr als vier Jahrhunderte später (1952) wurde in Basel das erste Elektroenzephalogramm (EEG) abgeleitet. Die Abteilung für EEG und Epileptologie am Universitätsspital Basel wurde durch Giuseppe Scollo-Lavizzari (1968-1997) aufgebaut. Er veröffentlichte wichtige Arbeiten in den Gebieten EEG, Epilepsie, Neuropharmakologie, Schlaf und Koma. Fast gleichzeitig entdeckten Basler Pharmafirmen entscheidende Medikamente zur Behandlung der Epilepsie, so die Benzodiazepine, Carbamazepin, Oxcarbazepin, Eslicarbazepin und Rufinamid. Bedeutende Beiträge zur Verbesserung der Epilepsietherapie wurden so u.a. von Leo Henryk Sternbach (Roche), Hans Allgeier, Walter Schindler oder Markus Schmutz (Ciba-Geigy/ Novartis) geleistet. Die Nachfolger von G. Scollo-Lavizzari auf dem Gebiet der Epileptologie, David Leppert (1998-2004) und Stephan Rüegg (seit 2004) setzten Arbeit und Forschung fort und erweiterten sie um den Status epilepticus sowie die Autoimmunepilepsien. Seit der Verfügbarkeit von räumlich hochauflösenden EEGs mit bis zu 256 Ableitungselektroden sowie leistungsfähiger Auswertungssoftware arbeitet eine multizentrische Forschungsgruppe unter der Leitung von Peter Fuhr an der Charakterisierung von Verlauf und Prognose chronischer Erkrankungen des ZNS mithilfe von quantitativem EEG.

Schlüsselwörter: Pharmakotherapie, Antiepileptika, Basel, Benzodiazepine, Carbamazepin, Status epilepticus, Neurointensivpflege, quantitatives EEG, chronische ZNS-Krankheiten

Contributions bâloises à l'électroencéphalographie et l'épileptologie

L'histoire de l'étude scientifique de l'épilepsie à Bâle remonte sans doute au moins à l'époque de Paracelse, qui décrivit ses causes, son diagnostic et son traitement alors qu'il était employé en tant que professeur de médecine durant près de deux ans (1527-1528). Le premier électroencéphalogramme fut réalisé à Bâle plus de quatre siècles plus tard, en 1952. Le service d'EEG et d'épileptologie de l'Hôpital universitaire de Bâle fut créé par Giuseppe Scollo-Lavizzari (1968-1997). Il publia d'importants travaux dans les domaines de l'EEG, de l'épilepsie, de la neuropharmacologie, du sommeil et du coma. Presque simultanément, des sociétés pharmaceutiques bâloises découvraient des médicaments déterminants dans le traitement de l'épilepsie et notamment les benzodiazépines, la carbamazépine, l'oxcarbazépine, l'eslicarbazépine et le rufinamide. Leo Henryk Sternbach (Roche), Hans Allgeier, Walter Schindler ou Markus Schmutz (Ciba-Geigy/Novartis), entre autres, ont ainsi contribué de manière significative à améliorer le traitement de l'épilepsie. Les successeurs de G. Scollo-Lavizzari dans le domaine de l'épileptologie, David Leppert (1998-2004) et Stephan Rüegg (depuis 2004) ont poursuivi les travaux et la recherche en les augmentant du statut épileptique et des épilepsies auto-immunes. Depuis que l'EEG à haute résolution spatiale avec jusqu'à 256 électrodes de recueil et qu'un logiciel d'analyse performant sont disponibles, un groupe de recherche multicentrique travaille sous la direction de Peter Fuhr à la caractérisation de l'évolution et du pronostic de maladies chroniques du SNC au moyen de l'EEG quantitatif.

Mots clés : Pharmacothérapie, médicaments antiépileptiques, Bâle, benzodiazépines, carbamazépines, status epilepticus, soins neurointensifs, EEG quantitatif, maladies chroniques du SNC

Preface

The following "historical" article is not written by historians, and all content is based on subjective selection, not covering all relevant topics and not mentioning all persons who obviously might have merited it. However, the manuscript relies on our best intentions, and all diligence and attention we could provide. Readers may pardon us for inevitable omissions.

Basel and epilepsy – the ancient times

The city of Basel has a longstanding record of contributions to the field of medicine resulting from the flourishing print industry (f. ex., Johann Froben and Johannes Oporinus) attracting many eminent late medieval and renaissance scientists, artists and philosophers like Erasmus of Rotterdam, Albrecht Dürer, and Vesalius. The city's University founded 1460 by the later Pope Pius II (Aeneas Piccolomini) added to the reputation of Basel as a center of erudition. Paracelsus (Philippus Theophrastus Aureolus Bombastus von Hohenheim; 1493-1541) was appointed lecturer at the University of Basel in 1527 where he broke with almost all customs and traditions of ancient medicine by publicly burning the works of the heroes of ancient medicine, like Galen, Celsus, and Avicenna. He introduced the outrageous concept of modern pharmacology and toxicology that all substances could be used as a drug and that only the dosage determines their helpful (i.e., pharmaceutical) or deleterious (i.e., toxic) effect. Since he also dared to give his lectures in German (and not Latin or Greek), he was forced to flee from the city one year later only in order to not be involved in hopeless legal proceedings. Regarding epilepsy, Paracelsus was not so progressive as he was on other topics. He held – contrary to Hippocrates – that epilepsy is a disorder not only originating from the brain, but also from the heart, the liver, the intestines and the limbs where the *spiritus vitae* is boiling and the resulting vapours cause the seizures. He recommended many remedies for epilepsy, like *spodium* (animal ash, mainly calcium phosphate), camphor, unicorn, etc., essentially "*served in a boiled egg*". But his favored recipe consisted of a lozenge of a mixture of several herbs, opium, and hyoscamus, bathed in hop juice, put into a quince, then covered with dough and baked. The "bread" is then crushed to powder and one part added to nine parts of *arcanus vitriolus* (oily suspension of sulphuric acid). It becomes clear that Paracelsus was still adhering to the sometimes magic potion-like mixtures of herbal, animal and mineral substances although he introduced a clear "chemical compound" (sulphuric acid, *vitriol*) into the pharmaceutical armamentarium against epilepsy [1].

The establishment of the neurological services/ department in Basel (1907)

Robert Bing (1878-1956) started in 1907 to practice neurology in the outpatient clinic of the Bürgerspital Basel, and later became the first full professor of neurology at the University of Basel. He wrote the first textbook of neurology in German and made important contributions to clinical neurology. However, the field of epilepsy was not his main focus; the same is true for his successor Felix Georgi (1893-1965) who was appointed 1951 as second head of the neurological outpatient clinic. He was able to expand the neurology services, to found a scientific lab and eventually to establish a neurological inpatient clinic. It was during his tenure that EEG was introduced.

The beginnings of electroencephalography in Basel (1952-1968)

The first EEG in the neurological outpatient clinic was recorded on July 10th, 1952 on an 8 channel machine. The name of the first patient examined was Hans Berger and thus – by chance – synonymous to that of the researcher who introduced the EEG into clinical neurology (**Figures 1a & b**). The EEG recordings in these initial times were supervised by experienced senior registrars, mainly Dr. Hans-Rudolf Richter, Dr. Hanspeter Rieder, and Prof. Hans-Rudolf Müller who also were in charge of the formation of the residents in EEG and epileptology.

Figure 1a: The well preserved first EEG journal of the Neurological Outpatient Clinic of the Bürgerspital Basel 1952/1953

The era of Prof. Giuseppe Scollo-Lavizzari (1968-1997)

Prof. Giuseppe Scollo-Lavizzari was appointed head of the division of EEG and Epileptology, and as attending physician at the Department of Neurology in 1968. He studied medicine, got his approbation, and did his first years of residency and his thesis in Rome. From 1960 onwards, he spent 8 years of formation in Zürich where he started as a resident at the Epilepsieklinik. Thereafter, he went as a research fellow to the Brain Research Institute of the University of Zurich and then

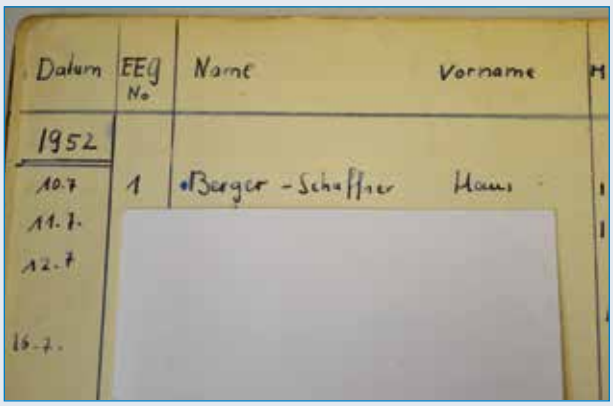

Figure 1b: The first entry in the EEG journal of the Neurological Outpatient Clinic of the Bürgerspital Basel dated July 10, 1952, portraying the name of a patient named Hans Berger, synonymous with the person who introduced human EEG into clinical neurological practice

changed to the EEG division (at that time in the Department of Neurosurgery (!) of the University Hospital of Zurich) where he remained for four years and was promoted to senior registrar before his appointment in Basel. Here, he finished his habilitation in Neurology, especially Clinical Neurophysiology in 1972 and was appointed professor in 1979.

During his time in Basel, he wrote more than 200 publications and became an internationally esteemed expert in EEG and epileptology: he remained during his life-long academic career in Basel despite that he had been invited by – among others overseas institutions. Key areas of his research were:

a. Sleep, epilepsy, and EEG

After his first studies in Zurich [2-6], he published an extensive study on the effect of sleep on EEG abnormalities remote from the lesion in structural-metabolic epilepsy [7]. Sleep deprivation was identified as a helpful activation method in the diagnosis of epilepsy [8, 9]. Together with his late wife, he wrote a comprehensive review on sleep, sleep deprivation, photosensitivity, and epilepsy [10]. Night sleep was continuously monitored by EEG and EMG in a case of subacute sclerosing panencephalitis [11]. He also reported the simultaneous EEG recording during cataplectic attacks showing that the events are non-epileptic [12]. Other publications dealt with absence ("petit-mal") status of adults [13, 14], and with the phenomenon of generalized epilepsy in association with subcortical structural alterations [15]. He was also interested in emerging new technologies, like spectral analysis of EEG activity [16] or cerebral computer tomography (CT) [17-20], and magnetic resonance imaging (MRI) [21]. In the late 80s, he was a member of a team using a "modern", multimodal approach (clinical examination, EEG, and head CT) for the differential diagnosis of senile dementia [22].

b. Pharmacological treatment of epilepsy

A second main interest was the pharmacological long-term treatment of epilepsy (reviewed in [23]), especially the study of GABAergic antiepileptic drugs. He pioneered the use of valproic acid [24] and clonazepam [25] in Switzerland. He evaluated the hypnotic efficacy and safety of midazolam in shift-workers [26]. He also pointed to the deactivation effect of diazepam on photosensitivity [27]. While studying the imido-azo-benzodiazepine compound flumazenil (Ro 15-1788), he became aware of the at least partial anticonvulsant activity of this drug which is nowadays used as the principal antagonist of $GABA_A$-receptor mediated currents [28, 29]. Further research tested the drug in patients with ethanol and carbamazepine intoxication and also as a diagnostic and therapeutic tool in patients with self-poisoning [30-32]; risks and benefits of its use in mixed drug intoxications were also reviewed [33].

c. The EEG of coma

Giuseppe Scollo-Lavizzari early recognized the potential of the EEG in the evaluation and prognostication of altered consciousness in critically ill patients and the recording of EEGs on patients in the intensive care unit (ICU) was daily routine. He systematically studied the prognostic value of EEG in post-anoxic coma after cardiac arrest [34] and also looked at the diagnostic impact of periodic lateralized discharges in herpes simplex encephalitis [35]. A double-blind placebo-controlled study looked at the efficacy of flumazenil in comatose intoxicated patients [36]. He was part of the group who detected the enormous prolongation of coma in patients under midazolam with concurrent renal failure, because the glucuronidated active 1-alpha-hydroxy-midazolam metabolite is excreted very slowly [37]. He described the clinical relevance of hyperammonemia associated with the use of valproic acid [38].

d. The EEG in liver diseases

Impaired consciousness is one hallmark of severe liver disease with porto-systemic encephalopathy. After exploration of lactulose as a treatment already in Zurich, he was in the group which almost 25 years later tested flumazenil as a treatment for this condition [39] and described the effect of this therapy on the EEG [40].

Epileptology: Contributions of the Basel pharmaceutical industry

Nobel laureate Leo Henryk Sternbach of the Basel-based pharmaceutical manufacturer Roche discovered the benzodiazepines as substances with strong sedative, hypnotic, anxiolytic, muscle relaxant and anticonvulsant activity in the 50s. From the mid-seventies onwards important contributions concerning the mechanisms of action of the benzodiazepines, above all the involvement of the inhibitory neurotransmitter GABA, were made by Willy Haefely and Hans Möhler [41]. Chlordiazepoxide (Librium®), the first drug of this class was approved in 1960 by the FDA, and Diazepam (Valium®) in 1963 [42, 43]. A large number of benzodiazepines, active against acute seizures and status epilepticus (midazolam, clonazepam, clobazam, etc.), were brought to the market in the following years. The anticonvulsant carbamazepine (Tegretol®) was synthesized by Walter Schindler at J.R. Geigy AG (now part of Novartis), Basel, in 1957 and from 1958 onwards developed for the treatment of the epilepsies. Subsequently, its therapeutic efficacy in trigeminal neuralgia was described in 1962 [44, 45]. The use of carbamazepine as an antiepileptic drug started 1963 in Switzerland and the UK, and 1967 in the USA [46-48]. The antiepileptic drug discovery program of Ciba-Geigy and Novartis (after the merger of 1996) of the 80s to the beginnings of the 21st century was led by Markus Schmutz, a leading expert in kindling and neuropharmacology of epilepsy [49-53]. During this period numerous research studies concerning the neurotransmitters GABA (e.g., $GABA_A$ and $GABA_B$ receptors; interactions with valproic acid, vigabatrin, anxiolytic pyrazolopyridines [54-66]), and glutamate (e.g., antagonism of NMDA- and AMPA-receptor-mediated glutamatergic transmission, metabotropic glutamate receptor 7 [67-82]), as well as other principles and animal models of seizures and epilepsies [53, 83, 84, 91] were published. He and his team played an essential part in the development of the antiepileptic drugs oxcarbazepine (Trileptal®) [85-90] and rufinamide (Inovelon®) [91].

Electroencephalography (EEG) and epileptology at the University Hospital Basel – the present (1997-2015)

After the retirement of Giuseppe Scollo-Lavizzari in 1997, the EEG lab and epileptology clinic became part of the Section of Clinical Neurophysiology headed by Peter Fuhr. From 1998, David Leppert took over the main responsibility for the EEG/epileptology part. During that time, they developed the nationwide guidelines for the treatment of status epilepticus (SE) approved by the Swiss Neurological Society [92]. Additionally, descriptions of both ictal asystolia and electrocerebral silencing during cardiac asystolia were published [93, 94].

In 2004, Stephan Rüegg was appointed head of EEG/epileptology. He is mainly interested in the neuropharmacology of epilepsy, into SE (especially nonconvulsive SE), neurocritical care, brain tumor-associated seizures [95-97], and autoimmune epilepsy. Together

with Peter Fuhr, Raoul Sutter, the team of the ICU of the University Hospital of Basel and an international network of epileptologists he published several papers and reviews on these topics [98-110]. He pioneered the use of intravenous levetiracetam in critically ill patients with seizures and SE [111], and of topiramate and lacosamide for refractory SE (RSE) [112, 113]. The group showed that implementation of continuous video-EEG in ICU patients increases diagnosis of non-convulsive SE, making these patients amenable to an earlier and specific treatment [114]. Looking for the identification of prognostic factors of SE, the group found that infections (at the first day) [115], acute phase proteins (like elevated C-reactive protein and low albumin levels) [116, 117], etiologies (like hypoxic encephalopathy and brain tumors) were associated with dismal outcome in SE [118], reviewed in [119]. The group recently observed in a retrospective study that anaesthetics for induction of therapeutic coma in the treatment of RSE were associated with an increased risk for death and infections [120].

Together with Annamaria Vezzani, Stephan Rüegg organized the first meeting on Inflammation, Immunity and Epilepsy (IIE) in Milan (Italy) [121-122], and he also published a comprehensive overview and editorials on the topic [123-125].

Electroencephalography is a neurophysiological method with a high temporal, but limited spatial resolution. To improve this disadvantage, the use of high-density array-EEG (nets with up to 256 electrodes connected to high-power amplifiers) has increasingly been implemented. Advanced computing offers the possibility to extract and calculate otherwise « hidden » information from these EEGs. With generous support by the Swiss National Science Foundation, these quantitative EEG (qEEG) methods are currently used in an international multicenter research program led by the Section of Clinical Neurophysiology (PI Peter Fuhr) for exploring course and prognosis of chronic disorders of the CNS, like multiple sclerosis, schizophrenia, Alzheimer's disease, and Parkinson's disease [126-137].

Electroencephalography (EEG) and epileptology – the future

In the next years, we will continue to optimize neuropharmacological treatment of SE, to better characterize patients with SE with respect to their types of SE, comorbidities, course and prognosis, and to identify helpful markers for individually tailored therapy of SE. The implementation of high-density array EEG and qEEG analyses in neurocritical care has a high priority, as we will establish (semi-)automated analysis of continuous EEG monitoring in the ICU. These steps will converge with the already well running qEEG studies in neurodegenerative and neuropsychiatric disorders.

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