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“Analysis and contextualisation of the work and life of the pharmacologists W. Wiechowski, E. Starkenstein and G. Kuschinsky with particular focus on their contribution to modern pharmacology”

PhD- thesis

PhD supervisor : Prof. PhDr. Petr Svobodný, Ph.D

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Explanation:

I declare herewith, that I have completed the thesis independently and have duly stated and quoted all sources and literature used to the best of my knowledge.

At the same time, I declare that this work has neither been used nor submitted to obtain any other academic degree before.

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Abstract

“Analysis and contextualisation of the work and life of the pharmacologists W. Wiechowski, E. Starkenstein und G. Kuschinsky with particular focus on their contribution to modern pharmacology”

“This dissertation explores three case studies of pharmacologists which had been the Chair of Pharmacology at the German University of Prague in the early to mid- 20th century and thereafter. Due to their different personal background and research interests, both their academic research work and also their personal lives are investigated, with regards to their contribution to modern pharmacology and also in terms of political victimization or preferential treatment. The underlying methodological concept has to be seen in Heidegger’s hermeneutic phenomenological philosophy, drawing from the understanding of the individual’s experiences, adding an interpretative view to his teacher’s perception of phenomenology, Edmund Husserl.”¹

Particularly original publications from all three pharmacologists are examined to establish each pharmacologists` research focus and methods applied as well as their contribution to an evidence oriented approach to pharmacotherapy, which can be seen on their extent of contribution to modern clinical trials. In addition personal files and correspondence, but also a semi- structured qualitative interview based on a topic guide of the analysed sources helped to (re)construct personal facets of the three cases.

“Thematically seen, all three pharmacologists are being reviewed in terms of their academic biography, including professional influences or direct academic collaborations. To understand socio-political influences, also personal stances on philosophical issues as well as humanist interests have been considered, e.g. their ideas on public health or wider health policies, professional development of healthcare professions or their relations to the pharmaceutical industry itself. Based on a “thick description” (Geertz), the results of this research demonstrate implications of ideological interferences on academic careers, and also consider Ehrenreich’s and Cole’s “Perpetrator- Victim- Bystander- Model”².

Keywords: Pharmacology- 20th century- phenomenology- case studies- conceptual framework of victimisation- German University Prague- Original Publication

¹ ZAWADZKI PATRICK, Die Pharmakologie in Prag. Biographische Annäherung an W. Wiechowski, E. Starkenstein und G. Kuschinsky in VIRUS – Beiträge zur Sozialgeschichte der Medizin, Band 21 (2022) page 255-260 (currently in print)

² Ibidem

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I. Introduction

1.1. Overview of theoretical approaches and methods

The overall aim of this thesis is to provide a distinctive contribution to social micro-history within the subfield of pharmacology. The period under study is the first and second Czechoslovak Republic as well as the German occupation until 1945 and developments thereafter. Micro-history can be distinguished from macro-historical approaches in terms of focus, as very specified events or aspects of social or cultural conditions are investigated on a small scale level.

Based on this focus, different contexts can be established, described in detail and understood over a longer period of time. Traditionally, micro-history deals with outstanding individuals, special situations or events that are meaningful and relevant to the bigger questions. The advantages that come with looking at historical events on the micro- level is both the specific perspective and the opportunity to delve into the details of particular situations and conditions.^{3,4}

Given the large time frame not all aspects can be considered within this research project, therefore a biographical approach was chosen, focusing on three pharmacologists: Prof. Wilhelm Wiechowski, Prof. Emil Starckenstein and Prof. Gustav Kuschinsky.

There is no clearly defined approach or single biographical method to choose from, which presents both challenges and opportunities for this type of research. Therefore a combination of various methods will be used which, besides the traditional narrative biography, will include other scientific methods from psychology, sociology or sources and data from the natural sciences. By merging and utilizing different approaches and sources a multidimensional approach can lead to greater authenticity and create meaning or help explain certain phenomena better. To achieve the above and to avoid *biographical illusion* hypotheses have been formulated for the three pharmacologists under study in order to refine research questions and focus on the scientific work and particular aspects of their lives.

³ SZIJARTO ISTVÁN, Four Arguments for Microhistory in: Rethinking History, Volume 6, Number 2 (2002)

⁴ MAGNUSSON SIGURDUR G. / SZIJÁRTÓ, ISTVAN M., What is Microhistory?: Theory and Practice in: (1st ed.). Routledge (2013)

According to Bourdieu, *biographical illusion* can and should be avoided by referring to social conditions and mechanisms⁵: « *Produire une histoire de vie comme le récit cohérent d'une séquence signifiante et orientée d'événements c'est peut être sacrifier à une illusion historique. (...) on ne peut en tout cas esquiver la question de mécanismes sociaux que favorisent ou autorisent l'expérience ordinaire de la vie comme unité et totalité* »

This involvement of sociological approaches offers the opportunity to avoid this linear, cartesian- like coherence in biographical research and to replace it with a more holistic understanding of the individual under study and the scientific work. It is therefore about a systematic analysis of sources, which is a initial deconstruction of each research subject and a following synthesis and reconstruction under specific and pre-defined aspects and questions.

In order to gain a depiction as holistic as possible on the one hand, and keep focus to the specific phenomenon under investigation on the other, the reciprocity and interaction of subject and society has to be made explicit. In this research, the focus will be clearly placed on the three subjects . Their research and their scientific environment or *life world* will be investigated as far as it is relevant for understanding and deeper insight. The thesis does not seek to fully and exhaustively examine several decades of scientific, political and personal shifts within the 20th century, but to explore and describe three examples of scientist and their scientific work within this time frame.

This phenomenological approach will seek to create a dualism between these two entities, that is a construction both of the subject under investigation and his *life world* , referring to the tradition of an *understanding sociology*.

There are, however, limits and boundaries to this research since the phenomenological approach cannot deliver an objective that is, immediately transferrable or a sociological analysis from which generalisations might be drawn, and nor does it aim to do so. Instead this thesis seeks to understand individual behaviour in a particular context and time in which it manifests itself by means of systematic examination and inductive interpretation.

The intended overlap of the phenomenological perspective and the “outward” social perspective can be found in the question of how and to what extent outward reality is constituted within the individual. In a way, the gradual construction of layers and different

⁵ BOURDIEU PIERRE, L'illusion biographique in: Actes de la recherche en sciences sociales, Vol. 62-63, L'illusion biographique (1986) page 70

dimensions in that *life world* can lead to a proto-sociological perspective, which in itself is a constituting element of social research.⁶

The connection between social theory and historical research can make valuable contribution to the expansion of historical enquiry and help to mitigate problems of historical explanation of the phenomena under study. As suggested by Tosh , several theoretical approaches or frameworks within the research process can help to reflect upon initial hypotheses and to weigh them against the evidence. Phenomenological research can help to make sense of problems referring to human experiences such as identity or power and hierarchies in societal contexts, which often exist on several levels. It ensures that personal aspects of an individual, such as identity, can simultaneously be investigated with political and socio-cultural contexts on a small- scale. This helps to understand the *inter-relatedness* of the several levels and dimensions that the human experiences holistically.⁷

1.2. Methodology: Phenomenology

Phenomenological science has to be understood as a science of experiences and to be clearly separated from exclusively positivist sciences which deal with a much narrower definition of this term. The experiences that are addressed in phenomenological research are not simply isolated observations, but rather a range of intentional or unintentional, real or potential experiences, which in their entirety form the stream of experiences.⁸ A fundamental and universal property of human consciousness within the phenomenological philosophy is *intentionality* , a dimension that embraces both past, present and potential future experiences, which form our horizon of experiences. More than pure sensual perception, intentionality characterizes the individual's ability to refer to something "real" like a physical object or something imaginative like a theoretical idea or characteristic in a deliberately, directed cognitive manner. By contrast to directed intentionality, sensual perceptions (*hyletisch-phenomenological*) add a further layer to the stream of an individual's experience.

⁶ RAAB, JÜRGEN/ PFADENHAUER M./ STEGMAIER P./ DREHER J./ SCHNETTLER B., *Phänomenologie und Soziologie : theoretische Positionen, aktuelle Problemfelder und empirische Umsetzungen*, Wiesbaden:VS Verlag für Sozialwissenschaften (2008)

⁷ TOSH, JOHN, *The Pursuit of History – aims, methods and new directions in the study of modern history* in: Pearson Education Limited. Fifth Edition (2010)

⁸ HUSSERL EDMUND, *Ideen zu einer reinen Phänomenologie und phänomenologischen Philosophie Erstes Buch: Allgemeine Einführung in die reine Phänomenologie* in: Sonderdrucke aus der Albert-Ludwigs-Universität Freiburg (Originalbeitrag erschienen in: Jahrbuch für Philosophie und phänomenologische Forschung, Verlag von Max Niemeyer (1913) page 65

A human's perception of an experience is gradually constituted by individual acts of perception and reflection at a certain point in time - "noesis". Through this intentional analysis of objects, the individual is capable of creating a meaning for himself or herself - "noema", sometimes in several steps of analysis. All sensual or directed intentional perception can be seen as real experience, whereas the individuals "noematic" interpretation of them represents an unrealistic correlate of it. ("irrealistischer Erlebnismoment").⁹ It must be emphasized that phenomenology strives to understand "Weseneigenschaften", that is the nature of events and experiences within the world instead of a sheer factual, empirical description of things.¹⁰

Within this philosophical line of thought we clearly see two dimensions: on the one hand, the horizon of experiences and on the other, the horizon of understanding.

This philosophical phenomenological approach is rooted in the work of Husserl and his student Heidegger, which differs both in metaphysical focus and result in different methods to describe it. Whereas Husserl's focus is of epistemological nature, his student Heidegger deals with ontological questions.

Heidegger's approach enables a historical access to knowledge by emphasizing temporality in all philosophical clauses:

*"Alle ontologischen Sätze sind, weil Aussagen über das Sein im Lichte der rechtsverstandenen Zeit, temporale Sätze (...)"*¹¹ and further *"Wir interpretieren das Sein aus der Zeit. Die Interpretation ist eine temporale. Die Grundproblematik der Ontologie als der Bestimmung des Sinnes des Seins aus der Zeit ist die der Temporalität"*¹²

The term *temporality* is used to express the condition of understanding of the *Da- Sein* in the context of time. Heidegger explicitly attaches importance to the dimension of time because "*temporality*" is manifested in all every-day experiences through a specific calculation of time, given we are generally aware of our life span with the dimensions of "Tod", "Sorge" "Entschlossenheit": "*Zeitlichkeit und Geschichtlichkeit*" and also "*Zeitlichkeit und Innerzeitlichkeit als Ursprung des vulgären Zeitbegriffs*"¹³

⁹ Ibidem, page 209

¹⁰ Ibidem, page 4

¹¹ HEIDEGGER MARTIN, Die Grundprobleme der Phänomenologie, in: Gesamtausgabe II Abteilung: Vorlesungen 1923-1944 Band 24, Limburger Vereinsdruckerei GmbH, (1975) page 461

¹² Ibidem, page 22

¹³ HEIDEGGER MARTIN, Sein und Zeit in: Elfte, unveränderte Auflage Max Niemeyer Verlag Tübingen (1967) page 235

The Heideggerian time span is not a strictly linear dimension and each present event can be called reality, but the state of „*Da-Sein*“ has to be understood as the entire period between birth and death and is necessarily timely.¹⁴ The term “*Sein*” and “*Seiend*” or “*Da-Sein*” cannot be used interchangeably as Heidegger points out its relevant ontological difference, which is that all that is actually, really in this world that we perceive is in fact “*Seiend*” and a product, a holistic background which can be understood as a horizon of understanding, the “*Sein*”. Phenomenological science aims for a gradual approach to an understanding of the “*Sein*” and its ontological structures, but it is not a clearly predefined or one way method but rather a philosophical attitude in conducting research.¹⁵

Husserlian transcendental phenomenology differs in the conception of the individual, who finds himself, or lives in a world of objects that the individual may direct his mind towards.¹⁶ This concept is called “*intentionality*” and is based on the assumption, that human experiences require this subject- object relationship, in which the “*res extensa*” can either have a practical, ontic meaning, such as a chair, house or tree, or is modified through intentionality to a value or a predication for the subject.¹⁷ By contrast, Heidegger’s concept of the *Da-Sein* both redefines and modifies this subject- object relationship of *res cogitans* and *res extensa* and also the term *intentionality*.

By further analysing the nature of human consciousness he rejects a strictly cartesian way of isolating the subject and object and elaborates on the nature of human consciousness, which is a combination of three entities: The content of our thoughts and reflections, the self - which is the individual - that is capable of cognitive and imaginative processes and the relationship between those two states. This is what Heidegger defines as intentionality and thereby broadens the understanding of the subject, while attaching further importance and stating that all subject and object relationships have to be a correlation in fact, as both entities cannot be understood separately.¹⁸

¹⁴ Ibidem, page 372ff.

¹⁵ HUSSERL EDMUND, Ideen zu einer reinen Phänomenologie und phänomenologischen Philosophie Erstes Buch: Allgemeine Einführung in die reine Phänomenologie (1913) page 461

¹⁶ HUSSERL EDMUND, Ideen zu einer reinen Phänomenologie und phänomenologischen Philosophie Erstes Buch: Allgemeine Einführung in die reine Phänomenologie (1913) page 50

¹⁷ Ibidem, page 67

¹⁸ HEIDEGGER MARTIN, Die Grundprobleme der Phänomenologie, in: Gesamtausgabe II Abteilung: Vorlesungen 1923-1944 Band 24, Limburger Vereinsdruckerei GmbH, (1975) page 221

The term of “*Existenz*” or existence illustrates this principle further on: “*Existieren besagt dann unter anderem : sich verhaltendes Sein bei Seiendem. Es gehört zum Wesen des Daseins, so zu existieren, dass es immer bei anderem Seienden ist*“.¹⁹

This quote shows, that the understanding of *Existenz* constitutes the nature of the *Dasein* and indicates its multiple possibilities to create and shape the social or political environment with and through others. The horizon of experience within this type of phenomenology looks at present experiences of the individual and postulates that objects, things are existent before any subjective experience.

By contrast to Husserl, Heidegger does not question the fact of being thrown into the world but acknowledges this fact instead. According to Heidegger, an individual is not only influenced by the perception of time, but also by the state of *In-Sein*, which is further composed of *Befindlichkeit* , *Verstehen* and *Rede*. Further important items within his approach to phenomenology are *Welt* and *Sorge*.

Humans have the intellectual capability to project their *In- Sein* to multiple (other) possibilities of *Sein* and thereby think about several possible relations to their world and to provide them with meaning for themselves. In this way they are able to interpret their world and this ability originates in the dimension of *Verstehen*, an analytic and interpretative elaboration of the *Da-Sein*.

The result of this multifactorial process of “*Verstehen*” can then be shared with others via language on an ontic level, but differs from “*Rede*” which is an ontological term. It is the articulation of “*Verstehen*” and as such also an interaction with and organization of the “*Welt*”.²⁰

Another property which constitutes the *In-Sein* is *Befindlichkeit* which goes beyond momentary feelings or subjective-emotional impressions of an individual, and as a mode of it, it is closely linked to the term of *Angst* . It does not address a specific fear of something or somebody but instead represents an inherent state of anxiety, as the danger or threat is vague and uncertain. *Angst* is a dimension that, in a way, absorbs the surrounding environment and thereby takes away the capability of the individual for the process of *Verstehen* in relation to this worldly environment.

¹⁹ Ibidem, page 224

²⁰ HEIDEGGER MARTIN, *Sein und Zeit* in: *Elfte, unveränderte Auflage* Max Niemeyer Verlag Tübingen (1967) page 162

This environment also plays a role in the generic term *Welt* and *Weltlichkeit* and *In-der-Welt-sein* which have meaning both on an ontic and ontological level. On the one hand, on a very fundamental and basic level, the term *Welt* can be understood as a description of the objects or people etc., that constitute the *Seiend*, and is linked to the *Umwelt*, which surrounds us. On a more abstract level, the existential-ontological term *Weltlichkeit* describes a structure of the *Sein*.

To methodologically link and to practically grasp this theoretical dimension, the term *In-der-Welt-sein* can be used to describe and discover the everyday phenomena, as it describes a form of *how* it is to be in this world. The question of what it is like to be in this world is further characterized by *Sorge*.

The term “*Sorge*” cannot be directly deducted from reality, and is referring to either the individual himself or herself or others in the sense of caring about other humans or the abstract term “*Welt*”²¹. Here again on an ontic level, this could be the (ecological) environment, the entire planet or even more abstract things like the social world a person is living in. If understood on an even more abstract level, the *Sorge* is a constituting structure to human’s existence, which refers to his or her “self” his or her “*Dasein*” and his or her “*Welt*” and therefore is not a specific, manifest worry about something or somebody but a more holistic state. The fact that by birth humans are exposed to their lives and have to choose between several possibilities to shape it is conceptualized as “*Geworfenheit*”, and within this state, the “*Sorge*” acts as a form of driver in the decision making process.²²

In this context, the “*Sein zum Tode*” plays an important role for the individual’s perception of his or her own existence, as the perceived death of others can be understood and transferred to someone’s own existence. Therefore the individual end of the “*Dasein*” can be objectively grasped, as death marks the border of the individual’s possibilities of experiences within the “*Da-Sein*”.²³

The underlying reason can be found in the temporality, “*Zeitlichkeit enthüllt sich als Sinn der eigentlichen Sorge*” which should not be mistaken with the general understanding of time, that manifests itself in an (objective) past, presence and future.²⁴ This ontological understanding of time acknowledges the ontic existence of objective time, but differs from this “realistic” concept of a tempo-spatial world, as - phenomenological time - is rather a

²¹ Ibidem, page 318

²² Ibidem, page 199

²³ Ibidem, page 237

²⁴ Ibidem, page 326

“horizon of time” within a stream of experiences. Therein, mental states- “*Befindlichkeiten*” such as “*Sorge*” or “*Angst*” are not something “*Seiend*” but structures of “*Sein*”.²⁵

This phenomenological theoretical framework by Heidegger is a philosophical idea that postulates the investigation of manifested experiences in order to explore a persons’ internal motivation, subjectivity and individual perceptions. It aims to describe the essential core of the phenomenon under investigation and to understand the individual, the environment and context in which he or she lives. It is the task of the researcher to gain an understanding by means of describing and analysing the individual subject’s interpretations of their environment, which can be dimensions such as their individual history, personal and professional background and the social world they live in.

Construction of meaning through lived experience is achieved by setting aside premises, prior conceptions and judgements or knowledge in the process of phenomenological reduction by means of bracketing them out the research process.²⁶ This also includes areas such as tradition or acquired scientific knowledge or even the researcher’s relationship with the topic under investigation. The process of eidetic reduction is an essential part within Husserl’s phenomenological philosophy as only the individual’s conscious, intentional experience is focused on and thereby all other worldly transcendental influences are manifested within this individual.

“Setzen wir alle diese Thesen außer Aktion, wir machen sie nicht mit, unseren erfassenden und theoretisch forschenden Blick richten wir auf das reine Bewusstsein in seinem absoluten Eigensein. Also das ist es was als das gesuchte phänomenologische Residuum übrig bleibt, übrig, trotzdem wir die ganze Welt mit Dingen, Lebewesen, Menschen und selbst inbegriffen ausgeschaltet haben. Wir haben eigentlich nichts verloren, aber das gesamte absolute Sein gewonnen, das, recht verstanden, alle weltlichen Transzendenzen in sich birgt, sie in sich konstituiert”²⁷.

The Heideggerian approach aims at the interpretation of phenomena rather than simply describing the essence of a phenomena in a Husserlian way. For Heidegger, human existence has no fixed or predefined meaning, but each individual has to make sense of his or her life and conscious decisions. In this context, he emphasises that all truth is relative to the *Sein* of the *Dasein*, and suggests that in his approach to phenomenology, unravelling the truth is to

²⁵ Ibidem, page 828ff.

²⁶ HUSSERL EDMUND, Ideen zu einer reinen Phänomenologie und phänomenologischen Philosophie Erstes Buch: Allgemeine Einführung in die reine Phänomenologie (1913) page 115

²⁷ Ibidem, page 94

discover possibilities of the “*Da-Sein*” which implies several possibilities of perceptions: “*Wahrheit als Entdecken einer Seinsart des Da-Seins*”.²⁸

Heidegger defines his hermeneutic phenomenology as a gradual process to the understanding of entities such as “*Being- in the world*” of an individual that exists as being in the surrounding world and bringing out its cultural structures clearly.²⁹ This state, *Being-there*, allows humans to reflect and realize their own existence. Therefore, an individual’s consciousness and perceptions cannot be investigated without assumptions about the context and objective reality in which they are situated, but are co-dependent on each other.

In the case of this thesis, only Heidegger’s hermeneutic phenomenological framework can be utilized appropriately as several preunderstandings and assumptions about both of the subjects and their environments are considered in the first place. These are both on a personal and professional level of all three subjects under study, such as Kuschinsky’s membership in the NSDAP and the “Nationalsozialistischer Deutscher Dozentenbund” or Starkensteins affiliation to the Jewish faith and culture. Instead of bracketing this prior knowledge and implicit judgements, the preunderstandings of both phenomena will be made explicit and investigated under defined aspects throughout the research process. In doing so Heidegger’s principle of the hermeneutic circle, which is an iterative revision of the analysis and interpretation of the holistic *Da-Sein* to get to the meaning of the phenomenon under investigation.³⁰

1.3. Method: Case- study approach

The case study approach is a research method that can be utilized to investigate and systematically examine phenomena of the past and present, depending on their context. In this respect, the case study approach is in accordance with philosophical underpinnings from Heidegger’s phenomenology when the case or phenomenon under investigation cannot be clearly divided from their context and presuppositions or prior judgements are therefore not excluded from research.

According to Yin et al. case studies should be conducted and are applicable whenever phenomena cannot be manipulated or altered, which is particularly the case in a historical

²⁸ HEIDEGGER MARTIN, *Sein und Zeit* in: Elfte, unveränderte Auflage Max Niemeyer Verlag Tübingen (1967) page 227

²⁹ HEIDEGGER MARTIN, *Die Grundprobleme der Phänomenologie*, in: Gesamtausgabe II Abteilung Vorlesungen 1923-1944 Band 24, Limburger Vereinsdruckerei GmbH, (1975) page 466

³⁰ HEIDEGGER MARTIN, *Sein und Zeit* in: Elfte, unveränderte Auflage Max Niemeyer Verlag Tübingen (1967) page 310ff.

approach, as events, such as research projects in the 20th century already took place. Additionally, case studies can be a useful research strategy if contextual conditions, such as academic and life conditions or events are meaningful for the case and cannot be isolated from it.³¹ Individual cases can also help to answer specific questions as to how events took place and sometimes elucidate why they occurred in one way or another. Therefore the units of analysis should be defined beforehand, which are in this case the three pharmacologists : Gustav Kuschinsky, Emil Starkenstein and Wilhelm Wiechowski , particularly in the time frame of the first and second Czechoslovak Republic from 1918-1939 and the German occupation until 1945. In the case of Prof. Kuschinsky, the only one of the three pharmacologists that lived beyond 1945, the time thereafter will be included into this research too, where considered relevant to a rich presentation of the case.

Within this thesis, the case studies will be presented in an exploratory and descriptive manner when it comes to answering research questions regarding the “how” and “what” in both of their personal and professional lives. In this respect, the inquiry will be guided by research questions that will analyse their academic work based on original publications and will critically appraise their relevance for modern pharmacology in the first place. In addition to that, a comparison and contextualization of the three cases will elaborate aspects and signs of either victimization or preferential treatment within the years of 1938- 45. Initial hypotheses have been formulated as a reference point to each case study in order to make it feasible to grasp each phenomenon practically, while acknowledging the fact, that multiple subjective truths are conceivable for each case. The recognition of subjectivity within the phenomenological approach will be backed up with objective data, such as archival sources or publications. The hypotheses are naturally divers in each case, due to the time and circumstances in which they occurred:

- Prof. Wiechowski a case of a “normal” academic biography ?
- Prof. Starkenstein a case of personal and professional victimisation ?
- Prof. Kuschinsky a case of preferential treatment under the German occupation ?

The initial research questions that might be modified throughout the research process, asses the extent to which the three subjects had been either integrated into or excluded from scientific networks or professional organisations and to what extent an appreciation of their works can be found in today’s scientific communities. Furthermore, preconditions of the

³¹ YIN ROBERT K, The Case Study as a Serious Research Strategy in: Knowledge, 3(1) (1981) pages 97–114.

cases in terms of their personal background and life will be investigated as well as their academic development. In doing so, a contextualization of the individual biography to both the political and ideological conditions within each time span will be worked out gradually.

Case studies can be conducted either as a single-case study or in a multi- case format, depending on the context and nature of phenomena under investigation.³² This research will use, a holistic case study with a cross – case analysis, since a multiple case study would require more than three cases to deliver robust and reliable results and also demand different contexts of the individual cases. Though it is possible to argue that the personal and political situations might differ within the three case studies, it is undoubtedly true, that all of them faced political shifts within their lifetime, especially Starkenstein and Kuschinsky, even within the same political regime. Besides this common context of political shifts during their lifetime in an academic environment, all of the three subjects conducted research for a considerable amount of time at the then German Medical Faculty in Prague. It is recommended to use a single case approach if one group, in this case, scientists is the focus of research, and a deeper insight into this particular group in terms of analysis of academic achievement or victimization or preferential treatment in a political system is desired.³³

For this thesis, the three pharmacologists have been chosen for three major reasons, which relate to the period of time that they worked at the German University in Prague, their common research interests in pharmacology and their different personal backgrounds and fates. Additionally, all three cases are connected to each other, as they all held the same position, which also speaks in favour of a cross-case analysis. Prof. Wiechowski was succeeded by Prof. Starkenstein, who became an associate Professor for Pharmacology and Pharmacognosy in 1920 and obtained a position as tenured professor after Wiechowski's death on the June 30th 1929.³⁴ Following the foundation of the Protectorate of Bohemia and Moravia by the National-Socialist regime on March 16th 1939, Kuschinsky succeeded his banished predecessor Starkenstein on September 29th 1939 as an adjunct professor. From March 6th 1940 until 1945 he was a full professor of Pharmacology and Pharmacognosy.³⁵

For the data collection process, archival sources both from University archives and national archives, will be used in addition to, databases such as Ovid, which include a huge variety of

³² GUSTAFSSON JOHANNA T, Single case studies vs. multiple case studies: A comparative study (2017)

³³ BAXTER PAMELA / JACK SUSAN, Qualitative Case Study Methodology: Study Design and Implementation for Novice Researchers in: The Qualitative Report, 13(4) (2008) pages 544-559

³⁴ HLAVACKOVA LUDMILA / SVOBODNY PETR, Biographisches Lexikon der deutschen Medizinischen Fakultät in Prag 1883-1945 in : Karolinum- Verlag der Karls- Universität (1998) page 227

³⁵ Ibidem, pages 124 and 204

medical full-text publications relevant to this thesis. Depending on availability and willingness of descendants, oral history will also be considered and data will be acquired via qualitative in- depth interviews.

1.3.1 Qualitative in depth interview

Oral history has been described as a powerful tool to capture “*the lived experiences of a person*”³⁶ especially in cases of those who had been victimized and forgotten due to their status within a certain population group, “*a vehicle for outsiders and the forgotten to tell their stories*”³⁷.

Though having been a respected and accomplished researcher , Prof. Starkenstein’s case qualifies for this definition as he had been victimized and murdered by the Nazi regime and both his scientific and intellectual work partially fell into oblivion, subsequently. As shown in Šimůnek’s publication on this matter “disappeared science”³⁸, Prof. Starkenstein’s life and achievements are in general not adequately reprocessed and remembered.

As a illustrative example for that deficit, to this day no biographical nor additional data is displayed on the virtual memory book of the concentration camp in Mauthausen, where Starkenstein died in 1942.^{39,40}

Since Prof. Starkenstein cannot be interviewed himself anymore, nor none of his direct descendents as all of them have already deceased, his grandson had been asked to take part in the interview instead.

Walter van Emde Boas PhD, MD, is a professor emeritus, specialised in neurophysiology and neurology with a great number of peer- reviewed medical publications and memberships in professional medical associations such as the ILAE (International League against Epilepsy).

As his grandson, Prof. Walter van Emde Boas is through his mother Magdalene Starkenstein-van Emde Boas, a direct ancestor of Emil Starkenstein. Though having not met his grandfather personally, Prof. van Emde Boas still represents a valuable purposive sample to answer the defined research questions both on a professional and personal level, in order to

³⁶ JANESICK VALERIE, Oral history for the qualitative researcher : Choreographing the story in: The Guilford Press (2010)

³⁷ Ibidem page 1ff.

³⁸ ŠIMUNEK MICHAL, Disappeared Science Biographical Dictionary of Jewish Scholars from Bohemia and Moravia – Victims of Nazism, 1939–1945 in: Verlag: Pavel Mervart (2014)

³⁹ Email correspondence with the Specialist Library from April 12th 2021

⁴⁰ Online access of “raumdernamen.mauthausen-memorial.org” with the search term: “Emil Starkenstein” on December 15th 2021

refine and triangulate the obtained results from the scoping/narrative review of Starkenstein's research and publications by proxy.

Legewie provides a useful guidance to interpret and validate qualitative interviews with a biographical focus, considering phenomenological parameters such as "*Lebenswelt*", in which he distinguishes between "objective", "subjective" or "social", "*Seinbereiche oder Welten*".⁴¹

As quality criteria of these interviews, Legewie suggests attaching importance to engaging in a manner with the interviewee in which meaningful and thus scientifically utilisable information can be attained "*reflektierte Subjektivität des Verstehens*", referring to the interviewees statements and recollections but also the concrete conclusions drawn from them.⁴²

Within this qualitative context there criteria entail dimensions such as 1. "*Verständlichkeit*", 2. "*Wahrheit*", 3. "*Soziale Angemessenheit*" and 4. "*Aufrichtigkeit*" as well as two interview partners that at least have some commonalities within their 5. "*Lebenswelt*" in order to engage in a communicative process which facilitates a in- depth understanding.⁴³ To meet the criterion of comprehensibility (1), content- related questions were clarified through repeated inquiries and follow up questions in case an issue had not been exhaustively addressed or was ambiguous. The aspect of truthfulness (2) of the information had been assessed through congruent background information that had been obtained before the interview and also through a absence of inconsistencies in the statements of the interviewee.

In terms of assessing the aspect of (3) "social adequateness" in the interview process, in the sense of fulfilling (hierarchical) social roles , potentially leading to bias e.g. by leaving aside certain questions, a topic guide was used to agreed beforehand on the subjects being addressed and not to loose research focus or to omit important topics. The criterion of "*Aufrichtigkeit*" (truthfulness) is one of the most difficult ones to assess within the quality evaluation process as it involves obtaining a authentic access to the interviewees internal thoughts and attitudes on a particular topic as possible. Due to the fact that Prof. van Emde Boas engaged in all of the questions willingly and in fact did not excluded any questions, alongside with his report about positive achievements of his grandfather, but also difficult

⁴¹ JÜTTEMANN GERD / LEGEWIE HEINER, Biographie und Psychologie in: Springer Verlag Berlin, Kapitel IV Erträge biographischer Forschung in der Psychologie : Interpretation und Validierung biographischer Interview (1987) page 141

⁴² Ibidem, page 144

⁴³ Ibidem, page 145ff.

character traits e.g. “stubborn”, “not much of a family man” , has to be assessed positively with regards to this criterion.

Though differing in academic hierarchy, both interlocutors are healthcare professionals with a interest and understanding for pharmacology and history, laying the foundation in terms of “*Lebenswelt*” (*lifeworld*) (5) for the interview process, which was carried out after a initial “getting to know phase” via email.

The semi- structured interview focused on personal questions to explore further aspects of Starkenstein’s life, also basing on previous review of the literary evidence. To support and facilitate an in-depth conversation, prompts were given in dependence to the interviewee’s previous knowledge and ability to answer each research question. The following topic guide had been sent to Prof. van Emde Boas prior to the interview on May 9th 2021 and consent had been obtained to use the information given in the interview for the doctoral project. The actual interview took place virtually on May 13th via Skype® and a recording was created to capture all answers verbatim.

The interview aimes at revealing several additional information about Starkenstein’s personal and social life, especially in terms of victimization and his role as a father and grandfather which had not been accessible in detail through written resources yet. All information has to be handled as second/third hand information since they had been passed on from Magdalene Starkenstein- van Emde Boas to her son, Walter van Emde Boas verbally and additionally originate from previous exchange with other sources as well as direct review of Starkenstein’s correspondence by Prof. van Emde Boas.

Topic guide:

a) Questions regarding Prof. Starkenstein's contribution and relevance for modern pharmacology

- Basing on your own academic resume and experience, how would you classify Starkenstein's work in terms of breadth of research (disciplines, methodologies, research questions and focus) ?
- How would you assess his relevance for modern pharmacology, (That is pharmacotherapy based on experimentation and a clear evidence base) ?
- Which publications/ topics / research questions are you aware of that demonstrate his accomplishments of bridging his laboratory and clinical experiments to clinical and thus therapeutic use?
- What information do you have regarding his collaboration with allied health professions such as pharmacists and his conceptualization of joint and holistic patient care ?

b) Questions regarding his personality and personal life

- Did you engage in conversations with your mother about his affinity for humanities and art?
- Do you think he had a influence on her career as an art historian, how do you think this talent and interest was fostered by his upbringing? - How do you think he was raised and educated in order to develop his scientific inquisitiveness?
- Which role would his Jewish heritage and Judaism per se play in his life ? Would you describe him, according to your knowledge as an agnostic, liberal, orthodox person Would he consider himself as Czech/ Bohemian / Austrian ?
- Did you ever discuss (with your mother) his expulsion from his chair in Prague and how this concretely (negatively) affected his career?
- Do you have an idea how he managed to successfully continue his research in Amsterdam after that? What were his links to the Netherlands?
- Do you have any knowledge of political activism (this can include several levels of action) against the Nazi occupation?
- Could you tell me a little more about your grandmother- the wife of Prof. Starkenstein and her political attitude ?

- Did your mother ever mention or are you aware of any cardiovascular precondition of your grandfather, such as coronary heart disease? (This is relevant as the death certificate states this as cause of death, which is obviously to be questioned)
- Is your mother Magdalene the only child of your grandfather or were there other siblings, if so what happened to them after / during the holocaust?

1.3.2 Document analysis

The range of documents used as a source for each case study include primarily scientific publications, both medical and pharmaceutical journals, academic files but also personal correspondence and newspaper articles.

An interpretative approach has been chosen, as described by Ballstaedt⁴⁴, examining each document by certain previous assumptions, as formulated in the initial hypotheses each case study in terms of their personal life and also with regards to their role within the chosen framework. Within their scientific publications their relevance for modern pharmacology was being assessed, as a result of their research interest, applied methods and thematic scientific focus.

To ensure a preferably high extent of sociological comprehension *Verstehen* all documents have been interpreted in a multilevel process, regarding several questions in a cyclical hermeneutic process. This process was practically carried out through a detailed, thematic classification of each used publication into an excel sheet, which later helped to synthesize findings according to the formulated research questions on an interpretative meta-level, described in detail in subchapter 1.5.

In line with Ballstaedt's further suggestions, particularly relevant passages in the text were cited and referenced, literally in case interpretative conclusions were drawn.

1.4. Thick description by Geertz

The concept of a thick description as a way of conducting research was firstly described by Clifford Geertz and originally referred to ethnographic research within anthropological sociology. Over time, several other disciplines, research methodologies and methods have

⁴⁴ BALLSTAEDT STEFFEN-PETER, Zur Dokumentenanalyse in der biographischen Forschung in: Jüttemann, G., Thoma, H. (eds) Biographie und Psychologie. Springer, Berlin, Heidelberg (1987)

embraced this concept such as psychology , sociology and especially phenomenological and case study research.⁴⁵

Ponderetto suggests several central aspects of thick description that need to be considered throughout the entire research process. Those encompass the act of “accurately describing and interpreting social actions within the appropriate context in which the social action took place”⁴⁶ This also implies linking “*motivations and intentions*” to those social actions and presenting research in a way in which the recipient is capable of acquainting himself or herself with experiences of others.⁴⁷ In this respect, thick description can also be – depending on the way and manner in which it is presented – “*biographical*” and “*historical*”⁴⁸.

The overall aim of any thick description is to understand a certain culture within its genuine context, which is what the individual surrounds himself or herself with voluntarily or unwillingly. Instead of a set of rigid techniques thick description is achieved through an iterative way of reflecting on research topics and thereby an “*intellectual effort*”⁴⁹ The difference between a thin description and a thick one is, for example, the act of a meaningful interpretation of cultural phenomena, instead of a sheer depiction of them.⁵⁰ Geertz suggests to “*gain access to the conceptual world in which our subjects live, so that we can, in some extended sense of the term, converse with them.*”⁵¹ Within this biographical research, there is a practical limitation. Given the three subjects are deceased, it is not possible to engage directly with them. However, access to their conceptual world can be gained through archival sources which can encompass personal files on the one hand and their scientific work, consisting of scientific publications, abstracts and secondary literature on the other one. Additionally, an oral history approach in the form of qualitative in depth interviews with descendants could be considered to illustrate the subjects’ careers and lives through the eyes of others.

Although any research process including thick description and interpretation should follow a systematic manner in terms of analysis and evaluation, the cultural phenomena under

⁴⁵ PONTEROTTO JOSEPH G, Brief Note on the Origins, Evolution, and Meaning of the Qualitative Research Concept Thick Descriptio in: The Qualitative Report 11(3) (2006)

⁴⁶ Ibidem

⁴⁷ Ibidem, page 542

⁴⁸ Ibidem, page 545

⁴⁹ GEERTZ CLIFFORD, Thick Description: Toward an Interpretive Theory of Culture in: The Interpretation of Cultures: Selected Essays, New York: Basic Books (1973) page 312

⁵⁰ Ibidem, page 317

⁵¹ Ibidem, page 320

investigation cannot be understood in terms of exclusively positivist approaches, in which Geertz links his concept to phenomenological research concepts and philosophies.⁵²

Case-studies that follow this concept of Geertz can be used to draw inferences from individual experiences and can then be put into or compared with a theoretical framework, as it is envisioned with Ehrenreich's and Cole's framework within this research project.

1.5. Form of data analysis

This research will use thematic analysis given its suitability for examining data such as personal files from archival resources, the content of scientific data and also data derived from qualitative interviews for oral history. Any given data set will be iteratively read and the parts which are deemed relevant for answering the research questions will be incorporated into an excel sheet. Through a constant process of immersion and distancing from parts of the data versus its entirety and an open-minded and simultaneously reflective approach to the data, the research will seek convergence with Heidegger's principle of a hermeneutic circle. This explorative process will elicit initial repeating data fragments or patterns which will lead to themes, or "*patterns of meaning*"⁵³

This analytical process can be summed up in three major cognitive steps: exploration of the data, through the described iterative process, (thick)-description of the data through a meaningful, that is a differentiated approach to patterns in the data set and finally an interpretation of the derived themes into a meaningful contextualisation with regards to the research questions. The transferability of each analysed case depends on the execution of this three way process, especially in terms of making implicit findings explicit to the reader.

As there are three initial hypotheses to each case, which are embedded with two main research questions and an additional framework to guide them, this research project is framed precisely to utilize *Interpretative Phenomenological Analysis*, which could have been chosen otherwise as it is bound to phenomenological philosophy. Instead, thematic analysis, which is not explicitly restricted to a particular research methodology and has been broadly used e.g. in Grounded Theory, is consulted in this case. Due to the flexibility and generic term of

⁵² Ibidem, page 315

⁵³ SUNDLER ANNELIE, Qualitative thematic analysis based on descriptive phenomenology in: Nursing Open; 6:733-739 (2019) page 736

thematic analysis, a further specification is necessary to bring transparency and reliability to the research process, in accordance with Braun et al.⁵⁴

Instead of taking the entire data set into account in the analytical process, the complexity of sources, that are relevant to answer the research questions will be considered in a in- depth description and interpretation. Braun et. al distinguish between data- driven analytics and theoretical approaches, which focuses on certain aspects of a data set. As this research will be guided by predefined questions for each case, a theoretical approach to thematic analysis was chosen. As previously noted, not only an exploration and description of the cases, but also an interpretation will be executed, which will also apply to the derived themes.

1.6. Conceptual framework of victimization

In accordance with Heidegger's interpretative and reflexive approach to phenomenology, a conceptual framework of a perpetrator-bystander-victim will be applied to the research process as described by Ehrenreich and Cole.⁵⁵ Within this framework the relationship and dependencies of each group are symbolised as an equilateral triangle in which the victim group constitutes the base and is separated from the other two sides, which symbolize either the bystander or the perpetrator group. The reason behind the separation of the victim group with the triangle from the two other groups is the inability of the victims to take action against their persecution as they lack political "*power and legitimacy*" which is fully held by their opponents. Instead, the only way of escaping the destruction process of genocide, is to adapt to their situation by finding "*survival strategies*" and therefore to move from the right hand side of the triangle, to the left one, which symbolizes either resistance and rescue or implies forms of escape and hiding. The authors of this model also suggest, that victims might also act in a "*detrimental*" collaborating way with the perpetrator group by further isolating themselves within their own group. Individuals who are victimized by other groups with the political authority and means to do so, are often categorized by an entirely arbitrary ideology, which is "*socially constructed*".⁵⁶

By contrast, the bystander group, which finds itself on the left side of the triangle is directly linked to its right side, which stands for the perpetrator group. This implies the greater extent of opportunities for both groups as they can choose their level of involvement in the

⁵⁴ BRAUN VIRGINIA / CLARKE VICTORIA, Using thematic analysis in psychology in: Qualitative Research in: Psychology, 3 (2) (2006) pp. 77-101

⁵⁵ EHRENREICH ROBERT M / COLE TIM, The Perpetrator-Bystander-Victim Constellation: Rethinking Genocidal Relationships in: Human Organization; Oklahoma City Vol. 64, Iss. 3 (2005) pages 213-224

⁵⁶ Ibidem

“*destruction process*” and therefore also reject a direct participation in governmental policies. The bystander group can in its most basic shape, simply share ethnic or political properties with the perpetrator group and thereby gain legitimacy to shape and influence societal processes. Depending on their attitude towards governmental actions and policies, they – as a collective- will be capable of either accelerating or appeasing the perpetrators’ envisioned destruction process of the victimized group. In the worst case, that is, if the perpetrator group feels totally in line with the majority of the bystander group, a fast implementation of genocide will take place, which is indicated by Line C in the proposed model.

The group of the perpetrators can also be split into two extremes, which are linked to the bystander group by the apex of the triangle, which equals a “*direct participation*” in the genocide and is the most extreme version of the bystander group. The other end of the perpetrator line is marked by an elitist group which holds the biggest amount of legitimacy and power within the destruction process and can be classified as “*leaders and killers*” within this system. This group is equipped with the greatest amount of “*power, authority, legitimacy and control*” to steer the destruction process and attribute humans to individual social groups. Within a totalitarian system the only menace to these perpetrators are “*external forces*”, which might be “*military, political or diplomatic*” and can either terminate a political regime or in the worst case even unwillingly accelerate the destruction process, as the perpetrators will feel urged towards the right hand apex of this model.⁵⁷

Needless to say, it is especially hard to distinguish between bystanders who are in line with governmental policies and actions that aid in victimizing others but do not openly participate and low level perpetrators who might not necessarily fully agree with an ideology but still choose to aid indirectly in promoting a genocide. Ehrenreich and Cole place individuals like “*low-level military, paramilitary and civil bureaucrats who play minor roles in the destruction process and are motivated by opportunism, ideology, inertia or some combination thereof*” into an area which is “*closest to the top vertex*”⁵⁸. This means that people with any active involvement directly aimed at the extermination of the victim group must be labelled perpetrators.

The triangle shape of this proposed model for the relationship of the three group also hold a temporal- dynamic aspect in it, as the right hand side marks the “*fastest implementation of genocide*”, a state which the perpetrator group will strive to attain as quickly as possible,

⁵⁷ Ibidem

⁵⁸ Ibidem, page 217

whereas the victim group will try hard to strategically appease this policy and therefore move towards the left hand side of the triangle. Both individuals from the bystander and perpetrator group can vary their level of involvement according to personal or external motivation.

There are four prerequisites that need to be fulfilled in order to apply this framework to any research process, which all apply in the case of this doctoral research project: Firstly, there must be a *“dominant entity within a region- although not necessarily the majority- and posses the power, authority, legitimacy and control to instigate and implement a destruction process.”*⁵⁹ This is unambiguously the case within the Nazi occupation in years of 1939 until 1945 in which this conceptual framework will be applied essentially. In 1939 the then German University of Prague was factually proclaimed as *“Reich University”* Prague and thereby put under total control of the German power.⁶⁰

Secondly, *“actual or contrived stress must exist within the population of the region , which the perpetrators can exploit to foment the destruction process.”*⁶¹ This second premise also fully applies to the prevailing conditions at the *“Reich University”* in Prague as associate professors were either persecuted, replaced in favour of German scholars or even executed, as occurred in the case of Gjuric, Prochazka and Vacek and also Emil Starkenstein.⁶²

Thirdly, *“a subset of the population must be classifiable on the basis of some socially constructed distinction that can be used by the perpetrator group as a foundation for the creation of an ideology of an other who is supposedly responsible for the contrived or actual stress and thus must be eradicated.”*⁶³

During the German occupation , the Nazi *“biopolitical ideology”* was, in spite of resistance, inevitably imported to occupied Universities such as the Reichsuniversity in Prague, as they were centrally controlled by the Berlin ministry of education. Central aspects of this constructed concept of a racially unified society defined by the National Socialists became established in law such as in the Nuremberg Laws from 1935 or other eugenic laws.

⁵⁹ Ibidem, page 215

⁶⁰ HLAVACKOVA LUDMILA/ SVOBODNY P. / BRIZA J., History of the General University Hospital in Prague, Nova Forma, s.r.o Publishers for GUH Prague (2014)

⁶¹ EHRENREICH ROBERT M / COLE TIM, The Perpetrator-Bystander-Victim Constellation: Rethinking Genocidal Relationships in: Human Organization; Oklahoma City Vol. 64, Iss. 3 (2005) page 215

⁶² HLAVACKOVA LUDMILA / SVOBODNY P. / BRIZA J., History of the General University Hospital in Prague, Nova Forma, s.r.o Publishers for GUH Prague (2014)

⁶³ EHRENREICH ROBERT M / COLE TIM, The Perpetrator-Bystander-Victim Constellation: Rethinking Genocidal Relationships in: Human Organization; Oklahoma City Vol. 64, Iss. 3 (2005) page 215

The final and fourth premise that need to be applicable to a socio- political situation in order to apply this framework is a “constellation that only exists either leading up to or during a genocidal action and will collapse once the genocidal action is either completed, because a victim group is no longer extant or halted by some internal or external force, at which point the perpetrator group is nullified.”⁶⁴ This in fact also applies to the situation in Prague during the german occupation until the “Liberation Day” on May 9th 1945 which had been preceded by Czech resistance towards the occupying forces, advances of soviet troupes and thereby caused by external forces, opposed to the Nazi perpetrator group.

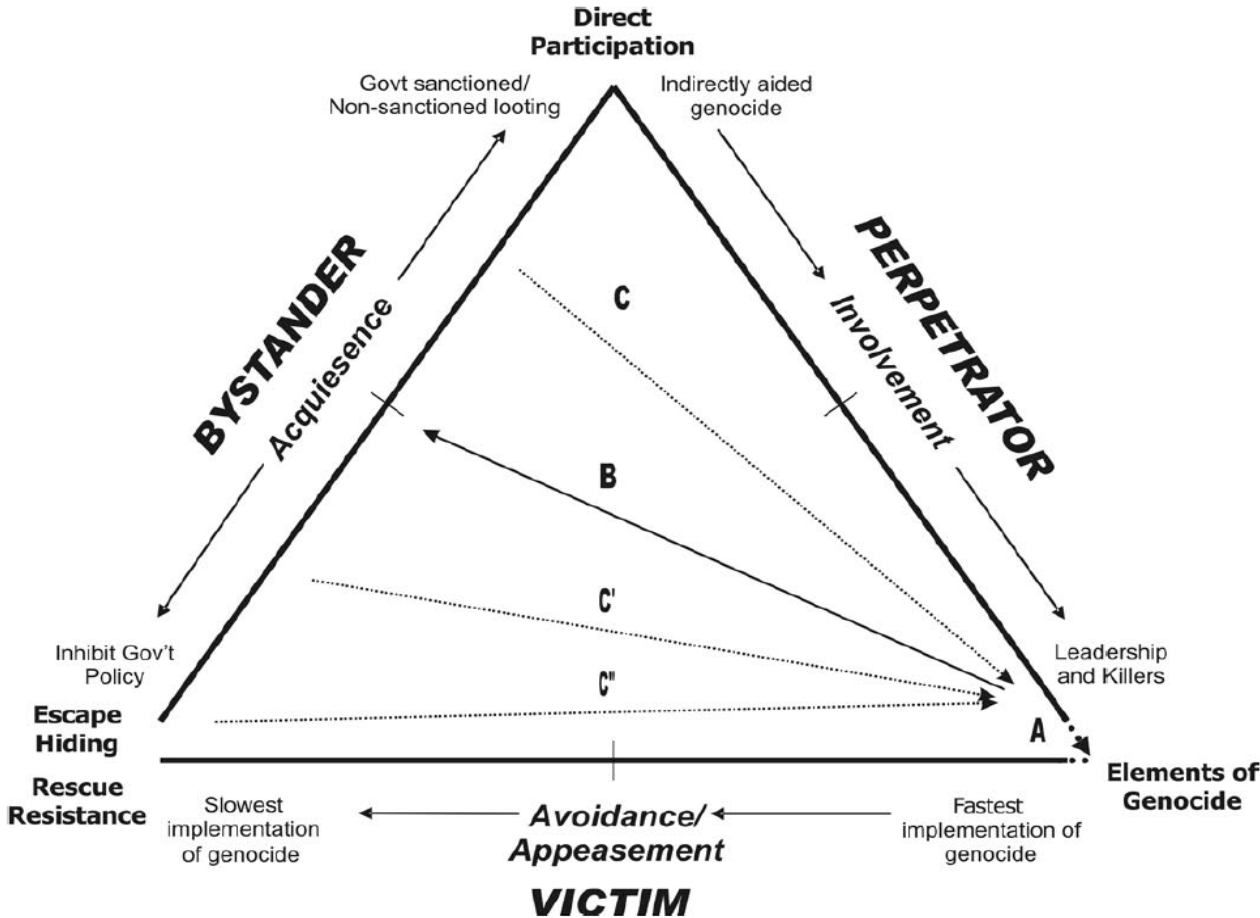


Illustration 1 from Ehrenreich and Cole: The Perpetrator- Victim- Bystander Model

⁶⁴ Ibidem
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1.7. The doctoral project in the context of previous research

Previous research on scholars in the 20th century at the German University in Prague has been conducted about a variety of personalities, both regarding ethnic and religious background, area of expertise and degree of scientific and political involvement.⁶⁵ This wide body of research also includes studies about individuals in the medical field and natural sciences, ranging from anatomy, embryology, neurosurgery, endocrinology to physics, botany, and chemistry. As a common ground within this research of the past, both the investigation of professional impact on each discipline and contextualisation into a political and historical dimension in association with their faculties and institutes, can be found e.g. in the years of 1939- 1945 where the “Gleichschaltung” of universities and other institutes of higher education took place.⁶⁶

Academic migration in the medical field and natural sciences within European universities such as Prague, Vienna or Berlin particularly also before and after the pivotal years of 1918 and 1945 have been investigated by researchers such as Petr Svobodný, Ludmila Hlaváčková, Alena Míšková and Mitchell G. Ash, Jan Surman and Felicitas Seebacher. Key concepts and terms to map and structure scientific exchange is suggested by Ash, as he introduces the terms “*geographic*” “*social*” and “*cultural mobility*” within German speaking universities and territories.⁶⁷ The mobility with regards to geography has to be understood as a perceived ranking with regards to career opportunities, prestige and influence associated with a particular university. Ash describes “*beginner*” “*intermediate*” and “*final destinations*” in terms of academic circulation and development within the years until 1918 in the Austrian Empire. Besides this choice of the most promising research institution in terms of career development, the aspect “*social mobility*” ensued from descent and other social preconditions such as paternal occupation and individual financial resources. The term “*cultural mobility*”, as defined by Ash, does not only assume command of the German language within the Austrian system, but also includes “*scientific practices*” and “*cultures*”.⁶⁸

This professional exchange was diminished in the interwar years 1918-1939 due to practical, financial and political obstacles at the German Medical Faculty of Prague, though other

⁶⁵ GLETTLER MONIKA/ MISKOVA ALENA, Prager Professoren 1938-1948: zwischen Wissenschaft und Politik in :Veröffentlichungen zur Kultur und Geschichte im östlichen Europa; Bd.17 (2001)

⁶⁶ Ibidem

⁶⁷ ASH MITCHEL G., The Natural sciences in the late Habsburg Monarchy: Institutions, networks, practices, in: Michal Kokowski, The Global and the local. The History of Science and the Cultural Integration of Europe, Proceedings of the 2nd ICESHS (2006)

⁶⁸ Ibidem

German faculties were even more seriously affected due to ideological burden both from Vienna and Prague.⁶⁹ From 1939- 1945 politically driven, one sided “academic circulations” were re-established by force, as the German University was incorporated into the academic system of the Third Reich, which effectively led to a expulsion of academics and unilateral appointment of professors with associations to the regime.⁷⁰

With regard to this doctoral project those pre- / inter- / and postwar tendencies of academic migration e.g. at the German University in Prague and the several concepts of mobility will help to understand each case in terms of career development or obstacles towards it.

Further research regarding specific physicians such as Otto Grosser, Hermann Hubert Knaus, Arnold Jirásek and Josef Charvát has been conducted at the Charles University of Prague by Svobodný, Hlaváčková and Míškova basing on prosopographic sources such as diaries, personal and professional correspondence, personal files, viva protocols and also annual reports, etc. Czech, German and Austrian Archives have also been involved in previous research, such as the university archive of Charles University in Prague, Vienna or Berlin. This doctoral project will continue to do so, as all the subjects of examination: Starkenstein, Kuschinsky and Wiechowski show touching points with Austria or Germany to various extent.

As discussed by Ash, the 19th (and 20th) century led to an emerging network of new (sub)-disciplines within the natural and medical sciences.⁷¹ This development also applies to modern Pharmacology, which can be understood as a an experimental subject at the interface of pharmaceutical and medical sciences. “*Modern Pharmacology*” as it is used within the dissertational project, describes the systematic “*study of the interactions of chemical agents with living matter*” and differs from other traditions such as “*materia medica*” especially in terms of focus and both interdisciplinary and causal inference of pharmacological effects.⁷² As such, modern pharmacology draws on a distinct exploration of both pharmacokinetic and pharmacodynamic properties of each substance. Pharmacokinetic parameters deal with aspects of liberation, distribution, elimination of drugs and their half- life in the human body

⁶⁹ SVOBODNY PETR, Die akademische Migration zwischen den medizinischen Fakultäten in Prag und Wien 1848- 1945, in : Strukturen und Netzwerke. Medizin und Wissenschaft in Wien 1848-1955 (2018)

⁷⁰ Ibidem, page 484f.

⁷¹ ASH MITCHEL G., The Natural sciences in the late Habsburg Monarchy: Institutions, networks, practices, in: Michal Kokowski, The Global and the local. The History of Science and the Cultural Integration of Europe, Proceedings of the 2nd ICESHS (2006)

⁷² PARASCANDOLA JOHN, Reflections on the History of Pharmacology: The 1980 Kremers Award Address in: Pharmacy in History, 22(4) (1980) 131-140

with inclusion of dimensions such as bioavailability or bioequivalence. In accordance with these specific aspects of each chemical compound or drug, its effect on the human or animal body, their pharmacodynamic profile, is also being investigated. Thereby, *Modern Pharmacology* tries to understand structure – reactivity relationships of chemical compounds with structures in the human body such as, receptors, ionchannels and enzymes in a qualitative and quantitative manner.

Previous research on the influence of institutions on the science of modern pharmacology such as the University of Dorpat, has been conducted by researcher such as Kuschinsky⁷³, Koppanyi⁷⁴ and Parascandola.⁷⁵ Often this research deals with outstanding representatives and pioneers of modern pharmacology such as Rudolph Buchheim, Claude Bernard or Oswald Schmiedberg and provides an overview over their academic achievements in terms of the discipline of pharmacology.

The necessity for further research has been pointed out before and still applies today: “ *There is thus much to be done in the history of pharmacology*”⁷⁶, and there are “*few historians who are devoting attention to this subject. Yet the history of pharmacology offers, I believe, much of interest to the scholar from the point of view of both intellectual and social history*”⁷⁷.

⁷³ KUSCHINSKY GUSTAV, The Influence of Dorpat on the Emergence of Pharmacology as a Distinct Discipline in “*Journal of the History of Medicine and Allied Sciences*, 23(3) (1968) 258-271

⁷⁴ KOPPANYI THEODORE, The Rise of Pharmacology in: *The Scientific Monthly*, 41(4) (1935) pages 316-324

⁷⁵ PARASCANDOLA JOHN, Reflections on the History of Pharmacology: The 1980 Kremers Award Address in: *Pharmacy in History*, 22(4) (1980) pages 131-140

⁷⁶ Ibidem

⁷⁷ Ibidem

II. Main Part

2. First Case: Prof. Wilhelm Wiechowski: Analysis and contextualisation of his professional and personal life

2.1. Academic biography

Prof. Wiechowski's academic career has been summarised in detail by Hedwig Langecker⁷⁸ and can be verified by several further sources^{79,80} such as written testimony by other colleagues^{81,82,83,84}, academic communications within newspapers^{85,86} or specialised press but also directly via original publications.^{87,88}

Wiechowski finished his medical studies at the German University of Prague in 1898⁸⁹ and engaged in direct clinical work for two years before becoming Pohl's scientific assistant defending his post-doctoral theses for Pharmacology⁹⁰ in 1906 and for Pharmacognosy two years later^{91,92} in 1908. After his appointment as an associate professor in recognition of his contribution to pharmacological and pharmacognostical⁹³ research domains through the

⁷⁸ LANGECKER HEDWIG, Wilhelm Wiechowski in: Lotos Nummer 77 (1929)

⁷⁹ WIECHOWSKI WILHELM, Personalakte in: Österreichisches Staatsarchiv,; AT-OeStA/AVA Unterricht UM allg. Akten 633.34 Wiechowski, Wilhelm, Professorenakt (1910)

⁸⁰ HLAVACKOVA LUDMILA / SVOBODNY PETR, Biographisches Lexikon der deutschen Medizinischen Fakultät in Prag 1883-1945 in: Karolinum- Verlag der Karls- Universität (1998)

⁸¹ SPIRO KARL, Erinnerung an Wilhelm Wiechowski in: Die Medizinische Welt – ärztliche Wochenschrift Nr. 6 (1929)

⁸² STARKENSTEIN EMIL, Wilhelm Wiechowski in: Deutsche Medizinische Wochenschrift, 55(5) (1929) pages 199–200

⁸³ STARKENSTEIN EMIL, Die Pharmakologischen Selbstversuche Purkinjes und Ihre Beurteilung nach dem heutigen Stande der Wissenschaft, Archive of Charles University Nr 198 Box 3, no year detectable on publication

⁸⁴ KNOLL FRITZ, Wilhelm Wiechowski in: Lotos - Zeitschrift fuer Naturwissenschaften – 77: 65 - Die Tätigkeit Wilhelm Wiechowskis im Verein Lotos (1929)

⁸⁵ Pharmazeutische Post Nr 33. vom Dienstag den 26. April 1910

⁸⁶ Wiener klinische Wochenschrift Nr. 27 1908

⁸⁷ JUNKMANN KARL , Über die Wirkung der sogenannten «Bitterstoffe» in: Archiv für experimentelle Pathologie und Pharmakologie 143 (1929) pages 368–380

⁸⁸ STARKENSTEIN EMIL, Sparsame Arzneiverordnung in : Beiträge zur ärztlichen Verordnung (1928)

⁸⁹ STARKENSTEIN EMIL, Die Pharmakologischen Selbstversuche Purkinjes und Ihre Beurteilung nach dem heutigen Stande der Wissenschaft, Archive of Charles University Nr 198 Box 3

⁹⁰ JUNKMANN KARL , Über die Wirkung der sogenannten «Bitterstoffe» in: Archiv für experimentelle Pathologie und Pharmakologie 143 (1929) pages 368–380

⁹¹ Ibidem

⁹² Wiener klinische Wochenschrift Nr. 27 1908

⁹³ WIECHOWSKI WILHELM, Pharmakognosie des Laubblattes von Magnifera indica (Habilitationsschrift) aus dem Österreichischen Staatsarchiv in: Lotos Band 56 Heft 5 (1908)

University of Vienna⁹⁴, Prof. Wiechowski returned to Prague in 1911 for a full professorship, succeeding Prof. Pohl, who had accepted a chair for Pharmacology in Breslau. ^{95,96,97}

The particulars of this appointment procedure can be retraced via several documents in his personal file **(III. 5)** found at the Austria State Archive, in which Prof. Hans Horst Meyer's advocacy for his colleague is documented, filling the vacancy of Prof. Löwi, who had previously been appointed as ordinary professor for Pharmacology and Pharmacognosy in Graz: “ *auf Anregung des Professors Dr. Meyer (...) die Ernennung des unbesoldeten außerordentlichen Professors der Pharmakologie an der deutschen Universität Prag , Dr. Wilhelm Wiechowski, zum Assistenten am pharmakologischen Institute der Universität in Wien beschlossen (...) nach seinem bisherigen wissenschaftlichen und lehramtlichen Leistungen wie auch auf Grund seiner vieljährigen Verwendung als Assistent an dem analogen Institute der deutschen Prager Universität (...)*“⁹⁸

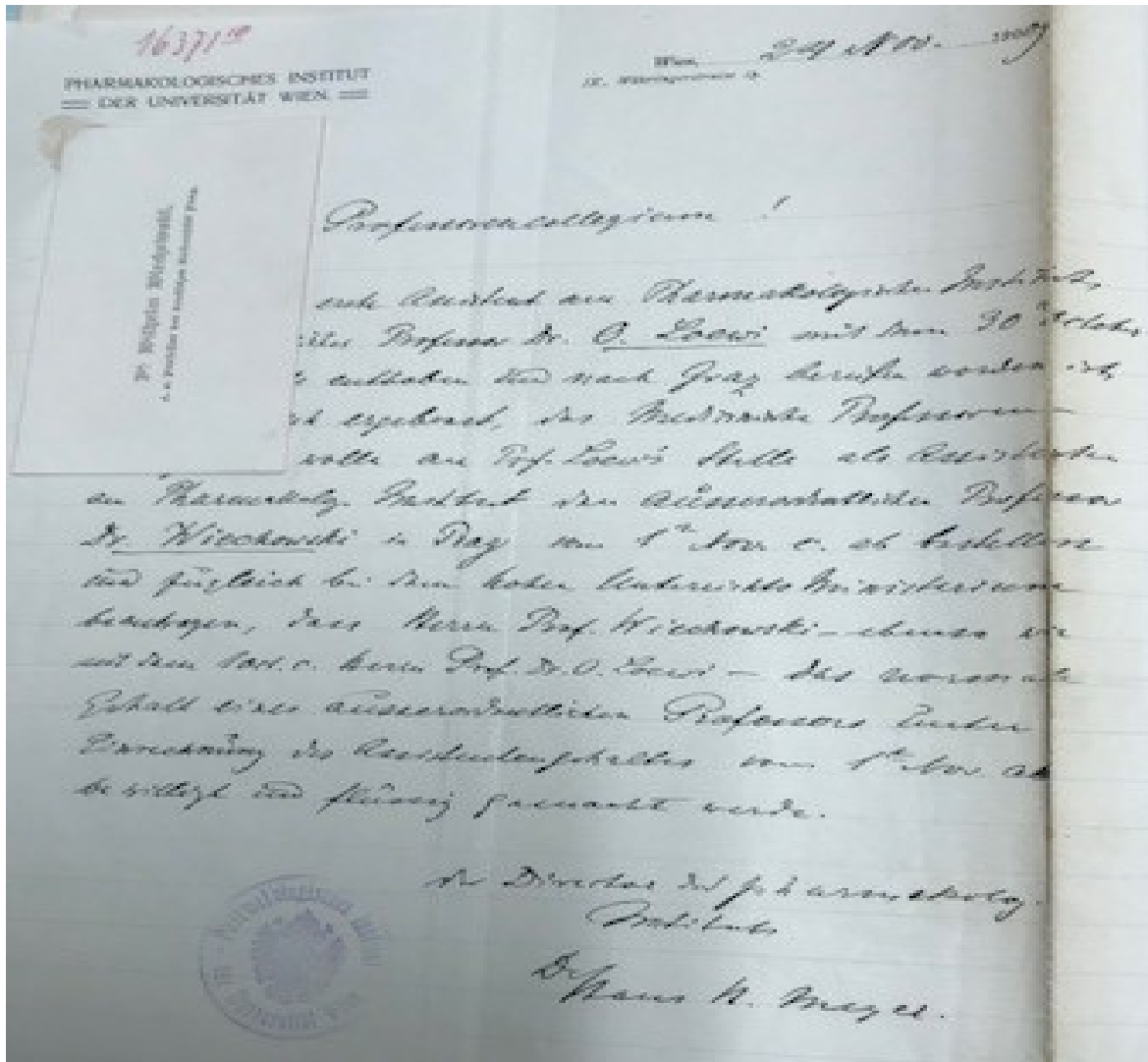
⁹⁴ Pharmazeutische Post Nr 33. vom Dienstag den 26. April 1910

⁹⁵ SPIRO KARL, Erinnerung an Wilhelm Wiechowski in: Die Medizinische Welt – ärztliche Wochenschrift Nr. 6 (1929)

⁹⁶ LANGECKER HEDWIG, Wilhelm Wiechowski in: Lotos Nummer 77 (1929)

⁹⁷ STARKENSTEIN EMIL, Wilhelm Wiechowski in: Deutsche Medizinische Wochenschrift, 55(5) (1929) pages 199–200

⁹⁸ WIECHOWSKI WILHELM, Personalakte in: Österreichisches Staatsarchiv, : AT-OeStA/AVA Unterricht UM allg. Akten 633.34 Wiechowski, Wilhelm, Professorenakt (1910)



III. 5: Handwritten letter of Prof. Meyer to his academic colleagues recommending Wiechowski for the upcoming personnel changes at the Pharmacological Chair in Vienna and informing his colleagues about further bureaucratic steps in this matter.⁹⁹

Besides his direct research assignments as a full professor in Prague, he also was in charge of establishing a new Institut of pharmacological studies, which he continuously adapted to his and his colleagues research needs: “ *Damals übersiedelte das pharmakologische Institut aus den bescheidenen Räumen des alten Hofmeisterinstituts in den Neubau am Albertov. Wiechowski bezog den Rohbau und widmete der Inneneinrichtung des Instituts seine ganze Kraft , ja er hat bei vielen Arbeiten selbst Hand angelegt und gerade damals kam ihm seine umfassende methodische Begabung, die ihm ermöglichte unüberwindlich erscheinende*

⁹⁹ Ibidem

*Schwierigkeiten zu besiegen sehr zu statten. (...) zu den best eingerichteten deutschen Instituten gehört“.*¹⁰⁰ Prof. Wiechowski attended several national and international conferences, often directly relevant to practical medicine, e.g. in terms of cardiovascular diseases²⁹⁴ or radium therapy “*Allgemeine biologische Wirkungen der Radium- und Röntgenstrahlen auf den Gesamorganismus: Prof. Wiechowski (Prag) Einwirkung der Radium- und Röntgenstrahlen auf Tumoren“.*¹⁰¹

The presiding committee within this conference, upon which Prof. Wiechowski was invited as a speaker, consisted of the Nobel laureates Marie Skłodowska-Curie and Ernest Rutherford.

2.1.2. Professional influences and direct academic collaborations

Wiechowski published a considerable number of publications in direct co-authorship with other researchers and colleagues from his Chair for Pharmacology and Pharmacognosy in Prague.^{102,103,104,105,106,107,108,109,110,111}

Besides these publications there is also a range of implicit intellectual influence and reflection on Wiechowski's research, at times also referenced directly by the authors.^{112,113,114,115,116}

¹⁰⁰ LANGECKER HEDWIG, Wilhelm Wiechowski in: Lotos Nummer 77 (1929)

¹⁰¹ Wiener Medizinische Wochenschrift Nr. 29 (1914) page 1693

¹⁰² HALPHEN HEDE (mitgeteilt von Wilhelm Wiechowski) Versuche an narkotisierten Froschherzen in: Archiv für experimentelle Pathologie und Pharmakologie 92, XXXIV (1922)

¹⁰³ STROSS WILHELM / JUNKMANN KARL, Über den Nachweis der toxischen Erregung des Vasomotorenzentrums in: Archiv für experimentelle Pathologie und Pharmakologie 131, 1–17 (1928) pages 18–44

¹⁰⁴ WIECHOWSKI WILHELM / ADLER, O., Melanin-Bildung aus organischen Stoffen. in: European Journal of Inorganic Chemistry Vol. 55; Iss. 9 (1922)

¹⁰⁵ WIECHOWSKI WILHELM / STRANSKY EMIL, Ueber das Vorkommen von Chelidonsäure in: Archiv der Pharmazie Vol. 258; Iss. 1 (1920)

¹⁰⁶ WIECHOWSKI WILHELM / LANGECKER HEDWIG, Das Pankreashormon in: Klinische Wochenschrift (1925)

¹⁰⁷ WIECHOWSKI WILHELM / STROB, WILHELM., Zur Pharmakologie des Kampfers in: Archiv f. experimentelle Pathologie und Pharmakologie 92, XXII (1922)

¹⁰⁸ WIECHOWSKI WILHELM, Über die experimentellen Grundlagen der Arzneibehandlung der Herzschwäche. Wiener Biologische Gesellschaft. Sitzung vom 15. Oktober 1923

¹⁰⁹ WIECHOWSKI WILHELM / KLAUSNER, E., Ueber die lokale Behandlung der Harnröhren gonorrhoe mit Silberglykosiden (Neoreargon) in: Deutsche Medizinische Wochenschrift (1925)

¹¹⁰ WIECHOWSKI WILHELM, HALPHEN HEDE, Die Uteruswirkung der Capsella Bursae Pastoris, in: Klinische Wochenschrift Nr. 16 (1922)

¹¹¹ WIECHOWSKI WILHELM / VON KNAFFL-LENZ E., Über die Wirkung von Radiumemanation auf Mononatriumurat in: Wiener klinische Wochenschrift Nr. 12 (1912) page 441

¹¹² HALPHEN HEDE (MITGETEILT VON WILHELM WIECHOWSKI) Versuche an narkotisierten Froschherzen in: Archiv für experimentelle Pathologie und Pharmakologie 92, XXXIV (1922)

¹¹³ JUNKMANN KARL / STROSS WILHELM, Pharmakologische Untersuchungen am überlebenden Ligamentum Rotundum Uteri in: Klinische Wochenschrift (1925)

¹¹⁴ STROSS WILHELM, Untersuchungen über die Wirkungsweise einiger Analeptika I. Mitteilung: Cardiazol in: Archiv für experimentelle Pathologie und Pharmakologie 114 (1926) pages 177–205

¹¹⁵ HANDOVSKY HANS, Ein Alkaloid im Gifte von Bufo vulgaris in: Archiv für experimentelle Pathologie und Pharmakologie 86 (1920) pages 138–158

In terms of direct collaborations Wiechowski often published research with assistants from the pharmacological Institute such as Wilhelm Stross, Oskar Adler, Emil Stransky or junior researchers such as Erwin Klausner from other medical departments like the dermatological Institute. Further examples of direct scientific cooperations, here also with external scientists such as Erich v. Knaffl- Lenz or colleagues Hede Halphen can exemplarily be shown on the publications “*Die Uteruswirkung der Capsella Bursae Pastoris*”¹¹⁷ or “*Über die Wirkung von Radiumemanation auf Mononatriumurat*”¹¹⁸ from 1922 and 1912 respectively.

Though not all publications mention Prof. Wiechowski as a contributing author explicitly, they do however frequently reference him either in terms of methodology^{119,120}, line of thought regarding the central research issue or simply regarding relevant preliminary work upon which the author draw from.¹²¹ In addition the majority publications state his chairmanship of the Pharmacology Institute in Prague at the time of their emergence^{122,123,124}, which in combination with several other written evidence by the authors themselves indicate the amount of his influence on those publications aswell: “*Die Herzwirkungen der bekannten Analeptika sind in unserem Institute planmäßig in der Aufstellung möglichst scharfer (kausaler) Indikationen untersucht worden (Wiechowski und Halphen, Junkmann, Stross Langecker). Es bedeutet eine Fortsetzung dieser Untersuchungen, drei jüngst als Analeptika in den Arzneyschatz eingeführte, synthetisch gewonnene Stoffe, das Cardiazol, das Coramin und das Hexeton, unter den gleichen Gesichtspunkten zu studieren.*”¹²⁵

This form of close collaboration can also be shown by the manner in which results from the joint, shared work had been communicated, e.g. in the context of congresses, in which Wiechowski was also acting vicariously at times and presented common research from the

¹¹⁶ JUNKMANN KARL, Über die Wirkung der sogenannten «Bitterstoffe» in: Archiv für experimentelle Pathologie und Pharmakologie 143 (1929) pages 368–380

¹¹⁷ WIECHOWSKI WILHELM / HALPHEN HEDE, Die Uteruswirkung der Capsella Bursae Pastoris in: Klinische Wochenschrift Nr. 16 (1922)

¹¹⁸ WIECHOWSKI WILHELM / VON KNAFFL-LENZ E., Über die Wirkung von Radiumemanation auf Mononatriumurat in: Wiener klinische Wochenschrift Nr. 12. (1912)

¹¹⁹ STROSS WILHELM / JUNKMANN KARL, Über den Nachweis der toxischen Erregung des Vasomotorenzentrums in: Archiv für experimentelle Pathologie und Pharmakologie 131 (1928) pages 1–17

¹²⁰ JUNKMANN KARL, Über die Wirkung der sogenannten «Bitterstoffe» in: Archiv für experimentelle Pathologie und Pharmakologie 143, (1929) pages 368–380

¹²¹ HANDOVSKY HANS, Ein Alkaloid im Gifte von Bufo vulgaris in: Archiv für experimentelle Pathologie und Pharmakologie 86 (1920) pages 138–158

¹²² Ibidem

¹²³ STROSS WILHELM, Untersuchungen über die Wirkungsweise einiger Analeptika I. Mitteilung: Cardiazol in: Archiv für experimentelle Pathologie und Pharmakologie 114 (1926) pages 177–205

¹²⁴ JUNKMANN KARL, Über die Wirkung der sogenannten «Bitterstoffe» in: Archiv für experimentelle Pathologie und Pharmakologie 143, (1929) pages 368–380

¹²⁵ STROSS WILHELM, Untersuchungen über die Wirkungsweise einiger Analeptika I. Mitteilung: Cardiazol in: Archiv für experimentelle Pathologie und Pharmakologie 114 (1926) pages 177–205

Pharmacological Chair: “*Hede Halphen : Versuche am narkotisierten Froschherzen (Mitgeteilt von Wilhelm Wiechowski)*”¹²⁶

2.1.2.1. Impact on Starkenstein and direct academic collaborations

Regular touchpoints and interactions can be confirmed both on a professional and personal level, particularly via academic publications^{127,128,129,130,131,132,133,134,135,136,137}, or a exchange of correspondence.^{138,139,140,141,142,143,144,145,146,147,148,149}

References to Wiechowski’s classification of diuretics and diaphoreticis and to his previous research regarding their therapeutic use “*Bedeutung der schweißtreibenden Tees*”¹⁵⁰ are explicitly mentioned by Starkenstein in his own considerations regarding this topic.

Further references can be found with regards to structure- effect- relationships¹⁵¹ with implications for pharmaceutical delivery forms and also research on other pharmacological

¹²⁶ HALPHEN HEDE (mitgeteilt von Wilhelm Wiechowski) Versuche an narkotisierten Froschherzen in: Archiv für experimentelle Pathologie und Pharmakologie 92, XXXIV (1922)

¹²⁷ STARKENSTEIN EMIL, Diuretika und Diaphoretika in: Sonderabdruck der ärztlichen Fortbildung (1928)

¹²⁸ STARKENSTEIN EMIL, Verhandlungen der deutschen pharmakologischen Gesellschaft Konstitution und Wirkung anorganischer Verbindungen in: Verlag von F.C.W Vogel in Leipzig (1926) Nr. 77 Box 2 Charles Archive

¹²⁹ STARKENSTEIN EMIL, Pharmakotherapie der Seekrankheit in: Medizinische Klinik (1927)

¹³⁰ STARKENSTEIN EMIL, Die Bedeutung der biochemischen Artenmerkmale für Entwicklungsgeschichtliche Fragen in: Journal of Physiologie in the USSR (1937)

¹³¹ STARKENSTEIN EMIL, Balneologie und Balneotherapie in: Internationaler Ärztlicher Fortbildungskursus (1931)

¹³² STARKENSTEIN EMIL, Wandlungen in der Adsorptionstherapie in: Sonderabdruck aus der Pharmazeutischen Presse (1930)

¹³³ STARKENSTEIN EMIL, Über die therapeutische Verwendung der Tierkohle in: Münchner medizinische Wochenzeitschrift Nr 1 (1915)

¹³⁴ STARKENSTEIN EMIL, Beiträge zur Physiologie und Pharmakologie des Purinhaushaltes in: Biochemische Zeitschrift (1920)

¹³⁵ STARKENSTEIN EMIL, Die Wertbestimmung der Adsorptionskraft von Medizinalkohlen in: Scientia Pharmaceutica (1935)

¹³⁶ STARKENSTEIN EMIL, Physiologische und pharmakologische Prüfung von Nauseamitteln in: Medizinische Klinik (1927)

¹³⁷ STARKENSTEIN EMIL, Der Einfluss experimentell pharmakologischer Forschung auf die Erkennung und Verhütung pharmakotherapeutischer Irrtümer in: Irrtümer der allgemeinen Diagnostik und Therapie sowie deren Verhütung (1923)

¹³⁸ STARKENSTEIN EMIL, family archives c.o. Dr. W. van Emde Boas, Netherland, file 013

¹³⁹ Ibidem, file 014 and 015

¹⁴⁰ Ibidem file 016 and 017

¹⁴¹ Ibidem file 012

¹⁴² Ibidem, letter from Anna Wiechowski to Starkenstein 17.07.1929

¹⁴³ Ibidem file 010

¹⁴⁴ Ibidem file 004

¹⁴⁵ Ibidem file 005

¹⁴⁶ Ibidem file 009

¹⁴⁷ Ibidem file 006/007/008

¹⁴⁸ Ibidem file 011

¹⁴⁹ Ibidem file 003

¹⁵⁰ STARKENSTEIN EMIL, Diuretika und Diaphoretika in Sonderabdruck der ärztlichen Fortbildung (1928)

questions in terms of modes of action and side effects in the context of therapeutic options against motion sickness^{152,153}: “*Von diesem Gesichtspunkt aus betrachtet würde das Atropin nach einer bestimmten Richtung hin als Nauseamittel wegen seiner hochgradigen zentralerregenden Wirkung direkt kontraindiziert erscheinen und es ist leicht denkbar, dass dieses Alkaloid trotz seiner vaguslähmenden Wirkung, eben wegen dieser zentral erregenden Komponente nicht zum vollen Erfolg bei der Seekrankheitstherapie führt (Wiechowski)*“¹⁵⁴ Additional connections to therapeutic concepts and interventions are reflected in relation to analytical fundamentals of balneotherapy¹⁵⁵ and concepts with medicinal charcoal “*Adsorptionstherapie*”.^{156,157,158}

Further links to Wiechowski’s research also feature his biochemical expertise and results, which Starkenstein then carries forward to investigate the degree of relationships within several organisms with regards to biotransformation and metabolic pathways.¹⁵⁹

Prof. Wiechowski’s preclinical methodology, particularly in terms of animal experimentation on several organ types, but also his method with dried organ powders were also taken up by Starkenstein, like in the case of Atophan.¹⁶⁰ The extent of the close and long-lasting collaboration of both pharmacologists was also directly voiced by Starkenstein in a publication in which he addressed Wiechowski as his mentor “*fast zwanzigjährigen Mitarbeit mit (seinem) verehrten Lehrer Wiechowski*”¹⁶¹ and emphasized his influence on his own academic career path “*seine geistige Mitarbeit*”¹⁶², but also many other research areas with clinical relevance during his chairmanship of the Pharmacological Institute: “*Harnsäure-*

¹⁵¹ STARKENSTEIN EMIL, Verhandlungen der deutschen pharmakologischen Gesellschaft Konstitution und Wirkung anorganischer Verbindungen in: Verlag von F.C.W Vogel in Leipzig (1926) Nr. 77 Box 2 Charles Archive

¹⁵² STARKENSTEIN EMIL, Pharmakotherapie der Seekrankheit in: Medizinische Klinik (1927)

¹⁵³ STARKENSTEIN EMIL, Physiologische und pharmakologische Prüfung von Nauseamitteln in Medizinische Klinik (1927)

¹⁵⁴ STARKENSTEIN EMIL, Pharmakotherapie der Seekrankheit in: Medizinische Klinik (1927)

¹⁵⁵ STARKENSTEIN EMIL, Balneologie und Balneotherapie in: Internationaler Ärztlicher Fortbildungskursus (1931)

¹⁵⁶ STARKENSTEIN EMIL, Wandlungen in der Adsorptionstherapie in: Sonderabdruck aus der Pharmazeutischen Presse (1930)

¹⁵⁷ STARKENSTEIN EMIL, Über die therapeutische Verwendung der Tierkohle in: Münchner medizinische Wochenzeitschrift Nr 1 (1915)

¹⁵⁸ STARKENSTEIN EMIL, Die Wertbestimmung der Adsorptionskraft von Medizinalkohlen in: Scientia Pharmaceutica (1935)

¹⁵⁹ STARKENSTEIN EMIL, Die Bedeutung der biochemischen Artenmerkmale für Entwicklungsgeschichtliche Fragen in: Journal of Physiologie in the USSR (1937)

¹⁶⁰ STARKENSTEIN EMIL, Beiträge zur Physiologie und Pharmakologie des Purinhaushaltes in: Biochemische Zeitschrift (1920)

¹⁶¹ STARKENSTEIN EMIL, Der Einfluss experimentell pharmakologischer Forschung auf die Erkennung und Verhütung pharmakotherapeutischer Irrtümer in: Irrtümer der allgemeinen Diagnostik und Therapie sowie deren Verhütung (1923)

¹⁶² *ibidem*

*Allantoinproblem und Beziehung zum Krankheitsgeschehen der Gicht, Adsorptionstherapie, Entzündungsprobleme , Uteruswirkung, Gefäßwirkung zentraler Analgetika, Spasmolytika und Kampferproblem, Expectorantia, Pharmakologie von Herzmitteln, pharmakologische Bedeutung des Ionengleichgewichts für die Therapie und darauf basierend die Pharmakologie des Mineralstoffwechsels und seine Bedeutung für die Balneologie (...)*¹⁶³

An extensive private correspondence between the two scientists from 1907 till 1928 displays both the professional as well as private content and the gradual development from a collegial cooperation to a amicable relationship.

Early letters dated June 17th 1910 and July 27th 1911 indicate their close collaboration at the pharmacological chair, with primarily professional content in the first place, e.g. regarding raw materials for compositions of pharmaceutical formulations “*Blütenpulver (Salvia Öle) (...) ossa sepiae (...)*Die Salbe ist kein Geheimnis mehr und scheint bereits perfekt zu sein”¹⁶⁴ while other topics pertain to technical questions “*eine Farbenmühle wie sie im Institut benutzt würd*”¹⁶⁵ in the context of Wiechowski’s laboratory research. Further correspondence deals with pharmacological questions such as effects of digitalis glykosides on pulse rate and thus their potential as a cardiac stimulant, also in reflection of recent scientific evidence: “*Nach einer neuesten Publikation (..) soll jede Digitaliswirkung eigentlich eine Ca- Wirkung sein und (...) die Empfindlichkeit gegen Ca steigern*”¹⁶⁶

Those letters do also provide information of their then current positions at the Pharmacological Chair, as Starckenstein is addressed as “*Lieber Herr Kollege*”¹⁶⁷ (...) “*Assistenten am pharmakologischen Institut der deutschen Universität Prag II*”¹⁶⁸ while Wiechowski is giving his regards to the soon to be departing Chair Prof. Pohl of the Pharmacological Institute: “*Bitte grüßen Sie Prof. Pohl, die Herren im Institut*”¹⁶⁹ Even exchange on holiday cards refers to Wiechowski’s activities as a speaker on medical topics as well as on those in scientific association like “*Lotos*”, suggesting Wiechowski’s incessant drive in terms of forging ahead with his research: “*Ich fürchte viele Tage werden nicht übrigbleiben von diesem heißem August*”.¹⁷⁰

¹⁶³ Ibidem

¹⁶⁴ STARKENSTEIN EMIL, family archives c.o. Dr. W. van Emde Boas, Netherland, file 004

¹⁶⁵ Ibidem file 005

¹⁶⁶ Ibidem file 010

¹⁶⁷ Ibidem file 004

¹⁶⁸ Ibidem file 005

¹⁶⁹ Ibidem

¹⁷⁰ Ibidem file 011

Nevertheless the prevailing professional content of those records, several letters account for a strong personal involvement in events¹⁷¹ that do not directly deal with academic questions, such as congratulations to the birth of Starkenstein's son "*Gratuliere zum Stammhalter* (letter dated 18.2 .1916)"¹⁷² or his military appointments within the Austro- Hungarian monarchy during his commitment in Radom, Poland "*Dozent Starkenstein, K u. K Regimentsarzt* (dated 21.11.16)"¹⁷³ Evidence for a further mutual involvement in family matters with quite private content can be shown during the First World War via a letter from October 2nd 1917, in which Wiechowski's wife, Anna asks Starkenstein for personal favours due to supply shortages in Prague: "*Fett (...) schwazen und weißen Zwirn (...) mein Mann hat sich zwar daran satt gegessen aber Witold (...) leidet jetzt chronischen Hunger ; (...) Es sind traurige Zeilen*"¹⁷⁴

Another letter by Anna Wiechowski from July 17th 1929, already after her husband's decease also depicts the long- lasting friendship and academic collaboration of both researchers being marked by both a transfer of knowledge and a targeted development of Starkenstein as Wiechowski's successor at the Pharmacological Institute in Prague: "*Sie wissen lieber Professor , daß es unser inniger Wunsch war kein Fremder möge Albertov übernehmen . Und ich darf Sie auch versichern , es ist der Wunsch unserer lieben Toten gewesen (...) In Freundschaft Ihre Anna Maria Wiechowski*"¹⁷⁵ Further evidence for a strong personal dimension within Wiechowski's and Starkenstein's collaboration, that also included their families in a amicable way can be derived from letters in which they address each other as "*Lieber Freund*"^{176,177} and send regards to their respective family members in a private manner: "*grüßen Sie Ihre Gemahlin und Ihre Kinder recht herzlich von mir*"¹⁷⁸

¹⁷¹ Ibidem file 003

¹⁷² Ibidem file 006/007/008

¹⁷³ Ibidem

¹⁷⁴ Ibidem file 009

¹⁷⁵ Ibidem letter from Anna Wiechowski to Starkenstein 17.07.1929

¹⁷⁶ Ibidem file 013

¹⁷⁷ Ibidem file 014 and 015

¹⁷⁸ Ibidem

2.1.3. Relation to the pharmaceutical sector in terms of collaboration and tensions

Prof. Wiechowski's collaboration with the pharmaceutical sector, concerns the field of research and development with Czech^{179,180,181,182} but also international pharmaceutical companies,^{183,184} as well as his interactions with the practicing pharmaceutical community.^{185,186,187}

Therapeutic innovations in an industry setting pertain to the field of dermatological¹⁸⁸, endocrinological^{189,190} and locally acting anti-infective treatments¹⁹¹, in addition his research also dealt with establishing standardized processes for the production of biological treatments¹⁹² and assessing their efficacy.

Market maturity was reached with the astringent ointment "*Olminol Dr. Stein*" basing on olive oil and 33 % aluminium in cooperation with the Prague based company "*Chemische Fabrik Norgine Dr. Viktor Stein- Aussig*"¹⁹³ and with a insulin preparation called "*Norgine*" produced according to Wiechowski's procedure with this North Bohemian Company^{194,195} in which he had been the head of the production process. Through this cooperation an economically priced alternative was established making it possible to supply hospitals and medical practices and thus patients in a much larger scale: "*Dadurch soll es den Spitälern ermöglicht werden. auch unbemittelte Zuckerkrankte mit Insulin zu behandeln.*"¹⁹⁶ According to Prof. Wiechowski's specifications in terms of standardisation and thus reproducible quality a Kombucha preparation "*Kombuchal*" had been manufactured, primarily for further investigating its future clinical use: "*Solange eine biologische womöglich meßbare Reaktion*

¹⁷⁹ Pilsner Tageblatt, October 29th 1923 page 2

¹⁸⁰ WIECHOWSKI WILHELM, Welche Stellung soll der Arzt zur Kombuchafrage einnehmen ? in: Beiträge zur ärztlichen Fortbildung (1928)

¹⁸¹ WIECHOWSKI WILHELM, Oelsaures Aluminium in: Medizinische Wochenzeitschrift Nr.34 (1921) page 1082 ff.

¹⁸² Pharmazeutische Post vom 13. März 1915 page 205

¹⁸³ Zeitschrift des Allgemeinen österreichischen Apothekervereines Nr. 46, 14. November 1914, page 474

¹⁸⁴ Freie Stimmen vom 6. Dezember 1923 page 4

¹⁸⁵ Pharmazeutische Post, Zukunftsfragen der Pharmazie 27. Oktober 1928

¹⁸⁶ Scientia Pharmaceutica, Wissenschaftliches Organ der Österreichischen Apothekerschaft, (1973) Heft 1, 41. Jahrgang

¹⁸⁷ Zeitschrift des Allgemeinen österreichischen Apothekervereines 2. Januar 1915 page 10

¹⁸⁸ WIECHOWSKI WILHELM, Oelsaures Aluminium in: Medizinische Wochenzeitschrift, Nr.34 (1921)

¹⁸⁹ Pilsner Tageblatt, October 29th 1923 page 2

¹⁹⁰ Freie Stimmen vom 6. Dezember 1923 page 4

¹⁹¹ Zeitschrift des Allgemeinen österreichischen Apothekervereines Nr. 46, 14. November 1914, page 474

¹⁹² WIECHOWSKI WILHELM, Welche Stellung soll der Arzt zur Kombuchafrage einnehmen ? in: Beiträge zur ärztlichen Fortbildung (1928)

¹⁹³ WIECHOWSKI WILHELM, Oelsaures Aluminium in: Medizinische Wochenzeitschrift Nr.34 (1921)

¹⁹⁴ Pilsner Tageblatt, October 29th 1923 page 2

¹⁹⁵ Freie Stimmen vom 6. Dezember 1923 page 4

¹⁹⁶ Ibidem

*des Kombuchasyrups nicht gefunden ist , ist es auch nicht möglich experimentell die Indikationen für dieses Arzneimittel zu konstruieren und seine Anwendung damit auf einen bestimmten Kreis von pathologischen Zuständen beschränken zu lehren*¹⁹⁷

Further touchpoints with the pharmaceutical industry concern the production process of medical charcoal with a Dutch company, in which he also was in charge both of the development of the production process but also quality control of the drugs. Prof. Wiechowski also investigated those adsorbents of other pharmaceutical companies like Merck from Darmstadt or Kahlbaum in Berlin in terms of their bioequivalence.¹⁹⁸ His willingness to cooperate with this industry sector also can be shown on his attendance and speaking engagements “*Über Tierkohle, deren Herstellung und Verwendung*” at social events and contexts that had been in a favourable position towards pharmaceutical companies.¹⁹⁹

With regards to practicing pharmacists in a community pharmacy setting, a more ambivalent behaviour can be stated according to several sources. On the one hand, Wiechowski actively participated in the actualization of pharmacopeias in terms of testing specifications based on his previous research, e.g. in a Hungarian one based on a ministerial decree.²⁰⁰ Additionally he reflected upon monographs in Austrian pharmacopeias in terms of optimization of pharmaceutical formulations, specifying indications of those manufactured formulas “*Bei Intertrigo, Brustarzenrhagaden, Dekunitus, Hämmorrhiden, Ekzemen*” for establishing a better therapeutic use.²⁰¹

On the other hand, his attitude toward pharmacists in a community setting, particularly regarding questions of occupational transitions in the face of industrialization processes “*Aus dem Gesagten geht hervor, daß die Apothekerei als Gewerbe im Absterben begriffen ist und daß es keineswegs dem in die Zukunft gerichteten Blicke wünschenswert erscheinen kann , druch irgendwelche künstlichen Maßnahmen diesen Absterbeprozess aufzuhalten oder zu verhindern*”²⁰², resulted in tensions between him and several members of the pharmaceutical profession.

Though a critical evaluation of Wiechowski’s entire article also displays his appreciation of his pharmaceutical colleagues, emphasizing their profound knowledge and skills in field of

¹⁹⁷ WIECHOWSKI WILHELM, Welche Stellung soll der Arzt zur Kombuchafrage einnehmen ? in: Beiträge zur ärztlichen Fortbildung (1928)

¹⁹⁸ Zeitschrift des Allgemeinen österreichischen Apothekervereines Nr. 46, 14. November 1914, page 474

¹⁹⁹ Pharmazeutische Post vom 13. März 1915 page 205

²⁰⁰ Zeitschrift des Allgemeinen österreichischen Apothekervereines 2. Januar 1915 page 10

²⁰¹ WIECHOWSKI WILHELM, Oelsaures Aluminium in: Medizinische Wochenzeitschrift Nr.34 (1921)

²⁰² Pharmazeutische Post, Zukunftsfragen der Pharmazie 27. Oktober 1928

research and development, *“Es muß auch als unumgänglich gefordert werden, daß die pharmazeutische Industrie nicht ausschließlich unter der Leitung chemischer Laboratorien, im Gegenteil insbesondere unter der Leitung pharmazeutischer Laboratorien zu stehen hat wenn sie die großen Entwicklungsmöglichkeiten, die in ihr schlummern ausbilden will.(...) zum Wohle des erkrankten Menschen“*²⁰³, his choice of words in terms of describing practical community pharmacists *“Apothekerei”*, rather displays his contemptuous attitude towards them.²⁰⁴

The fact that he later on and in consequence of negative feedback from the pharmaceutical community moderated his statements and further explained them²⁰⁵ does also speak for his generally positive feelings towards the pharmaceutical profession, emphasizing its need for continuous development and adaption to new developments and societal changes.

2.1.4. Personal affinities and potential familial impact on those

Prof. Wiechowski's personal affinities besides his academic research comprised political and social engagement work in various associations, philosophic and artistic interests underpinned by both humanist and pacifist ideas.

Evidence for political involvement can be given in terms of higher education matters, but also party political ones, both within the predominant and complex interplay of national interests at that time. Contentually, Prof. Wiechowski dealt with issues such as national autonomy of universities within senate sessions between Czech and German interests, in which he advocated for an independent decision making process: *“Jede Nation verwaltet sich selbst ihr Schulwesen. Jede Nation hat ihre eigenen Schulbehörden. sowie ihre eigenen beratenden Körperschaften.”*²⁰⁶ Elsewhere, he summoned a meeting in support of the Jewish rector of the University Prof. Steinherz, who faced antisemitic hostilities from several parts of the student body. Those attacks aimed at defaming the university rector not only basing on his ethnic – religious background but also bringing him into the proximity of alleged subversive interests: *“Wenn man ihm ferner einen Strick daraus zu drehen suche, daß er einen Saal des Karolinums, einem kommunistischen Abgeordneten, der am gleichen Tage eine tschechische Rede im Abgeordnetenhaus gehalten hat, zur Verfügung gestellt habe“*²⁰⁷

²⁰³ Ibidem

²⁰⁴ Ibidem

²⁰⁵ 41. Jahrgang Süddeutsche Apothekerzeitung Zeitschrift für Apotheker und Vertreter verwandter Berufszweige 1928 Nummer 104 / 105

²⁰⁶ Prager Tageblatt vom 18. Dezember 1920 page 3

²⁰⁷ Prager Tageblatt vom 22. November 1922 Nr. 273, page 3

Wiechowski proactively opposed those political currents , demanding both a vote of confidence in favour of Prof. Steinherz, and also a fundamental and cohesive opposition to those nationalistic attempts: “*Prof. Wiechowski protestiert in sehr energischer Weise dagegen daß die Resolution so formuliert werde als ob man einem Kompromß geneigt wäre. Wichtig ist auch daß man gegen die ganze Tendenz der der Vorgänge Stellung nehme. (...) Diesmal gehe es gegen den Rektor nächstens könne der Dekan, der Professor, der Student (..) herankommen*“²⁰⁸

Political involvement on a national level is documented within social democratic party, in which Wiechowski served as a state senator within the Czechoslovak Republic. Though his attachment to and personal dedication for interests of German speaking countries within his political activities, he is also described as being rather reluctant in executing his political mandate and more interested in his academic research: “*sobald als möglich wieder auf die Zugehörigkeit zum Parlament verzichtet*”²⁰⁹ and “*er war weder für seine eigene Person ein guter Politiker , noch auch für die Partei die er vertrat*”²¹⁰

The participants paying their last respect at his funeral give a hint of the extent of his networking besides direct colleagues, but included several public figures from university officials “*deutschen technischen Hochschule*”²¹¹, to politicians “*Gesundheitsministerium*”²¹² and former fellow party members but also representatives of associations such as “*Vereins deutscher Mediziner*”²¹³

Further work in several associations also included fine arts in the “*Verein deutscher bildender Künstler in Böhmen*” , in which he did not only participate as an ordinary member but in fact executed his duty as a committee member, e.g. as documented in the annual report from March 28th 1908.²¹⁴ Even though Wiechowski’s private activities, e.g. in associations display a wide spectrum, his scientific interest is here again represented in a disproportionately high manner. Meeting minutes from the natural science association *Lotos* depict numerous contributions to the discussion e.g. on October 26th 1909 “*Über die zerebrospinale*

²⁰⁸ Ibidem

²⁰⁹ SPIRO KARL, Erinnerung an Wilhelm Wiechowski in: Die Medizinische Welt – ärztliche Wochenschrift Nr. 6 (1929)

²¹⁰ STARKENSTEIN EMIL, Wilhelm Wiechowski, Worte des Gedenkens, gesprochen im Verein deutscher Ärzte in Prag am 18. Januar 1929 in: Sonderdruck aus Beiträge zur ärztlichen Fortbildung Nr 2 (1929)

²¹¹ STARKENSTEIN EMIL, family archives c.o. Dr. W. van Emde Boas, Netherland, file 016/017

²¹² Ibidem

²¹³ Ibidem

²¹⁴ Montagsblatt aus Böhmen vom 13. April 1908 page 7

*Pleozytose und ihre anatomischen Grundlagen*²¹⁵ or “*Fortsetzung der Diskussion über das chromaffine System*”²¹⁶ on January 26th 1910. Within these association activities, Wiechowski also gave talks, addressing current gaps in research “*Weder die Bildung noch das Schicksal des Adrenalins im Organismus ist bisher in eindeutiger Weise bekannt geworden*”²¹⁷ and contributed via book reviews “*Bayliss W. M: Das Wesen der Enzym Wirkung Dresden 1910*”²¹⁸ to scientific exchange.

Both artistic interest and a appreciation for philosophical questions²¹⁹ can be adjudged to Prof. Wiechowski as well, as his social and amicable environment did include several visual artists and writers, socialising with a range of outstanding personalities, such as Rainer Maria Rilke, Richard Teschner and Paul Leppin.²²⁰ His own understanding of metaphysical questions clearly exceeded natural scientific fundamentals and viewpoints “*Nach der von Wiechowski selbst entwickelten Anschauung über das geistige Leben können auch die ungesprochenen , aber ins All hinausgedachten Gedanken als belebende Materie befruchtend weiter wirken und von anderen aufgenommen warden*”²²¹ and also aimed at more holistic understanding of science, which would both consider humanist approaches with evidence from natural sciences: “*das Gefühl für die Einheit und Ganzheit des Organisierten, die sich ja jedem Denker beim Studium des Lebendigen unmittelbar aufdrängen*”²²².

There is several evidence suggesting that the familial background helped shaping Wiechowski’s interests both in the socio- political, but also within the pedagogical field.

Both of Wiechowski’s parents had been active within the pedagogical field²²³, providing a sound humanist education for all of their children, which then effectively all occupied themselves with education matters later on: “*Friedrich Wiechowski war Direktor des Deutschen Staatsrealgymnasiums in Prag, Siegfried war Professor an der Wiener*

²¹⁵ WIECHOWSKI WILHELM, Über die zerebrospinale Pleozytose und ihre anatomischen Grundlagen (Diskussionsbeitrag am 26. Oktober 1909) in: Naturwissenschaftliche Zeitschrift herausgegeben vom Deutschen Naturwissenschaftlich-Medizinischen Verein für Böhmen "Lotos" in Prag. Band 58 (1910)

²¹⁶ Ibidem

²¹⁷ Naturwissenschaftliche Zeitschrift herausgegeben vom Deutschen Naturwissenschaftlich-Medizinischen Verein für Böhmen "Lotos" in Prag." Band 58 (1910)

²¹⁸ Ibidem

²¹⁹ STARKENSTEIN EMIL, Wilhelm Wiechowski, Worte des Gedenkens, gesprochen im Verein deutscher Ärzte in Prag am 18. Januar 1929 in: Sonderdruck aus Beiträge zur ärztlichen Fortbildung Nr 2 (1929)

²²⁰ Ibidem

²²¹ STARKENSTEIN EMIL, family archives c.o. Dr. W. van Emde Boas, Netherland, file 016 and 017

²²² SPIRO KARL, Erinnerung an Wilhelm Wiechowski in: Die Medizinische Welt – ärztliche Wochenschrift Nr. 6 (1929)

²²³ STARKENSTEIN EMIL, Wilhelm Wiechowski, Worte des Gedenkens, gesprochen im Verein deutscher Ärzte in Prag am 18. Januar 1929 in: Sonderdruck aus Beiträge zur ärztlichen Fortbildung Nr 2 (1929)

Lehrerbildungsanstalt, Getrud Wiechowski war Begründerin des gymnastischen und rythmischen Turnens in Prag”²²⁴

Within those educational interests, his mother, Wilhemine Wiechowski had been actively involved in feminist and pacifist movements at that time , e.g. advocating for women’s rights in terms of equal rights and opportunities to engage in a variety of sport disciplines: “*Jugendspiele, Turnen, Wanderungen, Schwimmen, Eins- und Schneelauf*”²²⁵ The pacifist elements of her activities refer to a promotion of intercultural understanding among nations and thus a prevention of future war scenarios, which she later executed together with Wiechowski’s wife, Anna Maria.²²⁶

Those pacifist ideas also display themselves within Prof. Wiechowski’s adulthood, for instance via his engagement within the Lotos association, in which he vehemently opposed any military use of toxicological agents as a means of warfare. “*Unzulässigkeit einer solchen im wahrsten Sinne des Wortes barbarischen Kriegsführung. Wiechowski.*”²²⁷ Even during his doctoral studies, Wiechowski engaged in his mother’s and grandmother’s association activities “*Deutscher Verein zur Förderung des Wohles und und der Bildung der Frauen in Prag*“, here again to tackle the issue of education „*kleine Sünden in der Kinderstube*“.²²⁸

Further evidence for his social involvement with regards to public welfare can be verified by his non- profit approach or at least cost-effective solutions to drug production and development, utilizing his academic knowledge for practical causes as taken place within the “*Kriegsmedikamentenkomitee*”²²⁹

2.1.5. Final years and cause of death

Prof. Wiechowski’s last years have been marked by illness and gradual retreat into private life , characterized by his increasingly bad physical and psychological condition. Considerable private insights into this point of his life are accessible through diary entries of his, back then, attending nurse Ilse Kaiser, other sources such as obituaries but also first hand evidence like Wiechowski’s personal correspondence or publications²⁴⁵ reproduce important aspects of the circumstances of that time.

²²⁴ Grazer Volksblatt 21. April 1913

²²⁵ Ibidem

²²⁶ Neues Wiener Journal - Unparteiliches Tageblatt vom 16.November 1926 page 10

²²⁷ STARKENSTEIN EMIL / SCHLEIBNER F. / WIECHOWSKI W. / DEXLER H. /Bücherbesprechungen in: Lotos - Zeitschrift fuer Naturwissenschaften – 67-68 (1919) pages 189 – 200

²²⁸ Prager Abendblatt vom 25 Juni 1897 page 3

²²⁹ Pharmazeutische Presse vom 19. September 1914 page 314

The optimal management of a work- life balance seems to have been challenging for Wiechowski at times in his academic career, being involved in association work, the establishment of a new Pharmacological Institute in Albertov 7, industry cooperations and supervision of his colleagues and students in addition to his own research and development of innovative methods. Besides this immense workload, certain character traits might have acted disadvantageously on top of these commitments, which are described as being rather restless and short tempered with regards to his own and others progress: *“Freilich wer träge im Denken war , den konnte Wiechowski nicht brauchen”*²³⁰ and *“seine klaren und anregenden Vorlesungen in bester Erinnerung, in denen er mit zündender Begeisterung Altes und Neues und Neustes seinen Hörern vermittelte (...) dabei sich aufdrängende noch ungelöste Fragen war er bemüht rasch einer experimentellen Untersuchung zuzuführen“*²³¹

These estimates can further be underpinned with personal correspondence to Starkenstein, in which he urges him to organize the right laboratory materials, being indicative for his well organized but also micro- managing approach, especially with regards to third parties: *“Ich schreibe aber nicht direkt an die Leute (aus dem Fachgeschäft in Prag) weil ich fürchte , dass sie mir etwas ungeeignetes schicken”* and *“Ich wäre froh wenn ich die Sachen (...) bald hätte nachdem ich mit dem vergeblichen Suchen hier schon viel nützliche Zeit vertan habe“*²³²

This nearly constant involvement in affairs concerning his chair and colleagues did also not cease to exist at times of supposed personal rest, as seen on various letters²³³ and postcards²³⁴ from vacations but also according to accounts of Mrs. Kaiser: *“Seine Gedanken wanderten unablässig nach Prag, zur Stätte seiner Arbeit”* and *“ seine einzigen Freuden waren die Berichte seiner Mitarbeiter”*²³⁵ Wiechowski’s caring and altruistic personality traits, considering other’s well being is also displayed on interactions with people outside his academic sphere, in which he utilized his knowledge and position to make a positive impact on the life of others: *“Er unterhielt sich mit den Bauern des Dörfchens, lieh allen (...) ein williges Ohr und half in zahlreichen Fällen bei den damals grassierenden Darmerkrankungen mit seiner Tierhohle und seinen Kamillenglykosiden”*²³⁶

²³⁰ STARKENSTEIN EMIL, family archives c.o. Dr. W. van Emde Boas, Netherland „Wilhelm Wiechowski – Sein letztes Lebensjahr von Ilse Kaiser 1929“

²³¹ LANGECKER HEDWIG, Wilhelm Wiechowski in: Lotos Nummer 77 (1929)

²³² STARKENSTEIN EMIL, family archives c.o. Dr. W. van Emde Boas, Netherland, file 005

²³³ Ibidem file 013

²³⁴ Ibidem file 011

²³⁵ Ibidem „Wilhelm Wiechowski – Sein letztes Lebensjahr von Ilse Kaiser 1929“

²³⁶ Ibidem

Besides those positive, yet capacity- consuming characteristics of his personality, also argumentativeness and certain compulsion^{237,238} played of part of Wiechowski's multifaceted character, displaying several extremes within his social interactions. A gradual decline of his health can be shown through his stay at a sanatorium near Vienna, for which he partially handed over his teaching responsibilities to Prof. Starkenstein²³⁹, but also assumed on the significant change of his handwriting within his final years.^{240,241}

A personal letter dated February 28th 1928 to his colleague Starkenstein dealing with his state of health at that time and displays his stay in Baden for recreational and curative reasons "*Baden bei Wien Schwefelbäder Thermal Strandbad, Trinkkur, Traubenkur*", while Prof Wiechowski tries to deemphasize his exhaustion, focusing on his wife's concern about his health instead: "*guten Appetit*" and "*Bitte tun sie das Ihrige meine Frau zu beruhigen*"²⁴². Albeit his intentions to console his friends and family, his health condition deteriorated continuously, particularly towards the end of his life, being marked by social isolation, depression and substance abuse , particularly within the group of sedative and narcotic drugs "*Beruhigungsmittel*" and "*schmerzstillende und beruhigende Mittel*".²⁴³ Prior contact to narcotic drugs however within a scientific and research- driven context, can be verified earlier in his live, as seen on his publication "*Haschisch*"²⁴⁴, involving self- experimentation. Besides this academic context, there are reports about a regular private use as well as a exposure to other toxins as well: "*Experiment (Haschisch) auch im täglichen Leben gleichsinnig im Umgang mit Giften wurde (Alkohol, leider aber auch Narkotika)*" or "*chronischen Arsenvergiftung*"²⁴⁵.

Within this vicious cycle of substance abuse and depressive episodes, it remains unclear to which extent the exposure to those substances was an intended cure of underlying psychological problems "*eine schwere seelische Depression*"²⁴⁶ or indeed caused them in the first place. Though initially no physical illness could be diagnosed, cardiac problems are

²³⁷ SPIRO KARL, Erinnerung an Wilhelm Wiechowski in: Die Medizinische Welt – ärztliche Wochenschrift Nr. 6 (1929)

²³⁸ LANGECKER HEDWIG, Wilhelm Wiechowski in: Lotos Nummer 77 (1929)

²³⁹ Pharmazeutische Post vom 27. Juli 1929 page 361

²⁴⁰ STARKENSTEIN EMIL, family archives c.o. Dr. W. van Emde Boas, Netherland, file 012

²⁴¹ Ibidem file 004

²⁴² Ibidem file 012

²⁴³ Ibidem see Ilse Kaiser

²⁴⁴ WIECHOWSKI WILHELM, Wiechowski Haschisch in: Naunyn-Schmiedeberg's Archives of Pharmacology, Vol. 119; Iss. 5-6 (1927)

²⁴⁵ SPIRO KARL, Erinnerung an Wilhelm Wiechowski in: Die Medizinische Welt – ärztliche Wochenschrift Nr. 6 (1929)

²⁴⁶ STARKENSTEIN EMIL, family archives c.o. Dr. W. van Emde Boas, Netherland, see Ilse Kaiser

described within his final year: *“Er hatte Herzschmerzen (...) wurde eine Irritation des Herzens konstatiert”*²⁴⁷

Here again, certain cardiovascular risks such as arrhythmias, infarcts or cardiomyopathy have been reported in association with the abuse of cannabis²⁴⁸, alcohol^{249,250} and opioids²⁵¹ but also emotional stress²⁵². Being exposed to these factors to a greater or lesser extent throughout his later life, devoted to his work *“drei Tage lag er zu Bette, dann kam er ins Institut und jedermann sah, wie krank und gebrochen (...er...) war. Und doch arbeitete er”*²⁵³ Wiechowski finally died on December 19th 1929.

2.2. Analysis and contextualisation of his scientific research

2.2.1 Analytical methods and approaches used and developed by Wiechowski

Wiechowski's research often involved methodological questions with regards to concrete analytical methods^{254,255,256,257}, and also the development of own procedures in context to the underlying research^{258,259,260}. The majority of those publications originate from Wiechowski single-handedly, whereas in some cases he collaborated with his colleagues from the

²⁴⁷ Ibidem

²⁴⁸ MANOLIS THEODORA A./ MANOLIS ANTONIS A. / MANOLIS ANTONIS S., Cannabis Associated High Cardiovascular Morbidity and Mortality: Marijuana Smoke Like Tobacco Smoke? A Déjà Vu/Déjà Vécu Story? In: Mini Review in Medicinal Chemistry 2019;19(11) (2019) pages 870-879

²⁴⁹ GARDNER JASON D./ MOUTON AJ, Alcohol effects on cardiac function in: Comprehensive Physiologie Apr;5(2) (2015) pages 791-802

²⁵⁰ NISHIMURA MARIN / BHATIA H. / MA J./ DICKSON S. D. / ALSHAWABKEH L., ADLER E. / MAISEL A. / CRIQUI M : H. / GREENBERG B. / THOMAS I. C., The Impact of Substance Abuse on Heart Failure Hospitalizations in : The American Journal of Medicine. 2020 Feb;133(2) (2019) pages 207-213

²⁵¹ Ibidem

²⁵² ZHANG LILI / PIÑA ILEANA L., Stress-Induced Cardiomyopathy in: Heart Failure Clinics, Volume 15, Issue 1 (2019)

²⁵³ STARKENSTEIN EMIL, family archives c.o. Dr. W. van Emde Boas, Netherland, see Ilse Kaiser

²⁵⁴ WIECHOWSKI WILHELM, Ueber den Einfluss der Analgetica auf die intracranielle Blutcirculation, in :Naunyn-Schmiedeberg's Archives of Pharmacology (1902)

²⁵⁵ WIECHOWSKI WILHELM, Über experimentelle Beeinflussung des Contractionszustandes der Gefäße des Schädellinnern, in: Archiv für experimentelle Pathologie und Pharmakologie (1905)

²⁵⁶ HALPHEN HEDE (mitgeteilt von Wilhelm Wiechowski) Versuche an narkotisierten Froschherzen in: Archiv für experimentelle Pathologie und Pharmakologie 92, XXXIV (1922)

²⁵⁷ WIECHOWSKI WILHELM, Die Messung pharmakologischer Wirksamkeit am lebenden Tier , insbesondere die Ermittlung der minimal tödlichen Gabe und die biologische Definition von Maßpräparaten in: Naunyn-Schmiedeberg's Archives of Pharmacology Vol. 128; Iss. 1 Supplement (1928)

²⁵⁸ WIECHOWSKI WILHELM, Eine Methode zur chemischen und biologischen Untersuchung überlebender Organe in: Beiträge zur Physiologischen Chemie und Pathologie , Zeitschrift für die gesamte Biochemie (1907)

²⁵⁹ WIECHOWSKI WILHELM, Die Bedeutung des Allantoins im Harnsäurestoffwechsel Beiträge zur chemischen Physiologie und Pathologie in: Zeitschrift für die gesamte Biochemie Sonder Abdruck aus Band XI , Heft 3 und 4 (1907)

²⁶⁰ WIECHOWSKI WILHELM, Analyse des Harns in: Zum Gebrauch für Mediziner, Chemiker und Pharmazeuten zugleich Elfte Auflage von Neubauer-Huppert's Lehrbuch (1913)

pharmacological chair in Prague²⁶¹ or compared his reflections to previous evidence from other researchers²⁶². The great extent of those methodological conditions as well as the depth of content within his publications demonstrate Wiechowski's focus on scientific reproducibility and thus objectifying his research findings on the one hand and also enabling other researchers to follow his line of thoughts on the other one.²⁶³

In his research on intracranial blood circulation Prof. Wiechowski deals with a physiological method of Karl Hürthle, measuring a pressure differential between the carotid artery and brain-supplying arteries "*Circulus arteriosus willisii*", considering the complex neural and arterio-venous conditions in vivo: "*Dies hat jedoch nur Gültigkeit solange in den entsprechenden Venen keine Druckzunahme eintritt*"²⁶⁴ while recognizing the limits of this approach "*Das was hier von den intracraniellen Gefäßen gesagt worden ist, bezieht sich naturgemäß zum größten Teil oder ausschliesslich auf die Gehirngefäße; Gefäßveränderungen in den Gehirnhäuten allein lassen sich mit der angewandten Methode nicht erkennen*"²⁶⁵

Another extensive publication with similar content and objectives explains the physiological relationships within animals while focussing on a detailed portrayal of the needed surgical procedure to meet the subsequent pharmacological analysis and to prevent unintended effects: "*Es kamen zwei Präparationstypen zur Anwendung. Es wurden die Arteria carotis interna dextra, die Arteria carotis communis sinistra und deren Zweige 2 (...), die Arteria subclavia dextra an ihrem Ursprung von der Carotis communis dextra und ihre Zweige 2 und 3 (...) unterbunden; die Carotis externa sinistra und die A. subclavia dextra nach dem Abgange der A. vertebr, dextra bei 4 (...) angeschlungen*"²⁶⁶

As an example of methodological approaches in the style of Wiechowski both Stross' and Junkmann's research on sympathetic nerve cells in the medulla oblongata reference his scientific groundwork explicitly within the methods section of their publication: "*Zur Injektion in die A. vertebralis gingen wir entweder nach der Technik Wiechowskis vor, oder*

²⁶¹ HALPHEN HEDE (mitgeteilt von Wilhelm Wiechowski) Versuche an narkotisierten Froschherzen in: Archiv für experimentelle Pathologie und Pharmakologie 92, XXXIV (1922)

²⁶² WIECHOWSKI WILHELM, Ueber den Einfluss der Analgetica auf die intracranielle Blutcirculation, in: Naunyn-Schmiedeberg's Archives of Pharmacology (1902)

²⁶³ STROSS WILHELM / JUNKMANN KARL, Über den Nachweis der toxischen Erregung des Vasomotorenzentrums in: Archiv für experimentelle Pathologie und Pharmakologie 131(1928) pages 1–17

²⁶⁴ WIECHOWSKI WILHELM, Ueber den Einfluss der Analgetica auf die intracranielle Blutcirculation, in: Naunyn-Schmiedeberg's Archives of Pharmacology (1902)

²⁶⁵ Ibidem

²⁶⁶ WIECHOWSKI WILHELM, Über experimentelle Beeinflussung des Contractionszustandes der Gefäße des Schädellinnern, in: Archiv für experimentelle Pathologie und Pharmakologie (1905)

wir führten auf der rechten Seite in die in der unteren Halsgegend freigelegte Carotis herzwärts eine stumpfe Hahnkanüle soweit ein , daß ihre Spitze an der Verzweigungsstelle der Carotis dextra und Subclavia lag²⁶⁷

A stand- alone development of a biochemical procedure can be shown on the production of dried and pulverized animal organs, permitting both qualitative and quantitative conclusions in line with naturally occurring, physiological and biochemical properties of those organs.²⁶⁸ This procedure aimed at gaining and decrypting the metabolic essence of those organs at the same time, which Wiechowski identified as several proteins: “Das in dieser Weise vorgenommene Trocknen verändert weder die Eiweißkörper der Organe , noch schädigt es ihre Fermente. Das letztere wurde durch die Tatsache bewiesen, daß die Organe (Rinderniere, Rinderleber, Hundeleber) ihre Fähigkeiten , Harnsäure zu bilden und zu zerstören , Wasserstoffperoxyd zu spalten , sowie autolytisch zu zerfallen , durch das Trocknen nicht einbüßen“²⁶⁹ Within this chemical procedure unwanted cellular components and other accompanying substances are analytically separated to ensure a realistic comprehension of several biochemical reaction steps.

Further development of autonomous biochemical methods by Wiechoswki refer to the field of urin analysis, in which he defined the modalities of chemical separation processes as well as other methods. Those include the analytic determination of urin metabolites such as hippuric acid²⁷⁰ the determination of nitrogen, manufacturing instructions for chemical reagents and establishing limit values.²⁷¹

In collaboration with Hede Halphen, Prof. Wiechowski also addresses technical and methodological issues such as the physiological integrity and relating thereto informative value of the organ function, e.g. within cardiovascular research. In this respect he aims at drawing causative pharmacological conclusions through a previous elimination of physiological disruptive factors: “Die Narkose wird so lange fortgesetzt bis beim Austausch

²⁶⁷ STROSS WILHELM / JUNKMANN KARL, Über den Nachweis der toxischen Erregung des Vasomotorenzentrums in: Archiv für experimentelle Pathologie und Pharmakologie 131 (1928) pages 1–17

²⁶⁸ WIECHOWSKI WILHELM, Eine Methode zur chemischen und biologischen Untersuchung überlebender Organe in : Beiträge zur Physiologischen Chemie und Pathologie , Zeitschrift für die gesamte Biochemie (1907)

²⁶⁹ Ibidem

²⁷⁰ WIECHOWSKI WILHELM, Analyse des Harns in: Zum Gebrauch für Mediziner, Chemiker und Pharmazeuten zugleich Elfte Auflage von Neubauer-Huppert's Lehrbuch (1913)

²⁷¹ WIECHOWSKI WILHELM, Die Bedeutung des Allantoins im Harnsäurestoffwechsel Beiträge zur chemischen Physiologie und Pathologie in: Zeitschrift für die gesamte Biochemie Sonder Abdruck aus Band XI , Heft 3 und 4 (1907)

*des Kanüleninhalts gegen unvergiftete Ringerlösung auch nicht das geringste Anzeichen einer wiedereintretenden Tätigkeit bemerkt wird*²⁷²

However, the available methodological considerations are not only limited to the physiological and biochemical field but also pertain to mathematical principles, within the field of statistics. In this theoretical reasoning he sets a standard for the risk evaluation of pharmacons, such as the lowest lethal concentration, and further biomathematical models to assess mean values of toxicity data as well as relative toxicity, including species specific factors: *“Messungsergebnisse eines Merkmals nach Klassen steigenden Wertes gruppiert werden, in welche die Anzahl der Individuen eingetragen wird, deren Maß in die betreffende Klasse fällt (...) Für die immer mehr an Bedeutung gewinnenden biologischen Wertbestimmungen bzw. für die Wirksamkeitsdefinitionen der Vergleichspräparate ist die Berechnung von Mittel und Standardabweichung unumgänglich (...)”*²⁷³

a) Biochemical research and its context

Wiechowski's biochemical research focussed on understanding metabolic processes across species^{274,275}, as well as gaining further insights about biomolecular structures^{276,277,278} e.g. the chemical composition of bodily fluids, such as urine.²⁷⁹ The rationale behind those research projects was either triggered by interest in fundamental biological research with a strong focus on physiological processes within the human or animal bodies but also at times was carried out with the ulterior motive of contributing unmet needs in drug discovery and development:

²⁷² HALPHEN HEDE (mitgeteilt von Wilhelm Wiechowski) Versuche an narkotisierten Froschherzen in: Archiv für experimentelle Pathologie und Pharmakologie 92, XXXIV (1922)

²⁷³ WIECHOWSKI WILHELM, Die Messung pharmakologischer Wirksamkeit am lebenden Tier, insbesondere die Ermittlung der minimal tödlichen Gabe und die biologische Definition von Maßpräparaten in: Naunyn-Schmiedeberg's Archives of Pharmacology Vol. 128; Iss. 1 Supplement (1928)

²⁷⁴ WIECHOWSKI WILHELM, Über die Zersetzlichkeit der Harnsäure im menschlichen Organismus in: Archiv für experimentelle Pathologie 60, 185. (1909)

²⁷⁵ WIECHOWSKI WILHELM, Über Eigenschaften und Darstellung des harnsäurezerstörenden Fermentes der Rinderniere und Hundeleber in: Beiträge zur chemischen zur chemischen Physiologie und Pathologie (1907) page 247ff

²⁷⁶ WIECHOWSKI WILHELM, Die Produkte der fermentativen Harnsäurezersetzung durch tierische Organe von Wilhelm Wiechowski in: Beiträge zur Physiologischen Chemie und Pathologie, Zeitschrift für die gesamte Biochemie (1907) pages 295-310

²⁷⁷ WIECHOWSKI WILHELM, Eine Methode zur chemischen und biologischen Untersuchung überlebender Organe in: Beiträge zur Physiologischen Chemie und Pathologie, Zeitschrift für die gesamte Biochemie (1907)

²⁷⁸ WIECHOWSKI WILHELM, Die Bedeutung des Allantoin im Harnsäurestoffwechsel Beiträge zur chemischen Physiologie und Pathologie in: Zeitschrift für die gesamte Biochemie Sonder Abdruck aus Band XI, Heft 3 und 4 (1907)

²⁷⁹ WIECHOWSKI WILHELM, Analyse des Harns in: Zum Gebrauch für Mediziner, Chemiker und Pharmazeuten zugleich Elfte Auflage von Neubauer-Huppert's Lehrbuch (1913)

“Zur Gewinnung richtiger chemotherapeutischer Gesichtspunkte für den Menschen ist es daher oft nötig, in Würdigung dieser Erkenntnis die im Tierexperiment erhobenen Tatsachen auf ihre Gültigkeit für die menschliche Pathologie besonders zu prüfen. An diesem Punkte sind Studien angelangt, deren Ziel die Schaffung einer pharmakologischen Grundlage zur Gichttherapie ist.“²⁸⁰

Metabolic disorders, such as gout and gouty arthritis are closely linked to purine and urea metabolism which are then again characterized by hyperuricemia in case of pathological conditions. An in- depth understanding of those processes is essential to comprehend physiological manifestations such as joint pain, swellings or inflammation in order to treat them causally.

Wiechowski’s research on metabolism and elimination of those nucleid acids , did not only differentiate between the final products of that metabolism (III.4), such as allantoin in some animals, but also investigated the enzymatic equipment within individual organs and across species.²⁸¹

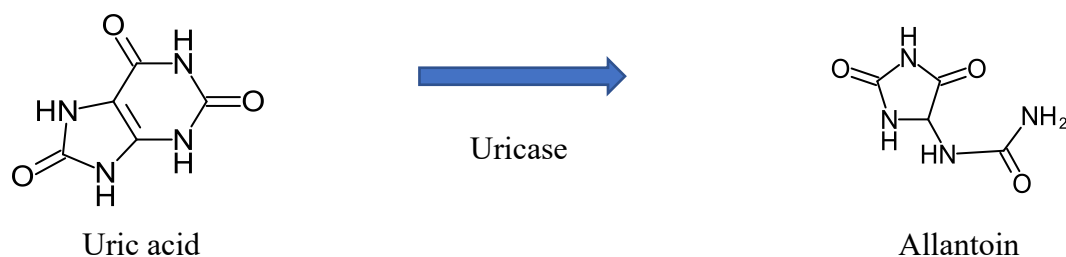


Illustration 4 : Metabolism of uric acid in some mammals except hominids such as homo sapiens who lack this enzyme

In those investigations Wiechowski is able to benefit from his previous methodological considerations, as he utilizes his dried and pulverized organ powders to scrutineer enzyme activities both in a qualitative and quantitative manner. By this means both the extent of efficacy , protein- protein interactions but also reaction conditions such as temperature , response time of the chemical reactants and also concentration ratios can be investigated under standardized conditions and as a result provide valid and meaningful conclusions about the enzymes. Implicitly enzyme substrate interactions are being examined in those

²⁸⁰ WIECHOWSKI WILHELM, Über die Zersetzlichkeit der Harnsäure im menschlichen Organismus in : Archiv für experimentelle Pathologie 60 (1909) page 185

²⁸¹ Ibidem

publications too, focussing on the biochemical conditions they need to fulfill their biological function:

“Das harnsäurezerstörende Ferment der Rinderniere und Hundeleber ist eine nur bei schwach alkalischer oder neutraler Reaktion wirkende Oxydase, (..) welcher die Zersetzung als Oxydation anspricht.”²⁸²

Prof. Wiechowski does not limit his research to directly detected metabolic end products but aims at decrypting numerous potential intermediates within the uric acid metabolism, experimenting on oxidative, hydrolytic reactions both in acid and alkaline liquid medium, mentioning metabolites such as *Alloxan*, *Uroxansäure* and *Glokokoll*.²⁸³ Though those substances are not a part of the physiological uric acid metabolism, Wiechowski elucidates the conditions under which they can be gained in laboratory scale and in doing so understanding the chemical reactivity of uric acid.²⁸⁴

Within this biochemical research, Wiechowski also deals with elements of nucleic acids, the purine bases and distinguishes between endogenous and exogenous supply and their effect on pathological conditions, also by comparing his own research to other authors: “Bei der Gicht ist die exogene Purinausscheidung verzögert”²⁸⁵.

b) Other basic chemical and pharmaceutical approaches

Besides biochemical research, particularly organic chemistry as well as pharmaceutical analytics play an important role in Wiechowski's research, accounting for his broad research portfolio both in terms of research content and methodology.

Within the domain of organic chemistry, naturally occurring pigments are being investigated in terms of technological opportunities for chemical modification and the behaviour of individual molecular groups within ozonisations, acetylation or other chemical reactions. In those chemical experiments both natural substances such as *Mangin* but also their metabolites like *Euxanthinsäure* are chemically defined with regards to pharmaceutically relevant parameters, e.g. optical activity, solubility, melting point or analysis of substance identity, according to their presumed substance category: “Mit $FeCl_3$ gibt das Mangin in alkoholischer

²⁸² WIECHOWSKI WILHELM, Über Eigenschaften und Darstellung des harnsäurezerstörenden Fermentes der Rinderniere und Hundeleber in: Beiträge zur chemischen Physiologie und Pathologie (1907)

²⁸³ WIECHOWSKI WILHELM, Die Produkte der fermentativen Harnsäurezersetzung durch tierische Organe von Wilhelm Wiechowski in: Beiträge zur Physiologischen Chemie und Pathologie, Zeitschrift für die gesamte Biochemie (1907) pages 295-310

²⁸⁴ Ibidem

²⁸⁵ WIECHOWSKI WILHELM, Analyse des Harns in: Zum Gebrauch für Mediziner, Chemiker und Pharmazeuten zugleich Elfte Auflage von Neubauer-Huppert's Lehrbuch (1913)

*und wässriger Lösung eine intensiv dunkelgrüne Farbe. Die Prüfung auf mehrwertige Phenole mittels Folinscher Lösung (Phosphorwolframsäure und Na₂CO₃) fiel stark positiv aus.*²⁸⁶

Further research with regards to organic chemistry deals with potential options to synthesize alkali-soluble pigments and to understand the chemical mechanism of their formation process. Over 382 individual molecules are being screened by Wiechowski and Adler collaboratively in order to identify applicable chemical laws within this process, concluding that only cyclic compounds are suitable for providing a positive reaction.²⁸⁷

In terms of applying methods of pharmaceutical analysis, quantifications of individual constituents such as chelidonic acid²⁸⁸ within mixtures of natural substances or procedures for obtaining pharmacologically active compounds are carried out.²⁸⁹

Focusing on ways of preserving those compounds *“Wegen des leichten Entstehens xanthochelidonsaurer Salze erfordert die Darstellung der Salze der Chelidonsäure besondere Vorsicht”*²⁹⁰, chemical modification is in some instances arranged by salt-precipitation, also in order to optimize factors such as stability and effectiveness, also under extended storage periods.²⁹¹

c) Animal and self- experimentations

Apart from the outlined in vitro experiments, Wiechowski also engaged in a variety of animal self- experimentation and test persons in a clinical or real life setting with primarily physiological and pharmacological content.

Within the animal experiments species characteristics e.g. with regards to neuronal circuits and their excitation both in physiological and pathophysiological conditions are examined: *“Die Kühlung des Kopfes hatte im Versuch VII und VIII eine merkliche Verengung der intrakraniellen Gefäße bewirkt, die nach dem Aufhören der Abkühlung wieder verschwand.*

²⁸⁶ WIECHOWSKI WILHELM, Über die Muttersubstanz des Indischgelb in: Archiv für experimentelle Pathologie u. Pharmakologie 97 (1923) pages 462–488

²⁸⁷ WIECHOWSKI WILHELM / ADLER, O., Melanin-Bildung aus organischen Stoffen. In: European Journal of Inorganic Chemistry Vol. 55; Iss.9 (1922)

²⁸⁸ WIECHOWSKI WILHELM / STRANSKY EMIL, Ueber das Vorkommen von Chelidonsäure in: Archiv der Pharmazie Vol. 258; Iss. 1 (1920)

²⁸⁹ WIECHOWSKI WILHELM, Über herzwirksame Glykoside in: Archiv für experimentelle Pathologie und Pharmakologie 92, XIX–XX (1922)

²⁹⁰ WIECHOWSKI WILHELM / STRANSKY EMIL, Ueber das Vorkommen von Chelidonsäure in: Archiv der Pharmazie Vol. 258; Iss. 1 (1920)

²⁹¹ WIECHOWSKI WILHELM, Über herzwirksame Glykoside in: Archiv für experimentelle Pathologie und Pharmakologie 92, XIX–XX (1922)

*Dagegen hat die Erwärmung des Kopfes nicht so prompt gewirkt.*²⁹² Additional research focusses on the potential of medicamentous impact on parameters such as increase or reduction of the body temperature of the laboratory animal with drugs like caffeine or anti-inflammatory medications such as Phenazon, or Aminophenazon etc.²⁹³

Another relevant aspect within those experiments relates to pharmacokinetic questions such as elimination and resorption but also metabolic and eliminatory processes. Those parameters are investigated by a range of type of applications, such as i.v. or s.c.- route of administration and also under fasting conditions or in the context of a special diet.²⁹⁴

These series of experiments also deal with a comparison of the relative effectiveness of traditional versus more innovative therapeutics, : *“Im Gegensatz zu den vorstehend geschilderten Versuchen in denen nur gelegentlich Drucksteigerungen geringen Ausmaßes gesehen worden waren, bewirkte Cardiazol sowohl bei intravenöser, als auch besonders bei intravertebraler Injektion fast regelmäßig Drucksteigerungen*²⁹⁵ but also serve for a pharmacological induction of experimental condition within the test animal , such as anaesthetising or parasympatholytic effects to improve the understanding for cerebral structures. Here again, Wiechowski’s affinity for development and optimizations of methods can be attested, as he is giving a talk on January 16th and 30th in Vienna within a conference of the morphologic and physiologic society. He presents a procedure which he had been developed in collaboration with his colleague C. Schwarz, about performing tolerable and minimally invasive investigations on a awake, non-anaesthetised animal: *“Methode der Anlegung von Blasen fisteln*”²⁹⁶

The rational basis for Prof. Wiechowski’s experimentation with laboratory animals was furthermore to assess levels of toxicity and critical values of pharmaceutical effects, e.g. with dogs and rabbits. Particularly renal and hepatic parameters represents basic points for the characterization of drug actions, as seen on investigations on cocaine: *“Dass das nicht wiedergefundene Cocain nicht etwa in der Leber zurückgehalten werde, davon überzeugten*

²⁹² WIECHOWSKI WILHELM, Ueber den Einfluss der Analgetica auf die intracranielle Blutcirculation, in: Naunyn-Schmiedeberg's Archives of Pharmacology (1902)

²⁹³ WIECHOWSKI WILHELM, Über experimentelle Beeinflussung des Contractionszustandes der Gefäße des Schädelinnern in: Archiv für experimentelle Pathologie und Pharmakologie (1905)

²⁹⁴ WIECHOWSKI WILHELM, Die Bedeutung des Allantoin's im Harnsäurestoffwechsel Beiträge zur chemischen Physiologie und Pathologie in: Zeitschrift für die gesamte Biochemie Sonder Abdruck aus Band XI , Heft 3 und 4 (1907)

²⁹⁵ STROSS WILHELM / JUNKMANN KARL, Über den Nachweis der toxischen Erregung des Vasomotorenzentrums in: Archiv für experimentelle Pathologie und Pharmakologie 131 (1928) pages 1–17

²⁹⁶ WIECHOWSKI WILHELM, Methode der Anlegung von Blasen fisteln in: Medizinische Klinik Nr. 18 (1911) page 713

wir uns dadurch~ dass bei einem mit der eben tödlichen Gabe vergifteten Hunde unmittelbar nach dem 1/2 Stunde später erfolgten Tode der Cocaingehalt der Leber bestimmt wurde. Dieser fand sich nicht größer als einer gleichmäßigen Verteilung des Giftes im Organismus entsprach. 5800 gr Hund erhielt 0,3744 Coc. pur. in 183 gr Leber warden gefunden: 0,008 Coc. pur.²⁹⁷

Further rationales for applying experimental animals besides the determination of possible health hazards have to be seen in dose- finding endeavours as well as assessing biological activity, e.g. in case of Insulin research. Herein, Wiechowski does not only seek to mitigate intraindividual sources of error due to origin or race of the animals concerned, but also aims at establishing reference samples, declaring himself in favour of using a relative biological activity instead of a absolute one “1/3 der an einem 24 Stunden hungernden 2 Kilo schweren Kaninchen den Blutzucker auf 45 mg % herabsetzenden Menge”²⁹⁸

Clinical observations and experiments on human test subjects were only conducted after comprehensive laboratory experimentations with animal or through chemical methods, both in vitro und in vivo. Wiechowski also investigated human tissue samples e.g. kidney and liver from the Institute of Pathology und Anatomy in Prague, which had been placed at his disposal by the institute directors and all had died from natural causes such as sepsis or malignant diseases.²⁹⁹

Concrete clinical observations from living tests persons were obtained as the medical need for new treatments occurred e.g. in a dysentery and other infectious diseases during the First World War in Prague³⁰⁰ and also in battlegrounds in Serbia³⁰¹. Those practical observations, basing on his broad experimental and theoretical knowledge also involved a systematical comparison between several accessible preparations of medicinal charcoal. This enabled a practical performance test under real- world conditions on the one hand and a more precise distinction in terms of adsorption power and thus therapeutic activity between the individual fabricators on the other one.³⁰²

²⁹⁷ WIECHOWSKI WILHELM, Ueber das Schicksal des Cocains und Atropins im Thierkörper, in : Naunyn-Schmiedeberg's Archives of Pharmacology (1901)

²⁹⁸ WIECHOWSKI WILHELM / LANGECKER H., Das Pankreashormon in: Klinische Wochenschrift (1925)

²⁹⁹ WIECHOWSKI WILHELM, Über die Zersetzlichkeit der Harnsäure im menschlichen Organismus in: Archiv für experimentelle Pathologie 60 (1909) page 185

³⁰⁰ Zeitschrift des Allgemeinen österreichischen Apothekervereines Nr. 46, 14. November 1914

³⁰¹ SPIRO KARL, Erinnerung an Wilhelm Wiechowski in: Die Medizinische Welt – ärztliche Wochenschrift Nr. 6 (1929)

³⁰² Zeitschrift des Allgemeinen österreichischen Apothekervereines Nr. 46, 14. November 1914

More risky and less developed or poorly understood pharmacological mechanisms and side effects of drugs were investigated by him in form of self- experimentations.

In order to assess the effects and metabolism of uric acid within the human body, Wiechowski injects himself several doses of it intravenously and subcutaneously or puts himself on a purine- and alcohol free diet. The level of self- sacrifice can particularly be seen in the restriction he imposed on himself also affecting his private life, but ultimately the danger and physical pain those injections had caused: *“mehrere Tage lang anhaltende Schmerzen und Muskelsteifigkeit an der Injektionsstelle”*³⁰³

Self-experimentation with cannabis are also reported by Prof. Wiechowski himself and refer to questions of efficacy as well as physiological (self-)observations such as cerebral and vegetative effects in comparison with other substance classes such as narcotics. Clinically relevant parameters like influences on blood pressure, heart rate, body temperature but also adjustments in dose frequency were investigated in order to deliver additional data for the preservation of an awake state and reflexes despite of the intake of psychoactive substances.³⁰⁴

There are also reports about less invasive self- experimentations with regards to other medical fields such as balneology, in which he examined the effect of pharmaceutically defined and analysed samples of water and their concrete effect on the pancreas and thereby stand in context of diabetes research. Here again several forms and routes of administration play a role, including both pharmacokinetic and pharmacodynamic aspects into his research.³⁰⁵ Other experiments pertain to the field of dermatology in which both local and systemic effects were examined with regards to their tolerability and safety: *“Wir haben diese Versuche auch auf die Haut und das Blut ausgedehnt und dabei gefunden, daß ihr Gehalt an Aluminiumäquivalenten in der gesunden Haut so groß ist , dass er die vorhandenn Ca- Äquivalente um das 5 fach übersteigt”*³⁰⁶

Prof. Wiechowski's experiments show a strong connection to his previous experimental research aiming to specify or to revise findings and initial hypotheses of in-vitro experiments

³⁰³ WIECHOWSKI WILHELM, Über die Zersetzlichkeit der Harnsäure im menschlichen Organismus in: Archiv für experimentelle Pathologie 60 (1909) page 185

³⁰⁴ WIECHOWSKI WILHELM, Haschisch in: Naunyn-Schmiedeberg's Archives of Pharmacology, Vol. 119; Iss. 5-6 (1927)

³⁰⁵ DIETRICH N.N./ KAMINER N.N, Handbuch der Balneologie medizinischen Klimaiologie und Balneogmphe Herausgegeben im Auftrage der Zentralstelle für Balneologie in: Georg Thieme Leipzig Band 4 (1924)

³⁰⁶ WIECHOWSKI WILHELM, Oelsaures Aluminium in : Medizinische Wochenzeitschrift Nr.34 (1921)

and to gain further knowledge connecting and evaluating both research findings amongst each other.

2.2.2. Further areas of natural scientific research

a) Physiology

Physiological investigations within Wiechowski's research work play an important part as an ancillary science to provide an in-depth understanding of biologic control circuits and causal relationships for further pharmacological experiments. They had been carried out particularly with regards to both physical and (bio)chemical processes within a range of organs in the cardiovascular³⁰⁷ and neurovascular^{308,309,310} field, he also addresses research questions with hormonal³¹¹ and enzymatic effects^{312,313}.

Understanding neurovascular structures in detail, at least initially within animal models, lay the foundation for establishing physiological contexts that could be therapeutically targeted and modified by pharmaceutical interventions: *“Das venöse System des Schädelinneren ist so reich verzweigt und besitzt namentlich nach den Sinus des Wirbelcanals so viele Abflusswege, dass eine an irgend einer Stelle sich ausbildende Stauung rasch ausgeglichen wird und keinen Einfluss auf die arterielle Circulation ausübt. Dafür sprechen wenigstens Versuche von (der) Abklemmung beider Jugularvenen am Halse von Kaninchen.”*³¹⁴

Within his hormonal and metabolic research, Prof. Wiechowski dealt with new options to regulate blood glucose levels e.g. by secondary plant substances that could have insulin-like characteristics. This research about glukokinines also included physiological effects on other organs such as the heart, uterus, the cardiac nerve system, addressing several physiological functions.³¹⁵

³⁰⁷ HALPHEN Hede (mitgeteilt von Wilhelm Wiechowski) Versuche an narkotisierten Froschherzen in: Archiv für experimentelle Pathologie und Pharmakologie 92, XXXIV (1922)

³⁰⁸ WIECHOWSKI WILHELM, Ueber den Einfluss der Analgetica auf die intracranielle Blutcirculation, in :Naunyn-Schmiedeberg's Archives of Pharmacology (1902)

³⁰⁹ WIECHOWSKI WILHELM, Über experimentelle Beeinflussung des Contractionszustandes der Gefäße des Schädelinneren in: Archiv für experimentelle Pathologie und Pharmakologie (1905)

³¹⁰ STROSS WILHELM / JUNKMANN KARL, Über den Nachweis der toxischen Erregung des Vasomotorenzentrums in: Archiv für experimentelle Pathologie und Pharmakologie 131 (1928) pages 1–17

³¹¹ WIECHOWSKI WILHELM / LANGECKER HEDWIG., Das Pankreashormon in : Klinische Wochenschrift (1925)

³¹² WIECHOWSKI WILHELM, Eine Methode zur chemischen und biologischen Untersuchung überlebender Organe in: Beiträge zur Physiologischen Chemie und Pathologie, Zeitschrift für die gesamte Biochemie (1907)

³¹³ WIECHOWSKI WILHELM, Die Produkte der fermentativen Harnsäurezersetzung durch tierische Organe von Wilhelm Wiechowski in: Beiträge zur Physiologischen Chemie und Pathologie, Zeitschrift für die gesamte Biochemie (1907)

³¹⁴ Ibidem

³¹⁵ WIECHOWSKI WILHELM / LANGECKER HEDWIG., Das Pankreashormon in: Klinische Wochenschrift (1925)

Physiological investigations regarding enzymatic functions aimed to link previously identified metabolites within in- vitro experimentations to in vivo correlates from substances identified both in animal and human samples: “*Der Hund scheidet eingeführtes Allantoin quantitativ aus, der Mensch dagegen nicht.*”³¹⁶ Wiechowski also reviews his findings from several methodological approaches, summarizing his findings and identifying needs for further research: “*das Schicksal des Allantoins im Tierkörper noch nicht völlig aufgeklärt; hier werden weitere Versuche anzuknüpfen sein*”³¹⁷

For all intents and purposes, the physiological extent of his research was a crucial part of ensuring to avoid confounding variables for the understanding of pharmacological effects, due to uncertainties or lack of knowledge in physiological structures.

b) Pharmacology

This tandem of physiological and pharmacological investigations can be demonstrated on a publication from his colleagues Junkmann and Stoss in 1925, while he held the chair for the Institute of Pharmacology und Pharmacognosy in Prague, being closely involved in research projects and carrying his methodologic mark.

Herein, connective tissue structures in the female pelvic area, the *ligamentum rotundum uteri* are tested for fundamental research in pharmacology, such as possibilities of neural stimulation in Tyrode solution and state variable such as temperature in the first place. Ensuing pharmacological experiments then compared the effect pharmacological substance classes such as alkaloids to those basic physiological results.³¹⁸

Evaluating substances for potential (later) therapeutic use or a critical assessment of already existing application fields: “*Er wurde früher als Sedativum bei Chorea m Epilepsie und Delirium tremens und als Anaphrodisiakum verwendet (...)*”³¹⁹ he also dealt with pharmacological testing of different types of muscle fibres to assess their effects within a variety of organs such as the heart or gastro-intestinal tract. Basing on a clearly defined pharmacological effect, such as an increase of the nervus vagus, he classified potential

³¹⁶ WIECHOWSKI WILHELM, Die Produkte der fermentativen Harnsäurezersetzung durch tierische Organe von Wilhelm Wiechowski in: Beiträge zur Physiologischen Chemie und Pathologie, Zeitschrift für die gesamte Biochemie (1907)

³¹⁷ Ibidem

³¹⁸ JUNKMANN KARL / STOSS W., Pharmakologische Untersuchungen am überlebenden Ligamentum Rotundum Uteri in: Klinische Wochenschrift (1925)

³¹⁹ WIECHOWSKI WILHELM / STROSS W., Zur Pharmakologie des Kampfers in: Archiv f. experimentelle Pathologie und Pharmakologie 92, XXII (1922)

therapeutic uses, e.g. within auricular fibrillation and restricted a rational use for other indications such as within the therapeutic class of cardiac analeptics.³²⁰

Prof. Wiechowski's effort to experimentally differentiate between verifiable pharmacological effects and rather non evidence based ones can also be shown on cardiac drugs. Those (electro)physiological experimentations regarding therapeutically relevant parameters such as the refractory period of the heart or cardiac output per minute are carried out with cardiovascular active agents like adrenaline, caffeine or camphor.³²¹ Basing on those experiments, Wiechowski also rejects the use of adrenaline to chronic cardiac insufficiency, instead he recommends its use in cases of excessive fall of blood pressure or other health emergencies such as cardiac arrest.³²²

Further considerations at the chair for Pharmacology bringing theoretical and practical pharmacological research and refer to Wiechowski's preliminary work in this field are dealing with pharmacological targets of analgesic drugs, here again evaluating presumed physiological structures of drug action, such as the *Vasomotorenzentrum*, examining the relative effectiveness of a range of compounds.³²³

c) Pharmaceutical Biology

Prof. Wiechowski's biological research, apart from his extensive biochemical studies mentioned before, comprises studies about pharmacologically active plant constituents^{324,325} and their pharmaceutical extraction, as well as research within the pharmacognosy^{326, 327} and the biological classification of plants.³²⁸

Performed investigations about secondary phytochemicals include a wide range of biogenic classes of compounds, such as anthraquinones, tannins and steroids and their glycosides. These phytochemicals, are derived from the wormwood plant (*artemisia absinthium*),

³²⁰ Ibidem

³²¹ WIECHOWSKI WILHELM, Über die experimentellen Grundlagen der Arzneibehandlung der Herzschwäche. Wiener Biologische Gesellschaft. Sitzung vom 15. Oktober 1923

³²² Ibidem

³²³ STROSS WILHELM, Untersuchungen über die Wirkungsweise einiger Analeptika I. Mitteilung: Cardiazol in :Archiv für experimentelle Pathologie und Pharmakologie 114 (1926) pages 177–205

³²⁴ WIECHOWSKI WILHELM, Über herzwirksame Glykoside in: Archiv für experimentelle Pathologie und Pharmakologie 92, XIX–XX (1922)

³²⁵ WIECHOWSKI WILHELM / HALPHEN HEDE, Die Uteruswirkung der Capsella Bursae Pastoris, in: Klinische Wochenschrift Nr. 16 (1922)

³²⁶ WIECHOWSKI WILHELM, Über die Muttersubstanz des Indischgelb in: Archiv für experimentelle Pathologie u. Pharmakologie 97 (1923) pages 462–488

³²⁷ WIECHOWSKI WILHELM, Pharmakognosie des Laubblattes von Magnifera indica (Habilitationsschrift) aus dem Österreichischen Staatsarchiv in; Lotos Band 56 Heft 5 (1908)

³²⁸ WIECHOWSKI WILHELM / STRANSKY EMIL, Ueber das Vorkommen von Chelidonsäure in: Archiv der Pharmazie Vol. 258; Iss. 1 (1920)

common yarrow (*achillea millefolium*), yellow gentian (*gentiana lutea*) and lily of the valley (*convallaria majus*) under standardized conditions ensuring a further chemical and pharmaceutical characterization.

Hereby, focus is put not only on fundamental chemical properties of those isolated compounds, but also biochemical processes such as their transport through biological membranes “*Die so erhaltenen Glykosidlösungen dialysieren leicht durch tierische Membranen*”³²⁹ as well as their pharmacological contexts, in which those compounds could be used, e.g. as cardiac glycosides.

Further research deals with secondary plant metabolism within botanical families of the cruciferous plants (*Brassicaceae*), the sweet grass family (*Poaceae*) and the amanita family (*Amanitaceae*).³³⁰ Wiechowski examines how uterotonic agents are formed within the sclerotium, a fungal parasite on these plants, generating knowledge about the chemical structure of those agents: “*Wir vermuten daher, daß die uterusaktiven Stoffe aller dieser Drogen überhaupt Produkte bakterieller Spaltung an sich wirkungsloser Bestandteile sind, die teilweise schon in der lebenden Pflanze vor sich geht.*”³³¹

Detailed studies about tannine- like substance called *Mangin* derived from the leaves of mango tree represent a detailed chemical analysis of the tannine and his metabolites, enabling a better understanding of their chemical constitution: “*Mit FeCl₃ gibt das Mangin in alkoholischer und wässriger Lösung eine intensiv dunkelgrüne Farbe. Die Prüfung auf mehrwertige Phenole mittels Folinischer Lösung (Phosphorwolframsäure und Na₂CO₃) fiel stark positiv aus.*”³³². This analysis also comprises possibilities of chemical modifications through reactions such as ozonizations, esterifications and acetylations with subsequent analysis of pharmaceutically relevant parameters like solubility, fusion point and optical activity to identify those metabolites more precisely.

Further research focusing on pharmacognosy also dealt with the mango tree, herein with the specific anatomical structures within leaf cross-sections which serve to identify and characterize the specific plant clearly: “*Das Mesophyll besteht unter der etwa 1/3 ausmachenden einreihigen Pallisadenschicht aus einem wenig oder gar nicht von*

³²⁹ WIECHOWSKI WILHELM, Über herzwirksame Glykoside in: Archiv für experimentelle Pathologie und Pharmakologie 92, XIX–XX (1922)

³³⁰ WIECHOWSKI WILHELM / HALPHEN HEDE, Die Uteruswirkung der Capsella Bursae Pastoris, in : Klinische Wochenschrift Nr. 16 (1922)

³³¹ Ibidem

³³² WIECHOWSKI WILHELM, Über die Muttersubstanz des Indischgelb in: Archiv für experimentelle Pathologie u. Pharmakologie 97 (1923) 462–488

Interzellularräumen durchlüfteten Gewebe isodimetrischer rundlicher Zellen, so dass hier statt des so häufig vorkommenden Schwammparenchyms ein kompaktes fest gefügtes Grundgewebe vorliegt (...) Ohne Zweifel ist dieses für Mangoblätter charakteristische Sekret identisch mit dem oben erwähnten (...) gelblichen Auswitterungen und ist die Hauptursache für das Auftreten der tief gelbbraunen Farbe beim Eintragen von Schnittblättchen in Laugen³³³ The basic scientific research character of this publication without direct practical implications for therapeutic uses can be explained by the mere fact that this work represents the habilitation thesis of Prof. Wiechowski within the field of Pharmacognosy and addresses theoretical academic questions.

The systematic analysis and collection of data for clearly defined substances within herbal essences also provided further basic research driven knowledge within the field of plant taxonomy, e.g. based on chemical similarities between the prevalent herbal constituents chelidonic acid and meconic acid. However, those taxonomic investigation, carried out within the plant families *Liliaceae*, *Araceae*, *Amaryllidaceae* were combined with preliminary pharmacokinetic characterization of some compounds with regards to a reasonable pharmaceutical administration³³⁴, also addressing more concrete practical applications.

2.3. Contribution to modern pharmacology

2.3.1. Contribution to preclinical research and clinical links within his basic research

Preclinical drug research and development aims at assessing drugs substance properties in terms of pharmacology, toxicology and carcinogenic effects, pharmacokinetics and thus the therapeutic potential of the investigated drug. In addition it provides information for safe starting doses, based on those preclinical experiments in vitro and usually in rodent and non-rodent mammals. Wiechowski focused both on pharmacodynamic as well as pharmacokinetic research.

With regards to those preclinically investigated substance properties, principles of the LADME model play a crucial role, also for the subsequent initiation of further clinical testing in humans, within Phase I clinical trials.

³³³ WIECHOWSKI WILHELM, Pharmakognosie des Laubblattes von *Magnifera indica* (Habilitationsschrift) aus dem Österreichischen Staatsarchiv in: Lotos Band 56 Heft 5 (1908)

³³⁴ WIECHOWSKI WILHELM / STRANSKY EMIL, Ueber das Vorkommen von Chelidonsäure in: Archiv der Pharmazie Vol. 258; Iss. 1 (1920)

This abbreviation stands for the liberation, adsorption, distribution, metabolism and elimination of pharmaceutical drugs, whereby the first part of this model (LAD) determines the onset of a pharmacological effect and (DM) its offset.

Prof. Wiechowski naturally investigated a range of pharmaceutically relevant parameters concerning drug characteristics, such as chemical reactivity, solubility etc. he did not decidedly carry out research within liberation processes of active drug components from dosage forms as done within dissolution or drug release tests, which is a domain of pharmaceutical research. While he carried out research about adsorptive mechanisms of pharmaceutical compounds on biological membranes³³⁵, he clearly focused his research on distributive and metabolic^{336,337} and eliminative³³⁸ aspects of pharmacological effects, often collectively^{339,340}.

Under Prof. Wiechowski's charge at the Chair of Pharmacology, a range of preclinical studies pertaining in- vivo toxicology in animals were conducted in Prague, e.g. assessing parameters such as lethal doses and relative toxicity: *“Die letale Dosis für 1 g Frosch beträgt vom Bufotalin 0,0000012 g, vom Alkaloid 0,0014 g, das erstere ist also 1167 mal giftiger.”*³⁴¹

Research by one of his students shows exemplarily how dose finding studies were conducted on isolated organs amidst potential clinical application before testing substances in several animals: *“Darüber und auch über das Verhältnis zwischen den für das Warmblüterherz nötigen Konzentrationen und den in meinen Versuchen für die Erzielung einer Leistungssteigerung am Froschherzen nötig gewesenen müssen erst Versuche am intakten Tier und Versuche über die Leistung des Warmblüterherzens Aufschluß geben.”*³⁴²

³³⁵ WIECHOWSKI WILHELM, Über herzwirksame Glykoside in: Archiv für experimentelle Pathologie und Pharmakologie 92, XIX–XX (1922)

³³⁶ WIECHOWSKI WILHELM, Die Produkte der fermentativen Harnsäurezerersetzung durch tierische Organe von Wilhelm Wiechowski in: Beiträge zur Physiologischen Chemie und Pathologie, Zeitschrift für die gesamte Biochemie (1907)

³³⁷ WIECHOWSKI WILHELM, Die Bedeutung des Allantoins im Harnsäurestoffwechsel Beiträge zur chemischen Physiologie und Pathologie in: Zeitschrift für die gesamte Biochemie Sonder Abdruck aus Band XI, Heft 3 und 4 (1907)

³³⁸ WIECHOWSKI WILHELM, Ueber das Schicksal des Cocains und Atropins im Thierkörper, in: Naunyn-Schmiedeberg's Archives of Pharmacology (1901)

³³⁹ WIECHOWSKI WILHELM, Analyse des Harns in: Zum Gebrauch für Mediziner, Chemiker und Pharmazeuten zugleich Elfte Auflage von Neubauer-Huppert's Lehrbuch (1913)

³⁴⁰ WIECHOWSKI WILHELM, Über die Zersetzlichkeit der Harnsäure im menschlichen Organismus in: Archiv für experimentelle Pathologie 60 (1909) page 185

³⁴¹ HANDOVSKY HANS, Ein Alkaloid im Gifte von Bufo vulgaris in: Archiv für experimentelle Pathologie und Pharmakologie 86 (1920) pages 138–158

³⁴² STROSS WILHELM, Untersuchungen über die Wirkungsweise einiger Analeptika I. Mitteilung: Cardiazol in: Archiv für experimentelle Pathologie und Pharmakologie 114 (1926) pages 177–205

Clinical links of this basic research can be observed within experimentations and considerations assessing therapeutical suitability of compounds for therapeutic use as anticoagulants³⁴³, cardiac drugs³⁴⁴, gastrointestinal treatments³⁴⁵, inflammatory processes³⁴⁶, or medicines against a variety of bacterial infections.^{347,348}

Within blood coagulation research, Prof. Wiechowski investigates the therapeutic potential of *Melaninsäuren* in which he presumes the colloidal structure of the component as a reason for the inhibition of blood clotting. In his hypothesis for a potential mode of action of those substances, a chemical precipitation of blood coagulation factors, such as the glycoprotein fibrinogen result in a prolonged blood coagulation time. Besides these efforts to understand mechanisms of drug action, focus is also put on assessing several dose dependent effects on various organs pertaining to cardio- pulmonary measurands such as heart rate, blood pressure or respiratory rate within laboratory animals. With regards to gathering information for later clinical use, the testing of several routes of application (i.v. or intraperitoneal injections etc.) serves as an indication for assessing the preservation of therapeutic effect and medical tolerability, e.g. in terms of acute toxicity.³⁴⁹ Chemical- pharmaceutical analytics is also used to screen out substances of toxicological concern e.g. metallic compounds and substituting them with chemical compounds bearing fewer health risks, while maintaining their therapeutic effects “*Es kann daher angenommen werden, das es eine adstringierende und antiphlogistische Tiefenwirkung auf die Haut wie das Bleioleat ausüben kann.*”³⁵⁰

Laboratory investigations carried out at Wiechowski's chair during his time as Head of the Department, explicitly state his influence especially in terms of methodology, e.g. chemical separation processes via extraction of plant mixtures with alcohol and ether. Thematically, amaroids are examined for their pharmacological profile here, a chemically quite heterogenous group, providing a well defined area of potential clinical application based on experimentally reproducible evidence: “*Jedenfalls sind das abgesehen von der*

³⁴³ WIECHOWSKI WILHELM / ADLER, O., Über Melaninsäuren und deren Wirkung im Tierkörper in: Archiv für experimentelle Pharmakologie und Toxikologie (1922)

³⁴⁴ WIECHOWSKI WILHELM / STOB W., Zur Pharmakologie des Kampfers in: Archiv f. experimentelle Pathologie und Pharmakologie 92, XXII (1922)

³⁴⁵ JUNKMANN KARL , Über die Wirkung der sogenannten «Bitterstoffe» in: Archiv für experimentelle Pathologie und Pharmakologie 143 (1929) pages 368–380

³⁴⁶ DIETRICH N.N./ KAMNER N.N, Handbuch der Balneologie medizinischen Klimaiologie und Balneogmphie Herausgegeben im Auftrage der Zentralstelle für Balneologie in: Georg Thieme Leipzig Band 4 (1924)

³⁴⁷ Zeitschrift des Allgemeinen österreichischen Apothekervereines Nr. 46, 14. November 1914

³⁴⁸ WIECHOWSKI WILHELM / KLAUSNER E., Ueber die lokale Behandlung der Harnröhrengonorrhoe mit Silberglykosiden (Neoreargon) in: Deutsche Medizinische Wochenzeitschrift (1925)

³⁴⁹ WIECHOWSKI WILHELM / ADLER, O. Über Melaninsäuren und deren Wirkung im Tierkörper in: Archiv für experimentelle Pharmakologie und Toxikologie (1922)

³⁵⁰ WIECHOWSKI WILHELM, Oelsaures Aluminium in: Medizinische Wochenzeitschrift Nr.34 (1921)

*geschmacksreflektorischen Steigerung der Magensekretion und der Beseitigung der Hungerkontraktionen die einzigen sichergestellten Wirkungen auf den Darm, welche zu einer Erklärung der therapeutischen Wirkung herangezogen werden können und die Anwendung dieser Stoffe bei spastischen Zuständen und bei einer Übererregbarkeit der Motilität begründen würden.*³⁵¹

Further interrelations of previous experimental laboratory research with impact on concrete clinical key problems of that time can also be demonstrated on his research on medical charcoal, e.g. for the use against dysentery. Jointly with researchers at his Chair, such as Dr. Adler, both theoretical and laboratory driven hypotheses were clinically tested and then again lead to new research questions: *“In der Zwischenzeit hat Prof. Wiechowski das Studium des Kohlenproblems von der rein experimentell wissenschaftlichen Seite aus fortgesetzt. Diese Studien haben dazu geführt, zunächst ein Verfahren zur Beruteilung der verschiedenen Kohlen auszuarbeiten.*³⁵²

The practical significance of his preclinical investigations becomes also evident by looking at combination drugs derived again from plant constituents such as anthraquinones that in combination with silver compounds were tested for their extent of depth penetration into human tissue. Basing on previously identified concentration ratios within each compounds, clinically promising candidates were developed, finally leading to drugs for a quantity manufacturing scale: *“Das Präparat welches sich bei unseren Versuchen in jeder Richtung bewährt hat, enthält rund 15 % Silber und 63 % Anthrachinonglykoside” (...)* *“Das Präparat ist in 5 % Lösung ebenso reizlos wie das bisher verwendete Gemenge von Anthrachinonglykosiden und Silbergelatose, das Reargon“.*³⁵³ Besides tests for finding the therapeutically purposeful dose also aspects such as biological compatibility and safety characteristics were tested, here also, such as done within other bacterial infections on patients, addressing a yet unmet medical need.

Basic research on both the qualitative and quantitative composition of mineral waters was investigated for its potential clinical relevance in terms of inflammatory and exsudative processes: *“Zur Erklärung dient bekanntlich die Hypothese der „Gefäßdichtung“; es erfolge*

³⁵¹ JUNKMANN KARL, Über die Wirkung der sogenannten «Bitterstoffe» in: Archiv für experimentelle Pathologie und Pharmakologie 143 (1929) pages 368–380

³⁵² Zeitschrift des Allgemeinen österreichischen Apothekervereines Nr. 46, 14. November 1914

³⁵³ WIECHOWSKI WILHELM / KLAUSNER E., Ueber die lokale Behandlung der Hamröhrengonorrhoe mit Silberglykosiden (Neoreargon) in: Deutsche Medizinische Wochenschrift (1925)

*nämlich eine Dichtung der Kittsubstanz zwischen den Endothelzellen. Nach Wiechowski sind auch kalziumarme Mineralwässer wirkungsvoll*³⁵⁴.

Wiechowski's in-vitro research e.g. *“Radiumemanation auf Mononatriumurat”* (...) *“Verschwinden der endogenen Blutharnsäure des Gichtikers und durch die Verkleinerung vorhandener Harnsäureablagerungen (..) bestätigt zu werden* ³⁵⁵ often aimed at understanding wider clinical research questions with practical implications for treatment, such as within gout therapy, by also testing hypotheses for their validity in vivo and thereby criticising premature and hasty conclusions of other researchers to therapeutic qualities in humans: *“Unerwarteterweise wurde aus diesen Versuchen geschlossen, daß die Emanation die Fermente des Nucleinstoffwechsels aktiviert habe (...) und der Beweis abgeleitet daß (...) (die) Radiumemanation (...) auch für den menschlichen Organismus seine Gültigkeit hat*³⁵⁶

3. Prof. Emil Starkenstein: Analysis and contextualisation of his professional and personal life

3.1.1. Academic biography

Prof Starkenstein's academic career has been comprehensively described by Šimůnek³⁵⁷, Hais³⁵⁸, Senius³⁵⁹ and Junkmann³⁶⁰ either under the viewpoints of his medical and educated middle class background, his Jewish decent and the persecution of the National Socialists but also with regards to research links to his mentor Wiechowski.

Concordantly all authors, as well as other sources^{361,362}, describe his descent from physicians *“the Starkenstein family had provided district physicians to Ronsperg uninterruptedly for more than 300 years”*³⁶³ and also other Jewish intellectuals *“He was related to the famous*

³⁵⁴ DIETRICH N.N. / KAMINER N.N, Handbuch der Balneologie medizinischen Klimaiologie und Balneogmphe Herausgegeben im Auftrage der Zentralstelle für Balneologie in: Georg Thieme Leipzig Band 4 (1924)

³⁵⁵ WIECHOWSKI WILHELM / VON KNAFFL-LENZ E., Über die Wirkung von Radiumemanation auf Mononatriumurat in: Wiener klinische Wochenschrift Nr. 12 (1912) page 441

³⁵⁶ Ibidem

³⁵⁷ ŠIMŮNEK MICHAL, Disappeared Science Biographical Dictionary of Jewish Scholars from Bohemia and Moravia – Victims of Nazism, 1939–1945 in: Verlag: Pavel Mervart (2014)

³⁵⁸ HAIS IVO M., Biospecific sorption, Prague, 1910: Emil Starkenstein (1884-1942) in: Journal of Chromatography 376:5-9” (1986)

³⁵⁹ SENIUS KARL E.O , Emil Starkenstein 1884- 1942 The life and work of a German pharmacologist in :Naunyn- Schmiedeberg's Archives of Pharmacology (1984)

³⁶⁰ JUNKMANN KARL, Emil Starkenstein in: Naunyn-Schmiedeberg's Archiv für Experimentelle Pathologie Und Pharmakologie, 204(1-3) (1947) pages 13–19

³⁶¹ VAN EMDE BOAS Walter, qualitative interview via Skype on May 13th 2021

³⁶² Archive of the Charles University, collection of registry books of the German University in Prague, inventory No. 3, Registry book of doctors of the German Charles-Ferdinand University in Prague/German University in Prague (1904–1924), page 117

³⁶³ SENIUS KARL E.O , Emil Starkenstein 1884- 1942 The life and work of a German pharmacologist in :Naunyn- Schmiedeberg's Archives of Pharmacology (1984)

*rabbi and Talmudic scholar Eleasar Löw*³⁶⁴ quite likely influenced his decision to also become active in the academic and medical segment. Starting his own studies in 1903/1904 and finalising it with his medical doctorate on May 10th 1909 under the supervision of Prof. Pohl, evidence of this first greater academic milestone can be found at the Archive of Charles University.³⁶⁵

Unlike the other authors, Šimůnek also touches upon Starkenstein's other academic study programmes of "*chemistry and botany at the (...) same university, without (...) finishing these studies*"³¹² and his occupational activities in other medical specialities "*from May 1, 1909 as an assistant physician at the Institute for Dermatology and Pharmacology of the German Faculty of Medicine*".³⁶⁶ Before refining and developing his research interest towards pharmacological research, he also engaged in a variety of biochemical studies, as suggested by Hais, influenced by Wiechowski's biochemical research focus.³⁶⁷ Also Junkmann described Starkenstein's early work in tradition and association with his predecessor's metabolism related research³⁶⁸, from which he subsequently emancipated himself towards a more clinical and pharmacological research, habilitating himself both in pharmacology and pharmacognosy in 1913.^{369,370} This tendency of academic development was also manifested in his joint publication "*Die neueren Arzneimittel und die pharmakologischen Grundlagen ihrer Anwendung in der klinischen Praxis*" with Priv.-Doz. Dr. Skutetzky from 1914, addressing practical questions of pharmacotherapy.³⁷¹

Starkenstein's appointment to an associate Professor for both subjects in 1920 followed a well ordered and concerted transfer from his colleague Wiechowski^{372,373} and implied several

³⁶⁴ SIMUNEK MICHAL, Disappeared Science Biographical Dictionary of Jewish Scholars from Bohemia and Moravia – Victims of Nazism, 1939–1945 in: Verlag: Pavel Mervart (2014)

³⁶⁵ Archive of the Charles University, collection of registry books of the German University in Prague, inventory No. 3, Registry book of doctors of the German Charles-Ferdinand University in Prague/German University in Prague (1904–1924),

³⁶⁶ SIMUNEK MICHAL, Disappeared Science Biographical Dictionary of Jewish Scholars from Bohemia and Moravia – Victims of Nazism, 1939–1945 in: Verlag: Pavel Mervart (2014)

³⁶⁷ HAIS IVO M., Biospecific sorption, Prague, 1910: Emil Starkenstein (1884-1942) in: Journal of Chromatography 376:5-9 (1986)

³⁶⁸ JUNKMANN KARL, Emil Starkenstein in: Naunyn-Schmiedeberg's Archiv für Experimentelle Pathologie Und Pharmakologie, 204(1-3) (1947) pages 13–19

³⁶⁹ SENIUS KARL E.O , Emil Starkenstein 1884- 1942 The life and work of a German pharmacologist in : Naunyn- Schmiedeberg's Archives of Pharmacology (1984)

³⁷⁰ SIMUNEK MICHAL, Disappeared Science Biographical Dictionary of Jewish Scholars from Bohemia and Moravia – Victims of Nazism, 1939–1945 in: Verlag: Pavel Mervart (2014)

³⁷¹ STARKENSTEIN EMIL / SKUTETZKY, A., Die neueren Arzneimittel und die pharmakologischen Grundlagen ihrer Anwendung in der ärztlichen Praxis; zweite Auflage in : Verlag Julius Springer (1914)

³⁷² Starkenstein family archives c.o. Dr. W. van Emde Boas, Netherlands File 013

³⁷³ Ibidem Letter from Anna Wiechowski to Starkenstein 17.07. 1929

intermediate stages, such as Vice Dean and Dean of the Medical Faculty at the then German University in Prague^{374,375}.

3.1.2. Professional influences and direct academic collaborations

Wiechowski's influence on Starkenstein's academic work can be shown on various occasions, either through relevant groundwork and previous research or via direct collaborations.

Basing on Wiechowski's and Wiener's investigations on the enzymatic processes from 1907 "*Über Eigenschaften und Darstellung des harnsäurezerstörenden Ferments der Rindeniere und Hundeleber*"³⁷⁶ and the presented influence of alcohol on enzymatic activity, Starkenstein continued his research in this field, also with considering the results of Eugenio Centanni, Julius Pohl and Ivar Bang in this immunological and microchemical field.³⁷⁷

A further reference to Wiechowski's research can be shown in the field of diaphoretic and diuretic agents, as he points out the differences in possible pharmacological mechanisms referring to his mentor's classification of a water dependent and independent pathway: "*Diuretika die mit dem Wasser oder unabhängig davon in einer mehrminder elektiven Weise bestimmte Stoffe des Organismus durch die Niere zur Ausscheidung bringen können*"³⁷⁸. In his own subsequent research, Starkenstein also focusses on extrarenal factors such as blood and osmotic pressure in tissue water and aims at a further characterisation of mechanisms, e.g. with xathin derivatives like coffeein.³⁷⁹

Starkenstein's publication from 1919 "*Proteinkörpertherapie und Entzündungshemmung*"³⁸⁰ that deals with clinical and experimental experiments to inhibit inflammatory processes, also refers to Wiechowski's preceding research on this topic: "*Entzündungsexperimente in Prag*"³⁸¹ and seeks to discover a pharmacotherapeutic cure. In those experimentations Starkenstein demonstrates that no direct causal treatment for this indication can be achieved

³⁷⁴ SENIUS KARL E.O, Emil Starkenstein 1884- 1942 The life and work of a German pharmacologist in: Naunyn- Schmiedeberg's Archives of Pharmacology (1984)

³⁷⁵ SIMUNEK MICHAL, Disappeared Science Biographical Dictionary of Jewish Scholars from Bohemia and Moravia – Victims of Nazism, 1939–1945 in: Verlag: Pavel Mervart (2014)

³⁷⁶ WIECHOWSKI WILHELM, Über Eigenschaften und Darstellung des harnsäurezerstörenden Fermentes der Rindeniere und Hundeleber in: Beiträge zur chemischen zur chemischen Physiologie und Pathologie (1907)

³⁷⁷ STARKENSTEIN EMIL, Über die Unabhängigkeit der Diastasewirkung von den Lipiden in: Biochemische Zeitschrift- Beiträge zur Physiologie und Pathologie (1911)

³⁷⁸ STARKENSTEIN EMIL, Diuretika und Diaphoretika in: Sonderabdruck der ärztlichen Fortbildung (1928)

³⁷⁹ Ibidem

³⁸⁰ STARKENSTEIN EMIL, Proteinkörpertherapie und Entzündungshemmung (Experimentelle und klinische Untersuchungen) in: Münchner Medizinische Wochenzeitschrift (1919)

³⁸¹ Ibidem

through parenteral administration of proteins “*Milchinjektion*”, and thus refuting the hypothesis of a vaccine- like physiological effect. “*spezifisch wirksame Vakkzine*”³⁸²

His influence on Starkenstein also becomes evident in terms of a joint understanding of pharmacotherapy to systematically evaluate drugs subsequently to prescribe medicines in a rational and evidence based manner.³⁸³

This scientific mindset is reflected in many of Starkenstein’s publications while referring to a detailed understanding basing on their chemical and scientific nature, as shown with Wiechowski’s concept of “*Adsorptionstherapie*”^{384,385,386} or a comprehension of the complexity of natural remedies: “*absolut genommene Menge irgendeines bestimmten Amteiles ankommt, sondern vielmehr (...) in dem relativen Verhältnis zu suchen ist*”³⁸⁷

Academic communications or comments, also of controversial nature, were addressed by Starkenstein objectively, as he defended his research against critique from J. Herzog, who questioned that the combination drug “*Veramon*” represented a addition compound “*Zersetzung und Verminderung der Reinheit der benutzten Arzneistoffe*”³⁸⁸ and labelled it as a mixture or even grease “*Schmiere*” instead. Starkenstein clarified this misunderstanding as he pointed out that the correct chemical synthesis of this combination compound demands a precise maintenance of temperature for a clearly defined time to ensure a medication of high pharmaceutical quality.³⁸⁹ In a lecture, given by Starkenstein and other leading pharmacologists on February 17th 1926 to the German Pharmaceutical Society, the consensus for a interdisciplinary and rational approach to medication use was being addressed unanimously: Prof. Joachimoglu: “*wie wenig heute die Ärzte von Arzneiverordnungslehre verstanden und wie sehr sich die Ärzte durch die Inserate und sonstige Propaganda der chemischen Industrie beeinflussen (lassen)*”³⁹⁰ and Prof. Franz Müller : “*verlangte dass die heutige Pharmakologie in nähere Beziehungen zum praktischen Kliniker und Pharmazeuten*

³⁸² Ibidem

³⁸³ STARKENSTEIN EMIL, Sparsame Arzneiverordnung in: Beiträge zur ärztlichen Verordnung (1928)

³⁸⁴ STARKENSTEIN EMIL, Wandlungen in der Adsorptionstherapie in: Sonderabdruck aus der Pharmazeutischen Presse (1930)

³⁸⁵ STARKENSTEIN EMIL, Über die therapeutische Verwendung der Tierkohle in: Münchner medizinische Wochenzeitschrift Nr 1 (1915)

³⁸⁶ STARKENSTEIN EMIL / LANGECKER HEDWIG, Die Wertbestimmung der Adsorptionskraft von Medizinalkohlen in: Scientia Pharmaceutica (1935)

³⁸⁷ STARKENSTEIN EMIL, Balneologie und Balneotherapie in: Internationaler Ärztlicher Fortbildungskursus (1931)

³⁸⁸ STARKENSTEIN EMIL, Über das Veramon in: Berichte der deutschen Pharmazeutischen Gesellschaft (1922)

³⁸⁹ Ibidem

³⁹⁰ STARKENSTEIN EMIL, Die pharmakologischen Grundlagen der kombinierten Arzneitherapie in: Apothekerzeitung (1926)

gebracht werde.”³⁹¹ In response to iron research and chemical analysis of other pharmaceutical compounds Prof. Starkenstein insists on experimental proof for subsequent discussions, instead of subjective therapeutic experience: “*Die große Verwirrung, die im Laufe der Jahrzehnte in der Eisenfrage platzgegriffen hat, ist vornehmlich darauf zurückzuführen, dass vieles behauptet wurde, was niemals experimentell gefunden, geschweige denn experimentell bestätigt worden ist.*”³⁹²

Direct collaborations with Wiechowski can also be shown at the example of the pharmaceutical compound “*Atophan*”, which had been investigated in terms of various anticipated pharmacological benefits, such as antipyretic and analgesic effects, as well as a influence on the physiological uric acid-, allantoin- and purine metabolism.³⁹³ Those investigations also were reflected in Starkensteins further interest in the examination of further substances classes like non- opioid analgesic such as salicylic acid, acetanilide or pyrazolone derivatives.³⁹⁴

A number of collaborations can also be stated with Hedwig Langecker^{395,396,397}, particularly with regards to applied toxicological research questions and biogenic drugs and their pharmacological usability. In “*Die Wertbestimmung der Adsorptionskraft von Medizinalkohlen*”³⁹⁸ from 1935, both researchers differentiate the effectiveness of therapeutical concepts and measures to treat intoxications and also demonstrate the limits of particular substances to do so: “*Wir haben eine ganze Reihe von Faktoren kennengelernt welche die Forderung nach Kohlen mit maximaler Adsoptionskraft rechtfertigen*” (...) “*Bolus alba, Ferrihydroxid (...) folgen ganz anderen Gesetzen*“.³⁹⁹ This cooperation of transfer from academic research to practical applicability and thus application in clinical practice is also

³⁹¹ Ibidem

³⁹² STARKENSTEIN EMIL, Erwiderung in: Sonderdruck aus Klinische Wochenschrift (1928)

³⁹³ STARKENSTEIN EMIL, Über die Pharmakologie des Atophans in: Prager Medizinische Wochenzeitschrift (1913)

³⁹⁴ STARKENSTEIN EMIL, Fieber und Fiebermittel in: Sonderdruck aus Therapeutische Monatshefte 31 Jahrgang (1917)

³⁹⁵ STARKENSTEIN EMIL / LANGECKER HEDWIG, Die Wertbestimmung der Adsorptionskraft von Medizinalkohlen in: Scientia Pharmaceutica (1935)

³⁹⁶ STARKENSTEIN EMIL / LANGECKER HEDWIG, Über die Pharmakologische Wirkung einiger neuer Papaverinderivate in: Klinische Wochenzeitschrift (1931)

³⁹⁷ STARKENSTEIN EMIL / LANGECKER HEDWIG, Vergiftungen in: Klinische Fortbildung (1935)

³⁹⁸ STARKENSTEIN EMIL, Die Wertbestimmung der Adsorptionskraft von Medizinalkohlen in: Scientia Pharmaceutica (1935)

³⁹⁹ Ibidem

reflected in Starkenstein's and Langenecker's guide to the detection, prevention and adequate treatment of intoxications.⁴⁰⁰

Joint investigations about secondary plant constituents like papaverine, a isoquinoline alkaloid, reveal the relationship between the chemical structure and the spasmolytic effect, but also determine the degree of relative toxicity among several derivatives.⁴⁰¹

3.1.3. Further insights into Starkenstein's personal stances on specific social, philosophical and methodological topics in relation to other researchers

An impression of Starkenstein's notion of other individuals, besides the sole direct scientific-based interaction in the academic publications, is provided by obituaries, given talks during events of commemoration and conferences.

Starkenstein's appreciation of pioneers in various academic disciplines, mentors and colleagues can be sensed through the detailed and individualized orations e.g. in the context the "*Krombholz Feier*" taking place at the Medical Faculty of the "German University" in Prag from January 27th 1933. In his talk on the physician and natural scientist, Starkenstein's affinity with philosophical and literary sources becomes evident, as he quotes Saint Augustin referring to moral values such as freedom "*libertas*" and unity "*unitas*" while critically weighing them against each other and finally upholding the principle of individual responsibility inside and outside of academia:" *überall, ganz besonders im akademischen Leben, Fälle wo Einigkeit das Gebot der Stunde ist und zur unbedingten Notwendigkeit werden muß. Und dann gibt es Fälle, wo Zweifel aufkommen, ob wirklich die Notwendigkeit vorhanden ist, die ein gemeinsames gleichartiges Handeln notwendig macht. Hier mögen besonders Fragen der Welt- und Lebensanschauung entscheidend sein und in einem solchen Falle muß die Freiheit des Handelns dem einzelnen gewahrt bleiben.*"⁴⁰²

With regards to the commemorative speech for Julius Krombholz, Starkenstein particularly acknowledges the altruistic efforts for his students, in terms of the establishment of caritative foundations "*Krombholz- Stiftung*"⁴⁰³ and providing means of education and practical support e.g. "*Reisestipendium*"⁴⁰⁴ in daily life.

⁴⁰⁰ STARKENSTEIN EMIL / LANGECKER HEDWIG, Vergiftungen in : Klinische Fortbildung (1935)

⁴⁰¹ STARKENSTEIN EMIL / LANGECKER HEDWIG, Über die Pharmakologische Wirkung einiger neuer Papaverinderivate in : Klinische Wochenzeitschrift (1931)

⁴⁰² STARKENSTEIN EMIL, Krombholz- Feier : Gedenkrede für Julius Vinzenz Krombholz, Medizinische Fakultät der Deutschen Universität in Prag und Verein deutscher Ärzte in Prag in: Medizinische Klinik (1933)

⁴⁰³ Ibidem

⁴⁰⁴ Ibidem

Analysing Purkinje's achievements in terms of physiology, Starkenstein describes two main qualities, which both researchers have in common and share professionally and personally: The first characteristic pertains to their experimental approach as shown on laboratory-, animal-, self- experimentation etc. and their ongoing effort to emancipate their main fields of research, physiology or pharmacology respectively, from other medical sciences. In Starkenstein's case this meant a conceptual delimitation of this controlled experimentation based, Modern Pharmacology from the *Materia Medica* or other pharmacopeia-like collections of documents. The second characteristic relates to their common affinities to literature and their linguistic abilities: *“Die Sprache in der Purkyne bei der Wiedergabe seiner Selbstversuche und bei der Schilderung des Erlebens einer Camphervergiftung zu uns spricht , ist nicht jener trockene Ton, den wir von so vielen wissenschaftlichen Arbeiten her kennen , sondern eine Sprache , in der nur ein Freund Goethes auch als wissenschaftlicher Schriftsteller zu uns sprechen kann.“*⁴⁰⁵

Insights about Starkenstein's perception of his mentor and predecessor Wiechowski with respect to philosophical questions about one's life work and existence can be referenced from his speech on the occasion of Wiechowski's death, given on January 18th 1929. Here Starkenstein describes the complexity of his predecessor's attitude and thinking towards topics that are inaccessible towards a “objective” natural scientific thinking and yet still played a part in Wiechowki's life:

“Wiechowskis Leben was das Leben eines Naturforschers von klassischer Reinheit und trotzdem war er nicht ganz frei von metaphysischer Einstellung“ (...) „ganz sonderbare Anschauungen über Seele und Seelenleben“ (...) " *gehe nichts verloren und darum können seiner Vorstellung nach auch geistige geleistete Arbeiten nicht untergehen*⁴⁰⁶

Given the fact that Starkenstein, also according to his own recollections⁴⁰⁷, had been knowing Wiechowski for 23 years, beginning in 1905 it is reasonable to say, that this assessment is based on far- reaching personal communication and knowledge about his colleague, especially as it is made at the end of the shared academic and personal collaboration.

⁴⁰⁵ STARKENSTEIN EMIL, Die Pharmakologischen Selbstversuche Purkinjes und Ihre Beurteilung nach dem heutigen Stande der Wissenschaft Nr 198 Box 3, no year detectable on publication

⁴⁰⁶ STARKENSTEIN EMIL, Wilhelm Wiechowski, Worte des Gedenkens, gesprochen im Verein deutscher Ärzte in Prag am 18. Januar 1929 in: Sonderdruck aus Beiträge zur ärztlichen Fortbildung Nr 2. (1929)

⁴⁰⁷ Ibidem

3.1.4. Involvement in higher education and health policy with regards to inter-professional cooperation

In addition to Starkenstein's interpersonal academic relations and indirect links with other researchers, further touchpoints can be stated through involvement and interest in higher education and health policy, which particularly involved questions of pedagogy, didactics as well as interdisciplinary cooperation with other health professionals.

The fact that university and higher education policies can be interlinked with health care policy is shown by Starkenstein in his publication about the medical profession from 1933. Herein he deals with the increase in medical specialisation and the shift in work load due to the establishment of social health insurance for the general public and a resulting strain on individual and quality patient care.⁴⁰⁸ In dealing with this process, he juxtaposes both technically and analytically enhanced tools in medical care with physician's personal capabilities and skills "*Instinkt*" and "*Intuition*" for patient's adequate treatment and diagnosis: "*Wir sehen somit, dass Intuition nicht mit Instinkt verwechselt werden darf, bei dem alles ohne direkte Erfahrung, von innen heraus vererbt, zum Ausdruck kommt, während Intuition nur die Auswirkung gesammelter Erfahrungen ist, die aber ins Unterbewusstsein zurückgedrängt und im rechten Augenblick schnell herangezogen auch schnell und richtig verwertet werden.*"⁴⁰⁹

It becomes evident in the overall view, that Starkenstein deems the focused, goal orientated and analytical action as important as the quick and spontaneous "intuitive" action within medical practice, depending on context and situation, to meet the demands within medical practice.

Further reflexions with health policy focus deal with interprofessional collaboration with other healthcare professionals such as pharmacists, inter alia to ensure patient safety.⁴¹⁰ As an example of Starkenstein's comprehension of this cooperation he reports about erroneous medical prescriptions due to either nomenclature or unclear dimension specifications regarding dosage, which lead to a fatal intoxication and subsequent death of the patient. Though he assumes the major responsibility to be with the prescribing physician, he also

⁴⁰⁸ STARKENSTEIN EMIL, Instinkt und Intuition in der Forschung, im Studium und im ärztlichen Berufe in: Einheitsbestrebungen in der Medizin (1933)

⁴⁰⁹ Ibidem

⁴¹⁰ STARKENSTEIN EMIL, Adrenalin -Vergiftung, tödliche, als Folge fehlerhafter Arzneiverordnung in: Sammlung von Vergiftungsfällen (1934)

states a partial negligence on the part of the pharmacists, which would have to correct this error contentually and would have to discuss this with the physician and make contact with him regarding this matter. This understanding of reciprocal control and constructive collaboration, does not only suggest a progressive attitude and appreciation within the healthcare workforce, but also practically implements his academic research on rational pharmacotherapy.

Further references in support of pharmacist's professional consolidation as a health care professional can be seen in Starkenstein's comment with regards to their professional accountabilities in terms of both patient's and drug safety.⁴¹¹ With respect to medications per se, the pharmacist has to ensure pharmaceutical quality of each preparation and to prevent a counterfeiting of medicines by all possible means. Patient's safety is then ensured through a exclusive access to drugs via pharmacies accompanied with expert advice to meet patient's questions e.g. on combination drugs, indications and their rational use:

*“Dem Apotheker muß daher auch die ausschließliche Abgabe der Stoffe vorbehalten bleiben, für deren Anwendung nach wie vor die Regeln der Medizin , für die Zubereitung die der Pharmazie in Geltung sind.“*⁴¹²

Here again Starkenstein requests mutual responsibility for a constructive collaboration, as he desires physicians to be more knowledgeable on all aspects of medications, starting on a fundamental chemical level *“Kentniss der chemischen Zusammensetzung”*⁴¹³ to practical clinical considerations which affect pharmacotherapy: *“Applikationsmöglichkeit, Schnelligkeit des Wirkungseintritts. toxische Nebenwirkungen, Preis, etc.”*⁴¹⁴

Efforts to make an impact on higher education policy can be seen on his contributions to curricula and reforms of professional and study regulations both for physicians¹⁴¹ and for pharmacists.^{415,416} In a publication from Mai 6th 1933, Starkenstein deals with the definition of medical specialisations, conditions that apply for obtaining them and the meaningfulness of their clear distinction to additional designations for professional use such as practitioners

⁴¹¹ STARKENSTEIN EMIL, Diätetika in: Sudetendeutsche Apothekerzeitung (1936)

⁴¹² Ibidem

⁴¹³ STARKENSTEIN EMIL, Über Anwendung und Auswahl der Schlafmittel in: Beiträge zur ärztlichen Fortbildung (1921)

⁴¹⁴ Ibidem

⁴¹⁵ STARKENSTEIN EMIL, Zur Reform des pharmazeutischen Studiums - Ideal und Wirklichkeit - Erweiterte Begrüßungsansprache des Vertreters der medizinischen Fakultät Prof. Emil Starkenstein bei der Hauptversammlung deutscher angestellter Apotheker in Prag, Nr. 190 Box 3, Archive Charles University Prague, no year detectable on publication

⁴¹⁶ STARKENSTEIN EMIL, Gegenwart, Zukunft und Vergangenheit der Pharmazie in: Apothekerzeitung (1934)

within the field of balneology “*Badeärzte*”⁴¹⁷, that do not meet these criteria. As a means of standardisation and objectivization within professional development and further learning in the medical field, Starkenstein addresses a government decree dealing with those regulations and recommends that medical specialisations should only be officially recognized if they are based on sound scientific fundamentals.

This systematic classification can be grounded on organ function such as cardiology, dermatology, neurology etc. or on more generalised subjects like laboratory physicians or radiologists. In contrast, a physician that deals with therapies in fields such as balneology, could not be called a specialist within this definition, as there is no scientific sound evidence to support this remedial method, nor does it imply a specific set of organs or physiological role within the human body. Starkenstein therefore classifies this teaching rather as a part within general medicine or as a subject of further research within the academic field, e.g. in pharmacology to further understand this principle of healing:

*“Lehre von den für therapeutischen Zwecke verwendeten Quellwässern , Mooren , Schlämmen und ähnlichen natürlichen Heilprodukten“*⁴¹⁸

With regards to the development of pharmaceutical studies and professional development, Starkenstein emphasizes the shared interest of optimized patient care and the need from both professions to engage in this constructively: *“Das dritte Interessensgebiet schließlich ist jenes , auf welchem sich Pharmazie und Medizin begegnen und von dem aus dem letzten Endziel beider Disziplinen zugestrebt wird: die Heilung der Kranken.“*⁴¹⁹ Thereby it becomes apparent that he conceptualizes this form of cooperation to be based on principles of equivalence and true partnership instead of rigid hierarchies between the two professions: *“Schwester sei , nicht Dienerin , die Pharmazie der Medizin“*⁴²⁰ In order to prepare pharmacists adequately for this role he and his colleagues successfully apply contentual and practical modifications to the pharmaceutical curriculum in 1936/1937 summer and winter semester at the German University in Prague before the German occupation. Those modifications primarily represent intensifications and expansions of clinical- analytical competencies to strengthen pharmacist’s public perception as a health care professional and

⁴¹⁷ STARKENSTEIN EMIL, Das Studium der Balneologie und Klimatologie der Facharztitel für Klimatologie und die Vorraussetzung für seine Erwerbung in Beiträge zur ärztlichen Fortbildung Nr. 9, 1933

⁴¹⁸ Ibidem

⁴¹⁹ STARKENSTEIN EMIL, Zur Reform des pharmazeutischen Studiums - Ideal und Wirklichkeit - Erweiterte Begrüßungsansprache des Vertreters der medizinischen Fakultät Prof. Emil Starkenstein bei der Hauptversammlung deutscher angestellter Apotheker in Prag, Nr. 190 Box 3, Archive Charles University Prague, no year detectable on publication

⁴²⁰ Ibidem

clear distinction from sheer commercial professions: “*Einfach klinische Laboratoriumsmethoden (...) Untersuchungen von Blut, Harn, Stuhl, Magensaft, Sputum und Liquor*” or „*Allgemeine und Spezielle Toxikologie*“ and „*Pharmakologie und Pharmakognosie für Pharmazeuten*“⁴²¹

Further recommendations regarding a expedient development of pharmaceutical studies towards a diversified academic health care profession are given by Starkenstein also in terms of extension of studies as well as linking theoretical subjects to their practical applicability. This meant that the traditionally taught subjects at pharmacy school such as biology, chemistry etc. should also be clinical and patient- related questions which occur in pharmaceutical practice through patient- interaction, e.g. in a pharmacy.⁴²² This appeal for a expansion of education and involvement of pharmacists into therapeutic safety and patient care can also be shown on Starkenstein’s reports about errors and misscommunications in prescription and pharmacist’s shared responsibility and interest to prevent them for patient’s safety.⁴²³

Starkenstein’s understanding and involvement did also imply socio- cultural aspects in the context of higher education policy, as shown in his considerations regarding the situation at the German University in comparison to other Universities in the “German Reich”. Here, he demands the unaltered maintenance of bilingual communication in both Czech and German in everyday academic life as well as in affiliated hospitals.

In general he advocated for a peaceful and fair mode of social interaction, while criticising nationalistic movements “*nationale Quertreibereien*” which might interfere with this coexistence.⁴²⁴ In addition to his demand to uphold national identities and diversities on both sides he also clearly declares himself in favour of the retention of autonomy within matters of research, teaching and clinical practice.⁴²⁵

Prof. Starkenstein’s interest and affinity to pedagogy and education also apart from his own lectureship and teaching activities can be demonstrated on his involvement on learning objectives and methods of learning, not only at universities, but also in middle schools. His perception of education also seeks to foster an environment that individually supports students

⁴²¹ Ibidem

⁴²² STARKENSTEIN EMIL, Gegenwart, Zukunft und Vergangenheit der Pharmazie in: Apothekerzeitung (1934)

⁴²³ STARKENSTEIN EMIL, Thallium Vergiftung , akute , als Folge fehlerhafter Arzneiverordnung und Arzneigabe in: Sammlung von Vergiftungsfällen (1934)

⁴²⁴ STARKENSTEIN EMIL, Von Deutschen Hohen Schulen in: Deutsche Medizinische Wochenschrift (1931)

⁴²⁵ Ibidem

basing on their capabilities and offers a high orientation on personal development, rather than on interests and reforms which aim at a standardisation and simplification of education.

In those considerations he makes the case for a comprehensive humanistic education, based on a variety of languages, such as Latin, ancient Greek, French etc., equipping the student's with the capability of autonomous learning, rather than with a predefined skill for a special purpose:

“Es soll nur erwähnt werden, wie sehr der Lateinunterricht die Grundlage für das leichte Erlernen einer ganzen Reihe von Sprachen darstellt und wie sehr es die Kenntnis der lateinischen Sprache jedem Wissenschaftler erleichtert, sich in der Fachliteratur der verschiedenen Sprachräume zurecht zu finden.”⁴²⁶

Besides his demand for a broad education, he also accentuates the need for physical activities in curricula for middle schools and the greater consideration of age-appropriate, developmental and psychological needs for students and the integration of those factors into educational practice at schools: *“Nichts scheint mir subjektiver als die Beurteilung der Unruhe und Störung im Unterricht und nichts nimmt auf die Physiologie des wachsenden Kindes weniger Rücksicht als die Beurteilung und Bestrafung dieser kindlichen Eigenschaft.”⁴²⁷*

Following the example of other well-read researchers, Starkenstein recommends a concrete choice of compendia for physicians in the style of a study library, covering at least six domains of specialist literature, in order to meet all professional needs for up-to-date-information.

*„Spezialliteratur des Fachgebietes“, „Fortschritt der Forschung“, „Zusammenfassende Monographien und Handbücher“, „größere Lehrbücher“, „Hilfskompendien“, „fachliche Zentralblätter“, „Wochenzeitschriften“.*⁴²⁸

3.1.5. Relation to the pharmaceutical sector as seen in collaborations and criticism

Previous research by Jezdinsky and Senius has given an overview about Starkenstein's life and work, provided in form of summary information, also about collaborations with the

⁴²⁶ STARKENSTEIN EMIL, Hochschulwissen und Mittelschulwissen - Allgemeine Betrachtungen über Lehrplan, Lehrziel und Lehrmethodik in: Zeitschrift Hochschulwissen (1930)

⁴²⁷ Ibidem

⁴²⁸ STARKENSTEIN EMIL, Der Arzt und sein Buch in: Schriften des Philobiblon Rudolph M. Rohrer Verlag /Brünn Sonderdruck aus PhiloBiblon X,7,1, Charles Archive no year or number detectable on publication

pharmaceutical industry, particularly in Jezdinsky's publication from 2006. The authors describe the time frames from 1919 to 1934 and 1939 to 1941 basing on a selection of original publications and previous biographers and chronologically list Starkenstein's collaboration with two Pharmaceutical companies: *Schering- Kahlbaum A.G. Berlin*⁴²⁹ and the *Amsterdamsche Chininefabriek*⁴³⁰. While particularly three medications *Veramon*, *Vasano*, and *Ferrostabil*, resulted from this direct industry collaboration, as shown by Jezdinsky⁴³¹, there is little information in Senius' publication about the actual content and relevance about the publications in the dutch exile, just as further publications must be reflected upon to understand Starkenstein's relation to the pharmaceutical sector more comprehensively.

Though particularly those three drugs are mentioned by Jezdinsky, it is likely that Starkenstein's basic research had a wider impact on drugs that reached market maturity and clinical use. As seen through advertisements by Schering- Kahlbaum A.G. Berlin in *Medizinische Mitteilungen* from 1933 for *Atophanyl* a combination drug of Atophan and salicylic acid or a analgesic ointment containing Atophan against musculoskeletal problems.⁴³²

The business concepts of both pharmaceutical companies seem to have been varying inasmuch ACF, the Amsterdamsche Chininefabriek, has put his focus on pharmaceutical trade and the production of pharmaceutical products, rather than primarily on research and development.^{433,434} Schering- Kahlbaum A.G. Berlin instead represented a pharmaceutical company that concentrated on therapeutic innovations, which can also be backed up by the fact that ACF today is a part of the *Phoenix Group*⁴³⁵, a leading pharmaceutical wholesaler, whereas the former German company Schering- Kahlbaum A.G. shows links to today's research-based pharmaceutical companies *Bayer Healthcare and Berlin-Chemie Menarini*.

⁴²⁹ JEZDINSKY JAROSLAV, Emil Starkenstein- one of the most important personalities of European continental pharmacology in the period between the two world wars in: *Neuroendocrinology Letters*, Volume 27, No 5. (2006)

⁴³⁰ SENIUS KARL E.O , Emil Starkenstein 1884- 1942 The life and work of a German pharmacologist in: *Naunyn- Schmiedeberg's Archives of Pharmacology* (1984)

⁴³¹ JEZDINSKY JAROSLAV, Emil Starkenstein- one of the most important personalities of European continental pharmacology in the period between the two world wars in: *Neuroendocrinology Letters*, Volume 27, No 5 (2006)

⁴³² STARKENSTEIN EMIL, Probleme und Untersuchungsergebnisse auf dem Gebiete der Pharmakologie des Eisens in: *Medizinische Mitteilungen* (1933)

⁴³³ VAN DER HOOGTE ARJO, Science in the service of colonial agro-industrialism: The case of cinchona cultivation in the Dutch and British East Indies, 1852–1900 in. *Studies in History and Philosophy of Biological and Biomedical Sciences* (2014)

⁴³⁴ JONG DE H. W, Remedie of pijnstillers? De werking van combinatiebewegingen in de farmaceutische industrie in: *GEWINA / TGGNWT*, volume 22, issue 1 (2012)

⁴³⁵ Ibidem

This distinction is relevant to Starkenstein's relationship with the pharmaceutical industry insofar as the far longer collaboration occurred with Schering-Kahlbaum and was characterized by then innovative therapeutic approaches, instead of focusing on the synthesis of already known compounds or simple modifications of known chemical structures.

It may be well assumed that the end of this constructive cooperation, in 1934, was rather due to the political climate and circumstances, rather than on professional discordances, which is also suggested by Jedzinsky.⁴³⁶

Although the ACF focused on the production of specific known pharmaceuticals such as "*the semi-finished product quinine sulphate*"⁴³⁷, Starkenstein adapted his basic research to the new conditions that he faced in the Dutch exile, while naturally addressing the secondary plant substance quinine and its potential for various indications, that resulted in a international transfer of knowledge e.g. to Spain, France, Italy or English-speaking countries, basing on translations of his research output.^{438,439,440,441,442.}

In at least five publications^{443,444,445,446,447} Prof. Starkenstein pursued pharmacological basic research on this topic, focusing on questions whether direct plant extracts with their naturally occurring mixtures of substances or a direct synthesis of chemically isolated compounds

⁴³⁶ JEZDINSKY JAROSLAV, Emil Starkenstein- one of the most important personalities of European continental pharmacology in the period between the two world wars in: *Neuroendocrinology Letters*, Volume 27, No 5 (2006)

⁴³⁷ VAN DER HOOGTE ARJO, Science in the service of colonial agro-industrialism: The case of cinchona cultivation in the Dutch and British East Indies, 1852–1900 in: *Studies in History and Philosophy of Biological and Biomedical Sciences* (2014)

⁴³⁸ STARKENSTEIN EMIL, Ein Beitrag zur Erklärung der "erregenden" Wirkungen des Chinins als Folge einer Enthemmung in: *Archives internationales de pharmacodynamie et de thérapie* (1939)

⁴³⁹ STARKENSTEIN EMIL, The stimulating action of Quinine explained as a result of abolished inhibition in: *Archives Internationales de Pharmacodynamie et de Thérapie* Tomo. LXII, fasc. II Gand Parigi (1939)

⁴⁴⁰ STARKENSTEIN EMIL, L'action excitante de la quinine expliquée par la neutralisation d'une inhibition Préexistante (1939)

⁴⁴¹ STARKENSTEIN EMIL, L'azione „Eccitante“ della Chinina spiegata con la neutralizzazione di una inibizione preesistente in: *Archives Internationales de Pharmacodynamie et de Thérapie* Vol. LXII, fascicolo II Gand Parigi (1939)

⁴⁴² STARKENSTEIN EMIL, La Accion „Estimulante“ de la quinina puesta en claro como supresion de una inhibicion preexistente in: *Archives Internationales de Pharmacodynamie et de Thérapie* Tomo. LXII, fasc. II Gand Parigi (1939)

⁴⁴³ STARKENSTEIN EMIL, Pharmakologische Analyse der Chinaalkaloide II Mitteilung : Die Wirkung der Chinaalkaloide auf das Hirudopräparat in: *Archives Internationales de Pharmacodynamie et de Therapie* (1941)

⁴⁴⁴ STARKENSTEIN EMIL, Ein Beitrag zur Erklärung der "erregenden" Wirkungen des Chinins als Folge einer Enthemmung in: *Archives internationales de pharmacodynamie et de thérapie* (1939)

⁴⁴⁵ STARKENSTEIN EMIL, Pharmakologische Analyse der Chinaalkaloide I: Mitteilung Das Chinaproblem in: *Archives Internationales de Pharmacodynamie et de Therapie* (1941)

⁴⁴⁶ STARKENSTEIN EMIL, Pharmakologische Analyse der Chinaalkaloide III Mitteilung: Die Wirkung der Chinaalkaloide auf den Darm in: *Archives Internationales de Pharmacodynamie et de Therapie* (1941)

⁴⁴⁷ STARKENSTEIN EMIL, Pharmakologische Analyse der Chinaalkaloide IV Mitteilung: Die Wirkung der Chinaalkaloide auf das Ösophagus- Magenpräparat des Frosches in: *Archives Internationales de Pharmacodynamie et de Therapie* (1942)

possessed more therapeutic potential. This questions on molecular and drug profiling were also combined with research on dosage, standardisation of extracts and structure – activity relationships: “*Verständnis dafür vermitteln, dass z.b. Chinin auf bestimmte Organe stärker wirkt als das isomere rechtsdrehende Chinindin...*”⁴⁴⁸ Additional to his laboratory research, Starkenstein gathered in his accustomed manner knowledge and evidence also by comprehensive literature reviews, differentiating individual effects of the main and secondary alkaloids of some species of the plant genus *Cinchona*, also considering animal experimentation^{449,450} and pharmaceutical formulation. Within these publications he links pre-clinical to clinical research and describes pharmacological mechanisms of quinine in a manner which is still valid today: “*Verlängerung der Refraktärperiode der Muskelfibrillen und eine Verminderung ihrer Erregbarkeit sowie der der motorischen Endplatte*”⁴⁵¹.

In this respect he continued his scientific research in this industrial setting, instead of turning towards other occupational activities that would have also been open for him, being a physician. His final research publications also represent a kind of back reference to his previous work and colleagues, but also prove his profound interest in a in depth-understanding of pharmacological mechanisms combined with clinical and therapeutical applicability in a industrial context.

While both authors concentrate on the productive scientific output of this industry collaboration, little consideration has been given to Starkenstein`s personal thoughts and attitude towards the pharmaceutical sector with regards to other aspects.

Commercial pressure and lobbying interests of this industry, appearing as layman- advertising and the aspiration to turn pharmacies into drug stores which do not primarily concentrate on specialist advice but on sales and profit maximisation are viewed critically by Starkenstein: „*Das durch Krise und andere Ursachen verminderte Absatzgebiet für Arzneimittel suchen die Arzneimittelerzeuger dadurch zu vergrößern , daß sie für den Arzneimittelabsatz auch dort sorgen , wo er weder nötig , noch gerechtfertigt ist; und dies erreichen sie dadurch, das sie*

⁴⁴⁸ STARKENSTEIN EMIL, Pharmakologische Analyse der Chinaalkaloide I: Mitteilung Das Chinaproblem in: Archives Internationales de Pharmacodynamie et de Therapie (1941)

⁴⁴⁹ STARKENSTEIN EMIL, Pharmakologische Analyse der Chinaalkaloide II Mitteilung : Die Wirkung der Chinaalkaloide auf das Hirudopräparat in: Archives Internationales de Pharmacodynamie et de Therapie (1941)

⁴⁵⁰ STARKENSTEIN EMIL, Pharmakologische Analyse der Chinaalkaloide IV Mitteilung :Die Wirkung der Chinaalkaloide auf das Ösophagus- Magenpräparat des Frosches in: Archives Internationales de Pharmacodynamie et de Therapie (1942)

⁴⁵¹ STARKENSTEIN EMIL, Pharmakologische Analyse der Chinaalkaloide III Mitteilung :Die Wirkung der Chinaalkaloide auf den Darm in: Archives Internationales de Pharmacodynamie et de Therapie (1941)

sich mit Umgehung von Arzt und meistens auch von Apotheker - direkt ans Publikum wenden.“⁴⁵²

Further points of criticism concern the abundance of pharmaceutical compounds and combinations that are not aimed at a therapeutical optimisation with regards to chemical incompatibilities, side effects but only feature molecular modifications or changes in composition with no proven clinical effect.^{453,454}

In this respect Starckenstein also deals objectively with antiemetic drugs of other pharmaceutical companies and evaluates them basing on pharmacological and therapeutical aspects, in accordance with other researchers, as done on “*Nautisan*” by “*Chemosan A.G. Wien*”, which turned out to be insufficient in terms of efficacy or “*Chloretan*”, a narcotic that should generally not be used in this indication.⁴⁵⁵ The great extent of appreciation in principle of the pharmaceutical sector, consisting of pharmacists and the pharmaceutical industry can be substantiated through Starckenstein’s remarks from a talk appreciating pharmacists as specialists regarding medications “*qualifizierter Fachmann*”⁴⁵⁶ and services of the pharmaceutical industry “*Fabriksspezialität, die höchste Erfüllung der Apothekerkunst*”⁴⁵⁷.

3.1.6. Personal attitudes, affinities and interests beyond sheer natural science and medical research

Starckenstein’s intellectual curiosity did not only involve his primary area of research but did in fact expand to other thematic areas , such as Jewish cultural history^{458,459,460,461} and

⁴⁵² STARKENSTEIN EMIL, Gegenwart, Zukunft und Vergangenheit der Pharmazie in: Apothekerzeitung (1934)

⁴⁵³ STARKENSTEIN EMIL, Pharmakologische Grundlagen für die Einführung kombinierter Arzneien in: Fortschritte der Therapie (1928)

⁴⁵⁴ STARKENSTEIN EMIL, Die Aufgaben der Pharmakopoe für den Arzt und die Arzneiverordnung für den Apotheker und die Arzneibereitung und für die Arzneimittel- Industrie in: Beiträge zur ärztlichen Fortbildung (1930)

⁴⁵⁵ STARKENSTEIN EMIL, Physiologische und pharmakologische Prüfung von Nauseamitteln in: Medizinische Klinik (1927)

⁴⁵⁶ STARKENSTEIN EMIL, Die pharmakologischen Grundlagen der kombinierten Arzneitherapie in :Apothekerzeitung (1926)

⁴⁵⁷ Ibidem

⁴⁵⁸ STARKENSTEIN EMIL, Kräuterbücher Eine Quelle für Medizin-, Natur-, Kunst-, und Kulturgeschichte (1928)

⁴⁵⁹ STARKENSTEIN EMIL, Juden- Namen in: Der B’Nai B’Irth Monatsblätter der Grossloge für den Cechoslovakischen Staat (1925)

⁴⁶⁰ STARKENSTEIN EMIL, Die Juden in der Medizin des Mittelalters in: Selbstwehr zum 1. Weltkongress jüdischer Ärzte in Tel- Aviv Nr. 175a Archiv Box 3, Archive (Starckenstein Nr 152- 215) no year detectable on publication

⁴⁶¹ STARKENSTEIN EMIL, Musa ben Maimun, der Arzt des Mittelalters Nr. 175 Archiv Box 3, Archive, no year detectable on publication

onomastics , both medical and pharmaceutical history^{462,463,464} , and also displayed a huge interest in literary topics⁴⁶⁵ and linguistic talent^{466,467} . In addition, several publications provide further insights into his own professional development^{468,469} and attitude towards humanities research⁴⁷⁰ , family background and his knowledge about his ancestors^{471,472,473} .

Basing on the store of knowledge from ancient herbal books and other written sources , Prof. Starkenstein acknowledged both the value in term of culture and art history and thereby also their potential to generate or re-active knowledge for future use. By the example of the written heritage of the Italian physician and natural scientist Matthiolus from the 16th century, Starkenstein deals with his artistic graphical representation of pharmaceutical techniques for drug production, as seen on distillation devices.⁴⁷⁴ Looking at a digitalised German version from 1563 of the Italian original, one can also notice the alphabetical and indication based order in which Matthiolus aimed at summarising therapies “*Wider die gebrechen des gesamten Hauptes*”⁴⁷⁵ or other physiological and anatomical considerations, as well as concrete pharmaceutical formulations for specific indications: “*Cardamomöle mit Anis und Wein.*”⁴⁷⁶ for “*Appetit oder begird zum essen zu bringen*”⁴⁷⁷ In this style of these previous systematization efforts and approach to provide accessibility for wider audiences, one can understand Starkenstein’s affinity for Matthiolus’ work with regards for his interest in learning from the past.

⁴⁶² STARKENSTEIN EMIL, Das Kräuterbuch des Matthiolus in: II. Alte Bücher Charles Archive, neither Number Nor year detectable on publication

⁴⁶³ STARKENSTEIN EMIL, Les vieux herbiers francais in: Le feuillets Medicaux no 1 (1932)

⁴⁶⁴ STARKENSTEIN EMIL, Nachtschatten in: Folia Medici Heft Nr. 4 (1937)

⁴⁶⁵ STARKENSTEIN EMIL, Der Arzt und sein Buch in: Schriften des Philobiblon Rudolph M. Rohrer Verlag /Brünn Sonderdruck aus PhiloBiblon X, 7, 1, Charles Archive, no year or number detectable on publication

⁴⁶⁶ STARKENSTEIN EMIL, Julius Pohl zum 70. Geburtstage, in: Klinische Wochenschrift. 10. Jahrgang, Nr. 44 (1931)

⁴⁶⁷ STARKENSTEIN EMIL, Gegenwart, Zukunft und Vergangenheit der Pharmazie in: Apothekerzeitung (1934)

⁴⁶⁸ STARKENSTEIN EMIL, Universitäten und Forschungsinstitute in Südamerika, Verein deutscher Ärzte in Prag und Biologische Sektion des Lotus in Prag in: Medizinische Klinik (1928)

⁴⁶⁹ STARKENSTEIN EMIL, Pharmakotherapie der Seekrankheit in: Medizinische Klinik (1927)

⁴⁷⁰ STARKENSTEIN EMIL, Organ und Organismus unter pharmakologischem Einfluß 1936 in: Sonderausdruck - Kongreß für synthetische Lebensforschung, Verhandlungsbericht Marienbad; Prag . J.G. Calvesche Universitätsbuchhandlung (1937)

⁴⁷¹ STARKENSTEIN EMIL, Sparsame Arzneiverordnung in: Beiträge zur ärztlichen Verordnung (1928)

⁴⁷² STARKENSTEIN EMIL, Die Pharmakologie in Prag und ihr Anteil an der Entwicklung der pharmakologischen Forschung und des pharmakologischen Unterrichts in: Medizinische Klinik (1929)

⁴⁷³ STARKENSTEIN EMIL, Über die Vererbung einer branchiogenen Fistel - Ein Beitrag zur Familienforschung in: Medizinische Klinik (1928)

⁴⁷⁴ STARKENSTEIN EMIL, Das Kräuterbuch des Matthiolus in: II. Alte Bücher Charles Archive, neither Number Nor year detectable on publication

⁴⁷⁵ MATTIOLI PIETRO ANDREA, New Kreüterbuch (1563) retrieved on 22/01/2020 from

https://openlibrary.org/books/OL25471279M/New_Kre%C3%BCterbuch

⁴⁷⁶ Ibidem

⁴⁷⁷ Ibidem

Further reflections of pharmaceutical and medical history follow up with written records of scientific and non-specialist provenance that do not only focus on their substantive content in terms of pharmacotherapy but again trace the development and links of knowledge across several epochs, as passed down by copperplate engravings and manuscripts from monasteries. His transfer of this knowledge to (then) current issues are seen in assessing the potential of plants and their extracts of those ancient sources in comparison to chemically synthesized single compound medications of today: *“les herbes médicinales (...) exercent une action d'ensemble plus précieuse que leurs principes isolés obtenues sous for cristallisée.”*⁴⁷⁸

Within Starkenstein's observations of herbal books he also incorporates multiethnic aspects of cultural history *“Juden, Griechen Römern und Arabern”*⁴⁷⁹ and their impact and contribution to medical science. In this respect he also seeks to understand their principles of healing from a philosophical point of view, not only basing on aspects of their direct applicability to modern use. Thereby he strives for reconciling or at least understanding both positivistic and transcendental approaches *“kabalistischer Zeichenkunst, in talmudischer Gesetzesliteratur”*⁴⁸⁰ with modern knowledge related to pharmacotherapy and healing principles. Biographical research, in order to illustrate social habits and their origin, also played a role in Starkenstein's studies about Jewish scholars⁴⁸¹ such as *“Musa ben Maimun”*⁴⁸² a middle eastern Jewish philosopher and physician from the Middle Ages. In this reflections he deals with concrete religious and cultural traditions and customs of the three main monotheistic religions, Judaism, Christianity and Islam as well as their historical links and developments, e.g. in terms of dietary laws and rules of hygiene: *“So wie in den religiösen Formulierungen des Islams in der Prophetenreihe Moses ebenso wie Christus vorkommen, so wurde auch jetzt, 2000 Jahre nach Moses und 600 Jahre nach Christus (...) in die neue Religion hinübergenommen.. (...) insbesondere zahlreiche hygienische Vorschriften (...) Beschneidungs- und Sexualvorschriften, an die Speisegebote erinnert.”*⁴⁸³

Starkenstein's appreciation of his biographee is becoming apparent through the certain ton of his publication in which he presents him as a multifaceted, sophisticated scholar and practical

⁴⁷⁸ STARKENSTEIN EMIL, Les vieux herbiers français in: Le feuillet Médical no 1 (1932)

⁴⁷⁹ STARKENSTEIN EMIL, Kräuterbücher Eine Quelle für Medizin-, Natur-, Kunst-, und Kulturgeschichte (1928)

⁴⁸⁰ Ibidem

⁴⁸¹ STARKENSTEIN EMIL, Die Juden in der Medizin des Mittelalters in: Selbstwehr zum 1. Weltkongress jüdischer Ärzte in Tel-Aviv Nr. 175a Archiv Box 3, Archive (Starkenstein Nr 152- 215) no year detectable on publication

⁴⁸² STARKENSTEIN EMIL, Musa ben Maimun, der Arzt des Mittelalters Nr. 175 Archiv Box 3, Archive, no year detectable on publication

⁴⁸³ Ibidem

physician, driven by the urge for knowledge and also being characterized by a liberal and free- thinking spirit: *“seine Anordnungen trifft Maimonides ohne jedes Vorurteil und in manchen Fällen auch unbekümmert um religiöse Vorschriften (...)”*⁴⁸⁴ Through further direct quotes of Musa ben Mainum , additional personal attitudes of Starkenstein can be established, as he shows respect for fixed regulations, such as cultural customs, but also requests individual decision basing on conscience as well as rational considerations. With regards to medical ethics and practice, he also expresses admiration of a moral that puts patients well being and interests into the centre of a physicians actions and shows reminiscences of spirituality in *"Morgengebet des Arztes"*⁴⁸⁵

Starkenstein’s further biographical research with respect to Goethe display parallels to his analysis of the life and work of the jewish scholar Mus ben Maimun with regards to their joint polymath-like and altruistic personality: *”Möge stets der Goethesche Genius des Allgemeinmenschlichkeit , der persikopischen Lebensbetrachtung und klassischen Weisheit den Leitstern vorantragen für unser ärztliches Denken und Handeln.”*⁴⁸⁶

Prof. Starkenstein’s interest in semitic culture and heritage is also reflected upon in his philological lay research with regards to the ethnic origin of words or terms which contain the word stem Jew or Jewish, as in *“Judenkraut”*⁴⁸⁷, *“Judenporzellan”*⁴⁸⁸ or *“Judensteuer”*⁴⁸⁹. In touching upon the etymology of such designations he also discloses misconceptions and prejudices about Judaism as well as outlining political and religious persecution and discrimination of this specific community. In doing so he also demonstrates a substantial historical knowledge, revealing the financial exploitation the Jewish community suffered e.g. under Frederick the Great in 1787, or Christian authorities which imposed taxes on them based on their ethnicity and thus causing fiscal inequality to other citizens. Starkenstein also shows that various terms which had been used by the general public often implied a racist undertone or at least proof for concrete reservations, as they contain stereotypical images that allegedly remind of Jewish- orthodox characteristics or habiti, such as long beards or orthodox hats in the plants *Achillea Millefolium* or *Physalis Alkekengi* respectively. By unmasking those prejudices and scrutinising the underling cause for those generalisations in common parlance, Starkenstein creates awareness for this issue, also with regards to other

⁴⁸⁴ Ibidem

⁴⁸⁵ Ibidem

⁴⁸⁶ STARKENSTEIN EMIL, *Arznei und Gift im Leben Goethes* in: *Beiträge zur ärztlichen Fortbildung* (1932)

⁴⁸⁷ STARKENSTEIN EMIL, *Juden- Namen* in: *Der B’Nai B’Irth Monatsblätter der Grossloge für den Cechoslovakischen Staat* (1925)

⁴⁸⁸ Ibidem

⁴⁸⁹ Ibidem

minorities, such as people of colour: *“Eine Verächtlichmachung ist hier etwa ebenso gegeben , wie bei der Farbenbezeichnung "mohrenschwarz"; denn nach Ansicht des Mohren gibt es hierfür andere Vergleichsobjekte“*.⁴⁹⁰

Further areas of interest pertain to literature and particularly to poetry and aphorisms, as shown on several references to Johann Wolfgang Goethe, Friedrich Schiller^{491,492} , with a significant emphasis on Goethe’s person and oeuvre.^{493,494,495,496,497,498,499,500,501} Those references and citations such as *“Zu neuen Ufern lockt ein neuer Tag“*⁵⁰² or *“Was man an der Natur Geheimnisvolles pries, das wagen wir verständig zu probieren, und was sie sonst organisieren ließ, da lassen wir kristallisieren“*⁵⁰³ give evidence of Starkenstein’s profound knowledge about the first and second Part of Faust and his linguistic abilities to transfer those lines to other occasions and context like professional education⁵⁰⁴ or at his inaugural lecture for Pharmacology and Pharmacognosy at the German University in Prague.⁵⁰⁵

Apart from his affinities towards arts, literature and history his scientific curiosity towards social sciences and humanities, even along with methodological considerations to link and to differentiate them to and from the natural sciences, can be stated on Starkenstein’s reflections

⁴⁹⁰ Ibidem

⁴⁹¹ STARKENSTEIN EMIL, Gemeinsame Wege der Pharmakologie und Pharmazie vom Heilkraut zur modernen Pharmakopoe - Vortrag gehalten in der österreichischen pharmazeutischen Gesellschaft in Wien, am 19. Februar 1937- Sonderdruck in: Pharmazeutisches Monatsheft (1937)

⁴⁹² STARKENSTEIN EMIL, Gegenwart, Zukunft und Vergangenheit der Pharmazie in: Apothekerzeitung (1934)

⁴⁹³ STARKENSTEIN EMIL, Julius Pohl zum 70. Geburtstage, in: Klinische Wochenschrift. 10. Jahrgang, Nr. 44 (1931)

⁴⁹⁴ STARKENSTEIN EMIL, Balneologie und Balneotherapie in: Internationaler Ärztlicher Fortbildungskursus (1931)

⁴⁹⁵ STARKENSTEIN EMIL, Der Arzt und sein Buch in: Schriften des Philobiblon Rudolph M. Rohrer Verlag /Brünn Sonderdruck aus PhiloBiblon X, 7, 1, Charles Archive, no year or number detectable on publication

⁴⁹⁶ STARKENSTEIN EMIL, Arznei und Gift im Leben Goethes in: Beiträge zur ärztlichen Fortbildung (1932)

⁴⁹⁷ STARKENSTEIN EMIL, Instinkt und Intuition in der Forschung, im Studium und im ärztlichen Berufe in: Einheitsbestrebungen in der Medizin (1933)

⁴⁹⁸ STARKENSTEIN EMIL, Musa ben Maimun, der Arzt des Mittelalters Nr. 175 Archiv Box 3, Archive, no year detectable on publication

⁴⁹⁹ STARKENSTEIN EMIL, Organ und Organismus unter pharmakologischem Einfluß 1936 in: Sonderausdruck - Kongreß für synthetische Lebensforschung , Verhandlungsbericht Marienbad; Prag . J.G. Calvesche Universitätsbuchhandlung (1937)

⁵⁰⁰ STARKENSTEIN EMIL, Die Pharmakologischen Selbstversuche Purkinjes und Ihre Beurteilung nach dem heutigen Stande der Wissenschaft, Archive of Charles University Nr 198 Box 3

⁵⁰¹ STARKENSTEIN EMIL, Die Pharmakologie in Prag und ihr Anteil an der Entwicklung der pharmakologischen Forschung und des pharmakologischen Unterrichts in Medizinische Klinik (1929)

⁵⁰² Ibidem

⁵⁰³ STARKENSTEIN EMIL, Balneologie und Balneotherapie in: Internationaler Ärztlicher Fortbildungskursus (1931)

⁵⁰⁴ Ibidem

⁵⁰⁵ STARKENSTEIN EMIL, Die Pharmakologie in Prag und ihr Anteil an der Entwicklung der pharmakologischen Forschung und des pharmakologischen Unterrichts in Medizinische Klinik (1929)

on holism and holarchy.⁵⁰⁶ In the context he examined the nature of biological holism following the considerations of Meyer-Albrich and dealt with complex physiological contexts and processes within the human body, as being found in the cardiovascular or cerebral system.

Starkenstein arranges several organs with their natural functions into physiological high-level control units, such as the brain with the embedded respiratory centre, and also further subordinate organ functions, dividing them into three groups, depending on their hierarchical position. This physiological order of priority follows the principles of vital necessity within the entire organism, ranging from “low priority” organs such as ears, higher priority organs such as secretory glands up to organs pertaining to the central nervous system, with the highest rank possible. Those holistic considerations go beyond physiological questions on a medical level, as Prof. Starkenstein also deals with issues of medical ethics like the concept of death and life and hereby demonstrates the limits of natural sciences to define them ultimately and comprehensively: “*das Leben (...) sich nicht definieren (ließe) sondern nur charakterisieren (ließe)*”.⁵⁰⁷

Several publications provide some insights about Starkenstein’s personal background, particularly with regards to his ancestors and their profession, stating that, at least his father and grandfather had been working in the medical profession^{508,509,510}.

His genealogical interest which leads him to trace back his decent until the 14th century also suggest Starkenstein’s spiritual affinity to his own past and additionally give evidence for an applied culture within this family to pass down literary remains from generation to generation: “*zahlreicher in (seiner) Familie vorhandener literarischer Dokumente (...) bis zum Jahre 1450 in direkter Linie und bis etwa 1350 in einer Seitenlinie*”⁵¹¹ Here again, he successfully manages to link his research interest in history and humanities research with positivist methods and objects of investigation as he traces back the genetic inheritance of a fistula

⁵⁰⁶ STARKENSTEIN EMIL, Organ und Organismus unter pharmakologischem Einfluß 1936 in: Sonderausdruck - Kongreß für synthetische Lebensforschung, Verhandlungsbericht Marienbad; Prag. J.G. Calvesche Universitätsbuchhandlung (1937)

⁵⁰⁷ Ibidem

⁵⁰⁸ STARKENSTEIN EMIL, Sparsame Arzneiverordnung in: Beiträge zur ärztlichen Verordnung (1928)

⁵⁰⁹ STARKENSTEIN EMIL, Über die Vererbung einer branchiogenen Fistel - Ein Beitrag zur Familienforschung in: Medizinische Klinik (1928)

⁵¹⁰ STARKENSTEIN EMIL, Die Pharmakologie in Prag und ihr Anteil an der Entwicklung der pharmakologischen Forschung und des pharmakologischen Unterrichts in: Medizinische Klinik (1929)

⁵¹¹ STARKENSTEIN EMIL, Über die Vererbung einer branchiogenen Fistel - Ein Beitrag zur Familienforschung in: Medizinische Klinik (1928)

“*Vererbung einer branchiogenen Fistel*”, which according to his report had been occurred in his family in some generations.⁵¹²

Starkenstein’s exceedingly positive personal attitude towards lifelong learning and his function as a university lecturer, also shows close ties to the way he was brought up and educated in a manner which encouraged a tradition of knowledge – sharing and arouse interest for the medical profession. “*Gnade zuteil wird durch Lehren weiterlernen zu dürfen*”⁵¹³

Besides gaining in – depth specialist knowledge in his own scientific domains, his strong affinity towards a wide-ranging transfer of knowledge as well as its interdisciplinary acquisition and logical connection of several academic subjects, accounts for his holistic view on education and learning. This is also reflected in the fact that Starkenstein clearly favoured an independent and critical thinking to all aspects of research, basing on exhaustive studies of primary literature to draw conclusions independently and self-determinedly based on one’s own acquired base of knowledge, instead of focusing on other’s inferences.⁵¹⁴

Practical experiences outside the academic environment can be found in several study trips that include multiple European cities, and many countries in South America such as Brazil, Argentina, Uruguay etc. Although naturally those journeys were undertaken in connection to professional interests and observations, such as exchange on education, research and potential therapeutics, Starkenstein own description also displays a cultural interest for the countries per se “*Landschaftsbilder, Vegetation und Tierwelt*”⁵¹⁵. The fact that Starkenstein was not only a pure theorist without a sense of practical medicine and its applications can be refuted by looking at his activities as a practicing doctor on “*Monte Sarmiento*“ and “*Antonio Delfino*” for a Austrian shipping line in the years 1911 to 1933 within the time between terms.⁵¹⁶

Starkenstein’s own political beliefs might have rather been in the conservative spectrum, there is no actual evidence for any communist activities, which was suggested by the regime as they

⁵¹² Ibidem

⁵¹³ STARKENSTEIN EMIL, Die Pharmakologie in Prag und ihr Anteil an der Entwicklung der pharmakologischen Forschung und des pharmakologischen Unterrichts in: Medizinische Klinik (1929)

⁵¹⁴ STARKENSTEIN EMIL, Der Arzt und sein Buch in: Schriften des Philobiblon Rudolph M. Rohrer Verlag /Brünn Sonderdruck aus PhiloBiblon X, 7, 1, Charles Archive, no year or number detectable on publication

⁵¹⁵ STARKENSTEIN EMIL, Universitäten und Forschungsinstitute in Südamerika, Verein deutscher Ärzte in Prag und Biologische Sektion des Lotus in Prag in: Medizinische Klinik (1928)

⁵¹⁶ STARKENSTEIN EMIL, Pharmakotherapie der Seekrankheit in: Medizinische Klinik (1927)

arrested him “in 1941 on (alleged) criminal charges”⁵¹⁷. Regarding his sense of nationality and belonging to a certain state or ethnicity, Starkenstein is described as a multi-layered rather open minded person who embraced several aspects of his own background: “*Given the fact that he was born in Bohemia and lived in Czechoslovakia apart from the war years, as officer in the Austrian- Hungarian army, but he felt Czech, he felt certainly very Jewish*”⁵¹⁸

This multinational mindset can also be documented in the way he raised his children, as both of them still had been born in the Austrian- Hungarian Monarchy, his son Walter in 1915 and his daughter Magdalene in 1917, insisting on his children being fluent in Czech and German. The Starkenstein household fostered a broad humanist education, which besides languages and natural sciences included “*interests in art, travel, in music, opera (...) from very early on (...) he was keen on education*”⁵¹⁹

Profound interest towards religious as well as ethical- philosophical viewpoints, particularly with regards to Judaism can be shown on his correspondence, essays and even a manuscript of a self-composed novel which never had been published. The fact that Starkenstein even considered becoming a rabbi at some point, before turning to his medical studies shows his firm roots and both intellectual and emotional attachment to Jewish culture. It can be assumed with a great level of certainty that his general attitudes towards religion had been rather moderate than ultra-orthodox and strictly conservative, one the one hand basing on the estimates of his grandson, but also on his own written testimony, advocating for a contemporary interpretation of religious laws and regulations.⁵²⁰ Within his publication about the Jewish scholar and physician “*Musa ben Maimun, der Arzt des Mittelalters*”⁵²¹ he clearly acknowledges the intellectual outcome of Jewish philosophical traditions and ethics, but at the same time adapts a critical and yet up to date approach to those traditions, rejecting principles of religious infallibility in a claim to absoluteness “*uneingeschränkter Autoritätsglaube*”.⁵²²

Although being described as rather “*stern*”, “*stubborn*”, “*demanding*” and “*not much of a family man*”⁵²³, being devoted to his research and education in itself, there also seems to be a quite open minded side to him as he reportedly encouraged his children to choose a career

⁵¹⁷ VAN EMDE BOAS Walter, qualitative interview via Skype on May 13th 2021

⁵¹⁸ Ibidem

⁵¹⁹ Ibidem

⁵²⁰ STARKENSTEIN EMIL, Hygienische und sanitäre Verhältnisse Polens in: Archiv für soziale Hygiene und Demographie (1917)

⁵²¹ STARKENSTEIN EMIL, Musa ben Maimun, der Arzt des Mittelalters Nr. 175 Archiv Box 3, Archive, no year detectable on publication

⁵²² Ibidem

⁵²³ VAN EMDE BOAS Walter, qualitative interview via Skype on May 13th 2021

path basing on their personal dispositions and capabilities and thereby fostering their talent, rather than predefining their development, basing on fixed ideas.

This way of his upbringing in this intellectual, multilingual and rather education – focussed Jewish household, also involved journeys abroad with his family, *“he would take the children on trips, involve them in travel, much of his travel was in part professional”*⁵²⁴ such as a visit in Moscow in 1936 with his daughter Magdalene to a scientific congress. According to her son, his mother came into contact there for the first time with simultaneous interpretation, leading to her great interest and subsequent learning of several languages.

While Starkenstein’s knowledge on a academic level is undisputed in the natural and medical sciences, the degree of expertise towards other academic disciplines, such as art (history) was less pronounced, *“I think he was not very knowledgeable, we inherited a couple of paintings, which most of them were not what he thought he was buying. They were good but not that good”*⁵²⁵.

Starkenstein himself acknowledges that his understanding within the humanities, e.g. within linguistic research has its limitations due to his academic background, which does not provide sufficient training for analysing and evaluating certain topics and research questions from scratch: *“Es wird hier ausdrücklich betont, daß es sich hier um keine wissenschaftliche Untersuchung handeln kann, da mir hierzu vor allem die obenerwähnten , hierfür unerläßlichen fachlichen Vorraussetzungen auf sprachwissenschaftlichem und folkloristischem Gebiete fehlen.”*⁵²⁶

3.1.7. Details about Starkenstein’s and his family’s forced migration after 1939

Those further aspects deal with Starkenstein’s actual, versus his intended journey after his expulsion from his professorial chair and teaching activities and also reveal additional aspects of his social sphere through his relationship to his family and professional networks. In addition the information obtained revealed a closer insight to Prof. Starkenstein complex personality in terms of political view, religious beliefs, parenting techniques and relation to and further characterization of his family as well as his attitude towards national affiliations. The assessment of Starkenstein’s academic and professional publications remained topical as naturally not all of the publications had been read in detail by the interviewee in advance but

⁵²⁴ Ibidem

⁵²⁵ Ibidem

⁵²⁶ STARKENSTEIN EMIL, Juden- Namen in: Der B’Nai B’Irth Monatsblätter der Grossloge für den Cechoslovakischen Staat (1925)

could confirm the major areas of his research and perceived focus areas that had been established before.

Starkenstein's motivation to leave Prague directly after his expulsion had been somewhat reluctant and cannot be described as a inconsiderate decision, as his daughter initially had to convince him to do so: "*he felt very offended by the fact that he had to leave, that his students suddenly were anti just because he was Jewish, and just because the facists took over.*"⁵²⁷ Basing on his grandson's description his subjective awareness regarding the danger of the incipient political situation initially had not been that alarming to him as "*he could not imagine that something really bad would happen because of his position, because of the role he had played before.*"⁵²⁸

The Netherlands had been Starkenstein's first intermediate stop and place of personal and professional refuge , as the Amsterdamse Kininefabriek did enable Starkenstein to resume his research activities, provided a certain income and also served as a storage for a part of his extensive library. In this process both Madgalene Starkenstein's who had emigrated to the Netherlands previously as well as the pharmacologists and university professors Ernst Laqueur and Jan Kok supported Starkenstein, latter ones through contacts and connections to the company. Both Starkenstein (with his wife) and his daughter initially seemed to have had the intention to move on to the United States of America and New Zealand respectively, but several practical circumstances "*he had problems of getting visa and by the time he did... or did not succeed the Germans where here*"⁵²⁹ prevented them from realizing their plan.

In Magdalene Starkenstein's case, just like in her brother Walter's both initially faced problems with the chance of finalising their studies while also trying to escape Prague at a certain time. While Mrs. Starkenstein finally managed to escape to the Netherlands and obtaining a doctorate in art history, the political situation did not allow her brother to specialise as a surgeon after his completion of his medical studies in Poland. The exact circumstances of his death remain unclear to his family until today, and there was no evidence traceable through online sources of the Red Cross , however it is known that he went to the Ukraine after finalization of his medical studies where he also was murdered through the Nazi regime: "*As far as we know (...) he is (...) one of the many, many Jews who perished in whatever way in the Ukraine (...) The story ends, we have a letter from a solicitor in Prague*

⁵²⁷ VAN EMDE BOAS Walter, qualitative interview via Skype on May 13th 2021

⁵²⁸ Ibidem

⁵²⁹ Ibidem

who claims that he had still correspondence from Walter from one of the camps, but we have never seen it”⁵³⁰

Starckenstein`s ordeal did not take place from Amsterdam to the concentration camp Mauthausen directly but lead to his abduction over several prisons in the Netherlands, Germany and eventually to the concentration camps in occupied Czechoslovakia and Austria: “And then he went to the jail in Scheveningen, from there he went to Kleve, from there he was moved to yet another ... I think in Prague... to Theresienstadt and (...) to Mauthausen”⁵³¹

3.1.8. Detention and assassination in the concentration camp Mauthausen

Enquiries that had been carried out about Prof. Starckenstein lead to two entries about himself within the database of the KZ memorial Mauthausen, one about his admission to the concentration camp on October 23rd 1942 with the signature MM/Y36a (**Illustration 3**) and another entry stating his death on November 6th 1942 with the signature MMY/46a. (**III. 4**)

The data about his detention prove that he was considered as a political prisoner by the Nazi regime, which is implied by the division of prisoners he was assigned to in the records (*Häftlingszugangsbuch*). The fascist regime classified the detainees into categories according to their ideology, such as *Zigeuner* or *Juden/Jüdinnen* but also distinguished prisoners due to the perceived political or active resistance against the Nazi dictatorship. This political classification could also be due to Prof. Starckenstein`s high international academic and intellectual profile and reputation, which was clearly not in line with the fascist ideology and agenda. According to his grandson, Prof. Starckenstein did not actively engage in political activities in his Dutch exile and his wife Marie is described a a-political person, yet Starckenstein was imprisoned by the Nazi regime as a political prisoner. Naturally Starckenstein was nevertheless socially and academically visible and exposed as he had been involved in university policies and was a member of several commissions and scientific associations, such as the *Lotos* , dealing with medical and natural scientific topics.⁵³²

The entries state his death after having been captured for approximately two weeks within the concentration camp due to cardiovascular complications (*Herzkranzgefäßerkrankungen, Herzschlag- see ill. 4: MMY/46a*) and therefore suggests a natural cause of death without any external influences.

⁵³⁰ Ibidem

⁵³¹ Ibidem

⁵³² STARKENSTEIN EMIL, Generalregister zu den Bänden 1- 60 (1850- 1912) in: *Lotos - Zeitschrift für Naturwissenschaften* – 63: 1 – 40 (1915)

Though this “diagnose” on the death certificate cannot easily be refuted in retrospect, as a underlying coronary heart disease could indeed cause a myocardial infarction leading to the death of the person affected, there remain open questions about the integrity of this statement. Firstly, the diagnosis of a coronary heart disease would have had to be ascertained through an autopsy and precise investigation of the heart, which is rather unlikely under the prevalent circumstances in the concentration camp Mauthausen. In addition, well- advanced chronic obstructive changes in the coronary arteries as a cause for a myocardial infarction, would very often also have caused clinical symptoms previously, such as *angina pectoris* and possibly to a reduced physical fitness and performance.

There is, to the author’s knowledge no evidence for a chronical heart disease of Prof. Starkenstein previous to his imprisonment in the concentration camp and also his several publications and continuous work especially from 1939 to 1941 and 1942 do not speak for a physical or mental impairment due to a chronic or worsening disease.^{533,534,535,536,537,538 ,539 ,540 ,541 ,542 ,543}

The fact that Starkenstein died shortly after being admitted to Mauthausen after had been captured in the Netherlands and the accompanied stress might of course have possibly lead to a heart attack, but even in this case one cannot assume a “natural” death. Given the harsh conditions of detention, the physical and mental abuse as well failure to render assistance and

⁵³³ STARKENSTEIN EMIL, Pharmakologische Analyse der Chinaalkaloide II Mitteilung : Die Wirkung der Chinaalkaloide auf das Hirudopräparat in : Archives Internationales de Pharmacodynamie et de Therapie (1941)

⁵³⁴ STARKENSTEIN EMIL, Ein Beitrag zur Erklärung der "erregenden" Wirkungen des Chinins als Folge einer Enthemmung in: Archives internationales de pharmacodynamie et de therapie (1939)

⁵³⁵ STARKENSTEIN EMIL, Pharmakologische Analyse der Chinaalkaloide I: Mitteilung Das Chinaproblem in :Archives Internationales de Pharmacodynamie et de Therapie (1941)

⁵³⁶ STARKENSTEIN EMIL, Pharmakologische Analyse der Chinaalkaloide III Mitteilung :Die Wirkung der Chinaalkaloide auf den Darm in: Archives Internationales de Pharmacodynamie et de Therapie (1941)

⁵³⁷ STARKENSTEIN EMIL, Pharmakologische Analyse der Chinaalkaloide IV Mitteilung :Die Wirkung der Chinaalkaloide auf das Ösophagus- Magenpräparat des Frosches in: Archives Internationales de Pharmacodynamie et de Therapie (1942)

⁵³⁸ STARKENSTEIN EMIL, Nervöse Hemmungen als Angriffspunkte pharmakologisch wirksamer Stoffe in :Acta brevia neerlandica (1939)

⁵³⁹ STARKENSTEIN EMIL, Schwermetalle und Blutbildung in: Overgedrukt uit Chemisch Weekblad (1940)

⁵⁴⁰ STARKENSTEIN EMIL, Beitrag zur Erklärung des Mechanismus der Adrenalinwirkung in: Acta Brevi Neerlandica de physiologica, pharmacologia, microbiologia E.A (1940)

⁵⁴¹ STARKENSTEIN EMIL, Die Differenzierung der druch die Phenanthrenderivate des Opiums und durch Apomorphin auslösbaren Krämpfe hinsichtlich ihrer Abhängigkeit von zentralen Hemmungen in: Archives Internationales de Pharmacodynamie et de Therapie (1941)

⁵⁴² STARKENSTEIN EMIL, Über ein Sauerstoffphänomen - Beitrag zur Analyse der Adrenalinwirkung und der Motorik überlebender glattmuskulärer Organe in: Archives Internationales de Pharmacodynamie et de Therapie (1941)

⁵⁴³ STARKENSTEIN EMIL, Der Purinstoffwechsel als Biochemisches Artmerkmal- Hamsäure Allatoinbestimmungen im Gibbonharn in: Acta Brevi Neerlandica de physiologica, pharmacologia, microbiologia E.A (1941)

medical care which then all present the external influences within the concentration camp as a cause of death and thus murder.

In the third place it also has to be considered that the National Socialists frequently displayed incorrect data on the inmates death certificates with the intention to conceal the true death cause and thereby voluntary killing and assassination for ideological reasons.

Further research within the database of the Red Cross also display documents about Prof. Starkenstein and his daughter Magdalene Starkenstein- van Emde Boas and his wife Marie, assigning himself to the prisoners number 13819. Information about his wife Marie Starkenstein- Weil further substantiates his detention for political reasons as their anti-fascist position of her entry states in dutch “*Bijzonderheden liberal positif*”.⁵⁴⁴ Another entry shows that both, Starkenstein and his spouse died in Mauthausen whereas their daughter Magdalene survived the prosecution of the Nazis and worked as a graduated art historian.⁵⁴⁵ According to the records of the database, there were no relevant financial reserves or property of monetary value left to Starkenstein and his wife at the time of their death,⁵⁴⁶ which also depicts their personal situation after Professor Starkensteins expulsion from his professorial chair at German University by the Nazi regime in 1939.

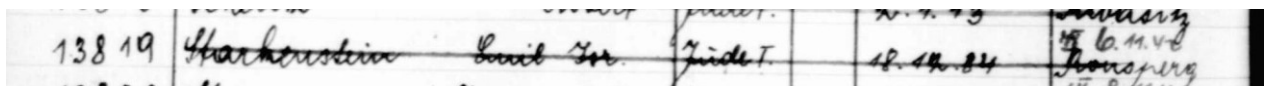


Illustration 3 (Signature MM/Y36a)

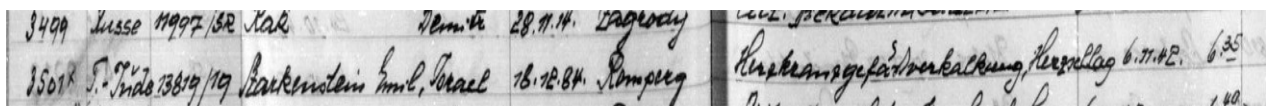


Illustration 4 (MMY/46a)

The average life expectancy decreased drastically from the years 1938 to 1945, depicting the harsh living conditions which included calculated chronic malnutrition and both physical and psychological abuse. This ill- treatment also culminated in several unethical human

⁵⁴⁴ STARKENSTEIN EMIL, Inhaftierungsdokumente aus dem Online Archive Arolsen vom 05.05.2021 Signatur 01020402243 Document ID: 130379931

⁵⁴⁵ STARKENSTEIN EMIL, Inhaftierungsdokumente aus dem Online Archive Arolsen vom 05.05.2021 Signatur 01020402277 Document ID 130283315, 1942

⁵⁴⁶ STARKENSTEIN EMIL, Inhaftierungsdokumente aus dem Online Archive Arolsen vom 05.05.2021 Signatur 01012603395, 1942

experimentations dealing with vaccines, hormones or nutrition physiology, of which the exact number of involved victims remains unclear.⁵⁴⁷

In line with the author's own findings and considerations, Prof. van Emde Boas also rejected the alleged cause of death, given on Starkenstein's death certificate, in fact stating his good health prior to his imprisonment: "*no indication of heart disease whatsoever – he was healthy- he didn't smoke he didn't drink*"⁵⁴⁸

According to conversations the interviewee had with his late mother, there were other theories about the actual circumstances of Starkenstein's death which have not been further documented or proven: "*Then there was a story from some other sources (...) that he died during experiments, that he was killed by phenol injections.*"⁵⁴⁹

Indications which could support this possible scenario are given by the fact that, the at that time accountable SS camp physician Dr. Eduard Krebsbach, incited the assassination of detainees through medically unfounded cardiac injections as part of unethical human experimentations which were aimed at the death of the involuntary test persons and lacked any scientific standard.⁵⁵⁰

3.1.9. Several levels and differentiated aspects of victimization

The victimization of Prof. Starkenstein can be documented on various levels both in a private setting and in his professional life. The private aspects of his victimizations are very obvious as they imply the deprivation of his liberty being imprisoned and displaced through various countries without having knowledge of his own fate and the one of his children and wife. Though the exact circumstances of his death remain unclear, there is no doubt that he (and probably his son Walter) are victims of the National Socialist dictatorship and its fascist ideology. Besides the immediate physical assaults and harm, psychological and social factors also have to be taken into consideration, as being prevalent on the loss of social networks and family ties but also through the arising nationalistic mobilization before and during the German occupation of then Czechoslovakia. Prof. Starkenstein's personal identification with and affinity to the German language and cultural environment and the fact that he had been socialized in a multi- ethnic Cisleithanian state, along with his service as a military physician

⁵⁴⁷ MARSALEK HANS, Die Geschichte des Konzentrationslagers Mauthausen, in: Österreichische Lagergemeinschaft Mauthausen, Wien 1980, 2. Auflage (1980)

⁵⁴⁸ VAN EMDE BOAS Walter, qualitative interview via Skype on May 13th 2021

⁵⁴⁹ Ibidem

⁵⁵⁰ MARSALEK HANS, Die Geschichte des Konzentrationslagers Mauthausen, in „Österreichische Lagergemeinschaft Mauthausen, Wien 1980, 2. Auflage (1980) page 185ff

and commanding officer under the Austro- Hungarian Monarchy⁵⁵¹, must have also caused distress to his own sense of belonging in context of those upcoming racist political streams. Further aspects of victimisation on a social level can be seen in the circumstance that Starkenstein was forced to flee Prague after a certain time and the resulting need to reorientate himself again in this new environment. This in effect also had far reaching effects not only for Starkenstein's immediate surviving family but also for science and the medical profession.

Starkenstein's Manual for Pharmacology *Lehrbuch für Pharmakologie, Toxikologie und Arzneiverordnung* had been published in an inaugural issue in 1938 by the company Franz Deuticke Leipzig, Wien but no further edition could be identified which had been published subsequently.⁵⁵² According to his grandson this publication "was suppressed by the Germans"⁵⁵³, though being even discussed for an English translation and wider distribution "there was a contract for an American publication that never came about"⁵⁵⁴ Financial hardship or at least shortages cannot be verified directly, but remain a reasonable presumption after Starkenstein had been expelled from University and had to earn a living at the Chininefabrik. The fact that no relevant asset was left to him and his family at the time of his death⁵⁵⁵ and also his daughter's need to sell his books to help to finance herself⁵⁵⁶, would also indicate victimization on this level.

3.2 Analysis and contextualisation of his scientific work

3.2.1 Methods and Methodology used in his laboratory and (pre)-clinical research

a) Basic pharmaceutical and chemical approaches and sciences

More than 220 publications have been reviewed and fully read under the aspects of scientific content, methodological approach, collaborations and both their relevance and contribution to modern pharmacology, whereby thematic duplicates had been excluded from the final summary. Prof. Starkenstein's academic accomplishments start with a variety of publications in basic sciences by primarily using qualitative and quantitative pharmaceutical

⁵⁵¹ STARKENSTEIN EMIL, Hygienische und sanitäre Verhältnisse Polens in: Archiv für soziale Hygiene und Demographie (1917)

⁵⁵² STARKENSTEIN EMIL, Katalog der deutschen Nationalbibliothek retrieved online on 12/02/2020 <http://dnb.info/361147678>

⁵⁵³ VAN EMDE BOAS WALTER, qualitative interview via Skype on May 13th 2021

⁵⁵⁴ Ibidem

⁵⁵⁵ STARKENSTEIN EMIL, Inhaftierungsdokumente aus dem Online Archive Arolsen vom 05.05.2021 Signatur 01012603395, 1942

⁵⁵⁶ VAN EMDE BOAS WALTER, qualitative interview via Skype on May 13th 2021

analysis^{557,558,559,560,561,562,563,564,565,566} to answer questions referring to chemical reactivity and solubility of compounds, e.g. enzymatic activity, oxidation states of ions, electrolytic dissociation and complexing of substances, precipitation reactions etc. In doing so, he has delivered concrete results to a more substantial and detailed understanding of the analytical accessibility of molecular groups and the suitability of chemical indicators, like “*Cochénille*” and “*Ferrocyanalium*” and their equivalence on volumetric analysis.⁵⁶⁷ In addition to that, Starkenstein put a focus on understanding aspects of stereochemistry by investigating phenomena such as optical activity in order to identify the mutual steric relation of atomic and molecular groups, thus answering questions of chemical constitution and configuration.^{568,569,570} He regularly investigated the effects of thermodynamic variables such as temperature, light, the amount of chemical substance and other accompanied conditions such as the PH- value within his basic experiments to then again draw conclusions for their impact on their durability and therapeutic usability⁵⁷¹, also with regards to enzymatic processes in the context of biological and biochemical research.⁵⁷²

⁵⁵⁷ STARKENSTEIN EMIL, Untersuchungen über das Verhalten der Uransalze zweibasischer Phosphorsäuren gegen Indikatoren in: Zeitschrift für analytische Chemie Vol.51(10) (1912)

⁵⁵⁸ STARKENSTEIN EMIL, Ionenwirkung der Phosphorsäuren in: Biochemische Zeitschrift (1911)

⁵⁵⁹ STARKENSTEIN EMIL, Über die Unabhängigkeit der Diastasewirkung von den Lipiden in: Biochemische Zeitschrift- Beiträge zur Physiologie und Pathologie (1911)

⁵⁶⁰ STARKENSTEIN EMIL, Über den Nachweis von Glykogen bei Meeresmolusken speziell bei Cephalopoden und Aplysien in: Hoppe-Seyler's Zeitschrift für Physiologische Chemie (1912)

⁵⁶¹ STARKENSTEIN EMIL, Über die pharmakologische Wirkung von kalziumfällenden Säuren und Magnesiumsalzen in: Wiener medizinische Wochenzeitschrift (1913)

⁵⁶² STARKENSTEIN EMIL, Die biologische Aktivität des Eisens ist lediglich eine Funktion der Ferroionen in: Klinische Wochenzeitschrift (1928)

⁵⁶³ STARKENSTEIN EMIL, Über das anorganische Eisen des Organismus in: Experimentelle Pathologie und Pharmakologie (1928)

⁵⁶⁴ STARKENSTEIN EMIL, Über die Bedingungen der Bildung lipidlöslicher Salze in gelösten Chlorid-Sulfatmengen in: Archiv für experimentelle Pathologie und Pharmakologie (1933)

⁵⁶⁵ STARKENSTEIN EMIL, Über eine im intermediären Eisenstoffwechsel entstehende Ferriglobulinverbindung in: Experimentelle Pathologie und Pharmakologie (1933)

⁵⁶⁶ STARKENSTEIN EMIL, Die Autoxydation der Ferrosalze und die Haltbarkeit ihrer Lösungen in: Archiv für Experimentelle Pathologie und Pharmakologie (1933)

⁵⁶⁷ STARKENSTEIN EMIL, Untersuchungen über das Verhalten der Uransalze zweibasischer Phosphorsäuren gegen Indikatoren in: Zeitschrift für analytische Chemie Vol.51(10) (1912)

⁵⁶⁸ STARKENSTEIN EMIL, Chemische Konstitution, physikalisch- chemische Eigenschaften und Pharmakologische Wirkung - Ein Beitrag zur Erklärung der chronischen Giftwirkung in: Klinische Wochenschrift (1936)

⁵⁶⁹ STARKENSTEIN EMIL, Beziehungen zwischen chemischer Konstitution und pharmakologischer Wirkung bei organischen Arsenverbindungen, Nr 15. Charles University Archive Box 1 no year detectable on publication

⁵⁷⁰ STARKENSTEIN EMIL, Die Bedeutung der Begriffe anorganisch, organisch und organisiert für die Arzneimittellehre in: Medizinische Klinik (1932)

⁵⁷¹ STARKENSTEIN EMIL, Die Autoxydation der Ferrosalze und die Haltbarkeit ihrer Lösungen in: Archiv für Experimentelle Pathologie und Pharmakologie (1933)

⁵⁷² STARKENSTEIN EMIL, Über den Nachweis von Glykogen bei Meeresmolusken speziell bei Cephalopoden und Aplysien in: Hoppe-Seyler's Zeitschrift für Physiologische Chemie (1912)

Besides anorganic chemistry, Starkenstein also conducted research within organic chemistry, e.g. in the drug synthesis of “Veramon” (III.2), a combination drug consisting of “Barbital” (5,5-Diethyl-(1H,3H,5H)-pyrimidin-2,4,6-trion) and “Aminophenazon” (4-Dimethylamino-1,5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-on.)⁵⁷³

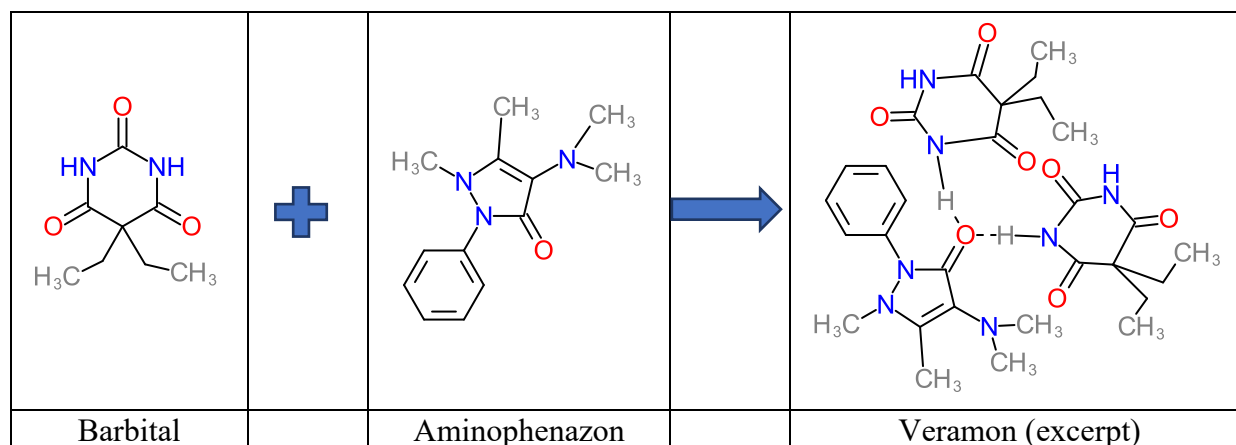


Illustration 2: Veramon and its educts in which Hertel (1931) suggests the reaction of the carbonyl group of the Aminophenazon (marked red) with two imido groups (marked blue) of the Barbital.⁵⁷⁴

Stability analyses of pharmaceutical compounds such as morphine in opium extracts for the purpose of investigating chemical stability and shelf life had been conducted by him in various dosage forms. Starkenstein’s causal understanding for chemical and physical properties and reactions establish the basis for further targeted development and search for reproducible pharmacotherapies.⁵⁷⁵

b) Animal experimentation

Basing on those chemical experiments Starkenstein frequently continued to investigate those findings on the living organism, using laboratory animals which included vertebrates such as mammals and amphibians. Those experiments included the examination of physiological parameters such as respiratory and heart rates, regulating nerval reflexes etc. in order to get a first impression on the effects the compound might have on living matter.⁵⁷⁶

⁵⁷³ STARKENSTEIN EMIL, Über das Veramon, in: Berichte der deutschen Pharmazeutischen Gesellschaft (1922)

⁵⁷⁴ HERTEL EDUARD, Die Struktur der Molekülverbindung im Veramon in: Zeitschrift für Physikalische Chemie, vol. 1931A, no. Supplement (1931) pp. 267-272

⁵⁷⁵ STARKENSTEIN EMIL, Die Bedingungen der Zerstörbarkeit des Morphins im Opium und im Opiumextrakt in: Archiv für experimentelle Pathologie und Pharmakologie (1937)

⁵⁷⁶ STARKENSTEIN EMIL, Ionenwirkung der Phosphorsäuren in: Biochemische Zeitschrift (1911)

In addition to that, Starkenstein also used animal models to determine the extent of toxicity in his experiments on those isolated organs but also on the entire cardiovascular and respiratory system and gastrointestinal tract, aiming at the investigation of metabolic states such as purine balance, inflammatory processes and glycosuria.⁵⁷⁷ Individual observations of drug actions in different animals were critically compared not only in terms of their direct effect, such as on the vegetative nervous system, but also in terms of the set up- of the individual experiment, e.g. depending on the use and concentration of chemicals, also in comparison with other researchers.^{578,579} Furthermore, cumulative and distributive processes in organs such liver and spleen or the blood stream respectively are here again linked to chemical properties of the observed drug, such as oxidative states and route of application. Concrete experiments, such as the Straub preparation of the heart were chosen to differentiate ionic and hormonally controlled effects⁵⁸⁰, and thus to elicit concrete mode of actions.

In the case of the drug *Atophan* those animal experimentations were crucial, as the compound displayed varying pharmacological effects, such as the influence on the purine metabolism, temperature regulation and influence on inflammatory processes that had not been fully understood.⁵⁸¹ Another example for experiments that involved animals, referred to the question how and under which circumstances analgesic effects could be measured scientifically sound, e.g. with drugs such as morphine and pyramidone with mice and guinea pigs. Hereby Starkenstein recognized species- specific differences and advised against a rash generalisation amongst effects in “animals” or even a general or direct transfer of those findings to humans.⁵⁸²

c) Pharmacokinetic and pharmacodynamic experiments

Starkenstein’s research often includes pharmacokinetic and pharmacodynamic aspects, where the influence of drugs is examined, e.g. in the case of inflammation and permeability by the usage of fluorescent pigments to visualize the transport of exsudates and the relocation of

⁵⁷⁷ STARKENSTEIN EMIL, Über die Wirkungen des Atophans in: Biochemische Zeitschrift (1920)

⁵⁷⁸ STARKENSTEIN EMIL, Zur Frage der Wirkung der Phenylchinolincarbonsäure (Atophan) auf das vegetative Nervensystem in: Zeitschrift für die gesamte experimentelle Medizin (1924)

⁵⁷⁹ STARKENSTEIN EMIL, Über das Schicksal des anorganischen Eisens in überlebenden Organen in: Experimentelle Pathologie und Pharmakologie (1928)

⁵⁸⁰ STARKENSTEIN EMIL, Über die Wirkungen des Atophans 1920 in: Biochemische Zeitschrift (1920)

⁵⁸¹ STARKENSTEIN EMIL, Über die Pharmakologie des Atophans in: Prager Medizinische Wochenzeitschrift (1913)

⁵⁸² STARKENSTEIN EMIL, Zur Methodik der Prüfung sachmerzstillender Mittel im Tierversuch in: Archiv für experimentelle Pathologie und Pharmakologie (1932)

fluids.⁵⁸³ Further research investigated distributive processes of drugs in the human body , depending on the degree of lipophilicity, which had been tested on narcotics⁵⁸⁴ and other substances: *“Die narkosefördernde Wirkung des Cholesterins ist von der Art der Zufuhr des Narkotikums abhängig; sie ist am deutlichsten bei intraperitonealer (...) und intravenöser oder subcutaner Zufuhr des Hypnoticums. Oral verabreichtes Cholesterin wirkt auch nach einem längeren Intervall nicht auf das intravenös verabreichte Schlafmittel fördernd, im Gegenteil manchmal (...) verzögernd.”*⁵⁸⁵

Other pharmacokinetic properties of drugs such as the process of resorption has regularly been investigated in different cell types and tissues such as the gastric mucous membrane, subcutaneous connective tissue, smooth muscles cells and other compartments of the organism.⁵⁸⁶ Within these experiments, again stereochemical properties of the drug and its metabolites are evaluated by Starkenstein , where he also shows understanding for the biotransformation of drugs and thus Phase I and II reactions:

“die gegenseitigen Beziehungen der Atome, also (..) Konstitution und Konfiguration” and *“Die Schwierigkeiten , die sich der Feststellung solcher Gesetzmäßigkeiten entgegenstellen, beruhen darauf, daß die pharmakologische Wirkung erst eine Folge jener, uns noch ganz unbekannt Reaktionen darstellt, die zwischen diesen Verbindungen (...) ablaufen”*.⁵⁸⁷

Classifying various types of chemical bindings also represents a part of those pharmacokinetic and pharmacodynamic considerations, as their influence on liberation, distribution, resorption is discussed by Starkenstein with regards to its implications for pharmacotherapy.⁵⁸⁸

The route of application of drugs, such as caffeine, through oral, intravenous or subcutaneous administration is then examined under the aspects of resorption, complexation and thereby questions of bioavailability in a application oriented setting.⁵⁸⁹ In the case of i.v. or s.c.

⁵⁸³ STARKENSTEIN EMIL, Die Beeinflussung der elektrostatischen Ladung der Gewebe durch Arzneistoffe in: Biochemische Zeitschrift (1931)

⁵⁸⁴ STARKENSTEIN EMIL, Beeinflussung der Narkose durch Cholesterin in: The Sechenov Journal of Physiology of the USSR (1931)

⁵⁸⁵ STARKENSTEIN EMIL / WEDEN, H, Zur Physiologie und Pharmakologie der Sterine IV in: Archiv für experimentelle Pathologie und Pharmakologie 182 (1936) pages 700–714

⁵⁸⁶ STARKENSTEIN EMIL, Zur Physiologie und Pharmakologie der Sterine II in: Archiv für experimentelle Physiologie und Pharmakologie (1936)

⁵⁸⁷ STARKENSTEIN EMIL, Chemische Konstitution , physikalisch- chemische Eigenschaften und Pharmakologische Wirkung - Ein Beitrag zur Erklärung der chronischen Giftwirkung in: Klinische Wochenschrift (1936)

⁵⁸⁸ STARKENSTEIN EMIL, Die Bedeutung der Begriffe anorganisch, organisch und organisiert für die Arzneimittellehre in: Medizinische Klinik (1932)

⁵⁸⁹ STARKENSTEIN EMIL, Die Koffeeinwirkung des schwarzen und des Milchkaffees in: Schweizerische Medizinische Wochenzeitschrift (1937)

adrenaline injections Starkenstein investigated the bioavailability and the uptake of the medication based on the increase of blood pressure.⁵⁹⁰

Other factors that influence this bioavailability of drugs, such as both structural and dynamic interactions, as in the case of iron complexes, in their various depot and transport forms also form an area of interest in Starkenstein's publications. Drug initiated side effects and interactions e.g. with narcotics, also played a crucial role in his research works, as shown with the experimental analysis with animals of *Pyramidon*. The then resulting side effects and thereby the pharmacodynamic effects are described as tetanic convulsions and an increase of heart and respiratory rate as well as blood pressure by Starkenstein.

Particularly with regards to addition compounds or pharmaceutical formulations, Prof. Starkenstein investigates a potential increase or reduction in efficacy between the pharmacologically active substances but also excipients or accompanying substances: "*Alkohol, Saponinen, Galle, Cholesterin*"⁵⁹¹. Chemical parameters that could influence pharmacokinetic properties and thereby the effectiveness of a drug also play a part of those considerations, bridging preclinical research with clinical aspects: *„eine Erhöhung der Wasserlöslichkeit bestimmter Verbindungen mit einer starken Schwächung ihrer pharmakologischen Wirkung verbunden sein kann, während umgekehrt Verminderung aber nicht vollständiges Aufheben der Wasserlöslichkeit bei gleichzeitiger Erhöhung der Lipidlöslichkeit eine Beschleunigung der Resorption, Änderung der Verteilung und der Bindung im Organismus und damit Steigerung der Gesamtwirkung zur Folge haben kann"*⁵⁹²

In general, animal experiments were the basis to answer his research interest, especially in cases that were ethically not suitable for human experiments. Patient⁵⁹³, healthy volunteer involvement⁵⁹⁴ or especially self-experiments^{595,596,597,598} were only performed in cases that

⁵⁹⁰ STARKENSTEIN EMIL, Haben subkutane Adrenalin- Injektionen eine blutdrucksteigernde Wirkung in: Medizinische Klinik (1934)

⁵⁹¹ STARKENSTEIN EMIL, Über die pharmakologische Wirkung von Additionsverbindungen und Gemengen in: Archiv für Experimentelle Pathologie und Pharmakologie (1934)

⁵⁹² Ibidem

⁵⁹³ STARKENSTEIN EMIL, Beiträge zur Therapie des Fleckenfiebers: Untersuchungen der Cerebrospinalflüssigkeit bei Fleckfieberkrankheiten in: Medizinische Klinik- Wochenzeitschrift für praktische Ärzte (1917)

⁵⁹⁴ STARKENSTEIN EMIL, Die Entstehung der endogenen Harnsäureausscheidung als Grundlage für die Bemessung der Arzneimitteldosen im Kindesalter in: Archiv für experimentelle Pathologie und Pharmakologie (1937)

⁵⁹⁵ STARKENSTEIN EMIL, Pharmakotherapie der Seekrankheit in: Medizinische Klinik (1927)

⁵⁹⁶ STARKENSTEIN EMIL, Über die diuretische Wirkung oral zugeführter Zuckerlösungen verschiedener Konzentration in Sonderabdruck aus der Festschrift für Prof. Dr. Emil Bürgi, (1932)

did not cause any harm and therefore were legitimate to perform. An example for Starkenstein's self-experiments are dealt with in "*Über die diuretische Wirkung oral zugeführter Zuckerlösungen verschiedener Konzentration*"⁵⁹⁹ where he operates with different concentrations of sugar solutions e.g. a 8 % concentrated one compared to physiological saline solution in order to explain varying retention and excretion rates of the human body.

Basing on previous biochemical investigations about renal excretion and elimination, Prof. Starkenstein also dedicates his research to pediatric topics such as age-adequate drug dosing for infants, young children and adolescents. These investigations, which he carried out twice per year, last for a remarkable time of eighteen years between 1919 until 1936. Besides age and gender-specific differences in this cohort he also includes physiological and endogenous factors as well as variables such as the infant's weight and height into his considerations. In doing so he modifies and elaborates back at that time used calculation formulas such as "*Dosis für Erwachsene x Anzahl der Jahre / 20*".⁶⁰⁰ As a proposed amendment based on his research he suggests the adjustment of the denominator in the formula for pediatric dosing and also stresses that nowhere near all drugs show the therapeutic index to rely on those formulas without risking overdosage and thus potential toxicity.⁶⁰¹

d) Literature reviews and appreciation of scientific theories and concepts

Starkenstein reviewed the, back in those days, current literature and publications of colleagues from a huge range of scientific disciplines, such as (pharmaceutical) biology^{602,603}, physiology⁶⁰⁴, pharmacology^{605,606}, etc. in order to compare and contrast his findings to the

⁵⁹⁷ STARKENSTEIN EMIL, Pharmakologische und chemische Untersuchungen über die wirksamen Bestandteile der *Urtica dioica* und *Urtica urens* in: *Archiv für experimentelle Pathologie und Pharmakologie* 172 (1933) pages 137–148

⁵⁹⁸ STARKENSTEIN EMIL, Über die Abhängigkeit der Diurese vom Salzgehalt und der Wasserstoffionenkonzentration des getrunkenen Wassers in: *Archiv für experimentelle Pathologie und Pharmakologie* 104, (1924) pages 6–22

⁵⁹⁹ STARKENSTEIN EMIL, Über die diuretische Wirkung oral zugeführter Zuckerlösungen verschiedener Konzentration in Sonderabdruck aus der Festschrift für Prof. Dr. Emil Bürgi, (1932)

⁶⁰⁰ STARKENSTEIN EMIL, Die Entstehung der endogenen Harnsäureausscheidung als Grundlage für die Bemessung der Arzneimitteldosen im Kindesalter in: *Archiv für experimentelle Pathologie und Pharmakologie* (1937)

⁶⁰¹ Ibidem

⁶⁰² STARKENSTEIN EMIL, Die Papaveraceenalkaloide in: *Handbuch der experimentellen Pharmakologie* (1924)

⁶⁰³ STARKENSTEIN EMIL, Über die Beeinflussung der Wirkung des schwarzen Kaffees durch Milchzusatz in: *Therapie der Gegenwart* (1932)

⁶⁰⁴ STARKENSTEIN EMIL, Diuretika und Diaphoretika in: *Sonderabdruck der ärztlichen Fortbildung* (1928)

⁶⁰⁵ STARKENSTEIN EMIL, Das Problem der humoralen, solidären und zellulären Wirkung und seine Beziehung zur Mineralstofftherapie in: *Medizinische Klinik* (1935)

ones of his colleagues or historical sources. In an immunological review Starkenstein takes into consideration previous pharmacological concepts and theories, such as the humoral pathology theory by Hippocrates and Galen that deals with the balance and imbalance of body fluids: *“Blut, Schleim. gelbe und schwarze Galle.”*⁶⁰⁷ Literature researches in state and academic archives e.g. in Prague, Vienna and Berlin also provided him with stimuli for the recollection of ancient remedies and their reassessment through modern technologies. Thereby he aimed at an assignment of several substances such as *“bolus alba”*, species of the aloe plant, *“Digitalis”* and extracts of opium in order to identify concrete active substances and to make them accessible for a therapeutic use.⁶⁰⁸

At the same time back then recent literature, so to speak, a up- to date review of the literature took place regularly within Starkenstein`s work, in order to synthesize findings and bring them up to date.^{609,610} In particular, intracellular processes that were methodologically and practically not accessible at those times, aroused his scientific interest with regards to pathogenesis and new therapeutic options: *“So ergibt sich die Notwendigkeit , immer mehr unsere Untersuchungsmethodik nach der Richtung hin zu vervollkommen, die uns ebenso die normalen wie die pathologischen endozellulären Vorgänge lehrt.”*⁶¹¹ With the onset of broader genetic research in the 20th century, his interest on those processes: *“intrazelluläre Vorgänge”*⁶¹² could be understood as a his comprehension for the upcoming importance of genetic factors in research.

3.2.2 Areas of natural -scientific & medical research

a) Toxicology

With regard to toxicological research, Starkenstein evaluates the degree of both chronical and acute toxicity of substances, e.g. by the determination of the relative, acute toxicity or lethal doses, in animal or in vitro- experimentations.^{613,614,615,616} To asses chronic toxicity, he

⁶⁰⁶ STARKENSTEIN EMIL, Arzneikunst im 17. Jahrhundert in Sonderabdruck der Monatszeitschrift in: Deutsche Arbeit (1910)

⁶⁰⁷ STARKENSTEIN EMIL, Das Problem der humoralen , solidären und zellulären Wirkung und seine Beziehung zur Mineralstofftherapie in: Medizinische Klinik (1935)

⁶⁰⁸ STARKENSTEIN EMIL, Arzneikunst im 17. Jahrhundert in Sonderabdruck der Monatszeitschrift in: Deutsche Arbeit (1910)

⁶⁰⁹ STARKENSTEIN EMIL, Zur Pharmakologie des Pituitrins in: Sonderabdruck der Prager Medizinischen Wochenzeitschrift (1912)

⁶¹⁰ STARKENSTEIN EMIL, Pharmakologische Analyse der Chinaalkaloide II Mitteilung : Die Wirkung der Chinaalkaloide auf das Hirudopräparat in: Archives Internationales de Pharmacodynamie et de Therapie (1941)

⁶¹¹ STARKENSTEIN EMIL, Die Bedeutung der Begriffe humoral , solidär und zellulär für die Analyse der Krankheitsentstehung und Kranheitsheilung in: Libro de Oro (1935)

⁶¹² Ibidem

⁶¹³ STARKENSTEIN EMIL, Ionenwirkung der Phosphorsäuren in: Biochemische Zeitschrift (1911)

accentuates the importance of clinical observations to confirm or reject the initial hypotheses and thereby to find the underlying causality of symptoms. There in his opinion, the well-directed interplay of clinical observations and laboratory research can lead to either to the mentioned deductive approach, but also serve to generate new pharmacological concepts and theories in an inductive manner.⁶¹⁷

His toxicological research on a molecular level can be demonstrated with his experimentations with bee poison and its haemolytic effects on cell membranes after i.v. injection in animals. The underlying initial hypothesis to explain these observed effects are either a structural similarity to the chemical group of the saponins or the same pharmacological target. Starkenstein finds the resulting toxic effect as an increased permeability of membranes in various organs: *“weitgehende Veränderungen der Permeabilität der Zellwände verschiedener Organe”*⁶¹⁸ and a pathological re-distribution of cholesterol: *“Cholesterinmobilisierung”*.⁶¹⁹ Starkenstein's investigations also point out the relevance of chemical properties on toxicological effects even within the same element: *“Ferriionen giftiger seien als die Ferroionen, so geht daraus schon das unterschiedliche Verhalten beider Oxydationsstufen eines und desselben Metalls deutlich hervor. Dieser Unterschied ist aber nicht nur ein quantitativer”*⁶²⁰ Further basic research refers to the splenic accumulation of pharmaceutical substances and toxins, such as carbon monoxide, hydrocyanic acid, nitrobenzene, acetanilide or several iron compounds. In detail this meant a controlled intoxication of laboratory guinea pigs, rats and cats with those substances and subsequent spectroscopic studies of blood from the carotid artery.⁶²¹

Aspects of clinical toxicity or detoxification are investigated in the case of the analgesic *Veramon* which consists of diethylbarbituric acid and pyramidon. Barbiturates are known to show a narrow therapeutic range and thus, if overdosed, a potential inhibition of the respiratory centre in the brain, resulting in a respiratory acidosis. In order to help to overcome

⁶¹⁴ STARKENSTEIN EMIL, Über die pharmakologische Wirkung von kalziumfällenden Säuren und Magnesiumsalzen in: Wiener medizinische Wochenschrift (1913)

⁶¹⁵ STARKENSTEIN EMIL, Über die Aufnahmefähigkeit der Milz für Arzneimittel und Gifte in: Medizinische Klinik (1929)

⁶¹⁶ STARKENSTEIN EMIL, Die Giftwirkung der Schwermetalle in: Forschungen und Fortschritte (1931)

⁶¹⁷ STARKENSTEIN EMIL, Zur experimentellen Analyse chronischer Vergiftungen in: Klinische Wochenschrift (1932)

⁶¹⁸ STARKENSTEIN EMIL, Beitrag zur pharmakologischen Wirkung des Bienengiftes in: Medizinische Klinik (1936)

⁶¹⁹ Ibidem

⁶²⁰ STARKENSTEIN EMIL, Die Giftwirkung der Schwermetalle in: Forschungen und Fortschritte (1931)

⁶²¹ STARKENSTEIN EMIL, Über die Aufnahmefähigkeit der Milz für Arzneimittel und Gifte in: Medizinische Klinik (1929)

and mitigate fatal adverse drug events Starckensteins aims at the development of drug combinations that reduce the dose of the barbiturates: *“In 0,4 g Veramon sind 0,28 g Pyramidon und 0,12 g Veronal enthalten.”*⁶²²

Basing on his experiments on respiratory rates and voluminal in animals Starckenstein draws the conclusion that the respiratory depressive effects can be worked against with the concomitant use of pyramidone: *“Hauptwirkung zu verstärken und Nebenwirkungen zu minimieren”*.⁶²³ The therapeutic idea to detoxify luxuries of everyday life such as nicotine or the then legally used cocaine are investigated by analytical means as well, whereby he exposes absurdity of such ideas, as the toxicity lies in the overdose of the drug per se or in case of nicotine also in the occurrence of toxic by products: *“Pyridin, Kohlenoxyd, Ammoniak und Blausäure”*⁶²⁴

Basing on his previous research, practically relevant questions, such as occupational intoxications, are presented by Starckenstein, e.g. in form of case- reports of a sub- acute poisoning with hydrogen sulfide gas and thereby evaluated pharmacologically in terms of their clinical symptoms.⁶²⁵ Further case reports and publications also deal with fatal intoxications due to prescription errors⁶²⁶ and the co- authorship on practical handbooks on their early recognition and adequate therapy to bridge basic knowledge and clinical applicability.^{627,628}

The link of qualitative analytic methods within forensic medicine, e.g. in case of potential suicides or murder cases respectively also play a role in Stakensteins toxicological research activities, where he demonstrated the informative value of a diligent and informed investigation of several human organs.⁶²⁹

⁶²² NAGEL V., Ueber die gute Verträglichkeit des Veramons in: Deutsche Medizinische Wochenzeitschrift (1926)

⁶²³ STARKENSTEIN EMIL, Die Toxizität des Veramons, Gemessen an seiner Wirkung auf die Atemgrösse in :Klinische Wochenschrift Vol.4(3) (1925)

⁶²⁴ STARKENSTEIN EMIL, Zur Frage der Entgiftung des Tabakrauches in Medizinische Klinik (1932)

⁶²⁵ STARKENSTEIN EMIL, Schwefelwasserstoff- Vergiftung , chronische , berufliche in: Sammlung von Vergiftungsfällen (1932)

⁶²⁶ STARKENSTEIN EMIL, Thallium Vergiftung , akute , als Folge fehlerhafter Arzneiverordnung und Arzneigabe in: Sammlung von Vergiftungsfällen (1934)

⁶²⁷ STARKENSTEIN EMIL / LANGECKER HEDWIG, Vergiftungen in: Klinische Fortbildung (1935)

⁶²⁸ STARKENSTEIN EMIL , Symptomatologie und Therapie der wichtigsten akuten Vergiftungen Nr. 27 Box 1, Archive Charles University Prague, no year detectable on publication

⁶²⁹ STARKENSTEIN EMIL, Zur Pharmakognosie der Hydnocarpus- und Gynocardiasamen Sonderabdruck in: der Naturwissenschaftlichen Zeitschrift Lotus Bd. 59, Heft 5 (1911)

b) Biology

Starkenstein`s work shows an involvement of knowledge from the field of pharmaceutical biology in particular in the field of pharmacognosy^{630,631,632,633} and phytotherapy⁶³⁴, but also deals with observations from other biological realms, such as the animal kingdom^{635,636}. Being aware of the fact that many natural extracts and materials in fact represent a mixture of several substances rather than clearly defined single ones, he directed his attention to the precise classification of pharmacologically active ingredients and their preparation and extraction of particular parts of the plant such as leaves, seeds and flowers. This classification represents the basis for a drug synthesis of specific compounds and pharmaceutical standardisation of extracts to gain a concretely defined content of ingredients to thereby positively affect therapeutic factors, such as exact dosability and chemical stability.

The profound interest for a further understanding of medically active constituents , can be shown on the example of extracts from “*urtica dioica*” and “*urtica urens*” , two plants of the *Urticaceae*, the stinging nettle family. Focusing on symptoms such as pruritus, burning sensations and swelling of the skin “*Quaddelbildung*” in self- and animal experiments, Starkenstein differentiates several compounds such as the causative formic acid from other components in the plant like phytosterols, flavonoids or coumarin derivates. Additionally, he discovered, that excessive heating or poorly stored, old plant material showed a limited pharmacological effect regarding the observed symptoms, probably due to catalytic reactions of the formic acid.⁶³⁷

Chemical in- depth investigations and classifications of alkaloids, such as morphine, that are obtained by plants of the *Papaveraceae* family also played a crucial role in Starkenstein`s biological research. Thereby he investigates both chemical properties such as resistance of

⁶³⁰ STARKENSTEIN EMIL, Die Papaveraceenalkaloide in: Handbuch der experimentellen Pharmakologie (1924)

⁶³¹ STARKENSTEIN EMIL, Pharmakologische und chemische Untersuchungen über die wirksamen Bestandteile der *Urtica dioica* und *Urtica urens* in: Archiv für experimentelle Pathologie und Pharmakologie 172 (1933) pages 137–148

⁶³² STARKENSTEIN EMIL, Zur Pharmakognosie der *Hydnocarpus*- und *Gynocardiasamen* Sonderabdruck in: der Naturwissenschaftlichen Zeitschrift Lotus Bd. 59, Heft 5 (1911)

⁶³³ STARKENSTEIN EMIL, Über die Beeinflussung der Wirkung des schwarzen Kaffees durch Milchezusatz in :Therapie der Gegenwart (1932)

⁶³⁴ STARKENSTEIN EMIL, Über Arzneikombinationen in: Prager Medizinische Wochenzeitschrift (1913)

⁶³⁵ STARKENSTEIN EMIL, Über den Nachweis von Glykogen bei Meeresmolusken speziell bei Cephalopoden und Aplysien in: Hoppe-Seyler`s Zeitschrift für Physiologische Chemie (1912)

⁶³⁶ STARKENSTEIN EMIL, Die Bedeutung der biochemischen Artenmerkmale für Entwicklungsgeschichtliche Fragen in: Journal of Physiology in the USSR (1937)

⁶³⁷ STARKENSTEIN EMIL, Pharmakologische und chemische Untersuchungen über die wirksamen Bestandteile der *Urtica dioica* und *Urtica urens* in: Archiv für experimentelle Pathologie und Pharmakologie 172 (1933) pages 137–148

morphine extracts against decay and bacteria, and its accessibility to titrimetric methods of analysis but also aspects chemical constitution of the molecule and his natural derivates. Within this publication Starkenstein clearly demonstrates a systematic analysis of the various compounds and thereby preparing the ground for a pharmacopoeia like summary of the relevant pharmacologically active compounds of the investigated plants.⁶³⁸ Guidance on the safe use of plants, depending on their level of phytochemicals such as oxalic acid in rhubarb, also are reflected within Starkenstein's research and provide practical and concrete answers, again basing on exact determination of the individual content in the organ or preparation in question.⁶³⁹ Further practical research involves the systematic classification of several plants which were used for oil extraction *Hydnocarpusöl* or *Gynocardiaöl* and subsequent margarine production through microscopic applications which served to distinguish toxic and non-poisonous species.⁶⁴⁰ Practical investigations from everyday life such as adding milk to coffee and the resulting implications on the pharmacological activity of the contained biological agents like caffeine are also being examined. The actual aim is to understand variations of active ingredients within several plants one the one hand but also to characterize their pharmacological properties correctly, e.g. in terms of complexation with other accompanying substances.⁶⁴¹

Within the realm of animals and plants, Starkenstein used both chemical and biochemical methods to define and differentiate species, basing on their individual purine metabolism: "*Unter Berücksichtigung der Endprodukte des Purinstoffwechsels folgende vier Gruppen unterscheiden: I. Kaltblütler (Fische und Amphibien) II. Vögel und Reptilien III. Säugetiere IV. Mensch und Menschenaffen.*"⁶⁴² In this context he describes Phase I reactions of biotransformation processes such as redox reactions systematically and points out genetic differences in species, such as the lack of certain enzymes in humans and other hominids: "*Da diese Fähigkeit (Harnsäureabbau) lediglich auf dem Vorhandensein einer Urikooxydase beruht, so ist eben das Verschwinden dieses Ferments bei höheren Affen und beim Menschen nur der Ausdruck des Rudimentärwerdens dieser nicht mehr notwendigen Funktion.*"⁶⁴³

⁶³⁸ STARKENSTEIN EMIL, Die Papaveraceenalkaloide in: Handbuch der experimentellen Pharmakologie (1924)

⁶³⁹ STARKENSTEIN EMIL, Ist Rhabarbermus giftig? Nr. 64. Box 2, Archive, no year detectable on publication

⁶⁴⁰ STARKENSTEIN EMIL, Zur Pharmakognosie der Hydnocarpus- und Gynocardiasamen Sonderabdruck in: der „Naturwissenschaftlichen Zeitschrift Lotus“ Bd. 59, Heft 5 (1911)

⁶⁴¹ STARKENSTEIN EMIL, Über die Beeinflussung der Wirkung des schwarzen Kaffees durch Milchzusatz in: Therapie der Gegenwart (1932)

⁶⁴² STARKENSTEIN EMIL, Die Bedeutung der biochemischen Artenmerkmale für Entwicklungsgeschichtliche Fragen in: Journal of Physiologie in the USSR (1937)

⁶⁴³ Ibidem

More recent findings from 2010 that also deal with the loss of this enzyme, suggest possible evolutionary reasons for this fact mentioned by Starkenstein, which are physiological and cognitive benefits in humans.⁶⁴⁴

c) Pharmacology

The areas within Starkenstein's pharmacological research are naturally widely spread and encompass both basic research^{645,646,647,648}, and also clinical aspects and research questions.^{649,650,651} His own understanding of *Modern Pharmacology* clearly differentiates between traditionally handed down and passed on healing methods one the one hand and empirical -experimental investigations that imply reproducible laboratory and in- vivo observations.⁶⁵² The perceived contribution to an in- depth pharmacological understanding is based not least because of the introduction of several objectifiable variables such as pathogenesis, experimental and observational conditions etc.

Within his basic pharmacological research he takes a close look at mechanisms of activation, stimulation or inhibition of individual pharmaceuticals and tries to differentiate those effects into a central or peripheral ones. Thereby he applies his physiological knowledge and observations in order to draw conclusions for the suspected underlying pharmacological cause: *“Atemfrequenz verlangsamt und Einatmung vertieft, so dass das Minutenvolumen gleich bleibt” (...)* *“Beweis, dass die Morphinaufregung der Katze als Folge einer zentralen Lähmung ist, lässt sich aber auch durch den antagonistisch- pharmakologischen Versuch einbringen”*⁶⁵³

⁶⁴⁴ ÁLVAREZ-LARIO BONIFACIO / MACARRÓN-VICENTE JESÚS, Uric acid and evolution in: *Rheumatology*, Volume 49, Issue 11 (2010)

⁶⁴⁵ STARKENSTEIN EMIL, Gibt es erregende Wirkungen des Morphins? In: *Prager Archiv für Tiermedizin und vergleichende Pathologie* (1926)

⁶⁴⁶ STARKENSTEIN EMIL, Antagonismus und Synergismus in: *Deutsche Medizinische Wochenzeitschrift* (1926)

⁶⁴⁷ STARKENSTEIN EMIL, Synergismus und Antagonismus in Veramon in: *Deutsche Medizinische Wochenzeitschrift* (1926)

⁶⁴⁸ STARKENSTEIN EMIL, Weitere Beiträge zur Pharmakologie und Physiologie des Eisens in: *Klinische Wochenschrift* (1926)

⁶⁴⁹ STARKENSTEIN EMIL, Verhandlungen der deutschen pharmakologischen Gesellschaft Konstitution und Wirkung anorganischer Verbindungen in „Verlag von F.C.W Vogel in Leipzig“ 1926 Nr. 77 Box 2 Charles Archive

⁶⁵⁰ STARKENSTEIN EMIL, Die pharmakologischen Grundlagen der kombinierten Arzneitherapie in: *Apothekerzeitung* (1926)

⁶⁵¹ STARKENSTEIN EMIL, Therapeutischer Wert und chemische Wertigkeit der Eisenpräparate in: *Therapie der Gegenwart* (1928)

⁶⁵² STARKENSTEIN EMIL, Das biologische Denken in der Pharmakologie in: *Die medizinische Welt* (1934)

⁶⁵³ STARKENSTEIN EMIL, Gibt es erregende Wirkungen des Morphins? In: *Prager Archiv für Tiermedizin und vergleichende Pathologie* (1926)

Starkenstein's pharmacological research often links (patho)-physiological questions such as inflammatory processes to Experimental Pharmacology and investigates locally restricted symptoms distinguishing them from systemic inflammatory diseases. This then in effect provided the rational basis for a in- depth understanding of future possible targets of the following pharmacotherapy.⁶⁵⁴ This principle and understanding of clinical and Experimental Pharmacology to understand as much presenting symptoms of a disease or medical condition as possible and then to differentiate them according to their relevance and accessibility for treatment can be seen as Starkenstein's maxime in research over all indications, particularly due to the fact that pharmacological effects often manifest themselves in various organs.⁶⁵⁵ Another example of this multidisciplinary approach within the medical sciences is looking at physiological determinants such as the mineral balance of the body or (colloid) osmotic pressure: *“Die Fähigkeit des Organismus den Gleichgewichtszustand in seinem Mineralhaushalt zu erhalten , ist die wichtigste Voraussetzung für die Erhaltung der Funktionen der Körperflüssigkeiten”*⁶⁵⁶

Further pharmacological research also aims at the differentiation of individual drug targets and the efficacy in combination preparations, such as antipyretics, narcotics or cardiac drugs.⁶⁵⁷

His considerations in terms of synergism and antagonism of drugs also lead to a refinement and a re-evaluation of pharmacological rules, as he identifies several single steps which then lead to a final pharmacological and then physiologically visible effect. As an example for that he mentions pharmacological actions on the heart , which can be differentiated into activation conduction and electrical propagation of the heart itself but also outside of cardiac- autonomic regulation like an innervation via the sympathetic of parasympathetic nervous system. In terms of Emil Bürgi's rule *“Arzneien mit gleichem Endeffekt geben bei Kombination ein additives Wirkergebnis, wenn sie gleiche, und ein überadditives wenn sie ungleiche pharmakologische Angriffspunkte haben”*⁶⁵⁸, Starkenstein criticises the oversimplification and

⁶⁵⁴ STARKENSTEIN EMIL, Symptomatische Therapie auf experimentell pharmakologischer Grundlage in: Therapeutisches Monatsheft (1917)

⁶⁵⁵ STARKENSTEIN EMIL, Klinische Pharmakologie. Theorie und Praxis am Krankenbette aus einem Vortrag am Feldärztlichen Abend in Lublin am 16. März 1918

⁶⁵⁶ STARKENSTEIN EMIL, Mineralstoffwechsel und Ionentherapie in: Deutsche Medizinische Wochenzeitschrift (1924)

⁶⁵⁷ STARKENSTEIN EMIL, Die pharmakologische Bewertung der Chinin-Digitaliskombination bei Herzkrankheiten in: Deutsche Medizinische Wochenschrift, 3/1922, Vol.48(13) (1922) pp.414-416

⁶⁵⁸ BÜRGI EMIL, Die Arzneikombinationen in: Berlin Verlag von Julius Springer (1938)

its limits to predict pharmacological interactions accurately and comprehensively.⁶⁵⁹ He also recommends to classify pharmaceutical compounds as specific in a pharmacological sense “*spezifische ätiologische Therapie*”⁶⁶⁰ in case they demonstrate a direct and causal relation to the symptom being present. In case of bactericidal effects, Starkenstein classifies many antibiotics of his time as aetiologic and thus in a causal relation to the infection but labels them as “*nicht spezifisch*”⁶⁶¹, implying that exact pharmacological target still remained unclear.

In order to contribute to a more profound comprehension of pharmacological mechanisms and drug targets, Starkenstein integrates several physiological considerations inside and outside the target organ, while testing secretory, neural, and motoric functions and structures as holistically as possible. Those experimentations can be demonstrated on his quantitative analysis of forced diuresis by the drug *Atophan* considering previous fluid intake and route of administration: “*Gleichzeitig wird von Atophan die Ausscheidung von Harnsäure und Azeton, während die Chloride nur parallelgehend mit der Diurese vermehrt ausgeschieden werden (...) Als Ursache dieser Wirkungen kann einerseits eine direkte Beeinflussung der sezernierenden Elemente, andererseits eine lähmende hemmender Nerven (Sympathikuslähmung) angenommen werden. Diese Frage wird als unentschieden diskutiert*”⁶⁶² Another multidisciplinary example for linking physiological knowledge to pharmacological use can be stated on his research on respiratory processes where he deals with neurochemical, physical-chemical and mechanical processes such as oxygen-uptake, transport in the human body and respiratory stimulation of depression caused by pharmaceutical compounds. At the same time he describes pharmaceutical properties of expectorants based on their chemical structure and establishes their pharmacological and thus pharmacotherapeutic potential: „*Die früher als Hustemittel bezeichneten Saponinhaltigen Drogen erweisen sich als stark sekretolytisch wirkend, wobei als Grundlage dieser Wirkung die Wechselbeziehung der Saponine mit den Sterinen und eine dadurch bedingte Permeabilitätssteigerung angenommen werden muss.*”⁶⁶³

⁶⁵⁹ STARKENSTEIN EMIL, Antagonismus und Synergismus in: Deutsche Medizinische Wochenzeitschrift (1926)

⁶⁶⁰ STARKENSTEIN EMIL, Die Definition der ätiologischen Therapie und der unspezifischen omnizellulären Resistenzsteigerung und Ihre Bedeutung der Infektionskrankheiten in: Tierärztliches Archiv (1922)

⁶⁶¹ Ibidem

⁶⁶² STARKENSTEIN EMIL, Über die pharmakologische Beeinflussung der Nierenfunktion in: Experimentelle Pathologie und Pharmakologie (1922)

⁶⁶³ STARKENSTEIN EMIL, Pharmakologie der Atmung Vortrag am 8. Ärztlichen Fortbildungskurs in den Kurorten der Hohen Tatra von 31. Mai bis 4 Juni 1936

The role of iron metabolism e.g. with regards to erythropoiesis is one central part of Starkenstein's pharmacological research, in which he also reflects upon physiological theories "*Bausteintherapie*" and "*Reiztherapie*"⁶⁶⁴, at a time in which concrete hormonal influences e.g. via erythropoietin were unknown. Despite this missing link, Starkenstein conclusions basing on his and others experiments, suggested correctly that both theories were not conclusive or outright completed, as the information base was insufficient: "*Eisen... eine Reizwirkung aufs Knochenmark als Blutbildungsstätte (...) darüber lagen mehr Vermutungen als experimentelle Beweise vor.*"⁶⁶⁵

Further pharmacologically extensive investigations concern adaptive and innate immune responses in regards to white blood cell activity, in which Prof. Starkenstein describes a inhibitory effect of *Atophan* on leukocytes⁶⁶⁶, a assumed connection to calcium homeostasis⁶⁶⁷ and potential electrostatic interaction and shift of fluids leading to a reduced permeability of capillary vessels.⁶⁶⁸

d) Pharmacotherapy

Basing on those basic pharmacological considerations, Starkenstein also draws conclusions for practical and bedside implications in clinical pharmacotherapy, in order to minimize drug interaction and accumulation: "*Eine derartige gegenseitige Beeinflussung mehrerer gleichzeitig verordneter Arzneimittel kann eine vollkommene Änderung ihrer Wirkung zur Folge haben, die sich ebenso im Sinne gesteigerten als auch herangesetzten Effektes äußern kann*"⁶⁶⁹. By classifying pharmaceuticals as single or combined drugs, "*Simplica*" and "*composita*", he advocates that prescription of medication should be based on causal factors instead of treating various symptoms. Thereby he references not only the diverse pharmacological possibilities of drug actions, but also biological and chemical incompatibilities that can be caused by galenic formula, solubility, blending behaviour or even chemical reactions between individual substances.⁶⁷⁰

⁶⁶⁴ STARKENSTEIN EMIL, Zur Analyse der pharmakologischen und Physiologischen Wirkungen des Eisens in: Institut de recherches physiologiques de moscou (1935)

⁶⁶⁵ Ibidem

⁶⁶⁶ STARKENSTEIN EMIL, Die Wirkung der Phenylchinolinkarbonsäure (Atophan) auf die Leukozyten in: Deutsche Medizinische Wochenzeitschrift (1922)

⁶⁶⁷ STARKENSTEIN EMIL, Die physiologischen und pharmakologischen Grundlagen der Kalziumtherapie in: Therapeutische Monatshefte (1921)

⁶⁶⁸ STARKENSTEIN EMIL, Die Beeinflussung der elektrostatischen Ladung der Gewebe durch Arzneistoffe in: Biochemische Zeitschrift (1931)

⁶⁶⁹ STARKENSTEIN EMIL, Die pharmakologischen Grundlagen der kombinierten Arzneitherapie in: Apothekerzeitung (1926)

⁶⁷⁰ Ibidem

Further recommendations on pharmacotherapy basing on previous research can be found in the treatment of kinetosis “*Pharmacotherapie der Seekrankheit*”⁶⁷¹ and “*Die Seekrankheit*”⁶⁷², where he pays attention to the genesis of objective and subjective vagotonic symptoms: “*Unlustgefühle, Niedergeschlagenheit, Schwäche, Müdigkeit, Angstgefühle, Apathie, Willenlosigkeit. (...) Störungen der Darmfunktion*”⁶⁷³ Instead of being satisfied with the treatment of those symptoms, Starkenstein’s objective is to recommend a causal therapy of the vestibular organs through a evaluation of the treatment with hypnotic, sedative or anticholinergic actions. Basing on previous experiments with dogs, and then self-experimentations in order to assess the spectrum of adverse events, Starkenstein recommends a combination of hyoscyamine and scopolamine, two alkaloids that show a positive therapeutic synergism and antagonism in terms of side effects. Those (pre)- clinical experiments, Starkenstein also compares his findings to more than six hundred case reports dealing with motion sickness and concludes by not only advising on the drug combination but also the correct timing of its intake:

*„Wir hatten die Erfahrung gemacht, dass die prophylaktische Verabreichung bei Beginn der Reise oder spätestens beim Anfang des Unwohlseins , jedenfalls aber noch bei rechtzeitig vor dem Erbrechen , sowohl hinsichtlich des absoluten Erfolges , als auch hinsichtlich der Zeitdauer der Wirkung , die besten Ergebnisse zeigte.“*⁶⁷⁴

Within his reflections of pharmacotherapeutic concepts and drug use, Starkenstein committed himself also to questions in the field of *balneology*⁶⁷⁵, pharmacological intervention on inflamed mucous membranes⁶⁷⁶, therapeutic narcosis induction⁶⁷⁷, dietetics and nutritional supplements⁶⁷⁸ or “*Adsorptionstherapie*”⁶⁷⁹.

In the context of balneology, Starkenstein gave a talk in Carlsbad in 1930 about medically used thermal waters in which he aimed at a contextualisation of their hypothetical effects with his knowledge about chemical reactions of the individual components in those natural

⁶⁷¹ STARKENSTEIN EMIL, *Pharmakotherapie der Seekrankheit* in: *Medizinische Klinik* (1927)

⁶⁷² STARKENSTEIN EMIL, *Die Seekrankheit* in: *Neue deutsche Klinik* (1932)

⁶⁷³ STARKENSTEIN EMIL, *Pharmakotherapie der Seekrankheit* in: *Medizinische Klinik* (1927)

⁶⁷⁴ *Ibidem*

⁶⁷⁵ STARKENSTEIN EMIL, *Balneologie und Balneotherapie* in: *Internationaler Ärztlicher Fortbildungskursus* (1931)

⁶⁷⁶ STARKENSTEIN EMIL, *Die pharmakologische Beeinflussung entzündeter Schleimhäute (Zum Problem der Wirkung von Augen-, -Mund-, - und Gurgelwassern)* in: *Medizinische Klinik* (1933)

⁶⁷⁷ STARKENSTEIN EMIL, *Verein deutscher Ärzte in Prag* in: *Medizinische Klinik* (1933)

⁶⁷⁸ STARKENSTEIN EMIL, *Diätetika* in: *Sudetendeutsche Apothekerzeitung* (1936)

⁶⁷⁹ STARKENSTEIN EMIL, *Wandlungen in der Adsorptionstherapie* in: *Sonderabdruck aus der Pharmazeutischen Presse* (1930)

remedies. Thereby he made clear, that from a scientific point of view, both the nature of the ionic bounds of each salt, its dissociation and also subsequent chemical reactions in the water play a role in pharmacological activity: “*In vielen Fällen (ist) die Wirkung des Kations von dem jeweiligen Anion so weitgehend abhängig, dass in einzelnen Fällen die Wirkung des Kations also des eigentlichen Arzneistoffes vollkommen aufgehoben wird, wenn es mit dem unrichtigen Anion verbunden erscheint.*”⁶⁸⁰ Due to the complexity of possible chemical reactions and the lack of knowledge of the exact elements that might lead to the anticipated medical effects, Starkenstein pointed out the limitations to fabricate artificial water- soluble crystals as medicinal products in the laboratory: “*Heute wo wir die die große Bedeutung des Erhaltenbleibens des natürlichen Ionengemisches als Grundlage für die Wirkung immer deutlicher erkennen, gewinnt auch die Forderung immer größere Bedeutung, die natürliche Heilkraft in unveränderter Form zu erhalten. Versuche durch chemische Methoden die "wirksamen Bestandteile" zu isolieren und womöglich am liebsten zur Kristallisation zu bringen, können zu keinem vollen Erfolg führen, da sich die Kraft der von der Natur organisierten Gemenge nicht restlos auf die daraus gewonnenen Kristalle übertragen lässt.*”⁶⁸¹

Further reflections on prophylaxis and therapy also comprise more sensitive areas of the human body such as inflamed mucous membranes in the eye or the naso- pharyngeal tract. Besides mentioning physical measures “*Schleimhautwaschung*”⁶⁸² he differentiates pharmacological effects into astringents, antiphlogistic drugs or antiseptic substances while considering local and systemic causes. Finally, clinical recommendations, basing on that pharmacological pre- analysis are given which can be shown exemplarily on the treatment option of sore throats: Starkenstein suggests the use of oral dosage forms that ensure a long retention time in the throat, which could be achieved by a chewing gum with medical additives more easily than with drug in pill or liquid form: „*allein schon wegen der besseren Durchfeuchtung der Mund- und Rachenhöhle ein therapeutischer Wert zugesprochen werden kann, dann aber auch weil durch das lange Verweilen des Stoffes in der Mund - und Rachenhöhle, jener Kontakt zwischen Arzneistoff (...) und Mund- und Rachenschleimhaut erreicht wird, der dem Ziele der Therapie entsprechend hier angestrebt wird.*”⁶⁸³

⁶⁸⁰ STARKENSTEIN EMIL, Balneologie und Balneotherapie in: Internationaler Ärztlicher Fortbildungskursus (1931)

⁶⁸¹ Ibidem

⁶⁸² STARKENSTEIN EMIL, Die pharmakologische Beeinflussung entzündeter Schleimhäute (Zum Problem der Wirkung von Augen-, - Mund-, - und Gurgelwassern) in: Medizinische Klinik (1933)

⁶⁸³ Ibidem

In a oral presentation from October 20th 1933, Prof. Starkenstein focusses on the therapeutic influence of narcotics in terms of onset of their effect and route of application. He identifies factors such as lipophilicity and dissociation processes in quantitative extraction and distribution experiments and divides narcotics into those with a immediate onset of pharmacological action e.g. and those with a delayed one. He emphasizes the boundaries of clinical controllability of injectable anesthetics, compared to inhalation anesthesia and advocates for a moderate use of narcotics with a rapid onset such as barbituric acid derivates.

As the duration of the pharmacological effect of intravenously applied anesthetics also depends on distributive, metabolic as well as on elimination processes, he thereby also considers accumulation through a saturation of metabolic capacities of the human body: *“Abbau von Arzneistoffen im Körper sehr bald ein Maximum erreicht hat”*⁶⁸⁴ In this context, Starkenstein points out the nonlinearity of dose and effect to mitigate the risk of toxic overdoses in practical use: *“ Wir müssen uns vor Augen halten, daß der Abbau der in den Kreislauf gebrachten Substanz nicht gleichmäßig vor sich geht (...) Es darf aus diesem Grunde nicht geschlossen werden , daß eine Dosis , die für eine 15 Minuten lange Narkose brauchbar ist, verdoppelt werden soll. , wenn eine halbstündige Narkose erforderlich ist“*⁶⁸⁵

Within the broad area of possible therapeutic remedies, Starkenstein clearly distinguishes pharmacotherapeutic concepts basing on pharmaceutical interventions from dietetics and nutritional science. In doing so he accentuates the privileged position of medical substances with regard to their underlying pharmacological action and also in terms of its legal implications: *“Waren (...)entgegen diesen Grundsätzen, offizinelle oder für Heilmittel erklärte Stoffe enthalten, oder die als Heilmittel angepriesen werden, sind keine Lebensmittel”*.⁶⁸⁶

With contrast to pharmaceuticals, he defines slimming aids and ailments to reduce weight differently, as they simply vary in terms of composition, compared to ordinary food: *“Es zählen namentlich nur Zubereitungen zu den diätetischen Präparaten , die auf Trockensubstanz bezogen ,einen höheren Gehalt an Eiweißkörpern besitzen als die normale Nahrung“*⁶⁸⁷

The therapeutic use of adsorbents within a range of clearly defined medical indications in the gastrointestinal tract such as dyspepsia or bacterial intoxications are investigated by

⁶⁸⁴ STARKENSTEIN EMIL, Verein deutscher Ärzte in Prag in: Medizinische Klinik (1933)

⁶⁸⁵ Ibidem

⁶⁸⁶ STARKENSTEIN EMIL, Diätetika in: Sudetendeutsche Apothekerzeitung (1936)

⁶⁸⁷ Ibidem

Starckenstein in terms of the pharmacotherapeutic concept of “*Adsorptionstherapie*”.⁶⁸⁸ *Carbomucil*, a combination preparation of medicinal charcoal and bulking agents practically combines the ability to bind toxins due to the large internal surface of the medicinal charcoal and to eliminate them with aid of the stimulating effect of the bulking agents on the intestinal peristalsis.

Starckenstein recommends the use of this combination in case of uncomplicated non- acute complaints such as “*Gärungsdyspesien*”⁶⁸⁹ or “*Sommerdiarrhöen der Kinder bei einfachen Magen- und Darmkatarrhen*”⁶⁹⁰, whereas he advises against its use in case of intoxications which demand a rapid detoxification. He demonstrates the further beneficial physiological aspects of this simultaneous use of both substances which are the enhancing effects on bulking agents on the medicinal charcoal, as the adsorption capacity is maintained through the moisturing effect of the bulking agent on the intestine: “*Durch die Kombination der Kohle mit dem erwähnten Quellstoff dagegen wird bewirkt , daß der Quellstoff dauernd Wasser durch den Darm mitführt, so daß er der Kohle selbst gewissermaßen während der ganzen Passage durch den Darm ein feuchtes Milieu schafft, wodurch die Kohle bis zum Verlassen des Darms ihre Adsorptionskraft behält.*”⁶⁹¹

e) Pharmaeconomy and prescriptions

Starckenstein evaluated drug actions not only in pharmaceutical, pharmacological or clinical aspects⁶⁹² but also in terms of their pharma-economic value.^{693,694}

In his view, medical prescriptions did not only present a simple written communication between physician and pharmacists, but in fact a testimony of the physician’s capability regarding his scientific knowledge, medical skills as seen in diagnosis and therapy but also proof of personal liability towards the patient. Expressing strong criticism with regards to those obligations, he opposes a stereotype- like use of medicines without addressing patient’s individual needs. Instead he suggests a three step process in prescribing, starting with a exhaustive analysis of all presenting symptoms followed by a individualised combination of

⁶⁸⁸ STARKENSTEIN EMIL, Wandlungen in der Adsorptionstherapie in: Sonderabdruck aus der Pharmazeutischen Presse (1930)

⁶⁸⁹ Ibidem

⁶⁹⁰ Ibidem

⁶⁹¹ Ibidem

⁶⁹² STARKENSTEIN EMIL, Die allgemeinen pharmakologischen Grundlagen für eine rationale Arzneiverordnung in: Ergebnisse der gesamten Medizin Nr. 69b Charles Archiv Box 1 no year detectable on publication

⁶⁹³ STARKENSTEIN EMIL, Sparsame Arzneiverordnung in: Beiträge zur ärztlichen Verordnung (1928)

⁶⁹⁴ STARKENSTEIN EMIL, Neue pharmakologische Richtlinien für die Eisentherapie in: Medizinische Klinik (1926)

medications, serving to reset all organ functions to a normal and healthy state, while reducing inter-medication errors and side effects at the same time. Besides those pharmacological interactions he also deals with pharmaceutical interactions which could limit optimal drug effects: “*Neutralisation, Entmischung oder Unmischbarkeiten, Löslichkeiten, Fällungsreaktionen, Oxydationsreaktionen*”.⁶⁹⁵

Via data from health insurances and drug codices the two extremes of either therapeutic nihilism on the one hand and a exorbitant drug production or prescription on the other one are reviewed critically. His critique refers to the enormous increase of “me- too” drugs and their marketing without therapeutic benefit or a clear medical indication, which accelerate patient’s demand for further treatment options and thereby again encourage further production of medications by the pharmaceutical sector.

Starkenstein describes these phenomena as “*Arzneihunger*” and the process of a almost exponential growth of supposed therapeutic options without clinical proof as a “*Circulus vitiosus*”.⁶⁹⁶ He takes offence at the enormous price spread of substances that are chemically totally identical or pharmacologically ineffective: “*unwirksamer Ferripräparate*” and “*chemisch vollständig identische Arzneistoffe , die sich nur durch ihren Namen unterschieden (---) enorme Preisunterschiede aufweisen können.*”⁶⁹⁷

The observed data includes statistical analysis of 17.718 prescriptions from the year 1921 in the region of Berlin and a comparison of the amount of available drugs from 1894 with around 400 pharmaceuticals to a number of 20000 drugs in 1920.⁶⁹⁸ A further publication also mentions in detail the excessively high numbers of iron tablets and other formulations and also indicates the socioeconomic burden its irrational use creates for the public.^{699,700}

In this area of tension that involves stakeholders such as patients, physicians, pharmacists and public health insurances, Starkenstein points out the complexity of bringing together their responsibilities , interests and needs. In the first place, the difficulty to translate basic research and its findings into concrete guidelines requires not only academic research but also practical clinical experiences in order to deliver valid recommendations for the prescribing

⁶⁹⁵ STARKENSTEIN EMIL, Die allgemeinen pharmakologischen Grundlagen für eine rationale Arzneiverordnung in: Ergebnisse der gesamten Medizin Nr. 69b Charles Archiv Box 1 no year detectable on publication

⁶⁹⁶ STARKENSTEIN EMIL, Sparsame Arzneiverordnung in: Beiträge zur ärztlichen Verordnung (1928)

⁶⁹⁷ Ibidem

⁶⁹⁸ Ibidem

⁶⁹⁹ Ibidem

⁷⁰⁰ STARKENSTEIN EMIL, Neue pharmakologische Richtlinien für die Eisentherapie in: Medizinische Klinik (1926)

process. In addition those expert recommendations then have to weigh up patient's interests and preferences with the best clinical evidence and also consider the demand for austerity in the case of national health funds. In this process of pluralistic interests, Starkenstein puts patients interests and their protection first before other considerations and highlights the significance of physician's therapeutic freedom : "*Dem Patienten freie Aeztewahl, dem Arzte freie Medikamentenwahl*"⁷⁰¹ In this context it also becomes obvious that this therapeutic freedom should base on the prerequisite of objective and critical assessment of the patients condition in terms of diagnosis and treatment and high ethical standards: "*stets nur das zu verordnen, was er sich selbst verordnen würde, wenn er krank wäre und wenn er die Medikamente selbst bezahlen müsste.*"⁷⁰² In his opinion this process could render a governmental overregulation unnecessary and thereby also bridge common interests also in terms of economy and patient's safety: "*die imperative Behinderung freizügiger Arzneiverordnung seitens des praktischen Arztes als eine falsche Methode bezeichnet werden muss um zu einer sparsamen und doch rationellen Arzneitherapie zu kommen*".⁷⁰³

3.3. Contribution to modern pharmacology

Contribution to modern pharmacology according to the interviewee

In line with the author's previous findings, Prof. van Emde Boas confirmed the main topics of Starkenstein's research within several pharmaceutical and chemical compounds such as "*iron, opiates, (...) pain killers (...) Veramon*"⁷⁰⁴ and also emphasized his achievements within a further pharmacological understanding of combinations drugs and especially their sound synergism in order to minimize adverse events and maximise therapeutic effects. Due to the fact that Prof. van Emde Boas did not read the entire academic work of his grandfather by himself, no details within the publications could be discussed with him.

3.3.1. Systematization and standardization, contribution to the development of modern pharmacopoeia and medical guidelines

The continuous process of systematization, standardization and harmonisation of pharmacopoeia e.g. from the former Austrio- Hungarian monarchy *Pharmacopoeia Austriaca octava* and more recent Czech editions, helped to define a clear pharmaceutical quality and thereby ensured therapeutical safety for patients. In this context, he criticises the unprecise

⁷⁰¹ STARKENSTEIN EMIL, Die Medikamentenverordnung der Krankenversicherungsanstalten sowie der Heilfonde und das Prinzip der sparsamen Arzneiverordnung in: Beiträge zur ärztlichen Fortbildung (1929)

⁷⁰² Ibidem

⁷⁰³ Ibidem

⁷⁰⁴ VAN EMDE BOAS Walter, qualitative interview via Skype on May 13th 2021

declaration of pharmaceutical compounds or preparations, as shown on sixty supposedly different medications, which in fact all consisted of the identical one compound, acetylsalicylic acid.⁷⁰⁵ Starkenstein's aspirations to contain the oversupply of medications that did not represent a true therapeutical innovation, but were in fact "me- too" products, were also reflected in his endeavour to create unified standards within the League of Nations: "*Schaffung einer internationalen für alle Staaten geltende Universal-Pharmakopöe*"⁷⁰⁶ Prof. Starkenstein discusses several ways of classifying those drugs both systematically and empirically e.g. through their chemical characteristics, alphabetically, physiological organ functions or their pharmacological effects on organs. At the same time he points out the difficulties in terms of physiological- pharmacological nomenclature as a more defined understanding for causative processes is required in order to avoid too wide definitions, that in effect then remain meaningless, e.g. "*Roborantia*".⁷⁰⁷

He also addressed questions regarding future areas of competence in this matter and emphasized pharmacists' primary ability and responsibility to be a driver in this necessary process: "*Indes sind diese Kenntnisse des Arztes doch nur mehr oder weniger theoretische und (...) nur ein kleiner Ausschnitt aus der Gesamterfahrung der Arzneibereitung, die der Apotheker in seinem Berufe erwirbt. Hinsichtlich dieses Hauptteiles der gesetzlichen Verordnungen, die in den Pharmakopoen enthalten sind, muss daher wohl dem Apotheker das erste Wort gelassen werden.*"⁷⁰⁸

Further areas of systematization involved the nomenclature of drugs in order enable a definite identification especially for physicians within the context of clinical use^{709,710} as well as recommendations edited in the manner of medical guidelines.⁷¹¹

Starkenstein pointed out the potential difficulties that emerged from naming medications after properties of the underlying raw material components "*Rohmaterial aus Pflanzen-, Tier- oder*

⁷⁰⁵ STARKENSTEIN EMIL, Die Aufgaben der Pharmakopoe für den Arzt und die Arzneiverordnung für den Apotheker und die Arzneibereitung und für die Arzneimittel- Industrie in: Beiträge zur ärztlichen Fortbildung (1930)

⁷⁰⁶ Ibidem

⁷⁰⁷ STARKENSTEIN EMIL, Tonika und Roborantia - Empirisch eingeführte Arzneimittel und ihre experimentell-pharmakologische Analyse in: Schweizerische Medizinische Wochenschrift (1934)

⁷⁰⁸ STARKENSTEIN EMIL, Die Aufgaben der Pharmakopoe für den Arzt und die Arzneiverordnung für den Apotheker und die Arzneibereitung und für die Arzneimittel- Industrie in: Beiträge zur ärztlichen Fortbildung (1930)

⁷⁰⁹ STARKENSTEIN EMIL, Zur Nomenklatur in Arzneimittelwerken (Nr 67.) Box 1 no journal or year detectable on publication

⁷¹⁰ STARKENSTEIN EMIL, Herkunft und Bedeutung der Arzneimittelnamen in: Naturwissenschaftliche Zeitschrift Lotos (1922)

⁷¹¹ STARKENSTEIN EMIL, Über Anwendung und Auswahl der Schlafmittel in: Beiträge zur ärztlichen Fortbildung (1921)

*Mineralstoffen*⁷¹² such as morphologic or physiological characteristics etc. instead of the explicit chemical IUPAC nomenclature. His concern was to facilitate the international unification of medically and practically used names for drugs for stakeholders in the prescription process, particularly physicians and pharmacists, acknowledging however that those names can also be chosen basing on origin, effectiveness or mode of action, indication area or function of the drug or even the discoverer.⁷¹³ Starkenstein's reflections on this matter suggest that he favoured an approach that helped to clearly distinguish drugs, and thus specific molecules to limit an excessive use of invented names, that either do not have any relation to the mentioned categories or lead to a multiple designation for one compound.

Systematically acquired knowledge and its summarisation in medical recommendations can be shown exemplarily in Starkenstein's publication about hypnotic and sedative drugs. Herein he discusses aetiology, pathophysiological aspects and clinical symptoms of insomnia and also differentiates between other diseases "*sekundäre Schlaflosigkeit*"⁷¹⁴, where sleeplessness is just a symptom instead of being the actual illness: "*Überreizung der Großhirnrinde*"⁷¹⁵

In further analogy with today's medical guidelines, Starkenstein also deals with the most relevant pharmacotherapeutic options to deal with insomnia and classifies the prevalent medications into sedative and hypnotic drugs, basing on their level of efficacy, mode of action, route of application and also their economic value.

3.3.2. Rational, evidence based pharmacotherapy

One of the most outstanding accomplishments of Starkenstein is his contribution to the development of a rational use of carefully previously investigated pharmaceutical compounds and thereby enforcing the principle of a more evidence based use of medications. In this respect he also managed to link preclinical, in- vitro experiments and knowledge to medical application and pharmacotherapeutic concepts. As an example of this approach, the complex of symptoms such as inflammation, pain, swelling, rash etc. is being addressed via a targeted antiphlogistic pharmacotherapy in "*Pharmakologie der Entzündung*"⁷¹⁶. Initially, pathophysiological causes such as leukocyte activation, changes in permeability and osmotic

⁷¹² STARKENSTEIN EMIL, Zur Nomenklatur in Arzneimittelwerken (Nr 67.) Box 1 no journal or year detectable on publication

⁷¹³ STARKENSTEIN EMIL, Herkunft und Bedeutung der Arzneimittelnamen in: Naturwissenschaftliche Zeitschrift Lotos (1922)

⁷¹⁴ STARKENSTEIN EMIL, Über Anwendung und Auswahl der Schlafmittel in: Beiträge zur ärztlichen Fortbildung (1921)

⁷¹⁵ Ibidem

⁷¹⁶ STARKENSTEIN EMIL, Pharmakologie der Entzündung in: Handbuch der normalen und pathologischen Physiologie (1929)

and activity within the inflamed tissue or other factors referring to the inflammation cascade are being carefully investigated. Only after investigating the underlying factors, Starckenstein addresses the potential pharmaceutical interventions, basing on also the previously investigated mode of actions of drugs e.g. “*Emmolentia*” or “*Muciliaginosa*” or astringents etc.⁷¹⁷ On this specific example, Starckenstein’s principle of synthesizing the best available evidence through preclinical animal experimentation, by defining the efficacy and safety of compounds, can be shown. This was followed by the inclusion of clinical experiences to assess real- world data and additionally a regular review of the literature to compare and contrast his findings with others.

Starckenstein’s consideration of that topic was not limited to academic research but also dealt with practical and legislative aspects of a rational, evidence based pharmacotherapy, as shown in his expert statement referring to a discussed amendment of pharmaceutical law from 1926. In essence, the subject matter of these negotiations referred to a more precise regulation of the pharmaceutical manufacturing process, as well as the way of distributing drugs and pharmaceuticals according to the current state of knowledge. This in fact also implied a more rigorous market access process for new drugs, which had to prove a truly innovative character as shown in superiority in either efficacy, better tolerability regarding side effects or at least advantageous aspects in terms of stability.⁷¹⁸ He mentions the successful development the following antipyretics and analgesic substances, which he considers as a therapeutic progress:

“*Cortex salicis - Acidum salicylicum- Natrium salicylicum*” and “*Acetanilid- Phenazetin*”
“*Antipyrin - Pyramidon*”⁷¹⁹

In order to assess and evaluate drugs systematically and objectively he suggests a comprehensive questionnaire, evaluating both the qualitative and quantitative composition of the pharmaceutical product and also addressing questions of safety etc. Besides his practical recommendations for drug approval, he also aimed at limiting business -to- layman advertisement ““*Kampf gegen die Prospektlüge*”⁷²⁰ , and also at clear and unambiguous declaration of preparations along with legal obligation to ensure the strict adherence to the stated ingredients.

⁷¹⁷ Ibidem

⁷¹⁸ STARKENSTEIN EMIL, Die Forderung genauer und unverschleierter Deklaration der Arzneimittel - Ein Aufruf an die gesamte Aerzteschaft zur Mitarbeit an der Rationalisierung der Arzneiverordnung und der Bekämpfung des Kurpfuschertums in: Beiträge zur ärztlichen Fortbildung (1933)

⁷¹⁹ Ibidem

⁷²⁰ Ibidem

Further evaluative efforts were undertaken not only in terms of precise classification and identification of pharmaceutical compounds but also with respect to their therapeutic interchangeability, basing on pharmacological and clinical aspects: *“Cardiazol das Erregungsmittel des Atem - und Vasomotorzentrums durch Digitalis zu ersetzen , bedeutet völlige Unkenntniss der Grundregeln der Arzneiverordnung. Ein Patient im Kollaps würde diesen “Ersatz“ mit dem Leben zu bezahlen haben!”*⁷²¹ It can be clearly stated on this example, that Starkenstein rejected a medically unfounded substitution of medications based on either pure political or economic motivations and instead focused on patient- centred interests and propagated therapeutic freedom of physicians in this context.⁷²²

In a academic talk in front of the Austrian Pharmaceutical Society on February 19th 1937 he evaluates the development from historic sources pertaining phenomena of healing principles such as subjective religious- mystical experiences, natural medicine and alchemical deliverances of healing.⁷²³ Though Starkenstein advocates for a objective evaluation and assessment of such reports, he acknowledges their historical value and potential benefit for future pharmacotherapy if investigated scientifically: *“Eine solche Geschichtsforschung lehrt uns auch das Gute , Wertvolle, Brauchbare unseres Arzenischatzes richtig zu werten und es von jenem wertlosen Ballast zu trennen , für den die Bezeichnung “Schatz” keineswegs gerechtfertigt ist.”*⁷²⁴ Starkenstein does explicitly not dismiss aspects of self-healing capacities of the individual *"vis medicatrix naturae"*⁷²⁵ a priori, but he conveys clearly that there needs to be a distinction between recoveries that are due to adaptive and innate immune responses of the human body and medical interventions on the other hand :

*"Wir werden es daher verständlich finden , daß überall dort wo der Arzt im Stadium der Selbstheilung irgendein Mittel verabreicht , also dann , wenn schon danke der dem Körper selbst innewohnenden Kräfte die Heilung einsetzt, dem verabreichten Mittel der Erfolg der sichtbar werdenden Heilung zugeschrieben wurde."*⁷²⁶

Starkenstein's stance on homeopathy and natural remedies such as herbal medicine varies widely, as he exposes the scientific limitations of the first concept explicitly and emphasizes

⁷²¹ STARKENSTEIN EMIL, Die pharmakologische Beurteilung des "Verzeichnisses" inländischer Heilmittel , die als Ersatz der ausländischen empfohlen werden in: Ärztliche Nachrichten (1932)

⁷²² Ibidem

⁷²³ STARKENSTEIN EMIL, Gemeinsame Wege der Pharmakologie und Pharmazie vom Heilkraut zur modernen Pharmakopoe - Vortrag gehalten in der österreichischen pharmazeutischen Gesellschaft in Wien, am 19. Februar 1937- Sonderdruck aus: Pharmazeutisches Monatsheft (1937)

⁷²⁴ Ibidem

⁷²⁵ Ibidem

⁷²⁶ Ibidem

the opportunities for drug discovery in terms of naturopathy. His critique on homeopathy is basing on the lack of causality and experimental reproducibility “*falschen Verallgemeinerung*”⁷²⁷ of the subjective observations “*Zufallsbeobachtungen*”⁷²⁸ that this theory is based on. In addition Starkenstein points out that those individual observations are generalized in a unscientific manner and thereby lead to false assumptions for pharmacotherapy.

The systematic investigation of medical plants and other naturally occurring living organisms based on analytical experimentation by contrast, contains the potential to isolate relevant pharmacologically active compounds and to make them available for therapeutic use in his opinion.⁷²⁹

His research on the appropriate treatment to cure typhus fever lead him to examine the cerebrospinal fluid of patients via serological testing and thus identifying the presence of absence of pathogens. Those methods helped to scientifically disprove medication schemes which were used but not causative to the underlying disease, e.g. camphor and digitalis or colloidal silver.⁷³⁰ According to his grandson, Starkenstein was considered an expert for the treatment of epidemic typhus, and was even sought out in the concentration camp for help when there was an outbreak during the Second World War.⁷³¹

3.3.3. Public Health aspects

The concept of Public Health has been defined in various ways throughout the last decades and frequently involves aspects of disease prevention and health promotion, as being reflected in several WHO definitions e.g. “*The art of applying science in the context of politics so as to reduce inequalities in health while ensuring the best health for the greatest number*”⁷³², basing on Acheson et al. (1988)⁷³³.

⁷²⁷ STARKENSTEIN EMIL, Gibt es ein Heilprinzip - Behandelt angesichts der Geschichte der Heilkunde in: Sonderabdruck aus Einheitsbestrebungen in der Medizin - Kongreß zur Förderung medizinischer Synthese und ärztlicher Weltanschauung - Verhandlungsbericht der 2. zwischenstaatlichen Tagung in Marienbad 14.- 17. 09. 1932

⁷²⁸ Ibidem

⁷²⁹ Ibidem

⁷³⁰ STARKENSTEIN EMIL, Beiträge zur Therapie des Fleckenfiebers: Untersuchungen der Cerebrospinalflüssigkeit bei Fleckfieberkrankheiten in: Medizinische Klinik- Wochenzeitschrift für praktische Ärzte (1917)

⁷³¹ VAN EMDE BOAS Walter, qualitative interview via Skype on May 13th 2021

⁷³² NAKAJIMA HIROSHI, The World Health Report 1998; in: Life in the 21st century: A vision for all. Geneva World Health Organization (1998) page 141

⁷³³ ACHESON DONALD, Public health in England in: The report of the committee of inquiry into the future development of the public health function, London, HMSO (1988)

Starkenstein dealt with those public health issues throughout his academic work, and focused on questions on hygiene^{734,735}, education and migration⁷³⁶, prevention of intoxications in both professional⁷³⁷ and personal domains^{738,739}, whereby he linked his clinical and pharmacological expertise with possible solutions of those social and cultural questions. Those suggestions for a improvement in terms of hygiene implied measures both on a individual and governmental level, advocating for medical care of vulnerable groups especially in terms of access to sanitary facilities and means of birth control, as well as the prevention of tuberculosis.⁷⁴⁰

A congress report of Starkenstein also displays his involvement and interest in issues such as dental hygiene, sanitary legislation both on municipal and federal level and public baths with regards to their purpose for public health.⁷⁴¹

Further aspects of disease prevention and health promotion aimed at raising awareness for the risks of acute intoxications within a every-day household context, due to improper storage, confusion between plants, but also dangers of chronic intoxications due to heavy metals or semimetals caused by the use of pewterware or arsenical substances in wallpapers and plaster.⁷⁴² In a case report from 1932, dealing with occupational poisoning, Starkenstein assesses the patient's health not only basing on the pathophysiological components, but also includes aspects of mental health in his considerations, considering the state of health thereby holistically through the involvement of psycho-social factors: *“Die Begutachter sehen in diesem ganzen Symptomkomplex eine Parallele zur sogenannten traumatischen Neurose: bei dieser entwickelt sich nach einem Unfall, zumal wenn er mit einer Hirnschädigung oder mit*

⁷³⁴ STARKENSTEIN EMIL, Hygienische und sanitäre Verhältnisse Polens in: Archiv für soziale Hygiene und Demographie (1917)

⁷³⁵ STARKENSTEIN EMIL, Die Einweihung des Deutschen Hygiene Museums in der II Internationalen Hygiene- Ausstellung in Dresden Nr. 170 Box 3, no year detectable on publication

⁷³⁶ STARKENSTEIN EMIL, Hygienische und sanitäre Verhältnisse Polens in: Archiv für soziale Hygiene und Demographie (1917)

⁷³⁷ STARKENSTEIN EMIL, Schwefelwasserstoff- Vergiftung , chronische , berufliche in: Sammlung von Vergiftungsfällen (1932)

⁷³⁸ STARKENSTEIN EMIL, Zur Frage der Entgiftung des Tabakrauches in: Medizinische Klinik (1932)

⁷³⁹ STARKENSTEIN EMIL, Vergiftungsmöglichkeiten in Schule und Haus und ihre Verhütung in: Hochschulwissen (1930)

⁷⁴⁰ STARKENSTEIN EMIL, Hygienische und sanitäre Verhältnisse Polens in: Archiv für soziale Hygiene und Demographie (1917)

⁷⁴¹ STARKENSTEIN EMIL, Die Einweihung des Deutschen Hygiene Museums in der II Internationalen Hygiene- Ausstellung in Dresden Nr. 170 Box 3, no year detectable on publication

⁷⁴² STARKENSTEIN EMIL, Vergiftungsmöglichkeiten in Schule und Haus und ihre Verhütung in: Hochschulwissen (1930)

einem starken Schreck einhergeht ein neurasthenischer, meist stark hysterisch verstärkter Krankheitskomplex”⁷⁴³

Here again, the evidence suggests that, in accordance with current definitions of health, “*Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity.*”⁷⁴⁴, Starkenstein involved several of those public health aspects, might they be individual, social, physiological or mentally driven into his professional work.

As a part of his efforts in public health, he also engaged in health education of the general public through societal commitment in non-profit associations such as “*Deutsche(r) Verein zur Verbreitung gemeinnütziger Kenntnisse in Prag*”⁷⁴⁵ and “*Lotos*”.⁷⁴⁶ On these occasions Prof. Starkenstein contributes to adult and national education e.g. in terms of folk medicine and the development of pharmacological understanding for those therapies also for lay audiences. His motivation to participate in this non- academic lectures can be seen in providing information in the first place, but at the same time to strengthen their individual responsibility and thereby to empower those communities, particularly in terms of preventing diseases: “*Wissen ist Macht und Wissen über das Geschehen, das sich beim Krankwerden ebenso wie beim Gesundwerden abspielt , gibt uns Macht und richtiges Verständnis über unser Handeln , das uns vor Krankheit bewahren kann*”⁷⁴⁷

3.4. Cross- case comparison of Prof. Starkenstein and Prof. Wiechowski

3.4.1. Areas of scientific research and contribution to modern pharmacology

Naturally there are a variety of commonalities in association with Wiechowski’s and Starkenstein`s research which is firstly due to their close academic collaboration and their linked teaching obligations, and also stemming from their overall approach to asses new drugs and chemical components in a way that necessarily affected several natural scientific and medical subjects.

⁷⁴³ STARKENSTEIN EMIL, Schwefelwasserstoff- Vergiftung , chronische , berufliche in: Sammlung von Vergiftungsfällen (1932)

⁷⁴⁴ WORLD HEALTH ORGANISATION; Basic documents, Forty- sixth edition, Including amendments adopted up to 31 December 2006.

⁷⁴⁵ STARKENSTEIN EMIL, Erkrankung und Heilung - Die Erforschung von Ursachen des Krankwerdens und des Gesundwerdens als Grundlage unserer Heilmethoden in: Sammlung gemeinnütziger Vorträge (1935)

⁷⁴⁶ STARKENSTEIN EMIL, in: Lotos Naturwissenschaftliche Zeitschrift, Band 67/68 (1920)

⁷⁴⁷ STARKENSTEIN EMIL, Erkrankung und Heilung - Die Erforschung von Ursachen des Krankwerdens und des Gesundwerdens als Grundlage unserer Heilmethoden in: Sammlung gemeinnütziger Vorträge (1935)

Within the chemical and pharmaceutical sciences both researchers utilized qualitative and quantitative pharmaceutical analysis, anorganic and organic chemistry to precisely characterize and understand substances on their molecular level, a necessity to draw exact conclusions and to predict later pharmacological activity of compounds. This also expanded to their nearly analogical way of conducting animal experiments, in which both researchers regularly included a variety of species and a spectrum of organ and tissue types to answer their preclinical research. Further common features are displayed in the choice of their involvement of physiological, biological, biopharmaceutical and toxicological aspects within answering wider pharmacological questions, however by looking at the concrete research output, more differentiating factors begin to emerge.

Though both dealt with biochemical research and shared a mutual interest in purine metabolism, Prof. Wiechowski's activities within this field are more extensive, particularly with regards to methodology, as seen on the developed procedure of pulverized animal organs, but also within biochemical analytics of body fluids and other fields such physiology and statistics. Starkenstein considered methodological implications as well within his research, however with the intention to ensure validity and to optimize systematic processes and thereby usually not with the underlying intention to create new methodological accesses. By contrast, Starkenstein put a greater emphasis on systematically examining toxicity profiles of chemical and pharmaceutical agents and linking those findings to further clinical observations, taking into account practical occupational and forensic questions. Wiechowski's research in this respect was usually limited to investigating those parameters with regards to drug metabolism and immediate physiological effects instead of wider clinical questions and implications.

The level of invasiveness within the conducted self-experimentation differed considerable between the two researchers, with Wiechowski performing painful experiments e.g. with uric acid injections or those holding the potential for severe addiction e.g. with cannabis. Starkenstein limited his self-experiments to less hazardous components such as glucose or salt water preparations for oral use or locally restricted dermal applications investigating the effects of non-toxic plant components.

Within the field of pharmaceutical biology Wiechowski's research addressed more fundamental questions dealing with the areas of taxonomy and secondary plant metabolism, which do not directly demonstrate a concrete association to therapeutic use. Though Starkenstein equally addressed those and other pharmacognostic questions he additionally

published data referring to medical and other application based issues, that involved recommendations for the safe or appropriate use of plants and their products. An analogy can be seen within the domain of physiology, in which Prof. Wiechowski aimed at further understanding of causal physiological and pathophysiological relations as a groundwork for establishing targets for subsequent pharmacological experiments, bringing them together with previous conclusions of other research. With this in mind, Starckenstein increased the clinical orientation of his pharmacological research in comparison to his predecessor, benefiting from his methodologically sound and thus explanatory research with regards to physiologically regulatory circuits and their pharmacological potential.

Building on this approach and at times on concrete results, Starckenstein put several pharmacological mechanisms into more concrete terms within pharmacotherapeutic approaches as seen on anti-inflammatory therapies, or the treatment of kinetosis etc. Although Wiechowski also established concrete pharmacotherapeutic concepts such as adsorptive therapy or the insuline treatments, his focus on theoretical basis and methods occupied a great deal of his work. Starckenstein, partly due to the good cooperation, but also due to genuine interest was then able to add further clinical but also pharmaeconomic aspects to his research and thereby to expand to further selected aspects of a rational and evidence based pharmacotherapy.

A quite illustrative example of understanding previous basic research correctly and of abstracting findings can be shown via the publication "*Richtige Beobachtungen und falsche Schlussfolgerungen*"⁷⁴⁸ from 1923. Here, Starckenstein explains how to deal with basic research information in accordance with practically and clinically obtained information in order to provide sound and informed decision for future pharmaceutical interventions, pointing out potential interpretation failures that need to be respected: "*Tatsächlich gibt es zwischen richtiger Theorie und richtig gedeuteter Erfahrung gar keine Gegensätze*" and "*unrichtigen Theorie verarbeitet*" or "*einfachen chemischen (Reaktionen)*" and "*biologischen Reaktionen*" and "*Zwischenglieder(n) geknüpfte(r) Folge(n)*".⁷⁴⁹

Herein he is differentiating between presenting symptoms and causative mechanisms of individual diseases, which need to be understood comprehensively in the first place before tackling them in the longer term. This in effect aimed to both promote and communicate academic research to broader health care circles, helping to implement academic findings on a

⁷⁴⁸ STARKENSTEIN EMIL, *Richtige Beobachtungen und falsche Schlussfolgerungen* in: *Grenzgebieten von Theorie und Praxis* (1923)

⁷⁴⁹ *Ibidem*

much broader scale in practice, which also has been documented in his efforts to address public health aspects explicitly.

Also in his own assessment , Starkenstein depicts the development within the Pharmacological Department in Prague under Wiechowski's influence as a reorientation towards biological and thus physiological elements within the pharmacological research that paved the way for later more refined clinical observations and questions: *“Die reine Chemie war zu jenen Zeiten als die experimentelle Pharmakologie geschaffen wurde , in ihrer Hauptrichtung Problemen nachgegangen , die eine direkte Beziehung zur Biologie nicht erlaubte”* and *“ausreichende Kenntniss der Drogen neue Wege für die pharmakologische Problemstellung erkannte”*⁷⁵⁰

3.4.2. Differences and similarities in the relation to the pharmaceutical sector

Though both Wiechowski and Starkenstein aimed at rationalising the use of medicines jointly, Starkenstein's direct contributions to a systematization and standardization of modern pharmacopeia and medical guidelines remain more pronounced, as seen in various publications on concrete indications and assistance in the development on a regulatory level. Wiechowski also played his part within individual test specification but was generally fewer involved in the establishment of guidelines and even less in legislative or economic considerations with regards to drugs.

An even more distinctive feature has to be seen in their relationship towards pharmacists in a community setting. While Wiechowski was quite pessimistic regarding the future prospects of the pharmaceutical profession within this primary care setting, though generally acknowledging their capabilities, Starkenstein rather envisioned the potential of a targeted cooperation while also providing more constructive ways of joint patient care. On the other hand, Starkenstein was criticizing excessive commercial developments driven by the pharmaceutical industry concretely and publicly, whereas Wiechowski indirectly aimed at altering social inequalities by implementing a socio-economic and thus affordable production for the general public. Both researchers maintained long- lasting and successful cooperations to pharmaceutical companies resulting in several medications and pharmaceutical products, however the cooperation within Starkenstein's exile in the Netherlands was due to external factors, to secure his and his families living after his expulsion from the University in Prague.

⁷⁵⁰ STARKENSTEIN EMIL, Die Pharmakologie in Prag und ihr Anteil an der Entwicklung der pharmakologischen Forschung und des pharmakologischen Unterrichts in: Medizinische Klinik (1929)

3.4.3. Degree of socio-political activities and humanist interests

Both researchers played an active part within higher education policies , however with quite different thematic focus and interests. Whereas Prof. Starkenstein was more involved in concrete pedagogic questions in term of didactics but also refining established structures within healthcare professions, Prof. Wiechowski rather focused on wider socio-political issues, apart from concrete occupational questions in the strict sense. This can be documented on his efforts for a national autonomy of universities but also in his vote of confidence in favour of politically discriminated individuals such as Jewish scholar Prof. Steinherz, but also in his activities as a member of the social democratic party and networks to other political institutions on a governmental level. According to his grandson, Prof. van Emde- Boas, Starkenstein had privately been rather conservative, but generally speaking an apolitical person, particularly in terms of public activities. *“He was in favour of the Czech Republic (...) but he was not actively participating in politics others than the activities in university (...) he was in all kinds of commissions etc.”*⁷⁵¹

Humanistic interests, such as art, historical contexts or religious matters were also quite pronounced with Wiechowski and Starkenstein , yet both individuals differed in terms of their concrete individual field of interest. While Starkenstein displayed a far- reaching curiosity in Jewish but also pharmaceutical and medical history with individual research, Wiechowski rather engaged in socialising in artistic circles and engaged in socio-political activities, also in the scope of associations. Basing on the several referenced sources , especially Starkenstein’s own publications and in – depth knowledge of German literature can be verified that exceeded common knowledge in this field, whereas Wiechowski’s focus of interest seemed to have been within visual fine arts and handicraft.^{752,753,754,755}

In a letter from Anna Wiechowski to Emil Starkenstein after her husband’s passing, dated March 19th 1929, she reports about a personal gift that she made her husband on a Christmas

⁷⁵¹ VAN EMDE BOAS Walter, qualitative interview via Skype on May 13th 2021

⁷⁵² LANGECKER HEDWIG, Wilhelm Wiechowski in: Lotos Nummer 77 (1929)

⁷⁵³ Montagsblatt aus Böhmen vom 13. April 1908 page 7

⁷⁵⁴ STARKENSTEIN EMIL, family archives c.o. Dr. W. van Emde Boas, Netherland, correspondence between (file 021) Anna Wiechowski- Starkenstein dated March 13th 1929

⁷⁵⁵ SPIRO KARL, Erinnerung an Wilhelm Wiechowski in: Die Medizinische Welt – ärztliche Wochenschrift Nr. 6 (1929)

occasion, a piece of pentelic marble “*Pentelimarmor*” supposedly of antique provenance “*Es besteht kein Zweifel, daß das kleine Marmorstück von einer Säule des Panthenons stammt*”⁷⁵⁶

The fact that Wiechowski kept this present all his life at his worktable indicates, a certain interest in this cultural asset, might this be because of his personal sensitivities, a historico-cultural interest “*künstlerischen Neigungen*”⁷⁵⁷ or a combination of both. Further hints to his interest in visual arts and craftsmanship can also be stated via his status within art associations but also through his dedication to establish the Pharmacological Unit within the German University, in which he helped organising the interiors also practically: “*Wiechowski bezog den Rohbau und widmete der Inneneinrichtung des Instituts seine ganze Kraft, ja er hat bei vielen Arbeiten selbst Hand angelegt (...) So hat er dann auch in diesen Räumen ein Institut geschaffen, das er zeitlebens durch Verbesserungen und Neueinrichtungen weiter auszugestalten bemüht blieb*”⁷⁵⁸

Religious convictions and ethical considerations undoubtedly played a role in the life of both researchers, though with a different emphasis regarding their beliefs and different ways of putting their ethical beliefs into practice.

Starkenstein’s close connectedness to Judaism and Jewish culture but also philosophical questions can be established through his publications and personal genealogical research but also through his grandson’s assessment within the qualitative interview. Wiechowski did not seem to feel strong affiliations to particular religious groups, instead had a certain sympathy for the idea of a cosmic and metaphysical order of things, that probably exceeded monotheistic dogmas.^{759,760} Much of common ground can be found in both their humanist-pacifist life philosophy, which was displayed by social courage and advocacy for socially marginalised groups e.g. within political activities but also within their academic research.

⁷⁵⁶ STARKENSTEIN EMIL, family archives c.o. Dr. W. van Emde Boas, Netherland, correspondence between (file 021) Anna Wiechowski- Starkenstein dated March 13th 1929

⁷⁵⁷ SPIRO KARL, Erinnerung an Wilhelm Wiechowski in: Die Medizinische Welt – ärztliche Wochenschrift Nr. 6 (1929)

⁷⁵⁸ LANGECKER HEDWIG, Wilhelm Wiechowski in: Lotos Nummer 77 (1929)

⁷⁵⁹ STARKENSTEIN EMIL, family archives c.o. Dr. W. van Emde Boas, Netherland, correspondence between Wiechowski and Starkenstein files 016 and 017

⁷⁶⁰ SPIRO KARL, Erinnerung an Wilhelm Wiechowski in: Die Medizinische Welt – ärztliche Wochenschrift Nr. 6 (1929)

3.4.4. Extent of contribution to preclinical research, Phase I-IV studies

Drug discovery and development dates back to ancient times, with a steady and continuous advancement of the methods and mandatory requirements for their scientific exploration, especially after the Second World War, with a preceding establishment of official bodies such as the U.S Food and Drug Administration.⁷⁶¹ The goals of preclinical and clinical trials are to objectively examine and assess the potential of pharmaceutical compounds, to investigate optimal pharmaceutical formulations to ensure aspects such as stability and efficacy of the compound while also evaluating pharmacological and toxicological properties on various levels.^{762,763} (III.5.)

Besides methodical guidelines that emerged over time within the pharmacological and clinical research in the 20th century, ethical standards were prescribed by law in answer to unconscionable conduct also via experiments in humans under the Nazi regime *Nuremberg Code 1947*⁷⁶⁴ and further elaborated within the *Declaration of Helsinki in 1964*⁷⁶⁵. Those ethical principles for any kind of research involving humans, primarily aim at setting the framework conditions under which clinical research may be conducted, putting patient interest and rights before all other scientific interests, taking their informed consent as a necessary basis.⁷⁶⁶

⁷⁶¹ JENKINS JEAN / HUBBARD SUSAN, History of clinical trials in: *Seminars in Oncology Nursing* 7(4) (1991) pages 228–234

⁷⁶² Ibidem

⁷⁶³ VAN NORMAN GAIL A, Drugs, Devices, and the FDA: Part 1 in: *JACC: Basic to Translational Science*, 1(3) (2016) pages 170–179

⁷⁶⁴ JENKINS JEAN / HUBBARD SUSAN, History of clinical trials in: *Seminars in Oncology Nursing* 7(4) (1991) pages 228–234

⁷⁶⁵ Ibidem

⁷⁶⁶ Declaration of Helsinki, World Medical Association Declaration of Helsinki, Ethical Principles for Medical Research Involving Human Subjects, *Bulletin of the World Health Organization*, 79(4) (2001)

Research stage	Explanation of relevant characteristics
Preclinical research	<ul style="list-style-type: none"> • Comprehension of pathophysiology and identification of pharmacological targets • Identification of compounds that interact with those targets • In- vitro / In- vivo experiments in animal models to establish a preliminary safety (carcinogenicity/mutagenicity/ teratogenicity) and efficacy profile • Pharmaceutical formulation with regards to stability, purity and drug release processes including manufacturing methods
Phase 0	<ul style="list-style-type: none"> • Not explicitly stipulated by law • Testing of microdoses („<1% of dose calculated to produce a clinical effect”) • Used to select promising pharmaceutical compounds • Aims at understanding PK parameters within a first- in human application
Phase 1	<ul style="list-style-type: none"> • Limited number of patients, usually healthy volunteers (n= 20-80) • Safety and tolerability testing with ascending doses • Monitoring of common side effects
Phase 2	<ul style="list-style-type: none"> • Increase of sample size (n =100-300) with patients suffering from the medical condition being investigated • Activity and efficacy of the drug is investigated • Placebo- controlled clinically randomized trial • Less common side effects are investigated • Phase 2a (Proof of concept), 2b (dose finding)
Phase 3	<ul style="list-style-type: none"> • Takes place if phase 2 results demonstrate clinical benefits towards placebo or comparative therapy • Further increase of investigated patients (n= 1000-3000) • Crucial for a medications initial approval but also for subsequent additional indications • Involving patients with co-morbidities and various previous treatments
Phase 4	<ul style="list-style-type: none"> • Study after governmental market approval , (might be a part of approval studies in some cases) • Investigation of more real- world conditions (risk-benefit assessment) • Collecting of very rare side effects and potential off-label use of the medication • Study numbers depend on the defined clinical endpoints

Illustration 5: Schematic process of preclinical and clinical trials adapted after VAN NORMAN Gail A, Drugs, Devices, and the FDA: Part 1 in: JACC: Basic to Translational Science, 1(3) (2016) pages 170–179

Both Prof. Wiechowski's as well as Prof. Starkenstein's main research was terminated due to their decease before the end of World War II and hence before a structured clinical testing process became a compulsory element within the national and international drug approval process. The first reported placebo controlled clinical trial had been published in 1948⁷⁶⁷ and countries like Germany did not explicitly regulate clinical testing by law before 1976⁷⁶⁸ obliging pharmaceutical manufacturers only to register their medications before bringing them into circulation.⁷⁶⁹ In the revision of the Medicines Law (*Arzneimittelgesetz*) from 1976 the clinical admission and approval procedure was then explicitly mentioned and defined in paragraph § 22: "*die Ergebnisse der klinischen oder sonstigen ärztlichen, zahnärztlichen oder tierärztlichen Erprobung (klinische Prüfung)*"⁷⁷⁰

Although both Wiechowski and Starkenstein principal activities referred to basic pharmacological research as well as its applications and albeit clinical testing had not been part of common practice within drug research and development, there are certain analogies to present methods of testing substances within preclinical and clinical trials.

The major contribution within has to be seen within preclinical research activities, as both researchers dealt with an in-vitro characterization of pharmaceutical compounds pertaining to the stability, solubility, chemical optimization and modification of drugs and thus their therapeutic availability. This established the basis for further in-vivo research within animals, involving various organ functions such as heart, lung, gastrointestinal tract, subsequently characterizing various pharmacokinetic and – dynamic parameters, a prerequisite for rational dose finding in human use. Examples for research regarding the comprehension of clinical (patho)physiology and the search for pharmacological targets can be seen in Starkenstein's publication "*Die physiologischen und pharmakologischen Grundlagen der Kalziumtherapie*"⁷⁷¹ which describes a potential clinical use basing on his own research: "*Eine absolute Indikation der Kalziumtherapie wäre a priori dort zu geben, wo ein effektiv exogener Kalziummangel als Ursache von pathologischen Störungen in Betracht käme*"⁷⁷² or in "*Über die pharmakologische Beeinflussung der*

⁷⁶⁷ JENKINS JEAN / HUBBARD, SUSAN, History of clinical trials in: Seminars in Oncology Nursing 7(4) (1991) pages 228–234

⁷⁶⁸ Bundesgesetzblatt Teil I, Bonn 1 September 1976, Nr. 110 : Gesetz zur Neuordnung des Arzneimittelrechts page 2445

⁷⁶⁹ Bundesgesetzblatt Teil I, Bonn 19 Mai 1961, Nr. 33: Arzneimittelgesetz page 533

⁷⁷⁰ Bundesgesetzblatt Teil I, Bonn 1 September 1976, Nr. 110 : Gesetz zur Neuordnung des Arzneimittelrechts page 2445

⁷⁷¹ STARKENSTEIN EMIL, Die physiologischen und pharmakologischen Grundlagen der Kalziumtherapie in: Therapeutische Monatshefte (1921)

⁷⁷² Ibidem

*Nierenfunktion*⁷⁷³. Wiechowski's clinical links especially in terms of pharmacokinetics and -dynamics and toxicology have been described in detail in chapter 2.3.1., further examples of explorations to find new drug targets due to underlying interactions took place with biological compounds "Ueber das Vorkommen von Chelidonsäure"⁷⁷⁴ and concrete clinical formulations of the research issue being addressed : "Über den Einfluss der Analgetica auf die intracranielle Blutcirculation"⁷⁷⁵

Though both acute and chronic toxicity played a role within their research, no studies were conducted dealing with mutagenicity of teratogenicity explicitly, potentially also due to the fact that neither Starkenstein nor Wiechowski dealt with drug or substances affected. Though both were involved in pharmaceutical formulation processes and in case of Wiechowski even in concrete manufacturing methods^{776,777} none of both dealt with extensive drug release experiments, which also form a part of today's preclinical research. In its entirety it must be said that both Wiechowski's and Starkenstein approach to preclinical research activities as mentioned above were particularly structured, wide-ranging and exhaustive, given the time at which they had been conducted. Those experiments and considerations, frequently based on a profound review of the then actual scientific literature aided to objectify, systematise and critically investigate pharmacological modes of action and thus constituted to a sound basis for later clinical use of drugs.

The clinical investigation within human probands naturally had not been conducted with all their preclinically investigated drugs as both were not primarily and continuously practicing clinically, nor could they have been performed in standards that were later established and are standard of today's clinical practice, e.g. sample sizes of the tested persons, randomization and blinding processes or placebo-controlled clinical trials. The merit of Starkenstein and Wiechowski however, also in this domain of drug research becomes evident by looking at the aspects of today's clinical Phases 0 and 4 which had already been partially incorporated into their research, long before it became mandatory by law, thereby maximizing patient's safety and ensuring a rational clinical application.

⁷⁷³ STARKENSTEIN EMIL, Über die pharmakologische Beeinflussung der Nierenfunktion in: Experimentelle Pathologie und Pharmakologie (1922)

⁷⁷⁴ WIECHOWSKI WILHELM / STRANSKY EMIL, Ueber das Vorkommen von Chelidonsäure in: Archiv der Pharmazie Vol. 258; Iss. 1 (1920)

⁷⁷⁵ WIECHOWSKI WILHELM, Ueber den Einfluss der Analgetica auf die intracranielle Blutcirculation, in: Naunyn-Schmiedeberg's Archives of Pharmacology (1902)

⁷⁷⁶ Zeitschrift des Allgemeinen österreichischen Apothekervereines Nr. 46, 14. November 1914

⁷⁷⁷ Pilsner Tageblatt, October 29th 1923 page 2

Investigating pharmacokinetic and pharmacodynamic parameters in humans as it is done within Phase 0 studies, was carried out by Starkenstein as he tested various concentrations of salt or sugar- solutions that had been orally administered before.⁷⁷⁸ (see III. 6-8) Having observed, that the uptake and excretion processes obey concentration dependent effects of the respective oral formulation he deduced as possible clinical usage of those formulations as a diagnostic tool for diabetes mellitus “*klinisch verwertbare Pankreasfunktionsprüfung*”⁷⁷⁹. Further experiments dealing with pharmacokinetic and – dynamic parameters of saline solutions and their diuretic activity in humans basing on the chemical composition: “*Äquivalentkonzentration an Salzen sowie das bestimmte Isotonieverhältnis*”⁷⁸⁰, particularly the ratio of hydrogen ion concentration, free carbon dioxide and other components.

Further of Starkenstein’s clinical investigations deal with the long- term observation of secretion processes to assess and identify age appropriate dosing, which helped to understand biocompatibility of drugs in the pediatric population investigated.⁷⁸¹

Clinial observations to understand aspects of tolerability under real world conditions were conducted by Starkenstein in the case of the drug *Vasano*. In his function as a ship’s doctor he used this opportunity to investigate its favourable side effects profile “*vollständiger Ausschaltung der Giftwirkung*”⁷⁸² in comparison to other antiemetics, but also to practically confirm its efficacy “*eine therapeutische, hier analgetische Wirkung*”.⁷⁸³ These observations bear content related analogies to Phase 4 clinical trials and similarities to non- investigator initiated trials, as they also dealt with further post market authorized drugs and their risk-benefit assessment such as *Nautisan*, also in terms of convenience in form of favoured application routes e.g. in oral dosage or suppositories.⁷⁸⁴

Prof. Wiechowski’s clinical investigations also display analogies to Phase 4 and non-interventional studies, as both *Reargon* and *Neoreagon* are clinically investigated in a sample size containing 40 probands all suffering from gonorrhoea, the condition being investigated

⁷⁷⁸ STARKENSTEIN EMIL, Wasserhaushalt und Durststillung in: *Klinische Wochenschrift* (1927)

⁷⁷⁹ STARKENSTEIN EMIL, Über die diuretische Wirkung oral zugeführter Zuckerlösungen verschiedener Konzentration in: Sonderabdruck aus der Festschrift für Prof. Dr. Emil Bürgi (1932)

⁷⁸⁰ STARKENSTEIN EMIL, Über die Abhängigkeit der Diurese vom Salzgehalt und der Wasserstoffionenkonzentration des getrunkenen Wassers in: *Archiv für experimentelle Pathologie und Pharmakologie* 104 (1924) pages 6–22

⁷⁸¹ STARKENSTEIN EMIL, Die Entstehung der endogenen Harnsäureausscheidung als Grundlage für die Bemessung der Arzneimitteldosen im Kindesalter in: *Archiv für experimentelle Pathologie und Pharmakologie* (1937)

⁷⁸² STARKENSTEIN EMIL, Physiologische und pharmakologische Prüfung von Nauseamitteln in: *Medizinische Klinik* (1927)

⁷⁸³ *Ibidem*

⁷⁸⁴ STARKENSTEIN EMIL, Pharmakotherapie der Seekrankheit in: *Medizinische Klinik* (1927)

under real world conditions, including testing for the compound's activity "Die Injektionen mit Neoreargon wurden noch mindestens 3 Tage Lang, wo es angängig war , 7 Tage lang fortgesetzt. (...) Die durchschnittliche Behandlungsdauer betrug 5 Tage"⁷⁸⁵ off- label use "Schließlich sei noch mitgeteilt , daß bei der Vulvovaginitis der Kinder therapeutische Versuche mit Neorargon an den beiden Kinderkliniken der deutschen Universität in Prag gemacht worden sind, welche zu sehr aussichtsreichen Resultaten geführt haben"⁷⁸⁶ as well as reports about side effects: "Nach der Absendung des Manusripts erlangen wir Kentniss von den beiden Mitteilungen von R. Wiener und von L. Lissner über Steinbildung nach Reargonverwendung."⁷⁸⁷

An additional example of Wiechowski's clinical investigations in a observational manner can be seen on his experiences with medical charcoal in a real life setting⁷⁸⁸ or in his casuistries on cannabis.⁷⁸⁹

Wiechowski and Starckenstein meet high ethical standards within their research activities, even in accordance with today's principles, as determined within *seven categories* of ethical requirements for clinical research suggested by Emanuel EJ et al.⁷⁹⁰

Both researchers undoubtedly provided "scientific value"⁷⁹¹ by contributing to further understanding of pharmacological theory and the evidence based evaluation of pharmacotherapy by using "accepted scientific principles and methods"⁷⁹² of that time. In terms of "subject selection"⁷⁹³ for their clinical examinations and observations the two scientists did not perform risky research on participants, as they initially tested pharmacological interventions in vitro as well as in animal models and in addition only engaged in experiments with persons that involved a justifiable and reasonable intervention, with authorised medicines. Within Wiechowski's research, e.g. in case of sexually transmitted or gastro-intestinal infectious diseases, the justification for involving patients can be seen in the lack of efficient therapeutic alternatives on the one hand and the "favourable risk- benefit

⁷⁸⁵ WIECHOWSKI WILHELM / KLAUSNER E., Ueber die lokale Behandlung der Harnröhrenonorrhoe mit Silberglykosiden (Neoreargon) in: Deutsche Medizinische Wochenzeitschrift (1925)

⁷⁸⁶ Ibidem

⁷⁸⁷ Ibidem

⁷⁸⁸ Zeitschrift des Allgemeinen österreichischen Apothekervereines Nr. 46, 14. November 1914, page 474

⁷⁸⁹ WIECHOWSKI WILHELM, Haschisch in: Naunyn-Schmiedeberg's Archives of Pharmacology, Vol. 119; Iss. 5-6 (1927)

⁷⁹⁰ EMANUEL EZEKIEL J. / WENDLER D. / GRADY C., What Makes Clinical Research Ethical? In: JAMA. 2000;283(20) (2000) pages 2701–2711

⁷⁹¹ Ibidem

⁷⁹² Ibidem

⁷⁹³ Ibidem

ratio”⁷⁹⁴ of those therapies, compared to other ones of that time: ” *Die wesentliche Wirkung dieser Kombination liegt darin, daß die Injektionen schmerz- und reizlos sind und daher die Behandlung ohne Beschwerden und Schaden soweit intensiviert werden kann, daß in den meisten Fällen eine wesentliche Abkürzung der Behandlungsdauer erzielt wird.*”⁷⁹⁵

Aspects of objectivization and “*independent review*”⁷⁹⁶ were ensured through a triple approval consisting of Wiechowski, his co- author E. Klausner and several clinical investigators taking part in both the treatment its evaluation: “*Bemerkt sei, daß die Behandlung ausschließlich durch den Arzt vorgenommen wurde.*”⁷⁹⁷ As mentioned before, Starkenstein compared and contrasted his findings critically with other scientists , (see. 3.2.1d) adding to their objectification and reproducibility. It can be assumed in all likelihood that “*informed consent (enabling) a voluntary decision whether to enroll and continue to participate*”⁷⁹⁸ in the treatments had been reached by both researchers basing on the fact that those experiments were conducted in a physician- patient relationship and in situations in which the probands were able to express their free will and thereby considering the “*subjects autonomy and welfare*”⁷⁹⁹ Basing on the present literature review and inclusion of publications of both researchers the overlap and analogies with clinical Phases 1, 2 and 3 are as expected less pronounced , which is in the two latter ones due to their statistical standards for data, e.g. need for representative sample sizes as the condition for making statements about the efficacy, safety and tolerability for larger populations.

⁷⁹⁴ Ibidem

⁷⁹⁵ WIECHOWSKI WILHELM / KLAUSNER E., Ueber die lokale Behandlung der Harnröhren gonorrhoe mit Silberglykosiden (Neoreargon) in: Deutsche Medizinische Wochenschrift (1925)

⁷⁹⁶ EMANUEL EZEKIEL J. / WENDLER D. / GRADY C., What Makes Clinical Research Ethical? In: JAMA. 2000;283(20) (2000) pages 2701–2711

⁷⁹⁷ WIECHOWSKI WILHELM / KLAUSNER E., Ueber die lokale Behandlung der Harnröhren gonorrhoe mit Silberglykosiden (Neoreargon) in: Deutsche Medizinische Wochenschrift (1925)

⁷⁹⁸ EMANUEL EZEKIEL J. / WENDLER D. / GRADY C., What Makes Clinical Research Ethical? In: JAMA. 2000;283(20) (2000) pages 2701–2711

⁷⁹⁹ Ibidem

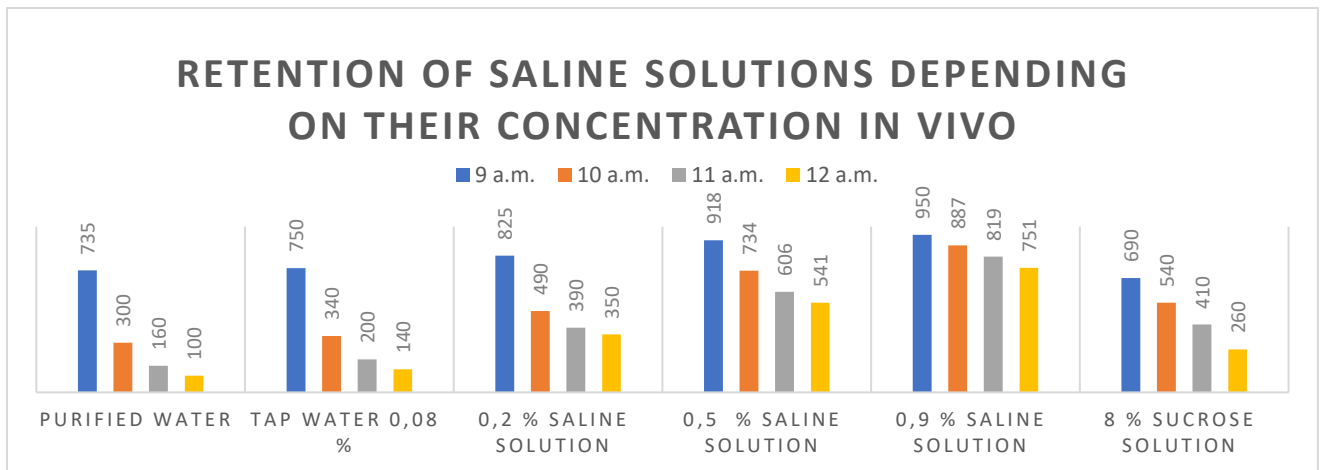


Illustration 6: Adaption and visualization of table 1 from “Wasserhaushalt und Durststillung”⁸⁰⁰ as an example for Starkenstein’s PK experimentation in humans in order to distinguish between diaphoretic and diuretic effects of various substances.

time	purified water	tap water 0,08 %	0,2 % saline solution	0,5 % saline solution	0,9 % saline solution	8 % sucrose solution
9 a.m.	735	750	825	918	950	690
10 a.m.	300	340	490	734	887	540
11 a.m.	160	200	390	606	819	410
12 a.m.	100	140	350	541	751	260

Illustration 7: Measured values of retained substances in the course of time as given in table 1 within the same publication.⁸⁰¹

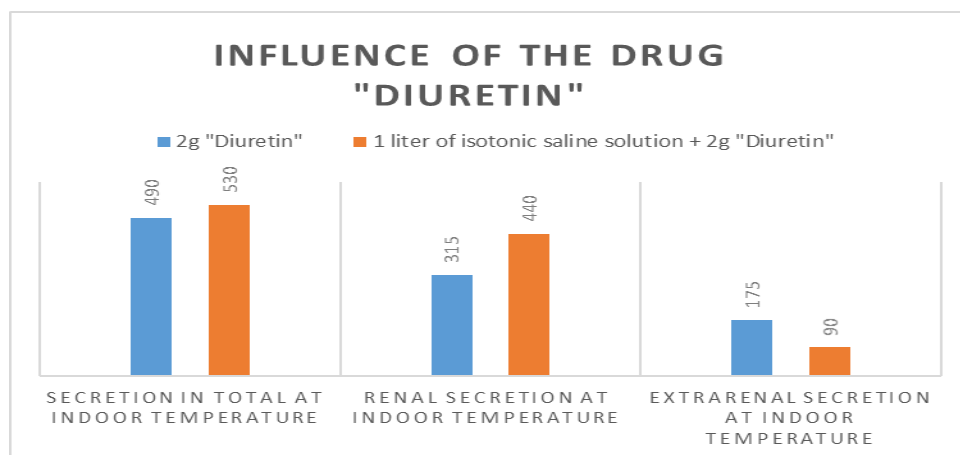


Illustration 8: Selected measurements of human renal and extrarenal excretion subject to “Diuretin”, chemically seen a double salt of theobromine-natrium and sodiumsaliylate adapted from “Wasserhaushalt und Durststillung”⁸⁰²

⁸⁰⁰ STARKENSTEIN EMIL, Wasserhaushalt und Durststillung in: Klinische Wochenzeitschrift (1927)

⁸⁰¹ Ibidem

⁸⁰² Ibidem

4. Third Case: Prof. Gustav Kuschinsky: Analysis and contextualisation of his professional and personal life

4.1. Academic biography

Detailed information about Kuschinsky's academic background and career can be found in personal files and documentation from the university archives both in Berlin and in Mainz.

Kuschinsky's medical studies took place in various cities in the German speaking area of the German Reich e.g. Berlin and Marburg⁸⁰³ and also the First Republic of Austria (Innsbruck) in the years 1922 until 1927,⁸⁰⁴ before taking his final exams on June 24th⁸⁰⁵ and obtaining the official license to practice medicine on July 4th 1928.^{806,807}

Within less than two years he subsequently completed his medical doctoral thesis at the University of Kiel, as apparent from his doctoral diploma, dated March 25th 1929 pertaining to a physio-pharmacological subject "*Ueber das Verhalten von Kalium und Valcium im Blute des Hundes beim Histaminschock*"⁸⁰⁸. The acquisition of some on- the job experience⁸⁰⁹ with regards to surgical but also other clinical skills such as anaesthesia had been obtained at this juncture as shown by work certificates , e.g. from a local hospital in Berlin- Zehlendorf, dated October 10th 1929.⁸¹⁰, as well as entries within personal academic records. The duration of these practical, in other words patient facing activities presented rather interim stages marked by a short time span of his career, as he returned to academia already in November 1929, with a temporary scientific assistant status and later, from 1.11.1931 to 28.2.1933 on a permanent one.⁸¹¹

His prevailing scientific affinity towards explorative pharmacological and physiological questioning culminated in the finalization of his habilitation project on February 21th 1933,

⁸⁰³ KUSCHINSKY GUSTAV, Universitätsarchiv Mainz Personalakte Kuschinsky im Universitätsarchiv Mainz, Ges 131 / S64/11 pages 74 -76

⁸⁰⁴ KUSCHINSKY GUSTAV, Personal file Kuschinsky in the University Archive Mainz "Der Verwaltungsdirektor bei der Friedrichs- Wilhelms Universität zu Berlin, Personalakten des Oberassistenten Dr Gustav Kuschinsky, angefangen 1.11.1931- 31.03.1940" pages 2 and 31

⁸⁰⁵ Ibidem, page 4

⁸⁰⁶ Ibidem

⁸⁰⁷ KUSCHINSKY GUSTAV, Universitätsarchiv Mainz Personalakte Kuschinsky im Universitätsarchiv Mainz, Ges 131 / S64/11 page 69, 71, 72ff

⁸⁰⁸ Ibidem

⁸⁰⁹ KUSCHINSKY GUSTAV, Personal file Kuschinsky in the University Archive Mainz "Der Verwaltungsdirektor bei der Friedrichs- Wilhelms Universität zu Berlin, Personalakten des Oberassistenten Dr Gustav Kuschinsky, angefangen 1.11.1931- 31.03.1940" pages 2 and 31

⁸¹⁰ Ibidem, page 8

⁸¹¹ KUSCHINSKY GUSTAV, Personal file Kuschinsky in the University Archive Mainz "Der Verwaltungsdirektor bei der Friedrichs- Wilhelms Universität zu Berlin, Personalakten des Oberassistenten Dr Gustav Kuschinsky, angefangen 1.11.1931- 31.03.1940" pages 2 and 31

upon which the Medical Faculty of Berlin granted the *venia legendi* in the subject of Pharmacology for Kuschinsky.^{812,813,814} By this, he acquired an academic rank as *Privatdozent* being valid for the entire German territory at that time' which then effectively ensured his continued employment according to academic directives "*Reichshabilitationsordnung*".⁸¹⁵

By this means, foreign teaching and research experiences, such as his stay at the *Tung-Chi* University in China from April 1933 until October 1936⁸¹⁶, where he held a full professorship within the Chinese university system⁸¹⁷, enabled his re-employment within the German education system, albeit in a demoted position, with regards to the one already held in China "*Der Herr Reichsminister hat Herrn Dr. Kuschinsky zugesichert, dass er bei seiner Rückkehr aus Shanghai als Dozent wieder eingesetzt wird. (...) Dekan*"⁸¹⁸ Further evidence for Kuschinsky's structural integration into the academic system of the German Reich shows itself by his biennial leave of absence that had been warranted by the Ministry of Science, Art and "*Volksbildung*", indicating his presumable return to a University on then German territory.⁸¹⁹

Similarly, Kuschinsky's short-lived scientific residence time in Graz, where he was summoned to continue his teaching and research with December 5th 1938, by a letter dated November 30th 1930⁸²⁰ or his shortly afterwards arising appointment to fulfill the obligations as a Professor for Pharmacology in Prague from September 11th 1939.⁸²¹ As a matter of fact, the structural basis for these vocational promotions had been the preceding and forced expulsion of the full Professors Loewi in Graz and Starckenstein in Prague for politically and ideologically motivated reasons of the Nazi regime.

Euphemistically portrayed and not truly describing the actual motivations of these nationalistic and racist processes in academia, the National Socialists tried to cover up this

⁸¹² Ibidem

⁸¹³ Ibidem, Page 4

⁸¹⁴ KUSCHINSKY GUSTAV, Universitätsarchiv Mainz Personalakte Kuschinsky im Universitätsarchiv Mainz, Ges 131 / S64/11 page 74 -76

⁸¹⁵ KUSCHINSKY GUSTAV, Personal file Kuschinsky in the University Archive Mainz "*Der Verwaltungsdirektor bei der Friedrichs- Wilhelms Universität zu Berlin, Personalakten des Oberassistenten Dr Gustav Kuschinsky, angefangen 1.11.1931- 31.03.1940*" pages 19ff

⁸¹⁶ KUSCHINSKY GUSTAV, Universitätsarchiv Mainz Personalakte Kuschinsky im Universitätsarchiv Mainz, Ges 131 / S64/11 page 74 -76

⁸¹⁷ KUSCHINSKY GUSTAV, Personal file Kuschinsky in the University Archive Mainz "*Der Verwaltungsdirektor bei der Friedrichs- Wilhelms Universität zu Berlin, Personalakten des Oberassistenten Dr Gustav Kuschinsky, angefangen 1.11.1931- 31.03.1940*" pages 2 and 31

⁸¹⁸ Ibidem pages 19ff

⁸¹⁹ Ibidem, Page 18

⁸²⁰ Ibidem, Page 50 and 51

⁸²¹ Ibidem, Page 67 and 73

replacement of scholars by speaking about free capacities within already established and staffed academic posts: “*vertretungsweise eine Professur an der Universität Prag (...) freigewordene Professur für Pharmakologie*”⁸²² and “*freie Planstelle (...) in der Medizinischen Fakultät der Deutschen Karls- Universität in Prag*”⁸²³

Kuschinsky had been instructed to take up his scientific activities in Prague as from January 1st 1940 and had been appointed as Associate Professor for life under this regime on March 6th 1940 “*Ich vollziehe diese Urkunde in der Erwartung, daß der Ernannte getreu seinem Diensteide seine Amtspflichten gewissenhaft erfüllt und das vertrauen rechtfertigt, daß ihm durch diese Ernennung bewiesen wird. Zugleich sichere ich ihm meinen besonderen Schutz zu. (...) Der Führer gez. Adolf Hitler*”⁸²⁴, further sources show that he had been created simultaneously to the managing director of the Pharmacological Institute upon his arrival.⁸²⁵

In the course of the looming defeat of the Nazi regime, Kuschinsky left Prague and returned to southern Germany, where he already on November 15th 1946 was appointed to a full professor at the University of Mainz for both Pharmacology and Toxicology⁸²⁶ and continued his academic career until his deferred retirement on March 31th 1972, aged sixty- eight.⁸²⁷ Kuschinsky died on November 17th 1992, aged 89, outliving his colleague Starkenstein for more than 50 years.⁸²⁸

4.1.2. Professional influences and collaborations

International exchange and occupational liaison played a part early on in Kuschinsky’s career, as seen on the participation on congresses^{829,830}, events for scientific socialising^{831,832,833} but

⁸²² Ibidem

⁸²³ Ibidem, page 106

⁸²⁴ Ibidem, page 105

⁸²⁵ Ibidem, page 75/76 and 81

⁸²⁶ KUSCHINSKY GUSTAV, Universitätsarchiv Mainz Personalakte Kuschinsky im Universitätsarchiv Mainz, Ges 131 / S64/11 page 9/10

⁸²⁷ Ibidem, page 79 and 83

⁸²⁸ KUSCHINSKY GUSTAV, Zeitungsausschnitte zu Kuschinsky, Signatur E 33, Blatt 3

⁸²⁹ KUSCHINSKY GUSTAV, Akten der medizinischen Fakultät Berlin 442 / Blatt 48

⁸³⁰ KUSCHINSKY GUSTAV, Personal file Kuschinsky in the University Archive Mainz “Der Verwaltungsdirektor bei der Friedrichs- Wilhelms Universität zu Berlin, Personalakten des Oberassistenten Dr Gustav Kuschinsky, angefangen 1.11.1931- 31.03.1940“ page 30

⁸³¹ KUSCHINSKY GUSTAV, Zeitungsausschnitte zu Kuschinsky, Signatur E 33, Blatt 1

⁸³² Ibidem, Blatt 2

⁸³³ Ibidem, Blatt 4

also through direct research collaborations e.g. with Hedwig Langecker^{834,835,836} , Heinz Lüllmann^{837,838,839,840,841,842 ,843} or support in the form of mentorship.^{844,845,846,847}

The participation in international congresses naturally involved those with pharmacological content, but also with related sciences, such as a Congress of Physiology in Zurich on August 1938, accompanied by Prof. Trendelenburg.⁸⁴⁸

Research trips, such as in July 1939 to attend a conference of the “*British Pharmacological Society*”⁸⁴⁹ is seized as an opportunity by Kuschinsky to engage in scientific exchange with other researchers and also to benefit from the knowledge of other working groups, e.g. in terms of laboratory methods “ *Auch ich persönlich kenne seit Jahren eine Reihe von britischen Pharmakologen . Das Institut von Prof. Burn ist in seiner Arbeitsrichtung bisher einzigdastehend. Es ist Zentralinstitut für biologische Auswertungen von Hormon und Vitaminpräparaten (...) zweckmäßig sein die dort angewandte Methodik zu lernen*”⁸⁵⁰

⁸³⁴ KUSCHINSKY GUSTAV, Universitätsarchiv Mainz Personalakte Kuschinsky im Universitätsarchiv Mainz, Ges 131 / S64/11 page 5 and Page 5(6)

⁸³⁵ KUSCHINSKY GUSTAV, Personal file Kuschinsky in the University Archive Mainz “Der Verwaltungs-Direktor bei der Friedrichs- Wilhelms Universität zu Berlin, Personalakten des Oberassistenten Dr Gustav Kuschinsky, angefangen 1.11.1931- 31.03.1940“ page 137/143/144

⁸³⁶ KUSCHINSKY GUSTAV / LÜLLMANN H. / MUSCHOLL E. Untersuchungen über die Einwirkung von verschiedenen Pharmaka auf die Spontanrhythmik des isolierten Hühneramnion, in: Naunyn - Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie 223 (1954) pages 369–374

⁸³⁷ KUSCHINSKY GUSTAV / LÜLLMANN H. / MUTSCHLER E. / WOLLERT U., Beziehungen zwischen der Struktur von Bisguanilhydrazonen und der Art ihrer Herzwirksamkeit in: Naunyn - Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie 251 (1965) pages 153–154

⁸³⁸ KUSCHINSKY GUSTAV / LINDMAR R. / LÜLLMANN H. / MUSCHOLL E., Der Einfluß von Reserpin auf die Wirkung der „Neuro-Sympathomimetica“ in: Naunyn - Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie 240 (1960) pages 242–252

⁸³⁹ KUSCHINSKY GUSTAV / LÜLLMANN HEINZ, Kurzes Lehrbuch der Pharmakologie und Toxikologie in: Thieme Verlag 11. neubearbeitete Auflage (1982)

⁸⁴⁰ KUSCHINSKY GUSTAV / LÜLLMANN H. / MUSCHOLL E., Untersuchungen über die Einwirkung von verschiedenen Pharmaka auf die Spontanrhythmik des isolierten Hühneramnion, in: Naunyn - Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie 223 (1954) pages 369–374

⁸⁴¹ KUSCHINSKY GUSTAV / FÖRSTER W. / LÜLLMANN H., Über adrenolytische Wirkungen von d,l,1-(4-oxyphenyl)-1-oxy-2-n-butylamino-aethan in: Naunyn - Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie 210 (1950) pages 23–30

⁸⁴² KUSCHINSKY GUSTAV / LÜLLMANN HEINZ, Über die Beziehungen der Barium-Ionen zum Acetylcholin in: Klinische Wochenschrift 28 (1950) pages 137–138

⁸⁴³ KUSCHINSKY GUSTAV / LÜLLMANN HEINZ, Über die Wirkung von synthetischem Hypertensin auf Kammer- und Vorhofsmuskulatur der Katze in: Klinische Wochenschrift 37 (1959) pages 928–931

⁸⁴⁴ KUSCHINSKY GUSTAV, Akten der medizinischen Fakultät Berlin 442 pages 46/ 53/ 58

⁸⁴⁵ KUSCHINSKY GUSTAV, Personalakte Kuschinsky (UK K 442) von 1932- 1940, Nummer 28

⁸⁴⁶ KUSCHINSKY GUSTAV, Akten der medizinischen Fakultät Berlin 442 / page 7-9

⁸⁴⁷ KUSCHINSKY GUSTAV, Personal file Kuschinsky in the University Archive Mainz “Der Verwaltungs-Direktor bei der Friedrichs- Wilhelms Universität zu Berlin, Personalakten des Oberassistenten Dr Gustav Kuschinsky, angefangen 1.11.1931- 31.03.1940“ page 41

⁸⁴⁸ Ibidem, Page 30

⁸⁴⁹ Ibidem, Page 41

⁸⁵⁰ KUSCHINSKY GUSTAV, Akten der medizinischen Fakultät Berlin 442 page 48

It can be assumed that Prof. Kuschinsky appreciated this form of scientific exchange and socializing as he, later on in post-war years, proactively initiated those get-togethers since the 1960's in his newly established academic base in the city of Mainz.^{851,852,853}

The preceding foundation under his leadership, of a medical-scientific association in 1951⁸⁵⁴ paved the way for those gatherings in which both researchers and clinicians from German speaking countries, but also the Netherlands, Bulgaria, Denmark and countries of the former Republic of Yugoslavia discussed pharmacological and toxicological topics.⁸⁵⁵ The opportunity and structural conditions that were prevalent after and in the 1950's in Mainz, as well as Kuschinsky's aptitude for organizing and to establish these events, were reflected in the attendance figures, such as about 600 participants in 1977 and following awards and honors.⁸⁵⁶

Long-lasting cooperations may be evidenced, as exemplified by the one with Prof. Hedwig Langecker, dealing with methodological questions of analytical techniques "*Eine mercurimetrische Bestimmung des Chlorids im Harn*"⁸⁵⁷, hormonal effects on diuresis in a series of subpublications "*Diurese, Filtration und Sekretion der Niere unter dem Einfluss verschiedener Pharmaka*"⁸⁵⁸ with a frequent formulation of research questions dealing with renal function.^{859,860}

Langecker acted in place of Kuschinsky on various professional occasions as well, as she undertook teaching and research-related commitments e.g. from 1.8.1943- 19.8. 1943 for private reasons or other professional obligations in March 1945.⁸⁶¹ Besides these vocationally documented touchpoints, one of Kuschinsky's publications from 1954 "*Untersuchungen über die Einwirkung von verschiedenen Pharmaka auf die Spontanrhythmik des isolierten*

⁸⁵¹ KUSCHINSKY GUSTAV, Zeitungsausschnitte zu Kuschinsky, Signatur E 33, Blatt 1

⁸⁵² Ibidem, Blatt 2

⁸⁵³ Ibidem, Blatt 4

⁸⁵⁴ Ibidem

⁸⁵⁵ Ibidem, Blatt 1

⁸⁵⁶ IBIDEM, Blatt 2

⁸⁵⁷KUSCHINSKY GUSTAV, Universitätsarchiv Mainz Personalakte Kuschinsky im Universitätsarchiv Mainz, Ges 131 / S64/11 page 5 and Page 5(6)

⁸⁵⁸ Ibidem

⁸⁵⁹ KUSCHINSKY GUSTAV, Über die Beteiligung der Tubulussekretion an der Harnbildung , in: Deutsche Medizinische Wochenschrift, 69(39/40) (1943) pages 695–697

⁸⁶⁰ KUSCHINSKY GUSTAV / LANGECKER, H, Über die Wirkung des Atropins auf die Nierenfunktion in: Naunyn-Schmiedeberg's Archives of Pharmacology 208(1) (1949) pages 35-36

⁸⁶¹ KUSCHINSKY GUSTAV, Personal file Kuschinsky in the University Archive Mainz "Der Verwaltungsdirektor bei der Friedrichs- Wilhelms Universität zu Berlin, Personalakten des Oberassistenten Dr Gustav Kuschinsky, angefangen 1.11.1931- 31.03.1940" page 137/143/144

*Hühneramnion*⁸⁶² is dedicated to his colleagues sixtieth birthday on a rather personal occasion, suggesting a rather pleasant collaboration through the years.

This publication, as many to follow, arose under the co-authorship of Prof. Heinz Lüllmann with whom Kuschinsky continued to collaborate for more than thirty years, publishing primarily within the area of the cardiovascular system^{863,864,865,866,867} but also issuing a pharmacological textbook⁸⁶⁸, that dealt with pharmacological principles and effects on a wider basis e.g. *“Heuristische Prinzipien der Pharmakologie d.h. Struktur- Wirkungs und Rezeptor - Bindungs- Untersuchungen”* and *“Endokrine Drüsen (...) Schilddrüse (...) Schilddrüsenhormone” (...)* *“Glatte Muskulatur (...) Therapeutische Aspekte (...) Therapie der Herzinsuffizienz”*⁸⁶⁹

A collaboration in the shape of academic mentoring persisted between Kuschinsky and Heubner during the 30's and 40's of the 20th century, as the latter one played a supporting role in Kuschinsky's academic progress. First and foremost Prof. Heubner created a positive appraisal of his mentee's scientific abilities, here concretely regarding his habilitation treatise *“So liefert die Arbeit (...) eine wertvolle wissenschaftliche Leistung , durch die der Verfasser seine Fähigkeit sowohl zur Formulierung von Problemen , wie zu ihrer experimentellen Bearbeitung (...) die Arbeit zur Annahme als Habilitationsschrift empfehlen zu dürfen”*⁸⁷⁰, which in effect also implied recommendations for his academic promotion: *“Unter diesen Gesichtspunkten bitte ich die Fakultät, dem von mir eigentlich nur weitergegebenen , aber*

⁸⁶² KUSCHINSKY GUSTAV / LÜLLMANN H. / MUSCHOLL E., Untersuchungen über die Einwirkung von verschiedenen Pharmaka auf die Spontanrhythmik des isolierten Hühneramnion, in: Naunyn - Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie 223 (1954) pages 369–374

⁸⁶³ Ibidem

⁸⁶⁴ KUSCHINSKY GUSTAV / LÜLLMANN H. / MUTSCHLER E. / WOLLERT U., Beziehungen zwischen der Struktur von Bisguanylhydrazonen und der Art ihrer Herzwirksamkeit in: Naunyn - Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie 251 (1965) pages 153–154

⁸⁶⁵ KUSCHINSKY GUSTAV / LINDMAR R. / LÜLLMANN H. / MUSCHOLL E., Der Einfluß von Reserpin auf die Wirkung der „Neuro-Sympathomimetica“ in: Naunyn - Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie 240 (1960) pages 242–252

⁸⁶⁶ KUSCHINSKY GUSTAV / FÖRSTER W. / LÜLLMANN H., Über adrenolytische Wirkungen von d,l,1-(4-oxyphenyl)-1-oxy-2-n-butylamino-aethan in: Naunyn - Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie 210 (1950) pages 23–30

⁸⁶⁷ KUSCHINSKY GUSTAV / LÜLLMANN H., Über die Wirkung von synthetischem Hypertensin auf Kammer- und Vorhofsmuskulatur der Katze in: Klinische Wochenschrift 37 (1959) pages 928–931

⁸⁶⁸ KUSCHINSKY GUSTAV / LÜLLMANN HEINZ, Kurzes Lehrbuch der Pharmakologie und Toxikologie in: Thieme Verlag 11. neubearbeitete Auflage (1982)

⁸⁶⁹ Ibidem

⁸⁷⁰ KUSCHINSKY GUSTAV, Akten der medizinischen Fakultät Berlin 442 / page 7-9

*doch mit Überzeugung vertretenen Wunsch einer raschen Habilitation des Herrn Dr. Kuschinsky zu willfahren*⁸⁷¹

Heubner also advocated for a future granting of Kuschinsky's academic degrees that had been either acquired abroad during his time in China, which had then been conceded in the form of a "*nichtbeamteter außerordentlicher Professor*" on February 19th 1939.^{872,873} Further evidence for this academic connection is also documented by a mutual participation in international congresses⁸⁷⁴ and governmental documents after the shortly after the Second World War.⁸⁷⁵

4.1.3. Extent of involvement in policies of the Nazi regime and political stances

The extent to which Kuschinsky had been (social)-politically integrated into domestic and foreign policies^{876,877} of the National Socialist regime through its governmental structures^{878,879,880,881,882} were reflected in a variety of privileges and amenities^{883,884,885,886,887} but also necessitated a simultaneous occurrence of several dependencies and concessions that had to be made.^{888,889,890,891,892,893,894}

⁸⁷¹ Ibidem

⁸⁷² KUSCHINSKY GUSTAV, Akten der medizinischen Fakultät Berlin 442 pages 46/ 53/ 58

⁸⁷³ KUSCHINSKY GUSTAV, Personalakte Kuschinsky (UK K 442) von 1932- 1940, Nummer 28

⁸⁷⁴ KUSCHINSKY GUSTAV, Personal file Kuschinsky in the University Archive Mainz "Der Verwaltungsdirektor bei der Friedrichs- Wilhelms Universität zu Berlin, Personalakten des Oberassistenten Dr Gustav Kuschinsky, angefangen 1.11.1931- 31.03.1940" page 41

⁸⁷⁵ KUSCHINSKY GUSTAV, Universitätsarchiv Mainz Personalakte Kuschinsky im Universitätsarchiv Mainz, Ges 131 / S64/11 page 6 (Sheet 1-14)

⁸⁷⁶ KUSCHINSKY GUSTAV, Akten der medizinischen Fakultät Berlin 442 pages 38/39 Letter

⁸⁷⁷ KUSCHINSKY GUSTAV, Personal file Kuschinsky in the University Archive Mainz "Der Verwaltungsdirektor bei der Friedrichs- Wilhelms Universität zu Berlin, Personalakten des Oberassistenten Dr Gustav Kuschinsky, angefangen 1.11.1931- 31.03.1940" page 2 and 31

⁸⁷⁸ Ibidem

⁸⁷⁹ Ibidem, page 3

⁸⁸⁰ Ibidem, page 21

⁸⁸¹ Ibidem, page 22

⁸⁸² Ibidem, page 111

⁸⁸³ Ibidem, page 106

⁸⁸⁴ Ibidem, page 62

⁸⁸⁵ Ibidem, page 125

⁸⁸⁶ KUSCHINSKY GUSTAV, Universitätsarchiv Mainz Personalakte Kuschinsky im Universitätsarchiv Mainz, Ges 131 / S64/11 page 11/17 (12)

⁸⁸⁷ KUSCHINSKY GUSTAV, Personal file Kuschinsky in the University Archive Mainz "Der Verwaltungsdirektor bei der Friedrichs- Wilhelms Universität zu Berlin, Personalakten des Oberassistenten Dr Gustav Kuschinsky, angefangen 1.11.1931- 31.03.1940" page 118

⁸⁸⁸ Ibidem, page 105

⁸⁸⁹ Ibidem, page 75/76/81

⁸⁹⁰ Ibidem, page 44/46/47/49

⁸⁹¹ Ibidem, page 41

⁸⁹² Ibidem, page 111

⁸⁹³ Ibidem, page 23

⁸⁹⁴ Ibidem, page 40

Especially at the outset of his career, one cannot speak about an increased political interest “1.3.1933. Innenpol. keine Betätigung”⁸⁹⁵ or involvement of Kuschinsky in any other divisions which would stand for any authority of the state, such as the military or national associations. However, emerging with his academic activities in Shanghai, China, implicit political motivations can be documented as well, as his research interests about traditional herbal Chinese Medicine “*Chinesische Drogen*”⁸⁹⁶ are also used to acquire insight knowledge for the benefit of his country of origin “*In China: Im Kulturpolitischen Interesse Deutschlands*”⁸⁹⁷, which also involved insights about the structural academic landscape.⁸⁹⁸

A sincere interest in political participation remains to be called into question, as seen by Kuschinsky’s comparatively late membership in political organisations of the National Socialists such as “*NSDAP Mitglied Anwärter seit Dezember 1937*”⁸⁹⁹ and “*NS Dozentenbund seit März 38*”⁹⁰⁰ as well as doubts or uncertainties regarding his political reliability and loyalty towards the Nazi regime, being uttered both by representatives of the then German state⁹⁰¹ and also former colleagues “*dass Herr Professor Kuschinsky im nationalsozialistischen Sinne nicht zuverlässig sei*”⁹⁰² Notwithstanding the rather lower genuine political interest in comparison to his academic and scientific ambitions, which had been also ascribed to him “*ließ sich Herr Prof. Kuschinsky stets von rein sachlich-wissenschaftlichen Gesichtspunkten leiten*”⁹⁰³, Kuschinsky had himself increasingly integrated into National Socialist structures, beginning with medical and professional associations “*NS - Ärztebund seit 12.3.36 Mitgliednummer 13162*”⁹⁰⁴ and “*NSB September 37 Mitgliednummer 8111140*”⁹⁰⁵ before only at a later point in time joining the wider political ones.⁹⁰⁶ A gradual but more increasing orientation towards these structures can be evidenced by his declaration to enter professional organisations in a timely manner “*Eintritt in NS -*

⁸⁹⁵ Ibidem, page 2 and 31

⁸⁹⁶ Ibidem

⁸⁹⁷ Ibidem

⁸⁹⁸ KUSCHINSKY GUSTAV, Akten der medizinischen Fakultät Berlin 442 / Blatt 38/39 Letter

⁸⁹⁹ KUSCHINSKY GUSTAV, Personal file Kuschinsky in the University Archive Mainz “Der Verwaltungsdirektor bei der Friedrichs- Wilhelms Universität zu Berlin, Personalakten des Oberassistenten Dr Gustav Kuschinsky, angefangen 1.11.1931- 31.03.1940“ page 3

⁹⁰⁰ Ibidem

⁹⁰¹ Ibidem, page 58-59

⁹⁰² KUSCHINSKY GUSTAV, Universitätsarchiv Mainz Personalakte Kuschinsky im Universitätsarchiv Mainz, Ges 131 / S64/11 page 6 (Sheet 1-14)

⁹⁰³ Ibidem

⁹⁰⁴ KUSCHINSKY GUSTAV, Personal file Kuschinsky in the University Archive Mainz “Der Verwaltungsdirektor bei der Friedrichs- Wilhelms Universität zu Berlin, Personalakten des Oberassistenten Dr Gustav Kuschinsky, angefangen 1.11.1931- 31.03.1940“ page 3

⁹⁰⁵ Ibidem

⁹⁰⁶ Ibidem, page 21

*Lehrerbund nach meiner Anstellung beabsichtigt*⁹⁰⁷ at the time of taking an official oath on October 29th 1936, in the context of his employment as university lecturer.

This efforts for memberships and cooperation with governmental structures disembogued in further professional entrustment with political tasks in the academic setting, effective as of September 30th 1939 „*In Entsprechung des Erlasses des Reichsministers für Wissenschaft, Erziehung und Volksbildung (...) ordnungsgemäße Übergabe des pharmakologisch-pharmakognostischen Institutes aus den Händen der stellvertretenden Leiterin Prof. Dr. Hedwig Langecker*“⁹⁰⁸, Mai 1940 “*Geschäfte des Leiters der Dozentenschaft an der hiesigen Universität zu beauftragen*”⁹⁰⁹ and “*gleichzeitig die Geschäfte des örtlichen Dozentenbundführers wahrnehmen sodass die bisher bestehende Personalunion erhalten bleibt. Eine beglaubigte Abschrift des Schreibens des Gaudozentenbundführers an mich vom 10 Mai 1940 füge ich bei.*“⁹¹⁰

The organizational anchoring and consolidation of Kuschinsky role in the National Socialist structures also coincided with further academic honors that were bestowed upon him “*Erlaß des Herrn Reichsministers für Wissenschaft, Erziehung und Volksbildung vom 23. März 1940 (...) mit Wirkung vom 1. Januar 1940 ab zum Direktor des Pharmakologisch-Pharmakognostischen Institutes der Deutschen Karls- Universität in Prag ernannt worden*“⁹¹¹ in a rather speedy manner that suggest party-political interests and support of associated groups „*von seiten des Dozentenbundes kein Einwand besteht*“⁹¹², which ultimately can be seen in the planned and orchestrated secondment of Kuschinsky by the Nazi administration, e.g. in Graz⁹¹³ or later in Prague.^{914,915} Further politically intended advantages, here in terms of safety for his physical well- being , resulted for Kuschinsky in his exemption from any military service due to his position and academic status “*aus zwingenden Gründen der Reichsverteidigung zur Erfüllung kriegswichtiger Aufgaben der Verwaltung des Ministeriums*

⁹⁰⁷ Ibidem, page 22

⁹⁰⁸ KUSCHINSKY GUSTAV, Protokoll der medizinischen Fakultät der deutschen Universität Prag Zeichen 3537/39, Betreff: Übernahme des pharmakologisch- pharmakognostischen Institutes durch Prof. Dr. Kuschinsky vom 30. September 1939

⁹⁰⁹ KUSCHINSKY GUSTAV, Personal file Kuschinsky in the University Archive Mainz “Der Verwaltungs-Direktor bei der Friedrichs- Wilhelms Universität zu Berlin, Personalakten des Oberassistenten Dr Gustav Kuschinsky, angefangen 1.11.1931- 31.03.1940“ page 111

⁹¹⁰ Ibidem

⁹¹¹ Ibidem, page 118

⁹¹² Ibidem, page 75/76/81

⁹¹³ Ibidem, page 50-51

⁹¹⁴ Ibidem, page 106

⁹¹⁵ Ibidem, page 75/76/81

für Wissenschaft , Erziehung und Volksbildung entgegen seinen persönlichen Wünschen vom Heeresdienste freigestellt“⁹¹⁶

Further amenities have to be seen in his foreseeable financial and social safeguarding through this collaboration either on a personal level or on a professional one.

First of all, the appointment as a full professor guaranteed a steady level of financial security for Kuschinsky⁹¹⁷, as this position was permanent “*nach Besoldungsgruppe H*”⁹¹⁸, adding to his previously acquired assets, as of July 19th 1939: “*Mein Barvermögen beträgt ca. 3000 RM, Mein Jahreseinkommen beträgt ca 10000RM*”⁹¹⁹ Basing on estimates of the German Central Bank as constituted on January 2021, one Reichsmark would be the equivalent of approximately 4,30 Euro today⁹²⁰, generating a yearly income of 43.000 Euro and savings of 12.000 Euro. According to the wage development within the German Reich, the average annual income amounted approximately 23.254 Euro, as calculated by an average weekly wage of 104 RM⁹²¹ on the base of 52 working weeks, bringing Kuschinsky an above- average earning in accordance with his academic qualification and expertise.

Invoices of further years also document the predictable and safe income both before 1945 “*Die Unterrichtsgeldgarantie für 1940 ist wie folgt gezahlt worden: I. Trimester 1940 1133,33 RM gezahlt am 26.2.1941, II. Trimester 1940 1133,33 RM gezahlt am 2.8.1940, III- Trimester 1940 1133,33 RM gezahlt am 30.01. 1941.*”⁹²² and additionally „*zugesicherte Unterrichtsgeldgarantie für die Zeit vom 1.1.- 31.12 1940 4000 RM, für die Zeit vom 1.1.- 31.12 1941 3000 RM, für die Zeit ab 1.1.1942 2000 RM*”⁹²³ but also in the early post war years as a result of his timely vocation to the vacant Chair of Pharmacology in Mainz in 1946.⁹²⁴

⁹¹⁶ Ibidem, page 125

⁹¹⁷ Ibidem, page 118

⁹¹⁸ Ibidem, page 106

⁹¹⁹ Ibidem, page 62

⁹²⁰ Kaufkraftäquivalente historischer Beträge in deutschen Währungen, Stand Januar 2021, gefunden online am 07.03.2021 bei der Deutschen Bundesbank: <https://www.bundesbank.de/resource/blob/615162/d55a20f8a4ecedd6d1b53e01b89f11c4/mL/kaufkraetaequivalente-historischer-betraege-in-deutschen-waehrungen-data.pdf>

⁹²¹ Lohnentwicklung im Deutschen Reich gefunden online am 07.03.2021 auf <https://de.statista.com/statistik/daten/studie/249961/umfrage/lohnentwicklung-im-deutschen-reich/#professional>

⁹²² KUSCHINSKY GUSTAV, Personal file Kuschinsky in the University Archive Mainz “Der Verwaltungsdirektor bei der Friedrichs- Wilhelms Universität zu Berlin, Personalakten des Oberassistenten Dr Gustav Kuschinsky, angefangen 1.11.1931- 31.03.1940“ page 135-136

⁹²³ Ibidem

⁹²⁴ KUSCHINSKY GUSTAV, Universitätsarchiv Mainz Personalakte Kuschinsky im Universitätsarchiv Mainz, Ges 131 / S64/11 page 11/17 (12)

Financial resources for a professional context, to fund and support Kuschinsky's research arose out of his collaboration with the *Deutsche Forschungsgemeinschaft* that facilitated his research within the areas of infectious diseases⁹²⁵, hormonal effects⁹²⁶ and also on diuretic substances⁹²⁷.

In a letter dated September 27th 1944, Prof. Kuschinsky reports on his results regarding dose-finding experiments with animals for the active tuberculosis treatment with pharmaceutical compounds, further reports to this centralized contact point for research *Reichsforschungsrat* deal with the mode of action of pituitary hormones, which he particularly investigates, alongside with other substances “*Sulfat/ Oleum Juniperi/ Kalciumacetat/Harnstoff/Salygran/Scillaren*”⁹²⁸ for their therapeutic potential for influencing renal functions. As indirectly stated on those reports, aspects of those experiments did also affect questions that could be seen as relevant for military purposes, as they refer to the treatment of intoxications “*Sie geben die Grundlage für die jetzt laufenden weiteren Untersuchungen der Diuretika (...) die auch für die Therapie der Nierenkrankheiten und die Ausscheidung von Giften bedeutungsvoll sind*”⁹²⁹ This is also supported by the fact that the grant for this entire antiinfective, hormonal and diuretic research had been extended for another year still in March 1944^{930,931} and dealt with practically relevant questions for medical care at those times “*Sind Rhodan- Salze imstande , die experimentelle Tuberkulose zu heilen?*”⁹³²

Further documents verify the granting of several allowances^{933,934} pertaining to laboratory equipment “*Thermo- Strohmuhr (...) 4785,55 RM*”⁹³⁵, “*2 Sätze Küvetten für Sauerstoff-*

⁹²⁵ KUSCHINSKY GUSTAV, Bundesarchiv Berlin- Lichterfelde, Bestandssignatur R 73 / Archivsignatur 12537, Sonderdrucke / Berichte , Aktennummer S 4891-5381(1721/10)-III/45

⁹²⁶ KUSCHINSKY GUSTAV, Bundesarchiv Berlin- Lichterfelde, Bestandssignatur R 73 / Archivsignatur 12537, Sonderdrucke / Berichte , hier an die Deutsche Forschungsgemeinschaft vom 1. April 1943, mit Eingang am 5. April 1943

⁹²⁷ Ibidem, Aktennummer S 4891-5380(1720/10)-III/45

⁹²⁸ Ibidem

⁹²⁹ KUSCHINSKY GUSTAV, Bundesarchiv Berlin- Lichterfelde, Bestandssignatur R 73 / Archivsignatur 12537, Sonderdrucke / Berichte , hier an die Deutsche Forschungsgemeinschaft vom 1. April 1943, mit Eingang am 5. April 1943

⁹³⁰ KUSCHINSKY GUSTAV, Bundesarchiv Berlin- Lichterfelde, Bestandssignatur R 73 / Archivsignatur 12537, Sonderdrucke / Berichte , Aktennummer S 4891-5381(1721/10)-III/45

⁹³¹ Ibidem, Aktennummer S 4891-5380(1720/10)-III/45

⁹³² Ibidem, here in Sonderdrucke and Berichte

⁹³³ Ibidem, here in Sonderdrucke and Berichte, Sachbeihilfen vom 12. Mai 1942 / Kur 4/16/4

⁹³⁴ Ibidem, here in Sonderdrucke and Berichte, Handwritten letter of Prof. Heubner

⁹³⁵ Ibidem, here in Sonderdrucke and Berichte “Kur 4/16/3-14744“

*Uhren und blutige Messung von Arterien und Venen des Hundes nach Krames als Ersatzküvetten für die gelieferte Apparatur an Herrn Prof. Dr. Kuschinsky*⁹³⁶

Dependencies and requisite concessions were a result of Kuschinsky's increasing involvement into both the academic and political structures of the National Socialist administration. The swearing-in process to a Professor for Pharmacology⁹³⁷, for a start, presupposed Kuschinsky's ethnic origins in line with the ideological constructions and beliefs⁹³⁸ of the National Socialist dictatorship "*deutschblütiger Abstammung*"⁹³⁹ and condoning the fact that these positions were based on the displacement of politically or ethnically unwanted scholars: "*freie Planstelle*"⁹⁴⁰ and "*Ich ersuche Sie im Wintersemester 1938/1939 in der Medizinischen Fakultät der Universität Graz die Vetreterung der durch das Ausscheiden des Prof. Loewis freigewordenen Professur für Pharmakologie wahrzunehmen und ihren Dienst spätestens am Montag den 5. 12. 1938 anzutreten.*"⁹⁴¹ At the same time, a official dissociation from any left-wing oriented body of thought had to be declared "*Auf die Anfrage betreffend Zugehörigkeit "Bund Deutsche Schlaraffia e.V." teile ich mit, daß ich dieser Organisation niemals angehört habe*"⁹⁴² as well as any political activities in this direction "*kommunistischen Hilfs- oder Ersatzorganisationen*"⁹⁴³ had to be dismissed clearly.

The structural integration, as also seen in organisations⁹⁴⁴ closely related to the NSDAP and the direct party membership "*NSDAP seit 1.5.1937, NSDoB seit 1.1.1938, NS Ärztebund seit 1937, Reichsdozentenschaft seit 1.11.1936, jedoch keine Militärverhältnisse*"⁹⁴⁵ accompanied Kuschinsky's academic career. This can also be seen on liabilities he incurred while being on congresses abroad, where he was expected to remain in exchange with organisations that were also linked to and controlled by the Nazi Party "*Ferner haben sich Prof. Dr. Heubner und Dozent Dr. Kuschinsky bei ihrem Auslandsaufenthalt nach Möglichkeit mit der örtlichen*

⁹³⁶ Ibidem, here in Sonderdrucke and Berichte, document dated 14.8.1943

⁹³⁷ KUSCHINSKY GUSTAV, Personal file Kuschinsky in the University Archive Mainz "Der Verwaltungsdirektor bei der Friedrichs- Wilhelms Universität zu Berlin, Personalakten des Oberassistenten Dr Gustav Kuschinsky, angefangen 1.11.1931- 31.03.1940" page 105

⁹³⁸ Ibidem, page 23

⁹³⁹ Ibidem, page 44/46/47/49

⁹⁴⁰ IBIDEM, PAGE 75/76/81

⁹⁴¹ IBIDEM, PAGE 50/51

⁹⁴² IBIDEM, PAGE 40

⁹⁴³ IBIDEM, PAGE 23

⁹⁴⁴ IBIDEM, PAGE 111

⁹⁴⁵ KUSCHINSKY GUSTAV, Universitätsarchiv Mainz Personalakte Kuschinsky im Universitätsarchiv Mainz, Ges 131 / S64/11 page 11/17 (12)

*Auslandsorganisation der NSDAP in Verbindung zu setzen, die von ihrer Reise unterrichtet werden wird*⁹⁴⁶

Aspects of Kuschinsky's conception of man and political worldview are reflected in letters and other official documents during 1934 and after 1945.^{947,948}

A handwritten letter from Shanghai, dated February 2nd 1934, displays both praise "*sind im allgemeinen sehr fleissig*"⁹⁴⁹ but also criticism "*Man muss die ostasiatische Ruhe bekommen aber nicht gleichzeitig die Inaktivität*"⁹⁵⁰ for the perceived mindset of the Chinese and their structures of university education. The tone in which this letter is written suggests a certain feeling of (imagined) superiority towards the social circumstances and people in Asian areas, especially in comparison to those ones allegedly present in German speaking countries: "*Die Chinesen lassen sich leicht blenden durch äußerlich prächtig aufgezoene Institute , wie das Rockefeller Institut in Peking*" (...) "*Da gilt es auf Qualität hinzuweisen (...) Leute zum Verständnis deutscher Qualität zu erziehen*"⁹⁵¹ Defiance the favourable impressions which Kuschinsky receives also about other cultures, there are references to be found which indicate a certain degree of nationalist thinking in his writing, particularly noticeable with regards to foreign policy developments: "*Der Austritt Deutschlands aus dem Völkerbund , das eine ungeheuer starke Wirkung gehabt hat, brachte Deutschland schon eine große Vermehrung des Ansehens das weiter im Steigen begriffen ist. Besonders von England wird wieder mit dem Machtfaktor Deutschland gerechnet, nicht mehr ablehnend wie anfangs, sondernd mehr und mehr anerkennend.*"⁹⁵² Several testimonies in writing suggest on the other hand, that Kuschinsky had been generally rather open- minded towards other nationalities and religions and within his actual behaviour at times helpful and partially supportive of marginalized groups under the Nazi terror. As these governmental documents date back to post- war years, care had been taken to critically balance the sources and to avoid to credit statements that could have either been caused in a relationship of dependence or as a courtesy aiming at gaining professional or other advantages.

⁹⁴⁶ KUSCHINSKY GUSTAV, Personal file Kuschinsky in the University Archive Mainz "Der Verwaltungsdirektor bei der Friedrichs- Wilhelms Universität zu Berlin, Personalakten des Oberassistenten Dr Gustav Kuschinsky, angefangen 1.11.1931- 31.03.1940" page 41

⁹⁴⁷ KUSCHINSKY GUSTAV, Universitätsarchiv Mainz Personalakte Kuschinsky im Universitätsarchiv Mainz, Ges 131 / S64/11 page 6 Sheet 1-14

⁹⁴⁸ KUSCHINSKY GUSTAV, Akten der medizinischen Fakultät Berlin 442 pages 38/39 Letter

⁹⁴⁹ Ibidem

⁹⁵⁰ Ibidem

⁹⁵¹ Ibidem

⁹⁵² Ibidem

The majority of these statements for Kuschinsky's defence originate from academic circles during his time in Prague, with consistently exonerating content⁹⁵³, which have however to be classified in some smaller parts as embellished or even partially untrustworthy, at a bigger extent of moderate informative value but at some parts of high plausibility and credibility in terms of his actions.

Exculpatory first hand statements of high plausibility and credibility can be instanced as an example on the declarations of scholars which Kuschinsky supported in their career during the German occupation in Prague, although they were not in-line with fascist ideas "*Dozent Dr. med. habil Werner Wolfram, frueher Oberarzt der Deutschen Uni. Frauenklinik in Prag (...) Kuschinsky (...) meine Habilitation unterstuetzt und gefoerdert hat, trotzdem ihm bekannt war, dass ich in erster Ehe mit einer Juedin verheiratet war, und in Parteikreisen als unzuverlaessig und gegnersich eingestellt angesehen wurde*"⁹⁵⁴ and „*Herr Professor Kuschinsky hat stets die Methoden des Nationalsozialismus abgelehnt und das System verurteilt. Mit der Behandlung der Juden war er nicht einverstanden und hat den persoenlichen Verkehr mit gemeinsamen juedischen Bekannten nicht abgebrochen*““(…)“*jedes Parteileben lehnte er ab und beiteiligte sich m.W. nicht daran*"⁹⁵⁵

Further highly credible sources of scientists that have not been connected with the National Socialist regime and even part of circles of resistance, attest Kuschinsky's benevolent behaviour as seen on Prof. Günther, at the Chair of Philosophy or Fr.Dr. Sladek, a catholic priest and pastoral worker. Prof. Günther was, according to his own objectively collidated statements seen as an opponent to the Nazi government "*trotz der öffentlich bekannten politischen "Unzuverlässigkeit" (siehe NS.-Monatshefte- Dezemberheft 1935*"⁹⁵⁶ and yet been actively supported by Kuschinsky in his academic career. In the case of Fr. Dr. Sladek, the witness does not only confirm Kuschinsky's support in this academic manner, but also indicates his actual political stances, which, according to his opinion had been much more moderate and liberal than his academic and political positions would have suggested: "*daß Prof. Kuschinsky in dieser und in anderen Fragen durchaus nicht den radikalen Parteistandpunkt teilte, ja überhaupt kein fanatischer Nationalsozialist war, sondern im Wissenschaftlichen einen streng sachlichen und im Weltanschaulichen einen weitherzigen,*

⁹⁵³ KUSCHINSKY GUSTAV, Universitätsarchiv Mainz Personalakte Kuschinsky im Universitätsarchiv Mainz, Ges 131 / S64/11 page 6 Sheet 1-16

⁹⁵⁴ Ibidem, Sheet 1

⁹⁵⁵ Ibidem, Sheet 4-6

⁹⁵⁶ Ibidem, Sheet 12

*toleranten Standpunkt vertrat*⁹⁵⁷ This impression can be objectified through the fact that Kuschinsky did help the catholic priest to remain in his functions at the German University in Prague even though this also implied a certain personal risk for Kuschinsky, as Prof. Sladek had been put under investigation for his engagement in catholic organisations: “*Gestapo und Sicherheitsdienst wegen meiner Tätigkeit als Studentenseelsorger in Prag und wegen meiner Arbeiten in der Katholischen Aktion und der katholischen Jugend vor und nach 1938 gegen mich Stellung genommen, so daß mir der Vorgänger Prof. Kuschinskys in der Prager Dozentenbundführung die erforderliche Zulassung verweigerte.*”⁹⁵⁸

Those colleagues are primarily physicians but also represent other academic fields, whose statements are plausible with regards to the fact that they represent independent conclusions from persons not having been affiliated to the regime. They are in line with other official documents as well, e.g. the point in time at which Kuschinsky was admitted to organizations of the Nazi Party, at times suggesting a certain level of reluctance to do so:

*„Mir ist bekannt , daß er Jahre hinsurch seinen Beitritt zu NSDAP verweigert hat, bis er schließlich 1938 starkem Druck nachgeben mußte. Er hat sich auch weiterhin in der Folgezeit von politische Betätigung fernhalten können“*⁹⁵⁹

Exonerating statements that have to be judged as being less indepent and objectifiable in certain parts are less trustworthy and thus moderately informative, as seen in statements of his former employes “*Sekretärin des Institutes (...) Elisabeth Jüstel*”⁹⁶⁰ or students “*Christa Meister cand.med*”⁹⁶¹ which at the time of their testimony, might have been apprehensive of potential professional disadvantages and in addition could not have comprehensively judged Kuschinsky’s political nor personal involvement.

Sources of limited or diminished credibility have to be seen in the statement of persons that had been directly or indirectly involved in the National Socialist system, as seen in memberships in the NSDAP oder military activites in favour of the regime.

As an example of this, Prof. Richter’s⁹⁶², Prof. Hamperl’s⁹⁶³ and Prof. Heubner’s^{964,965} testimonies have to be assessed cautiously since all researchers have themselves have not

⁹⁵⁷ Ibidem, Sheet 14

⁹⁵⁸ Ibidem

⁹⁵⁹ Ibidem, Sheet 8

⁹⁶⁰ Ibidem, Sheet 2

⁹⁶¹ Ibidem, Sheet 7

⁹⁶² HLAVACKOVA LUDMILA / SVOBODNY, PETR, Biographisches Lexikon der deutschen Medizinischen Fakultät in Prag 1883-1945 in: Karolinum- Verlag der Karls- Universität (1998)

clearly distanced themselves from the regime, remain ambiguously viewed researchers “*Eine grundsätzliche Gegnerschaft zum nationalsozialistischen Staat und nationalsozialistischer Hochschulpolitik kann dem Verhalten Heubners nicht entommen werden. Die Spielräume, die er im Umgang mit nationalsozialistischen Amtsträgern hatten nutze er in großem Maße*”⁹⁶⁶ having been active in armed forces⁹⁶⁷ or member of the NSDAP⁹⁶⁸, serving the regime.

Furthermore, parts of these statements display a fairly subjective and biased view on the actual events, e.g. in terms of Kuschinsky’s deployment to Prague, excluding any type of party- political interests or discrimination of others: “*Nach meiner Kenntnis hat also Kuschinskys Berufung nach Prag gar nichts mit Parteipolitik zu tun (Uebrigens war er ja erst vertretungsweise in Graz (...) auch dies gab ihm ein moralisches Anrecht auf eine der demnächst zu besetzenden Ordinariate.*”⁹⁶⁹

Overall, the evidence suggests that Kuschinsky, on a personal level and in part also on a professional one, did not entirely nor full- heartedly comply with the National Socialist agenda, as he continued to support people of various ethnic and religious backgrounds and also treated Czech colleagues with respect and not differently than German co-workers.⁹⁷⁰

On the other hand he allowed himself to be successively integrated into official functions, beginning with the NSDAP’s seizure of power “*bis 1932 hat eine aktive politische Beteiligung bei Dr. K. nicht vorgelegen*” (...) „*nach dem Umbruch 1933 sich beim NS Ärztebund in Changhai zur Verfügung gestellt*“⁹⁷¹ while at times succeeding in keeping either

⁹⁶³ GROSS DOMINIK, Between fiction and reality: Herwig Hamperl (1899–1976) and the Third Reich as reflected in his autobiography in: Pathology - Research and Practice, Volume 215, Issue 4 (2019)

⁹⁶⁴ SCHLEIERMACHER SABINE / SCHAGEN UDO, (HG.), Die Charité im Dritten Reich. Zur Dienstbarkeit medizinischer Wissenschaft im Nationalsozialismus, darin: Udo Schagen / Von der Freiheit – und den Spielräumen- Der Wissenschaft(ler) im Nationalsozialismus: Wolfgang Heubner und die Pharmakologen der Charité 1933 bis 1945, in: Ferdinand Schöningh, Paderborn (2008)

⁹⁶⁵ KUSCHINSKY GUSTAV, Universitätsarchiv Mainz Personalakte Kuschinsky im Universitätsarchiv Mainz, Ges 131 / S64/11 page 6 Sheet 13

⁹⁶⁶ SCHLEIERMACHER SABINE / SCHAGEN UDO, (HG.), Die Charité im Dritten Reich. Zur Dienstbarkeit medizinischer Wissenschaft im Nationalsozialismus, darin: Udo Schagen / Von der Freiheit – und den Spielräumen- Der Wissenschaft(ler) im Nationalsozialismus: Wolfgang Heubner und die Pharmakologen der Charité 1933 bis 1945, in: Ferdinand Schöningh, Paderborn (2008)

⁹⁶⁷ HLAVACKOVA LUDMILA / SVOBODNY, PETR, Biographisches Lexikon der deutschen Medizinischen Fakultät in Prag 1883-1945 in: Karolinum- Verlag der Karls- Universität (1998)

⁹⁶⁸ GROSS DOMINIK, Between fiction and reality: Herwig Hamperl (1899–1976) and the Third Reich as reflected in his autobiography in: Pathology - Research and Practice, Volume 215, Issue 4 (2019)

⁹⁶⁹ KUSCHINSKY GUSTAV, Universitätsarchiv Mainz Personalakte Kuschinsky im Universitätsarchiv Mainz, Ges 131 / S64/11 page 6 Sheet 13

⁹⁷⁰ Ibidem, Sheet 2

⁹⁷¹ KUSCHINSKY GUSTAV, Akte NS Dozentschaft Universitätsarchiv der HU Berlin (Ns- Doz, 1 Nr 169), Nummer 51

a low profile about his political ideas^{972,973} but also taking measures to ingratiate himself with supervisors⁹⁷⁴, governmental officials “*Heil Hitler! Kuschinsky*”⁹⁷⁵ or other Party members “*seine anständige Gesinnung und idealistische Haltung aus. er hat das Bemühen ein guter Nationalsozialist zu sein*”⁹⁷⁶, which then created a certain level of proximity to the National Socialist government. Both aspects play a role in understanding how he addressed the socio-political situation he found himself and his research endeavours, displaying in a sense two versions of himself, depending on the addressee.

4.1.4. Familial background, personal traits and interests apart from pharmacological research

Key features of Kuschinsky’s family background can be deduced from his academic personal files, just like his civil status at several times in his life^{977,978,979} whereas the life courses of his descendants are traceable via professional journals and publications.

Being born on January 10th 1904 into a protestant, non- academic parental home “*Gustav Kuschinsky, Kaufmann (...) Mutter Johanna Wittmoser*”⁹⁸⁰, several direct ancestors had been working in the agricultural sector.⁹⁸¹

Kuschinsky himself got married to the physician Ingeborg Maria Stöhr with whom he had three children in the following, Gisela born in Prague on April 20th 1942, Wolfgang Rainer Kuschinsky on March 15th 1944⁹⁸² and their son Klaus- Udo being born on October 9th 1939

⁹⁷² KUSCHINSKY GUSTAV, Personal file Kuschinsky in the University Archive Mainz “Der Verwaltungs-Direktor bei der Friedrichs- Wilhelms Universität zu Berlin, Personalakten des Oberassistenten Dr Gustav Kuschinsky, angefangen 1.11.1931- 31.03.1940“ page 58/59

⁹⁷³ KUSCHINSKY GUSTAV, Akte NS Dozentenschaft Universitätsarchiv der HU Berlin (Ns- Doz, 1 Nr 169), Nummer 7/12/20

⁹⁷⁴ KUSCHINSKY GUSTAV, Akten der medizinischen Fakultät Berlin 442 pages 38/39 Letter

⁹⁷⁵ KUSCHINSKY GUSTAV, Personal file Kuschinsky in the University Archive Mainz “Der Verwaltungs-Direktor bei der Friedrichs- Wilhelms Universität zu Berlin, Personalakten des Oberassistenten Dr Gustav Kuschinsky, angefangen 1.11.1931- 31.03.1940“ page 44/46/47/49

⁹⁷⁶ KUSCHINSKY GUSTAV, Akte NS Dozentenschaft Universitätsarchiv der HU Berlin (Ns- Doz, 1 Nr 169), Nummer 51

⁹⁷⁷ KUSCHINSKY GUSTAV, Personal file Kuschinsky in the University Archive Mainz “Der Verwaltungs-Direktor bei der Friedrichs- Wilhelms Universität zu Berlin, Personalakten des Oberassistenten Dr Gustav Kuschinsky, angefangen 1.11.1931- 31.03.1940“ page 4

⁹⁷⁸ Ibidem, page 132/ (140)

⁹⁷⁹ KUSCHINSKY GUSTAV, Universitätsarchiv Mainz Personalakte Kuschinsky im Universitätsarchiv Mainz, Ges 131 / S64/11 page 1

⁹⁸⁰ KUSCHINSKY GUSTAV, Personal file Kuschinsky in the University Archive Mainz “Der Verwaltungs-Direktor bei der Friedrichs- Wilhelms Universität zu Berlin, Personalakten des Oberassistenten Dr Gustav Kuschinsky, angefangen 1.11.1931- 31.03.1940“ page 2 and 31

⁹⁸¹ Ibidem, page 32 sheet 4

⁹⁸² Ibidem, page 132 / (140)

in Berlin.⁹⁸³ A certain extent of domestic imprint and influence with regards to occupational decisions can be assumed due to the fact that all three children became physicians themselves, either in academic or regulatory environment. His daughter Gisela worked as a expert for drug safety and therapy in association with various medical committees such as “*Arzneimittelschaft der deutschen Ärztekommision*”⁹⁸⁴, while his son Klaus- Udo conducted research within neuropharmacological “*Morphine catalepsy in the rat: relation to striatal dopamine metabolism.*”⁹⁸⁵ or physiological context respectively “*Physiology of cerebral blood flow and metabolism. Arzneimittelforschung.*”⁹⁸⁶

A set of personal traits become apparent through work and employer references which, all things considered, depict both his behaviour patterns and social intelligence.

Already at early stages of his academic career, Kuschinsky evinced a quite industrious attitude within his research, which is unanimously confirmed at various professional stages⁹⁸⁷ “*fleißig und ausdauernd mit wissenschaftlichen Problemstellungen befasst (...) u.a. tierexperimentelle Arbeiten (...) mit Erfolg durchgeführt*”⁹⁸⁸ and “*von all den gebotenen Gelegenheiten , sein Wissen und Können zu vertiefen , hat Dr. Kuschinsky mit Eifer und wissenschaftlichen Ernst Gelegenheit genommen*”⁹⁸⁹ In addition to his high work ethic, Kuschinsky seemed to have also been driven by great academic ambition, which does not only become evident through his supervisor’s assessment, but also through own words, describing the character of students who either do or do not engage in scientific activities themselves:

⁹⁸³ KUSCHINSKY GUSTAV, Universitätsarchiv Mainz Personalakte Kuschinsky im Universitätsarchiv Mainz, Ges 131 / S64/11 page 1

⁹⁸⁴ BRENNECKE RALPH, Medizinische Informatik und Statistik in: Datenquellen für Sozialmedizin und Epidemiologie (1981)

⁹⁸⁵ KUSCHINSKY KLAUS / HORNYKIEWICZ OLEH, Morphine catalepsy in the rat: relation to striatal dopamine metabolism in: European Journal of Pharmacology 19(1) (1972) pages 119-22.

⁹⁸⁶ KUSCHINSKY WOLFGANG, Physiology of cerebral blood flow and metabolism, in: Arzneimittelforschung 41(3A) (1991) pages 284-8

⁹⁸⁷ KUSCHINSKY GUSTAV, Universitätsarchiv Mainz Personalakte Kuschinsky im Universitätsarchiv Mainz, Ges 131 / S64/11 page 69 /71/72 ff

⁹⁸⁸ KUSCHINSKY GUSTAV, Personal file Kuschinsky in the University Archive Mainz “Der Verwaltungsdirektor bei der Friedrichs- Wilhelms Universität zu Berlin, Personalakten des Oberassistenten Dr Gustav Kuschinsky, angefangen 1.11.1931- 31.03.1940“ page 6

⁹⁸⁹ Ibidem, page 8

*“The more interested students were keen to have a doctor’s degree and came to his department to work upon a thesis. Only the weak ones were satisfied with the license alone and the title “practitioner””*⁹⁹⁰

His capabilities exceeded sheer scientific skills and knowledge according to the assessment of several contemporaries, as Kuschinsky was able to adapt to a range of social situations successfully *“ist menschlich sehr geschickt und anpassungsfähig”*⁹⁹¹ and was also successful in maintaining and establishing positive relationships to several groups, might they either be within a academic context *“auch mit den Studenten ein recht gutes Verhältnis unterhält”*⁹⁹² or a political one, e.g. with E. Landt *“NSD Dozentenbundführers der Universität Berlin , SA - Sturmführer der Standarte 1, Ortsgruppe Schmargendorf”*⁹⁹³ Further references to his rather socially intelligent behaviour certify ability to pursue his goals but to remain likeable^{994,995} at the same time *“seines Taktes und seines bescheidenen aber bestimmten Auftretens”*⁹⁹⁶

Little is known about his personal interests besides pharmacological research, however there are some publications about his stances on and involvement in the assessment of alternative medicines or evidence about his interest in certain aspects of history.

With regards to homeopathic agents, Kuschinsky does not directly advocate against their use, but does however clearly point out the lack of any scientifically sound proof for their pharmacological action, classifying them as placebo *“Die Verordnung wird zum Ritual, das Medikament hat Amuletfunktion (...) homöopathische Mittel (...) keine Haupt- oder Nebenwirkung besitzen“*⁹⁹⁷ As a corollary, his stance towards homeopathy becomes increasingly critical if homeopathic agents are ascribed factual pharmacological actions besides their suggestive and psychological ones *“billige Placebos die nur aus Milchzucker bestehen”*⁹⁹⁸, emphasizing their methodological relevance within clinical trials but not within

⁹⁹⁰ KUSCHINSKY GUSTAV, The Influence of Dorpat on the Emergence of Pharmacology as a Distinct Discipline in: Journal of the History of Medicine and Allied Sciences, 23(3) (1968) pages 258-271

⁹⁹¹ KUSCHINSKY GUSTAV, Akte NS Dozentschaft Universitätsarchiv der HU Berlin (Ns- Doz, 1 Nr 169), Nummer 7/12/20

⁹⁹² Ibidem

⁹⁹³ Ibidem

⁹⁹⁴ Ibidem

⁹⁹⁵ KUSCHINSKY GUSTAV, Personal file Kuschinsky in the University Archive Mainz *“Der Verwaltungsdirektor bei der Friedrichs- Wilhelms Universität zu Berlin, Personalakten des Oberassistenten Dr Gustav Kuschinsky, angefangen 1.11.1931- 31.03.1940“* page 8

⁹⁹⁶ KUSCHINSKY GUSTAV, Universitätsarchiv Mainz Personalakte Kuschinsky im Universitätsarchiv Mainz, Ges 131 / S64/11 page 69 /71/72 ff

⁹⁹⁷ KLEEDORFER GÜNTHER, Heilmittelkonsum in Österreich in: Soziale Sicherheit, Fachzeitschrift für die Sozialversicherung Heft 11 (1977) page 482

⁹⁹⁸ KUSCHINSKY GUSTAV, Über die Beurteilung der Wirkung neuer Arzneimittel in: Deutsche Medizinische Wochenschrift Nr. 36 (1955)

effective pharmacotherapy. Relating to other scientists, Kuschinsky's rather reserved attitude towards this therapeutic concept, not being based on scientific evidence becomes apparent as well "*Auch seine (Anm.:August Bier) Verteidigung der Homöopathie war durch nicht sehr kritische Beobachtungen beeinflusst*"⁹⁹⁹

There is some evidence that Kuschinsky was active in committees that critically and objectively evaluated the action of drugs or substances in scientific terms already before 1945¹⁰⁰⁰ and also subsequently in the 1960's and henceforth.¹⁰⁰¹ The core idea of those investigations was to contribute of principles ensuring pharmaceutical drug safety and rational drug use^{1002,1003}, which also implied using mathematical-statistical methods into the assessment of drugs, which in effect had been interpreted by some authors as an opposing position towards homeopathy "*Homöopathie feindlich gesonnenen Pharmakologen um Kuschinsky*"¹⁰⁰⁴

Kuschinsky's autobiographical recollections¹⁰⁰⁵ reveal further insights about his interests and grant an insight into his personal perspectives, especially on pivotal events in his life, such as career pathways. On a meta-level, further aspects of his personality are reflected indirectly, such as the anecdotal nature of his narration alongside with occasionally witty commentaries on the events, giving a hint of his sense of humour. In this regard one has to consider as well a certain level of subjectiveness in the interpretation of topics, or even an omission of rather unpleasant parts of his biography, which also allows certain assumptions about his personality.

Concrete interests besides his pharmacological research cover artistic¹⁰⁰⁶ and historic ones^{1007,1008} as well as travelling and foreign placements in particular. Kuschinsky describes

⁹⁹⁹ MANN GÜNTER / DUMONT FRANZ, *Medizin in Mainz. Praxis und Wissenschaft, Entwicklungen und Erinnerungen in: 40 Jahre Medizinische Fakultät und Klinikum 1946-1986.* Verlag: Mainz. Kirchheim (1986) page 222

¹⁰⁰⁰ JÜTTE ROBERT, *Von der Notwendigkeit, die Vergangenheit zu bewältigen: Homöopathie und Nationalsozialismus in: Allgemeine Homöopathische Zeitung.* 258 (2013) pages 6-9.

¹⁰⁰¹ KESSEL NILS, *Umstrittene Expertise. Der Beirat „Arzneimittelsicherheit“ in der bundesdeutschen Arzneimittelregulierung 1968-1976 / Controversial expertise. The “Scientific Advisory Committee for Drug Safety” and its role in drug regulation in the Federal Republic of Germany, 1968-1976 in: Medizinhistorisches Journal,* 44(1) (2009) pages 61–93”

¹⁰⁰² Ibidem

¹⁰⁰³ JÜTTE ROBERT, *Von der Notwendigkeit, die Vergangenheit zu bewältigen: Homöopathie und Nationalsozialismus in: Allgemeine Homöopathische Zeitung.* 258 (2013) pages 6-9

¹⁰⁰⁴ KESSEL NILS, *Umstrittene Expertise. Der Beirat „Arzneimittelsicherheit“ in der bundesdeutschen Arzneimittelregulierung 1968-1976 / Controversial expertise. The “Scientific Advisory Committee for Drug Safety” and its role in drug regulation in the Federal Republic of Germany, 1968-1976 in “Medizinhistorisches Journal,* 44(1) (2009) pages 61–93”

¹⁰⁰⁵ MANN GÜNTER / DUMONT FRANZ, *Medizin in Mainz. Praxis und Wissenschaft, Entwicklungen und Erinnerungen in. 40 Jahre Medizinische Fakultät und Klinikum 1946-1986.* Verlag: Mainz. Kirchheim (1986)

¹⁰⁰⁶ Ibidem, Page 220

occasions at his early years in Berlin at which he regularly was able to watch theatre productions of Max Reihhardt, or even worked as an extra within productions of the German State Opera of Berlin *“Mit guten Verbindungen zum Garderobenmeister der Staatsoper konnte ein Student auch als Statist fungieren. So bin ich einmal in einer hervorragenden Carmen- Aufführung als „Schwarzer Aquarillo“ aufgetreten, der hinter dem berittenen (!) Torero im Gefolge schreiten mußte.“*¹⁰⁰⁹

A certain level of interest in the history of medicine can be seen in his publication about the gradual evolution of pharmacological sciences in the 19th century including scientific-analytical and thus positivist findings. Herein, Kuschinsky deals with the key challenges of this process, due to anchored traditions based in materia medica or a rather clinical than research oriented approach to in depth pharmacological understanding *“ (...) pharmacology which was considered an applied science. Since the clinician did not always have enough time , he often chose someone who did not have the ability to become a good clinician to lecture on pharmacology”*¹⁰¹⁰. Instead of following empirical and handed down knowledge, laboratory methods were gradually incorporated into research to understand the exact mode of actions of drugs, which also required clearly chemically defined structures *“Experiments were performed with cardiac glycosides, caffeine and related purines, and heavy metals”*¹⁰¹¹ and related to organic functions, based on physiological experimentation e.g. *“vagal (autonomic) system, depressor nerve, perfusion of organs, gases in blood”*¹⁰¹²

Further historical references, with a much less specific content, rather used to classify and contextualize his own path of life are found in his autobiography, e.g *“Die Revolution im November 1918 hat zunächst wenig an dem Leben der Schüler geändert (...) Aber in der Nachkriegszeit kam es häufiger zu Störungen, Streiks usw. Ich mußte über den Stettiner Bahnhof fahren , in dessen Umgebung öfter Kämpfe zwischen Putschisten, Revolutionären und der Reichswehr tobten“*¹⁰¹³ or *„So habilitierte ich mich am 28.2.1933. Dies geschah noch*

¹⁰⁰⁷ KUSCHINSKY GUSTAV, The Influence of Dorpat on the Emergence of Pharmacology as a Distinct Discipline in: Journal of the History of Medicine and Allied Sciences, 23(3) (1968) pages 258-271”

¹⁰⁰⁸ MANN GÜNTER / DUMONT FRANZ, Medizin in Mainz. Praxis und Wissenschaft, Entwicklungen und Erinnerungen in: 40 Jahre Medizinische Fakultät und Klinikum 1946-1986. Verlag: Mainz. Kirchheim (1986) pages 220,230,237

¹⁰⁰⁹ Ibidem, page 220

¹⁰¹⁰ KUSCHINSKY GUSTAV, The Influence of Dorpat on the Emergence of Pharmacology as a Distinct Discipline in: Journal of the History of Medicine and Allied Sciences, 23(3) (1968) pages 258-271”

¹⁰¹¹ Ibidem

¹⁰¹² Ibidem

¹⁰¹³ MANN GÜNTER / DUMONT FRANZ, Medizin in Mainz. Praxis und Wissenschaft, Entwicklungen und Erinnerungen in: 40 Jahre Medizinische Fakultät und Klinikum 1946-1986. Verlag: Mainz. Kirchheim (1986) pages 219f“

nach altem Ritus. (Hitler hatte noch andere Sorgen. Der Reichstag brannte in jenen Tagen.)“¹⁰¹⁴

Despite those historical references, Prof. Kuschinsky does completely skip any of his memberships in National Socialist organisations, neither does he explain himself in this regard, nor the circumstances under which he found himself back then, throughout his entire memoir. Instead crucial parts of his autobiography such as his appointments to pharmacological chairs, both in Graz and Prague are portrayed euphemistically or at least quite unidimensional, suggesting either a temporarily representation of his predecessor Loewi in Graz or his move to Prague for personal and light-hearted reasons: *“Verschiedene Gründe veranlaßten mich nach Prag zu gehen. Das Institut bot eine wesentlich bessere Einrichtung. Aber auch das Leben in dieser schönen Stadt versprach reizvoll zu werden.“¹⁰¹⁵*

An authentic interest in travelling becomes evident, either in Kuschinsky’s various national and especially international journeys, seen on his academic biography in Berlin, Hamburg, Tübingen, Kiel and parts of former East Prussia, but also his detailed depictions of his triennial stay in China.¹⁰¹⁶, Austria, Switzerland, Italy, Scandinavia.¹⁰¹⁷

Those travelogues do not only emphasize Kuschinsky’s enthusiasm for exploring those places *“Peking (...) Was für eine Stadt! Was für prächtige Bauten! Nicht nur die riesigen Stadtmauern und Stadttore (...) sondern auch der mächtige Kaiserpalast (...) die großen künstlich angelegten Gewässer und vor allem im Süden der Stadt der Himmelstempel, eines der schönsten Gebäude , die ich kenne.“¹⁰¹⁸* but also deliver impressions on Kuschinsky’s respectful conduct with regards to interpersonal interaction. Being repelled by rituals of initiation within fraternity contexts which he experienced at his years of study *“Die vertilgten Alkoholmengen waren enorm. Es war barbarisch, wie sogenannte geistige Menschen sich benahmen”¹⁰¹⁹* or by condescending demeanour he witnessed during his stay in Peking *„Einige Europäer machten sich einen Spaß daraus , von Zeit zu Zeit eine Handvoll Silberdollars (...) auf die Tanzfläche zu werfen, damit die Mädchen sich darüber balgten, Ich schämte mich ein Europäer zu sein“¹⁰²⁰*, Kuschinsky’s sense of tact are also explicitly

¹⁰¹⁴ Ibidem, page 230

¹⁰¹⁵ Ibidem, page 240f

¹⁰¹⁶ Ibidem, page 231ff

¹⁰¹⁷ Ibidem, page 228

¹⁰¹⁸ Ibidem, page 234

¹⁰¹⁹ Ibidem, page 221

¹⁰²⁰ Ibidem, page 235

confirmed by other sources.¹⁰²¹ Further personal qualities show themselves by reading the memoir, which not only display Kuschinsky's ability to entertain and to formulate witty remarks, but also his sense of pragmatism "*Lubarsch war der gefürchtete Pathologe. Die Studenten mußten oft vor 6 Uhr aufstehen, um rechtzeitig zu seiner um 7 Uhr beginnenden Vorlesung zu kommen. Ein anderer Pathologe, Westerhöfer las nachmittags im Augusta – Hospital. Da man offiziell Prüfer gegeneinander austauschen konnte, tauschte ich Lubarsch gegen Westhöfer und konnte 2 Semester lang ausschlafen.*"¹⁰²² Further events in Kuschinsky's life are also characterized by that sense of pragmatism, which together with his ability to establish useful contacts is directly described by himself, on various occasion, also during the post war years in Wiesbaden. "*konnte aber die Lage dem neuen Oberbürgermeister vortragen, der die notwendigen Anweisungen geben ließ*"¹⁰²³ and „*Das Hindernis der Zonengrenze konnte ich durch einen Ausweis des Gesundheitsamtes überwinden*"¹⁰²⁴

Kuschinsky's touchpoints with the pharmaceutical sector pertained both an industrial and practicing setting¹⁰²⁵ as he engaged in research activities with substances being distributed by several companies and also played a role in education and training of pharmacists.^{1026,1027,1028,1029,1030}

In his role as a university teacher at the University in Mainz he collaborated together with other life scientists, to work out a case collection and compendium about several mechanisms of action of drugs, organised according to physiological organ functions. Hereby practical aspects of pharmacotherapy but also underlying experimental findings were pictured in detail "*Prinzip der Methode und Registrierung, Durchführung des Versuches, Reihenfolge der*

¹⁰²¹ KUSCHINSKY GUSTAV, Personal file Kuschinsky in the University Archive Mainz "Der Verwaltungsdirektor bei der Friedrichs- Wilhelms Universität zu Berlin, Personalakten des Oberassistenten Dr Gustav Kuschinsky, angefangen 1.11.1931- 31.03.1940" page 8

¹⁰²² MANN GÜNTER / DUMONT FRANZ, Medizin in Mainz. Praxis und Wissenschaft, Entwicklungen und Erinnerungen in: 40 Jahre Medizinische Fakultät und Klinikum 1946-1986. Verlag: Mainz. Kirchheim (1986) page 223

¹⁰²³ Ibidem, page 242

¹⁰²⁴ Ibidem, page 243

¹⁰²⁵ MANN GÜNTER / DUMONT FRANZ, Medizin in Mainz. Praxis und Wissenschaft, Entwicklungen und Erinnerungen in: 40 Jahre Medizinische Fakultät und Klinikum 1946-1986. Verlag: Mainz. Kirchheim (1986)

¹⁰²⁶ Scientia Pharmaceutica, Wissenschaftliches Organ der Österreichischen Apothekerschaft, Heft 2, 42. Jahrgang, in: Buchbesprechungen Kurs der Allgemeinen Pharmakologie und Toxikologie (1974)

¹⁰²⁷ Scientia Pharmaceutica, Wissenschaftliches Organ der Österreichischen Apothekerschaft, Heft 1, 41. Jahrgang, 1973

¹⁰²⁸ Scientia Pharmaceutica, Wissenschaftliches Organ der Österreichischen Apothekerschaft, Heft 3, 42. Jahrgang Buchbesprechungen 1974 page 201

¹⁰²⁹ Österreichische Apothekerzeitung, 17 Jahrgang, Folge 8, 1963, page 112

¹⁰³⁰ Österreichische Apothekerzeitung 17 Jahrgang ,Folge 24, 1963, page 380

*Effekte , (...) Kurvenbilder, und der tabellarischen Zusammenstellung der Ergebnisse.*¹⁰³¹

Further educational touchpoints with pharmacists can be seen the issuing in a pocketbook “*Taschenbuch der modernen Arzneibehandlung*”¹⁰³², particularly conceived to address pharmacists and physicians since it focused on applied pharmacotherapy and had been advertised in associated pharmaceutical journals. This pocketbook had been published in numerous editions and been translated into several languages¹⁰³³ and is still today available in updated versions with additional authors.¹⁰³⁴

Kuschinsky also took part in advanced training courses of the Federal Pharmacy Chamber of Germany, giving a lecture on Mai 21st 1963 in Meran¹⁰³⁵, dealing with the classification of diuretic drugs and their potential interactions with substances classes such as cardiac glycosides, combining scientific and practical questions.¹⁰³⁶

During his experiences as a medical practitioner before 1929, at his time in Shanghai from 1933 onwards but also in early and later post-war years, Kuschinsky also engaged in direct and practical interaction with his pharmaceutical colleagues at various occasions and levels, which he also deemed relevant to describe in his reminiscences.¹⁰³⁷

Due to his evidence based, rational approach to drug prescription he did also challenge current practice of some of his medical and pharmaceutical colleagues at that time and thereby also opposed commercial benefits due to extensive medication use “*Der Apotheker war mit mir nicht zufrieden. Meine Rezepte waren zu kurz. Er zeigte mir einige Muster, bei denen immer 8 bis 10 Einzelsubstanzen gemischt wurden, dabei oft Morphin in homöopathischer Dosis.*”¹⁰³⁸

At the same time, the knowledge about herbal medicines, being treasured by pharmacists in China and the concomitant potential to identify and discover new compounds that could then serve as medical substances, was appreciated by Kuschinsky.¹⁰³⁹ Evidence for positive and direct collaborations can also be seen in his time at the University of Mainz, where he choose

¹⁰³¹ Scientia Pharmaceutica, Wissenschaftliches Organ der Österreichischen Apothekerschaft, Heft 2, 42. Jahrgang, in: Buchbesprechungen Kurs der Allgemeinen Pharmakologie und Toxikologie (1974)

¹⁰³² Scientia Pharmaceutica, Wissenschaftliches Organ der Österreichischen Apothekerschaft, Heft 1, 41. Jahrgang (1973)

¹⁰³³ Scientia Pharmaceutica, Wissenschaftliches Organ der Österreichischen Apothekerschaft, Heft 3, 42. Jahrgang Buchbesprechungen (1974) page 201

¹⁰³⁴ LÜLLMANN HEINZ / MOHR KLAUS, Pharmakologie und Toxikologie, Arzneimittelwirkungen verstehen – Medikamente gezielt einsetzen in: 18. überarbeitete Auflage, Thieme Verlag (2016)

¹⁰³⁵ Österreichische Apothekerzeitung, 17 Jahrgang, Folge 8, 1963, page 112

¹⁰³⁶ Österreichische Apothekerzeitung 17 Jahrgang, Folge 24, 1963, page 380

¹⁰³⁷ MANN GÜNTER / DUMONT FRANZ, Medizin in Mainz. Praxis und Wissenschaft, Entwicklungen und Erinnerungen in: 40 Jahre Medizinische Fakultät und Klinikum 1946-1986. Verlag: Mainz. Kirchheim (1986)

¹⁰³⁸ Ibidem, page 226

¹⁰³⁹ Ibidem, page 232

a pharmacist as a researcher within his Pharmacological Institute¹⁰⁴⁰ and also fostered productive relations to local pharmacists to ensure an adequate drug supply to his patients.¹⁰⁴¹

Further indirect touchpoints with the pharmaceutical sector can be shown in his evaluation of newly registered or marketed pharmaceutical drugs, such as vitamin E preparations by various manufacturing companies *Evion*¹⁰⁴² by *E. Merck, Chem. Fabrik, Darmstadt*¹⁰⁴³ or *E-Viterbin*¹⁰⁴⁴ by *Knoll AG., Chem, Fabrik, Ludwigshafen am Rhein*¹⁰⁴⁵, in which Kuschinsky also entered his own research findings “*Vitamin E vermag die Wirkung der weiblichen Sexualhormone zu verstärken. Besonders wichtig ist die Corpus Luteum - artige Wirkung, welche die erfolgreiche Anwendung bei (...) Aborten verständlich macht.*”¹⁰⁴⁶

Recurrently he was provided with drug samples of pharmaceutical companies for his research, as documented in the case of *Fa. Kali- Chemie A. G.*¹⁰⁴⁷, *Firma E. Merck*¹⁰⁴⁸, *Fa. Chemiewerk Homburg*^{1049,1050}, *Firma Bayer*^{1051,1052}, *Fa. Gebr. Giulini GmbH*¹⁰⁵³, *Farbwerke Hoechst*^{1054,1055,1056} and *Firma Sandoz A.G.*¹⁰⁵⁷, *Chem. Fabrik Promonta G.m.b.H.*¹⁰⁵⁸ or

¹⁰⁴⁰ Ibidem, page 243

¹⁰⁴¹ Ibidem, page 242

¹⁰⁴² KUSCHINSKY GUSTAV, Kuschinsky "Wichtige neue Arzneimittel" in: Deutsche Medizinische Wochenschrift Nr.27/28 (1943)

¹⁰⁴³ Ibidem

¹⁰⁴⁴ Ibidem

¹⁰⁴⁵ Ibidem

¹⁰⁴⁶ Ibidem

¹⁰⁴⁷ KUSCHINSKY GUSTAV, Die Verhütung von Erschöpfungszuständen des Herzens durch Digitalissubstanzen. In: Klinische Wochenschrift 24 (1947) pages 502–503

¹⁰⁴⁸ KUSCHINSKY GUSTAV, Über Gefäßabdichtung durch Rutin in: Klinische Wochenschrift 27, (1949) page 317

¹⁰⁴⁹ KUSCHINSKY GUSTAV, Über die Wirkung von embryonalem Herzextrakt auf Herz und Nebennierenhypertrophie im Schwimmversuch in: Naunyn - Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie 205 (1948) pages 424–428

¹⁰⁵⁰ KUSCHINSKY GUSTAV / MUSCHOLL ERICH, Die Behandlung der experimentellen Quecksilbervergiftung mit 2,3 Dimercaptopropionsäure, in: Naunyn - Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie 223 (1954) pages 408–419

¹⁰⁵¹ KUSCHINSKY GUSTAV, Über die Wirkung luteinisierender Substanz auf die Funktion der lipoidhaltigen Zellen des Ovariums in: Archiv für experimentelle Pathologie und Pharmakologie 179 (1935) pages 717–721“

¹⁰⁵² KUSCHINSKY GUSTAV, Über die Wirkung luteinisierender Substanz auf den Hoden in: Archiv für experimentelle Pathologie und Pharmakologie 179 (1935) pages 722–725

¹⁰⁵³ KUSCHINSKY GUSTAV / REUTER H., Über den Wirkungsmechanismus von Ajmalin, in: Naunyn - Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie 242 (1961) pages 17–23

¹⁰⁵⁴ KUSCHINSKY GUSTAV / BRUNNER H. / MÜNCHOW O. / PETERS G., Der Einfluß von natürlichem und synthetischem Oxytocin auf endogene Kreatinin-Clearance, Salzausscheidung und Säureausscheidungsfähigkeit der Ratte und auf die Diurese des Menschen in. Naunyn - Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie 230 (1957) pages 80–89

¹⁰⁵⁵ KUSCHINSKY GUSTAV/ MUSCHOLL ERICH, Die Behandlung der experimentellen Quecksilbervergiftung mit 2,3 Dimercaptopropionsäure, in: Naunyn - Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie 223 (1954) pages 408–419

¹⁰⁵⁶ KUSCHINSKY GUSTAV / FÖRSTER W./ LÜLLMANN H., Über adrenolytische Wirkungen von d,l,1-(4-oxyphenyl)-1-oxy-2-n-butylamino-aethan in: Naunyn - Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie 210 (1950) pages 23–30

directly funded via industrial cooperations¹⁰⁵⁹ “*Die Arbeit wurde aus dem Roche - Fonds der deutschen Forschungsgemeinschaft unterstützt*“¹⁰⁶⁰ Notwithstanding those productive interactions, Kuschinsky did also criticise the advertisement “*Auch die Propaganda der Firmen (...) um sie für ihre Zwecke auszunutzen*”¹⁰⁶¹ and sales of medicinal products with similar or identical constituents with no proven or objective benefit, implying a conscious deception of the general public for financial reasons.

4.2. Analysis and contextualization of Kuschinsky’s scientific research

4.2.1 Physiology

One of Kuschinsky’s main scientific focus was fundamental research, taking into account various basic pharmacological aspects linked to physiological contexts, such as signal transduction^{1062,1063,1064} the measurement of stimulus thresholds^{1065,1066,1067} or the initial understanding of the mode of action of drugs and biogenic substances.^{1068,1069,1070,1071,1072}

¹⁰⁵⁷ KUSCHINSKY GUSTAV/ BRUNNER H. / MÜNCHOW, O. / PETERS, G., Der Einfluß von natürlichem und synthetischem Oxytocin auf endogene Kreatinin-Clearance, Salzausscheidung und Säureausscheidungsfähigkeit der Ratte und auf die Diurese des Menschen in: Naunyn - Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie 230 (1957) pages 80–89

¹⁰⁵⁸ KUSCHINSKY GUSTAV / HÄRTFELDER, G./ MOSLER, K. H., Über pharmakologische Wirkungen an elektrisch gereizten glatten Muskeln in: Naunyn - Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie 234 (1958) pages 66–78

¹⁰⁵⁹ KUSCHINSKY GUSTAV, Bundesarchiv Berlin- Lichterfelde, Bestandssignatur R 73 / Archivsignatur 12537, Sonderdrucke / Berichte, Sachbeihilfen vom 12. Mai 1942 / Kur 4/16/4

¹⁰⁶⁰ KUSCHINSKY GUSTAV, Über die diuretische Wirkung von Hinterlappen-Präparaten und Ihre Beziehung zur antidiuretischen Wirkung des Vasopressins in: Klinische Wochenschrift 18 (1939) pages 207–208

¹⁰⁶¹ KUSCHINSKY GUSTAV, Über die Beurteilung der Wirkung neuer Arzneimittel in: Deutsche Medizinische Wochenschrift Nr. 36 (1955)

¹⁰⁶² KUSCHINSKY GUSTAV / LÜLLMANN, HEINZ, Über die Beziehungen der Barium-Ionen zum Acetylcholin in Klinische Wochenschrift 28 (1950) pages 137–138

¹⁰⁶³ KUSCHINSKY GUSTAV, Über das Verhalten von Kalium und Calcium im Blut des Hundes beim Histaminshock. in: Z. Ges. Exp. Med. 64 (1929) pages 563–568

¹⁰⁶⁴ KUSCHINSKY GUSTAV / HATTINGBERG, M./ RAHN, K.H., Der Einfluß von Pharmaka auf Calciumgehalt und 45 Calciumaustausch der glatten Muskulatur der Taenia Coli vom Meerschweinchen in: Naunyn - Schmiedebergs Arch 253 (1966) pages 438–443

¹⁰⁶⁵ KUSCHINSKY GUSTAV / LÜLLMANN H. / MUSCHOLL, E., Untersuchungen über die Einwirkung von verschiedenen Pharmaka auf die Spontanrhythmik des isolierten Hühneramnion, in: Naunyn - Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie 223 (1954) pages 369–374

¹⁰⁶⁶ KUSCHINSKY GUSTAV/ HÄRTFELDER, G. / MOSLER, K.H., Über pharmakologische Wirkungen an elektrisch gereizten glatten Muskeln in: Naunyn - Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie 234 (1958) pages 66–78

¹⁰⁶⁷ KUSCHINSKY GUSTAV / LÜLLMANN H. / MOSLER, K.H., Über den Einfluß von Chinin, Papaverin und Temperaturherabsetzung auf die mechanische und elektrische Aktivität des isolierten Uterus der Ratte in: Naunyn-Schmiedebergs Archiv für Experimentelle Pathologie und Pharmakologie 237 (1959) pages 495–506

¹⁰⁶⁸ KUSCHINSKY GUSTAV / HILLE, U. / SCHIMASSEK, H., Über Histamin als Mittler-Substanz bei der Wirkung von Adrenochrom auf die Blutungszeit in : Naunyn - Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie 215 (1952) pages 48–51

¹⁰⁶⁹ KUSCHINSKY GUSTAV, Über die Bedeutung von Sulfhydrylgruppen für Prozesse am Aktomyosin in: Die Naturwissenschaften Heft 18 Jahrgang 38 (1950) pages page 425f.

In the course of investigations with smooth muscle tissue on several isolated organs, the interplay of ions, neurotransmitters and substances and their ability to affect muscarinic receptors at the neuronal-muscular junction are examined with regards to their interplay and subsequent physiological effects on the investigated target organ “*Wir müssen nach unseren Versuchen annehmen, daß auch für die rythmischen Spontanbewegungen von Darm und Uterus Acetylcholin eine Rolle spielen mag, und daß die Barium Ionen imstande sind die Produktion des Acetylcholin durch die Cholin- acetylase zu fürdern oder auf die acetylcholinabbauende Cholinesterase hemmend zu wirken.*”¹⁰⁷³

Further very fundamental investigations on physiological effects based on biochemical processes are examined via several drugs such as 2,4- dinitrophenol or adrenaline with regards to calcium homeostasis. Hereby kinetic characteristics of radioactively marked calcium isotopes were used to understand ionic mobility as a result of pharmacological cascades induced by those drugs “*Papaverin steigerte an der Taenia Coli die Aufnahme (...) und die Abgabe (...) von ⁴⁵Ca*”¹⁰⁷⁴ or „*Unter Adrenalin waren Aufnahme und Abgabe von ⁴⁵Ca an der Taenia Coli nicht verändert*“¹⁰⁷⁵

Effects of biogenic amines, such as histamin were investigated to understand caused electrolyte shifts within the bloodstream in the context of anaphylaxis. Those levels of potassium and hydronium ions are then again related to asses their relevance for other physiological parameters such as hematocrit or clinical manifestations like oedemas.¹⁰⁷⁶

Activation and excitation thresholds to evoke an action potential and a subsequent physiological effect also play a role within Kuschinsky’s physiological experiments. In a series of electric pulse protocols, physiological movement on smooth muscle tissue are investigated, to imitate their behaviour in vivo: “*Zur Reizung wurd Wechselstrom aus dem Netz (120 V) verwendet (...) Die Teizstärken betrug 0,5 - 20 V Wechselstrom (= 0,125 -5*

¹⁰⁷⁰ KUSCHINSKY GUSTAV / LINDMAR, R./ LÜLLMANN, H./ MUSCHOLL, E., Der Einfluß von Reserpin auf die Wirkung der „Neuro-Sympathomimetica“ in : Naunyn - Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie 240 (1960) pages 242–252

¹⁰⁷¹ KUSCHINSKY GUSTAV / LANGECKER, H, Über die Wirkung des Atropins auf die Nierenfunktion in: Naunyn-Schmiedeberg's Archives of Pharmacology 208(1) (1949) pages 35-36

¹⁰⁷² KUSCHINSKY GUSTAV / REUTER, H., Über den Wirkungsmechanismus von Ajmalin, in: Naunyn - Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie 242 (1961) pages 17–23

¹⁰⁷³ KUSCHINSKY GUSTAV/ LÜLLMANN, H., Über die Beziehungen der Barium-Ionen zum Acetylcholin in: Klinische Wochenschrift 28 (1950) pages 137–138

¹⁰⁷⁴ KUSCHINSKY GUSTAV / HATTINGBERG, M. / RAHN, K.H., Der Einfluß von Pharmaka auf Calciumgehalt und ⁴⁵ Calciumaustausch der glatten Muskulatur der Taenia Coli vom Meerschweinchen in: Naunyn - Schmiedebergs Arch 253 (1966) pages 438–443

¹⁰⁷⁵ Ibidem

¹⁰⁷⁶ KUSCHINSKY GUSTAV, Über das Verhalten von Kalium und Calcium im Blut des Hundes beim Histaminshock. In: Z. Ges. Exp. Med. 64 (1929) pages 563–568

*V/cm3) die Reizzeit 2 1/2 - 5 sec, die Unterbrechung 30-120 sec. Organe mit Spontanrhythmik wurden jeweils etwas frequenter gereizt als es der Eigenfrequenz entsprach*¹⁰⁷⁷

Other electrophysiological experiments dealt with a detailed description of activation processes of these evoked action potentials, characterising their monophasic or dual-phased course and thus their physiological effects on muscle tissue, also under the influence of pharmaceuticals.¹⁰⁷⁸ Besides activating substances, also inhibitory effects on neurotransmitters are used to either assess their potential to influence target structures or to provide an in- depth understanding to physiological connections “*Auch die Unwirksamkeit von Pentamethonium und Hexamethonium spricht für das Fehlen zumindest komplizierterer nervaler Elemente (intramurale Umschaltstellen)*”¹⁰⁷⁹

The examination of the mode of action had been investigated e.g. in terms of blood coagulation time, taking into account the relevance of biogenic amines such as histamine and their effect on other metabolites e.g. catecholamines.¹⁰⁸⁰ Other experiments also involved in the investigation of (formerly) authorized drugs such as the organic mercury compound *Salygran* with respect to their concentration- dependent effects on filamentproteins “*Polymerisation des Aktins und auf die Symplexbildung von Aktin und Myosin*”¹⁰⁸¹ and thus to identify their influence on functional groups such as sulfhydryl groups.

Additional research focused on grasping the mode of action of sympathomimetic drugs by assessing direct or indirect underlying effects, either receptor-mediated or through the release of neurotransmitters, which also incorporated the quantification of those and other pharmacological effects, based on the frequency of action potentials and the contractility of the myocardium.¹⁰⁸²

¹⁰⁷⁷ KUSCHINSKY GUSTAV/ HÄRTFELDER, G./ MOSLER, K.H., Über pharmakologische Wirkungen an elektrisch gereizten glatten Muskeln in: Naunyn - Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie 234 (1958) pages 66–78

¹⁰⁷⁸ KUSCHINSKY GUSTAV / LÜLLMANN, H. / MOSLER, K.H., Über den Einfluß von Chinin, Papaverin und Temperaturherabsetzung auf die mechanische und elektrische Aktivität des isolierten Uterus der Ratte in: Naunyn-Schmiedebergs Archiv für Experimentelle Pathologie und Pharmakologie 237 (1959) pages 495–506

¹⁰⁷⁹ KUSCHINSKY GUSTAV / LÜLLMANN, H. / MUSCHOLL, E., Untersuchungen über die Einwirkung von verschiedenen Pharmaka auf die Spontanrhythmik des isolierten Hühneramnion, in : Naunyn - Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie 223 (1954) pages 369–374

¹⁰⁸⁰ KUSCHINSKY GUSTAV / U. HILLE, U., / SCHIMASSEK, H., Über Histamin als Mittler-Substanz bei der Wirkung von Adrenochrom auf die Blutungszeit in : Naunyn - Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie 215 (1952) pages 48–51

¹⁰⁸¹ KUSCHINSKY GUSTAV, Über die Bedeutung von Sulfhydrylgruppen für Prozesse am Aktomyosin in: Die Naturwissenschaften Heft 18 Jahrgang 38 (1950) pages page 425f

¹⁰⁸² KUSCHINSKY GUSTAV / LINDMAR, R. / LÜLLMANN, H./ MUSCHOLL, E., Der Einfluß von Reserpin auf die Wirkung der „Neuro-Sympathomimetica“ in : Naunyn - Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie 240 (1960) pages 242–252

Effects on secretion and absorption within kidney tissue are investigated by Kuschinsky with various substances to assess both parameters such as the glomerular filtration rate or effects within the distal tubule to identify accessible targets “*Diese Wassersekretion lässt sich gleichzeitig mit der Phenolrotsekretion durch Atropin hemmen (...) Im Gegenteil wurde der Salygraneeffekt meist um 50 - 250 % gesteigert*“¹⁰⁸³ (...) “*Nicht nur den sezernierenden , sondern auch den rückresorbierenden Teil des Tubulusapparates hemmt*“¹⁰⁸⁴

The classification of antiarrhythmic agents also played a part of characterising drug actions in a more detailed manner, here concretely with two different kinds of alkaloids, which are analysed relating to their abilities to modify cardiac parameters “*Ajmalin und Chinidin vermindern die Kontraktionsamplitude des elektrisch gereizten Meerschwindenvorhofs.*”¹⁰⁸⁵ Both antiarrhythmic drugs are assigned to the same pharmacological class, blocking sodium channels, which is also in line with today’s knowledge about them “*Die Versuche sprechen für einen gleichen antifibrillatorischen Wirkungsmechanismus von Ajmalin und Chinidin.*”¹⁰⁸⁶

4.2.2 Pharmacological research

Naturally both pharmacological and physiological research display a certain level of thematic and methodic overlap, however the allocation had been made depending on the research focus, either dealing with questions of basic physiological understanding or with primarily analysing drug actions within a broader context, suitable for therapeutic intervention.

In this respect, an almost 360 degree view on pharmaceutical compounds, such as meta-sympathol had been conducted investigating their structure- effect relationship, in regards to physiological parameters such as blood pressure, vascular tone, effects on pulmonary and cardiovascular circulation but also toxicological ones, including lethal dose, therapeutic index or capturing symptoms of intoxication. Kuschinsky is also using other pharmacologically similar substances such as adrenaline to assess and to compare maximum therapeutic effects, such as saturation levels within maintenance treatment.¹⁰⁸⁷ Further research concentrating on a quite comprehensive pharmacological profiling of substances had been conducted with pyridine derivatives in the context of their tranquillizing potential. Here again, structure-

¹⁰⁸³ KUSCHINSKY GUSTAV / LANGECKER, H., Über die Wirkung des Atropins auf die Nierenfunktion in : Naunyn-Schmiedeberg's Archives of Pharmacology 208(1) (1949) pages 35-36

¹⁰⁸⁴ Ibidem

¹⁰⁸⁵ KUSCHINSKY GUSTAV / REUTER, H., Über den Wirkungsmechanismus von Ajmalin, in: Naunyn - Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie 242 (1961) pages 17–23

¹⁰⁸⁶ Ibidem

¹⁰⁸⁷ KUSCHINSKY GUSTAV / OBERDISSE, K., Die Kreislaufwirkungen des Meta-Sympatols ,in: Archiv f. experimentelle Pathologie und Pharmakologie 162 (1931) pages 46–55

effect relationships, pharmacokinetic and toxicologic parameters such as elimination, metabolism and evidence for accumulation, side effects and median lethal doses of drugs are gathered to assess first safety and tolerability data “nach mittleren Dosen etwa 0,4 g /kg ein leichtes Vibrieren der Muskeln (...) Durch Dosen bis 0,7 g / kg wurde niemals eine Ratte getötet“¹⁰⁸⁸ Particular interest to further distinct structural groups can be documented on Kuschinsky’s extensive research on derivatives of hydrazone^{1089,1090,1091,1092,1093,1094}

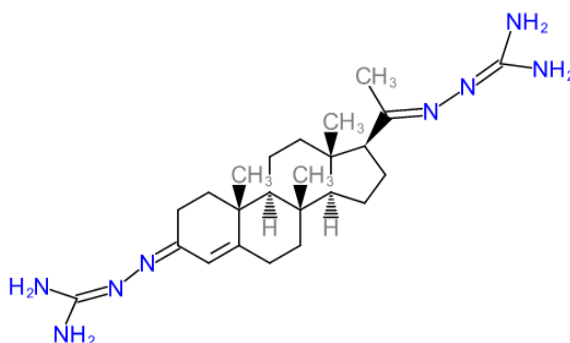


Illustration 9: Progesteron-bis-guanyl-hydrason (BG31) one investigated representative of this chemical class with a steroid as carrier substance

This research included the evaluation of the pharmacokinetic parameters such as the distribution within the bloodstream and the extent of adhesion to biological surfaces such as the erythrocyte membrane.¹⁰⁹⁵ Further pharmacokinetic research referred to eliminative

¹⁰⁸⁸ KUSCHINSKY GUSTAV / KRAUTWALD, A. / RIEDEL, H., Über die sedative Wirkung von Pyridinderivaten, in: Archiv für experimentelle Pathologie und Pharmakologie 193 (1939) pages 219–230

¹⁰⁸⁹ KUSCHINSKY GUSTAV / LÜLLMANN, H. / MUTSCHLER, E./ WOLLERT, U, Beziehungen zwischen der Struktur von Bisguanylhydrazonen und der Art ihrer Herzwirksamkeit in : Naunyn - Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie 251 (1965) pages 153–154

¹⁰⁹⁰ KUSCHINSKY GUSTAV / EHMER, A. / JAHR, K. / LÜLLMANN, H./ REUTER, H. / WOLLERT, U., Progesteronbisguanylhydrason als Vertreter einer neuen herzwirksamen Substanzgruppe in: Naunyn - Schmiedebergs Arch 247 (1964) page 342

¹⁰⁹¹ KUSCHINSKY GUSTAV / SCHMITTEL, K. / HOFMANN, P. / MUTSCHLER, E. / WOLLERT, U., Über die Eiweißbindung von Bisguanylhydrazonen in: Naunyn-Schmiedebergs Arch. Pharmak. u. Exp. Path. 257 (1967) page 328

¹⁰⁹² KUSCHINSKY GUSTAV / EHMER, A. / JAHR, K./ LÜLLMANN, H. / MUTSCHLER, E. / WOLLERT, U., Über die Wirkung einfacher Bisguanylhydrazone auf Herzgewebe in : Naunyn - Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie 247 (1964) page 343

¹⁰⁹³ KUSCHINSKY GUSTAV / HOFMANN, P. / MUTSCHLER, E. / WOLLERT, U., Die Verteilung von Progesteron- und Dodecandion-2,11-bisguanylhydrason im Meerschweinchenorganismus in : Naunyn-Schmiedebergs Archiv für experimentelle Pharmakologie und Experimentelle Pathologie 257, 288–289 (1967) pages 288–289

¹⁰⁹⁴ KUSCHINSKY GUSTAV / SCHMITTEL, K., Über die Verteilung von 3,3'-Dimethyl-4,4'-diacetyl-diphenyl-bisguanylhydrason im Erythrocyten in : Naunyn-Schmiedebergs Arch. Pharmak. u. Exp. Path. 260 (1968) pages 195–196

¹⁰⁹⁵ KUSCHINSKY GUSTAV / SCHMITTEL, K., Über die Verteilung von 3,3'-Dimethyl-4,4'-diacetyl-diphenyl-bisguanylhydrason im Erythrocyten in : Naunyn-Schmiedebergs Arch. Pharmak. u. Exp. Path. 260, 195–196“ (1968) pages 195–196

processes as measured by concentration measurements in pulmonary and renal tissue obtained from animal experimentations “*In der Elimination aus den verschiedenen Organen verhält sich BG 31 ähnlich wie BG 60 während sich BG 32 deutlich unterscheidet*”.¹⁰⁹⁶

But also investigations in the context of pharmacodynamic questions, such as the cardiac efficacy corresponding to their chemical structure “*Aus den unterschiedlichen Ergebnissen für die BGs mit verschiedenen Trägermolekülen ergibt sich, daß für das Verhalten dieser Substanzen im Organismus nicht allein die beiden Guanylhydrazongruppen verantwortlich sind.*”¹⁰⁹⁷ represent a part of this thematic focus. As an example for that, the substitution of functional groups are taken into consideration in order to modify sympathomimetic effects or to analyse the level of dependency of various concentrations on those effects.¹⁰⁹⁸ Relevant additional pharmacokinetic parameters such as plasma protein binding, directly influencing the level of drug activity are measured, here directly with human serum albumin.¹⁰⁹⁹

The structure- activity relationships^{1100,1101} also implied a direct comparison with other, already well-established cardiac glykosides or their aglycone like strophantin and digitoxigenin, which are also investigated with regards to electrophysiological parameters such as their influence on cardiac membrane potentials “*Zwei Zentren mit hoher Elektronendichte, die einen bestimmten Abstand voneinander aufweisen*”¹¹⁰² (...) “*Konjugierte Doppelbindung im ungesättigten Lactonring des Genins entspricht die konjugierte Doppelbindung im Guanylhydrazon- Rest an C20 und der Sauerstofffunktion an C3 des Genins wieder um eine konjugierte Doppelbindung im Guanylhydrazon- Rest an C3 der Steroide*”¹¹⁰³

¹⁰⁹⁶ KUSCHINSKY GUSTAV / HOFMANN, P. / MUTSCHLER, E. / WOLLERT, U., Die Verteilung von Progesteron- und Dodecandion-2,11-bisguanylhydrazon im Meerschweinchenorganismus in: Naunyn-Schmiedebergs Archiv für experimentelle Pharmakologie und Experimentelle Pathologie 257 (1967) pages 288–289

¹⁰⁹⁷ Ibidem

¹⁰⁹⁸ KUSCHINSKY GUSTAV / LÜLLMANN, H. / MUTSCHLER, E. / WOLLERT, U., Beziehungen zwischen der Struktur von Bisguanylhydrazonen und der Art ihrer Herzwirksamkeit in: Naunyn - Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie 251 (1965) pages 153–154

¹⁰⁹⁹ KUSCHINSKY GUSTAV / SCHMITTEL, K. / HOFMANN, P. / MUTSCHLER, E. / WOLLERT, U., Über die Eiweißbindung von Bisguanylhydrazonen in: Naunyn-Schmiedebergs Arch. Pharmak. u. Exp. Path. 257 (1967) page 328

¹¹⁰⁰ KUSCHINSKY GUSTAV / LÜLLMANN, H. / MUTSCHLER, E. / WOLLERT, U., Beziehungen zwischen der Struktur von Bisguanylhydrazonen und der Art ihrer Herzwirksamkeit in: Naunyn - Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie 251 (1965) pages 153–154

¹¹⁰¹ KUSCHINSKY GUSTAV / EHMER, A. / JAHR, K. / LÜLLMANN, H. / MUTSCHLER, E. / WOLLERT, U., Über die Wirkung einfacher Bisguanylhydrazone auf Herzgewebe in: Naunyn - Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie 247 (1964) page 343

¹¹⁰² KUSCHINSKY GUSTAV / A. EHMER, A. / JAHR, K. / LÜLLMANN, H. / REUTER, H. / WOLLERT, U., Progesteronbisguanylhydrazon als Vertreter einer neuen herzwirksamen Substanzgruppe in: Naunyn - Schmiedebergs Arch 247 (1964) page 342

¹¹⁰³ Ibidem

Further investigations on the same subject are also to be found on other cardio- and vasoactive substances representatives of sympathomimetic drugs such as ephedrine and its derivatives, also with deduced recommendations for pharmacotherapy “*Es ist also dann indiziert, wenn ein lang anhaltender Effekt auf die Gefäße erwünscht ist.*”¹¹⁰⁴ These pharmacotherapeutic suggestions frequently relate to several indications, such as moderate to severe hypotonia or positive effects on cardiac conduction and other beneficial pharmacological effects like reduced cardiac oxygen consumption induced by these drugs. At the same time side effects are also considered basing on the previous experiments: “*Das in den letzten Jahren häufig untersuchte Benzedrin, ein β - Phenylisopropylamin, zeichnet sich besonders durch starke zentrale Wirkungen aus, die zum Teil auch schon bei Ephedrin beobachtet wurden. Es erzeugt gehobene Stimmungslage, psychische und motorische Unruhe , lange Schlaflosigkeit usw.*“¹¹⁰⁵

This tight interlinking of basic pharmacological research to clinical application is also manifested through investigations on dose- response relationships, as well as duration of pharmacological action, therapeutic index and also aspects of practical applicability.¹¹⁰⁶ Underlying experiments also simulated this dose dependency on individual organs and tissue types, e.g. inhibitory or stimulatory effects, as seen on theophylline, caffeine, papaverine and chinine, which either have certain therapeutic potential or are of pharmacological and toxicological interest, based on their dosage.

Within parts of Kuschinsky’s rather clinical and thus application- oriented posing of scientific questions, performance- enhancing drugs were also explicitly investigated at times also with registered proprietary pharmaceuticals such as “*Kombetin- Böhringen*”¹¹⁰⁷, a intravenously administered cardenolide. Here not only implications for the medical treatment of pathological conditions are investigated “*Die gilt auch für klinisch sonst normale Herzen vor schweren operativen Eingriffen oder bei Beginn schwerer fieberhafter Erkrankungen*“¹¹⁰⁸ but also in healthy persons, which could according to Kuschinsky’s recommendations, benefit

¹¹⁰⁴ KUSCHINSKY GUSTAV, Kreislauftherapie mit Adrenalinverwandten Mitteln in: Klinische Wochenschrift 17 (1938) pages 145–148

¹¹⁰⁵ Ibidem

¹¹⁰⁶ KUSCHINSKY GUSTAV / FÖRSTER, W. / LÜLLMANN, H., Über adrenolytische Wirkungen von d,l,1-(4-oxyphenyl)-1-oxy-2-n-butylamino-aethan in: Naunyn - Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie 210 (1950) pages 23–30

¹¹⁰⁷ KUSCHINSKY GUSTAV, Die Verhütung von Erschöpfungszuständen des Herzens durch Digitalissubstanzen. In: Klinische Wochenschrift 24 (1947) pages 502–503

¹¹⁰⁸ Ibidem

from this hormone intake in situations of increased physical strain, to act as a stimulant via the inhibition of the cardiac transmembrane protein, the sodium- potassium ATPase.¹¹⁰⁹

Additional experiments with the thematic focus on identifying substances` pharmacological potential to serve as doping agents were conducted with corticoid hormones, here also with already marketable products such as *Cohormon* by the company *Fa. Chemiewerk Homburg*.¹¹¹⁰ Within this series of laboratory trials, animals are exposed to considerable physical stress “*Schwimmleistungen bis zur Erschöpfung*”¹¹¹¹ aiming at assessing the ultimate physical performance caused by the drug, in comparison to the untreated control group “*die Erschöpfungszustände waren teilweise hochgradig. Nur durch Wärmebehandlung gelang es , in diesen Fällen die Ratten am Leben zu erhalten*”¹¹¹² Besides those primarily investigated pharmacologically driven increase in physical performance, also safety aspects with regards to the applied doses are considered, e.g. cardiac hypertrophy and thus limitations for its potential later use in humans. Additional forms of application such as a subcutaneous administration of luteinising hormones also originating of pharmaceutical production “*Prolan*” (...) “*Firma Bayer*”¹¹¹³ and involve the investigation of their effects on reproductive effects on the animal ovary and follicle stimulation but also on male reproductive organs in laboratory rats.¹¹¹⁴

Both the histological and morphological examination of seminal vesicles and testicles, with particular focus on the Leydig cells, essential for testosterone production “*Bei männlichen Rattensäuglingen bewirkt luteinisierende Substanz aus Schwangerenharn (Prolan) eine Vermehrung der Zwischenzellen*”¹¹¹⁵ are investigated also though an assessment of pharmacologically induced increase in weight.

Experiments on the effects of subcutaneous injections of neuropeptides such as oxytocin and other peptide hormones such as vasopressin “*Tonephin*”¹¹¹⁶ or their antagonists

¹¹⁰⁹ Ibidem

¹¹¹⁰ KUSCHINSKY GUSTAV, Über die Wirkung von embryonalem Herzextrakt auf Herz und Nebennierenhypertrophie im Schwimmversuch in: Naunyn - Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie 205 (1948) pages 424–428

¹¹¹¹ Ibidem

¹¹¹² Ibidem

¹¹¹³ KUSCHINSKY GUSTAV, Über die Wirkung luteinisierender Substanz auf die Funktion der lipoidhaltigen Zellen des Ovariums in: Archiv für experimentelle Pathologie und Pharmakologie 179 (1935) pages 717–721

¹¹¹⁴ KUSCHINSKY GUSTAV, Über die Wirkung luteinisierender Substanz auf den Hoden in: Archiv für experimentelle Pathologie und Pharmakologie 179 (1935) pages 722–725

¹¹¹⁵ Ibidem

¹¹¹⁶ KUSCHINSKY GUSTAV, Über die diuretische Wirkung von Hinterlappen-Präparaten und Ihre Beziehung zur antidiuretischen Wirkung des Vasopressins in: Klinische Wochenschrift 18 (1939) pages 207–208

“Hypophysin”¹¹¹⁷ are evaluated with regards to their effects on diuresis “So ist z.B. nach 0,05 E Orasthin die Cl- Ausscheidung durchschnittlich 5 mal so hoch wie nach der entsprechenden Menge Tonephin.”¹¹¹⁸ Besides these different routes of administrations, exogenous factors on these observed pharmacological effects play a role in these comprehensive investigations such as thermal influences on the biological activity of those biochemical messengers. Basing on the complex functional interrelationships these experiments aim to assess individual factors within the hormonal feedback control and endocrinological axis. “Nach 2 Tagen Kälteeinfluss zeigten die Hypophysen ungefähr dieselbe thyreotrope Wirkung wie normale. (...) Eine Kälteeinwirkung von 1-3 Tagen nach vorheriger Wärmeeinwirkung von 9-11 Tagen zeigte ebenfalls keine Veränderung in der thyreotropen Wirksamkeit.”¹¹¹⁹ Other investigated external modifications such as sodium chloride intake or possible interventions with diuretic substances were measured on individual bodily organ parameters such as renal clearance, which also included considerations to antagonise one substance by another.¹¹²⁰

Kuschinsky’s overall approach to explore new therapeutic opportunities by bridging pharmacologically induced pathological states and assessing new drugs basing on a in- depth understanding of their chemical structure and resulting physiological effects can also be demonstrated on his experiments with di-mercaptopropionicacid (*DMPS*). The experimentally induced intoxication was brought about by *Salyrgan*, causing a variety of symptoms of cardiac poisoning as measured by blood pressure changes, anomalies within the electrocardiogram “*Verbreiterung des QRS - Komplexes (...) eventuelle Senkung der Mittelstrecke, Erhöhung von T (...) periodisches oder dauerhaftes Aussetzen des Kammerkomplexes, gelegentliches Kammerflattern oder - flimmern*”¹¹²¹ or renal malfunctions, as seen in the occurrence of protein in the urine of the investigated animals. The rationale of this experiment was to figure out whether this substance had the potential to reduce the toxic effects of the organomercury compound *Salyrgan* e.g. via complexation or redox reactions, and whether or not the investigated antidote *DMPS* did not present any health risk itself.

¹¹¹⁷ Ibidem

¹¹¹⁸ Ibidem

¹¹¹⁹ KUSCHINSKY GUSTAV, Über den Einfluss verschiedener Temperaturen auf die Sekretion des thyreotropen Hormons in: Archiv für experimentelle Pathologie und Pharmakologie 1935 Vol.179 (1935) pp.726-737

¹¹²⁰ KUSCHINSKY GUSTAV, Über den Gehalt des Harnes an Hinterlappenähnlichen Wirkstoffen in: Klinische Wochenschrift 18 Jahrgang Nr. 7 (1939)

¹¹²¹ KUSCHINSKY GUSTAV / MUSCHOLL, E., Die Behandlung der experimentellen Quecksilbervergiftung mit 2,3 Dimercaptopropionsäure, in: Naunyn - Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie 223 (1954) pages 408–419

Additional substance groups under investigation, such as flavonoid glykosides pertain to substances derived from natural sources with both antioxidative and protective effects e.g. on capillary vessels. Within Kuschinsky's experiments he also tested their pharmacological effect with regards to edemas within animals, measured on their potential to diminish their extent. *“Die Versuche ergeben, daß das Rutin bei direkter Einwirkung auf die Gefäße im Stande ist die Gefäßwände abzudichten“*¹¹²² Research on coumarin derivates and their effect on blood coagulation, as measured by prothrombin levels and also accompanied influences on vascular permeability in oral doses of 0,04 -0,1 mg /kg, enqueue themselves within subgroup of his investigations that aimed at eliciting pharmaceutical options to modify vascular elasticity and thus together with a reduction of blood coagulation factors to ameliorate hemodynamic conditions within the bloodstream.

4.2.3 Applied methods and methodological considerations within his research

Kuschinsky's spectrum of methods frequently involved several animal experiments at times also including healthy human volunteers, chemical-analytical methods, electrophysiological studies but also explicit methodological considerations.^{1123,1124 ,1125 ,1126 ,1127 ,1128}

Against the backdrop of addressing basic research as seen on pharmacological, physiological but also toxicological and application oriented pharmaceutical research , laboratory animals such as mice, dogs etc. were utilized. Here, the removal of several organs, to assess pharmacological effects on an organ and tissue level^{1129,1130,1131,1132,1133} , or direct

¹¹²² KUSCHINSKY GUSTAV, Über Gefäßabdichtung durch Rutin in: Klinische Wochenschrift 27 (1949) page 317

¹¹²³ KUSCHINSKY GUSTAV, Über die Wirkung von embryonalem Herzextrakt auf Herz und Nebennierenhypertrophie im Schwimmversuch in: Naunyn - Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie 205 (1948) pages 424–428

¹¹²⁴ KUSCHINSKY GUSTAV / BRUNNER, H. / MÜNCHOW, O. / PETERS, G., Der Einfluß von natürlichem und synthetischem Oxytocin auf endogene Kreatinin-Clearance, Salzausscheidung und Säureausscheidungsfähigkeit der Ratte und auf die Diurese des Menschen in: Naunyn - Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie 230 (1957) pages 80–89

¹¹²⁵ KUSCHINSKY GUSTAV / JUNGBLUT, P., Eine Methode zur Beurteilung des Nierengefäßtonus bei Mäusen in: Naunyn - Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie 225 (1955) pages 533–540

¹¹²⁶ KUSCHINSKY GUSTAV / HATTINGBERG, M. / RAHN, K.H., Der Einfluß von Pharmaka auf Calciumgehalt und 45 Calciumaustausch der glatten Muskulatur der Taenia Coli vom Meerschweinchen in: Naunyn - Schmiedebergs Arch 253 (1966) pages 438–443

¹¹²⁷ KUSCHINSKY GUSTAV, Methoden zur Prüfung diuretisch wirkender Stoffe in: Naunyn - Schmiedebergs Archive für experimentelle Pathologie und Pharmakologie 238 (1960) pages 195–218

¹¹²⁸ KUSCHINSKY GUSTAV / HILLE, U. / SCHIMASSEK, H., Über Histamin als Mittler-Substanz bei der Wirkung von Adrenochrom auf die Blutungszeit in: Naunyn - Schmiedebergs Archiv für experimentelle Pathologie und PHARMAKOLOGIE 215 (1952) pages 48–51

¹¹²⁹ KUSCHINSKY GUSTAV / LÜLLMANN, H., Über die Beziehungen der Barium-Ionen zum Acetylcholin in „Klinische Wochenschrift 28 (1950) pages 137–138

experimentations to investigate behavioral changes^{1134,1135} or (patho)physiological modifications^{1136,1137,1138,1139,1140,1141,1142} in vivo subject to pharmacological interventions, were undertaken.

Implying initial research questions such as dose- finding¹¹⁴³, or assessing tolerability in animals^{1144,1145}, often involving parameters like substance accumulation and habituation to them, but also pathological organ alterations. If relevant, such as in cases such as stimulants, also behavioural experiments were performed in which physiological limits were assessed “*Ratten täglich steigend 2- 8 Stunden im Laufrad bis zur Erschöpfung belastet, dabei gingen von 9 unbehandelten Tieren bereits nach einigen Tagen 7 zu Grunde, während 6 mit 0,15 g Strophanthin je 100 mg (...) nur 1 Tier ausgefallen war.*“¹¹⁴⁶

¹¹³⁰ KUSCHINSKY GUSTAV / LANGECKER, H, Über die Wirkung des Atropins auf die Nierenfunktion in: Naunyn-Schmiedeberg's Archives of Pharmacology 208(1) (1949) pages 35-36

¹¹³¹ KUSCHINSKY GUSTAV, Über die Wirkung luteinisierender Substanz auf die Funktion der lipoidhaltigen Zellen des Ovariums in: Archiv für experimentelle Pathologie und Pharmakologie 179 (1935) pages 717–721

¹¹³² KUSCHINSKY GUSTAV, Über die Wirkung luteinisierender Substanz auf den Hoden in: Archiv für experimentelle Pathologie und Pharmakologie 179 (1935) pages 722–725

¹¹³³ KUSCHINSKY GUSTAV / KRAUTWALD, A. / RIEDEL, H., Über die sedative Wirkung von Pyridinderivaten, in: Archiv für experimentelle Pathologie und Pharmakologie 193 (1939) pages 219–230

¹¹³⁴ KUSCHINSKY GUSTAV, Die Verhütung von Erschöpfungszuständen des Herzens durch Digitalissubstanzen. In: Klinische Wochenschrift 24 (1947) pages 502–503

¹¹³⁵ KUSCHINSKY GUSTAV, Über die Wirkung von embryonalem Herzextrakt auf Herz und Nebennierenhypertrophie im Schwimmversuch in: Naunyn - Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie 205 (1948) pages 424–428

¹¹³⁶ KUSCHINSKY GUSTAV, Über Gefäßabdichtung durch Rutin in: Klinische Wochenschrift 27 (1949) page 317

¹¹³⁷ KUSCHINSKY GUSTAV / MUSCHOLL, E., Die Behandlung der experimentellen Quecksilbervergiftung mit 2,3 Dimercaptopropionsäure, in: Naunyn - Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie 223 (1954) pages 408–419

¹¹³⁸ KUSCHINSKY GUSTAV, Über die Behandlung der experimentellen Glomerulonephritis mit Calcium in: Klinische Wochenschrift 24 (1947) pages 531–532

¹¹³⁹ KUSCHINSKY GUSTAV, Über den Einfluss verschiedener Temperaturen auf die Sekretion des thyreotropen Hormons in: Archiv für experimentelle Pathologie und Pharmakologie 1935 Vol.179 (1935) pp.726-737

¹¹⁴⁰ KUSCHINSKY GUSTAV, Über den Gehalt des Harnes an Hinterlappenähnlichen Wirkstoffen in: Klinische Wochenschrift 18 Jahrgang Nr. 7 (1939)

¹¹⁴¹ KUSCHINSKY GUSTAV, Methoden zur Prüfung diuretisch wirkender Stoffe in: Naunyn - Schmiedebergs Archive für experimentelle Pathologie und Pharmakologie 238 (1960) pages 195–218

¹¹⁴² KUSCHINSKY GUSTAV, Über das Verhalten von Kalium und Calcium im Blut des Hundes beim Histaminshock. in: Z. Ges. Exp. Med. 64 (1929) pages 563–568

¹¹⁴³ KUSCHINSKY GUSTAV / LANGECKER, H, Über die Wirkung des Atropins auf die Nierenfunktion in: Naunyn-Schmiedeberg's Archives of Pharmacology 208(1) (1949) pages 35-36

¹¹⁴⁴ KUSCHINSKY GUSTAV, Über die Wirkung luteinisierender Substanz auf den Hoden in: Archiv für experimentelle Pathologie und Pharmakologie 179 (1935) pages 722–725

¹¹⁴⁵ KUSCHINSKY GUSTAV / KRAUTWALD, A. / RIEDEL, H., Über die sedative Wirkung von Pyridinderivaten, in : Archiv für experimentelle Pathologie und Pharmakologie 193 (1939) pages 219–230

¹¹⁴⁶ KUSCHINSKY GUSTAV, Die Verhütung von Erschöpfungszuständen des Herzens durch Digitalissubstanzen. In: Klinische Wochenschrift 24 (1947) pages 502–503

Further research within the living test animal e.g. with frogs is performed in analogy with a method suggested by Trendelenburg¹¹⁴⁷ to assess vasoconstrictive effects or also via intoxication to emulate pathophysiological conditions “*experimentelle Masugi- Nephritis*”¹¹⁴⁸ or immunological connections.^{1149,1150}

Research with healthy volunteers concerned experiments with synthetic oxytocin in increasing doses to evaluate its effect on renal parameters “*an 10 freiwilligen gesunden Versuchspersonen (7 Männer und 3 Frauen) im Alter von 24 bis 36 Jahren von Mai bis Juli 1956 als Doppelblindversuche durchgeführt*”¹¹⁵¹ Further experiments with human test subjects also involved the testing of urine after application of diuretics such as Chlorothiazid, also under co- medication of glucocorticoids to addresses possible clinical implications for the treatment of edema and to compare these results with findings of the animal pretests.¹¹⁵²

Chemical and analytical methods, such as isotopic labelling for elucidating changes in ion concentrations¹¹⁵³ or experiments involving several (physio)chemical separation processes like centrifugation and subsequent complexation and extraction processes¹¹⁵⁴, concentration determination¹¹⁵⁵ or assessing binding affinities to erythrocytes¹¹⁵⁶ were relevant for answering pharmacokinetic and -dynamic effects.

¹¹⁴⁷ KUSCHINSKY GUSTAV, Über Gefäßabdichtung durch Rutin in: Klinische Wochenschrift 27 (1949) page 317

¹¹⁴⁸ KUSCHINSKY GUSTAV, Über die Behandlung der experimentellen Glomerulonephritis mit Calcium in: Klinische Wochenschrift 24 (1947) pages 531–532

¹¹⁴⁹ KUSCHINSKY GUSTAV, Über den Einfluss verschiedener Temperaturen auf die Sekretion des thyreotropen Hormons in: Archiv für experimentelle Pathologie und Pharmakologie 1935 Vol.179 (1935) pp.726-737

¹¹⁵⁰ KUSCHINSKY GUSTAV, Über den Gehalt des Harnes an Hinterlappenähnlichen Wirkstoffen in: Klinische Wochenschrift 18 Jahrgang Nr. 7 (1939)

¹¹⁵¹ KUSCHINSKY GUSTAV / BRUNNER, H. / MÜNCHOW, O. / PETERS, G., Der Einfluß von natürlichem und synthetischem Oxytocin auf endogene Kreatinin-Clearance, Salzausscheidung und Säureausscheidungsfähigkeit der Ratte und auf die Diurese des Menschen in: Naunyn - Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie 230 (1957) pages 80–89

¹¹⁵² KUSCHINSKY GUSTAV, Methoden zur Prüfung diuretisch wirkender Stoffe in: Naunyn - Schmiedebergs Archive für experimentelle Pathologie und Pharmakologie 238 (1960) pages 195–218

¹¹⁵³ HATTINGBERG, M. / KUSCHINSKY, G. / RAHN, K.H., Der Einfluß von Pharmaka auf Calciumgehalt und 45 Calciumaustausch der glatten Muskulatur der Taenia Coli vom Meerschweinchen. , 253(4) (1966) pages 438–443

¹¹⁵⁴ KUSCHINSKY G. / SCHMITTEL, K. / HOFMANN, P. / MUTSCHLER, E. / WOLLERT, U., Über die Eiweißbindung von Bisguanylhydrazonen in: Naunyn-Schmiedebergs Arch. Pharmak. u. Exp. Path. 257 (1967) page 328

¹¹⁵⁵ KUSCHINSKY G. / HOFMANN, P. / MUTSCHLER, E. / WOLLERT, U., Die Verteilung von Progesteron- und Dodecandion-2,11-bisguanylhydrazon im Meerschweinchenorganismus in: Naunyn-Schmiedebergs Archiv für experimentelle Pharmakologie und Experimentelle Pathologie 257(1967) pages 288–289

¹¹⁵⁶ KUSCHINSKY G. / SCHMITTEL, K., Über die Verteilung von 3,3'-Dimethyl-4,4'-diacetyl-diphenyl-bisguanylhydrazon im Erythrocyten in: Naunyn-Schmiedebergs Arch. Pharmak. u. Exp. Path. 260(1968) pages 195–196

A very extensive and recurrently used research method within Kuschinsky's publications have to be seen in his electrophysiological research, investigating electro(chemical) signal transmission on isolated organs and within the living laboratory animal.

One of those approaches involved the determination of muscle tonus and the investigation of possible drug-induced changes in the electrophysiological innervation of muscle tissue, as measured by their potential to have inhibitory or stimulating effects on action potentials¹¹⁵⁷ and electromechanical coupling.¹¹⁵⁸ Those experiments also helped to compare biological potency of individual components of either biogenic "Chinin" or "Papaverin" or physiological origin "Oxytocin" and "Acetylcholin".¹¹⁵⁹ Electrophysiological investigation within the isolated heart muscle tissue specifically addressed individual muscle groups, such as those of the heart ventricle or papillary ones, essential for a variety of physiological functions. Within these experiments both physiological characteristics under certain reference conditions were assessed "*Rechteckimpusen (...) Reizstärke supramaximal, Impulsdauer 1-8 msec (...) Reizfrequenz (...) 1-1,1 Hz bei 35 Grad Celsius und 0,8 Hz bei 28 Grad Celsius*"¹¹⁶⁰ and then compared to modified conditions in terms of pharmacological interventions with cardiac drugs such as beta-blockers or cardiac glycosides.

Within his experimentations an in depth analysis of the detected electric signals was performed while drawing conclusions to underlying pharmacological mechanisms of actions "*eine relativ starke Zunahme der Kaliumleitfähigkeit zu beschleunigter Repolarisation des Aktionspotentials*"¹¹⁶¹ and assessing further influences on drugs action "*Die negativ inotrope Wirkung von Noradrenalin am digitalisvorbehandelten Herzpräparat bei Hypothermie ist anscheinend weder für die beiden Substanzen spezifisch, noch ist die erniedrigte Temperatur Voraussetzung*"¹¹⁶²

¹¹⁵⁷ KUSCHINSKY GUSTAV / PORZIG, H. / SCHOLZ, H., Über Wechselwirkungen zwischen Digitoxigenin, Noradrenalin und Calcium am Myokard in: Naunyn-Schmiedebergs Archiv für Pharmakologie und Experimentelle Pathologie 260 (1968) pages 188–189

¹¹⁵⁸ KUSCHINSKY GUSTAV / LÜLLMANN, H. / MUSCHOLL, E., Untersuchungen über die Einwirkung von verschiedenen Pharmaka auf die Spontanrhythmik des isolierten Hühneramnion, in: Naunyn - Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie 223 (1954) pages 369–374

¹¹⁵⁹ KUSCHINSKY GUSTAV / LÜLLMANN, H. / MOSLER, K.H., Über den Einfluß von Chinin, Papaverin und Temperaturherabsetzung auf die mechanische und elektrische Aktivität des isolierten Uterus der Ratte in: Naunyn-Schmiedebergs Archiv für Experimentelle Pathologie und Pharmakologie 237 (1959) pages 495–506

¹¹⁶⁰ KUSCHINSKY GUSTAV / PORZIG, H. / SCHOLZ, H., Untersuchungen über Wechselwirkungen zwischen Digitoxigenin, Noradrenalin und Calcium unter Hypothermiebedingungen an isolierten Präparaten aus Säugetierherzen in: Naunyn-Schmiedebergs Archiv für Pharmakologie und Experimentelle Pathologie 261, (1968) pages 191–211

¹¹⁶¹ Ibidem

¹¹⁶² Ibidem

Due to the broad conceptual and methodological expertise within electrophysiological experimentation, Kuschinsky also engaged in methodical reflections to optimize the methods and to minimize possible sources of errors within his research, "*Gleichstromöffnungs- und Schließungszuckungen, faradische Ströme aus einem Induktorium oder Rechteckimpulse aus einem Reizgenerator... (...) mit allen diesen Variationen der elektrischen Reizung gleichartige Ergebnisse erzielen, wobei auch die bei den einzelnen Untersuchern verschiedene Anordnung der Elektroden ohne wesentliche Bedeutung ist*"¹¹⁶³ but also to estimate the validity of obtained results in terms of informative value for pharmacological conclusions „*am Uterus (...) nicht böllig befriedigend, da es sich um eine indirekte Beweisführung handelt*" (..) „*Besonders geeignet (...) zur Prüfung spamolytischer oder lähmender Stoffe.*"¹¹⁶⁴

Further methodological considerations mainly referred to statistics, but also dealt with methods of other authors¹¹⁶⁵ in a comparative perspective and also implied thoughts on animal experimentation.¹¹⁶⁶

Kuschinsky concentrated on adequate sample sizes and several dispersion measures¹¹⁶⁷ within his experiments "*Wegen der geringen Tierzahlen mußten relativ große Ausschläge in den Werten erreicht werden um ein gesichertes Ergebnis zu erhalten. Die (...) gefundenen Differenzen der Herz- und Nierengewichte liegen außerhalb des 5 fachen mittleren Fehlers der Differenz, sind also trotz der geringen Tierzahl statistisch gesichert*"¹¹⁶⁸ and also on other statistical analysis techniques such as regression analysis, statistical significance or confidence intervals^{1169,1170} „*Es werden Mittelwert (...) mittlerer Fehler des Mittelwertes mit*

¹¹⁶³ KUSCHINSKY GUSTAV / HÄRTFELDER, G. / MOSLER, K.H., Über pharmakologische Wirkungen an elektrisch gereizten glatten Muskeln in: Naunyn - Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie 234 (1958) pages 66–78

¹¹⁶⁴ Ibidem

¹¹⁶⁵ KUSCHINSKY GUSTAV / JUNGBLUT, P., Eine Methode zur Beurteilung des Nierengefäßtonus bei Mäusen in: Naunyn - Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie 225 (1955) pages 533–540

¹¹⁶⁶ KUSCHINSKY GUSTAV, Methoden zur Prüfung diuretisch wirkender Stoffe in: Naunyn - Schmiedebergs Archive für experimentelle Pathologie und Pharmakologie 238 (1960) pages 195–218

¹¹⁶⁷ KUSCHINSKY GUSTAV / HILLE, U. / SCHIMASSEK, H., Über Histamin als Mittler-Substanz bei der Wirkung von Adrenochrom auf die Blutungszeit in: Naunyn - Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie 215 (1952) pages 48–51

¹¹⁶⁸ KUSCHINSKY GUSTAV, Über die Wirkung von embryonalem Herzextrakt auf Herz und Nebennierenhypertrophie im Schwimmversuch in: Naunyn - Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie 205 (1948) pages 424–428

¹¹⁶⁹ KUSCHINSKY GUSTAV / BRUNNER, H. / MÜNCHOW, O. / PETERS, G., Der Einfluß von natürlichem und synthetischem Oxytocin auf endogene Kreatinin-Clearance, Salzausscheidung und Säureausscheidungsfähigkeit der Ratte und auf die Diurese des Menschen in: Naunyn - Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie 230 (1957) pages 80–89

¹¹⁷⁰ HATTINGBERG, M. / KUSCHINSKY, G. / RAHN, K.H., Der Einfluß von Pharmaka auf Calciumgehalt und 45 Calciumaustausch der glatten Muskulatur der Taenia Coli vom Meerschweinchen, in: Naunyn - Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie, 253(4) (1966) pages 438–443

der Zahl der Einzelwerte (n) in Klammern angegeben. Der Vergleich der Aufnahme - und Abgabekurven erfolgte mit Hilfe der Varianzanalyse“¹¹⁷¹

In addition to that Kuschinsky compared his applied methods to those of other researchers, such as in the case of experiments dealing with narcotics and their influence on renal blood distribution and function, visualized by specific dyes.¹¹⁷²

Concrete considerations to animal experiments per se are given in a publication from 1960 addressing the pharmacological testing of diuretics addressing testing in both human subjects and animals, pointing out key aspects to consider within some species “Über summarische Prüfungen von Diuretica an Meerschweinchen liegen nur wenig und an Goldhamster gar keine Ergebnisse vor, obgleich sich die Goldhamster wegen ihrer günstigen anatomischen Verhältnisse besonders gut für die Mikrokathetersierung der Nierenpapillen eignen.”¹¹⁷³

4.3. Contribution to modern pharmacology

4.3.1. Cardiovascular research

A large number of Kuschinsky's research projects concentrate on cardiovascular^{1174,1175,1176,1177,1178,1179,1180}, and allied renal questions, either on a basic research level or addressing clinical and therapeutic implications directly.

¹¹⁷¹ Ibidem

¹¹⁷² KUSCHINSKY GUSTAV / JUNGBLUT, P., Eine Methode zur Beurteilung des Nierengefäßtonus bei Mäusen in: Naunyn - Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie 225 (1955) pages 533–540

¹¹⁷³ KUSCHINSKY GUSTAV, Methoden zur Prüfung diuretisch wirkender Stoffe in: Naunyn - Schmiedebergs Archive für experimentelle Pathologie und Pharmakologie 238, 195–218“ (1960) pages 195–218

¹¹⁷⁴ KUSCHINSKY GUSTAV / REUTER, H., Über den Wirkungsmechanismus von Ajmalin, in: Naunyn - Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie 242 (1961) pages 17–23

¹¹⁷⁵ KUSCHINSKY GUSTAV / SCHMITTEL, K. / HOFMANN, P. / MUTSCHLER, E. / WOLLERT, U., Über die Eiweißbindung von Bisguanylhydrazonen in: Naunyn-Schmiedebergs Arch. Pharmak. u. Exp. Path. 257 (1967) page 328

¹¹⁷⁶ KUSCHINSKY GUSTAV, Über die Stellung des Sympatols in der Adrenalinreihe in: Naunyn-Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie 157 (1930) pages 114–115

¹¹⁷⁷ KUSCHINSKY GUSTAV / R. LINDMAR, R. / LÜLLMANN, H. / MUSCHOLL, E., Der Einfluß von Reserpin auf die Wirkung der „Neuro-Sympathomimetica“ in: Naunyn - Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie 240 (1960) pages 242–252

¹¹⁷⁸ KUSCHINSKY GUSTAV / SCHMITTEL, K., Über die Verteilung von 3,3'-Dimethyl-4,4'-diacetyl-diphenyl-bisguanylhydrazon im Erythrocyten in: Naunyn-Schmiedebergs Arch. Pharmak. u. Exp. Path. 260 (1968) pages 195–196

¹¹⁷⁹ KUSCHINSKY GUSTAV / PORZIG, H. / SCHOLZ, H., Über Wechselwirkungen zwischen Digitoxigenin, Noradrenalin und Calcium am Myokard in: Naunyn-Schmiedebergs Archiv für Pharmakologie und Experimentelle Pathologie 260 (1968) pages 188–189

¹¹⁸⁰ KUSCHINSKY GUSTAV, Personalakte Kuschinsky (UK K 442) von 1932- 1940, Nummer 28 and Nr. 1a, therein Kuschinsky G. (1935) Zur Pharmakologie des Kreislaufs, Vortrag gehalten auf der 52. Sitzung der Medizinisch Naturwissenschaftlichen Gesellschaft, Shanghai 12.1. 1935

Extensive research on pharmacological possibilities to influence cardiac functions, formed a basis to give specific recommendations on pharmacotherapy, as seen on the formulation of clear therapeutic indications, safe use of medications and prevention of adverse effects, such as toxicity.¹¹⁸¹

As an example of his precursory experimentation on electrophysiological animal studies with *Val-Hypertensin II*, a hypertension causing peptide hormone and its amides, can be stated which are investigated in relation to noradrenaline in terms of vasoconstrictive qualities and impact on cardiac contraction.¹¹⁸² At the same time, evaluations of antagonizing effects¹¹⁸³ on several tissues, not only the myocardium directly and also competitive actions of these investigated compounds play a role within Kuschinsky's basic experimentations "*Am Uterus der Ratte und der Maus zeigte Butylsympathol gleichfalls hemmende Wirkungen. Die hemmenden Wirkungen des Adrenalins waren nicht aufzuheben.*"¹¹⁸⁴ Direct cardiac properties such as positive inotropic^{1185,1186} or antiarrhythmic ones¹¹⁸⁷ alongside with clarifications whether an effect is receptor-mediated or indirectly induced via the release of neurotransmitter^{1188,1189} and the assessment of selectivity to specific organs¹¹⁹⁰ also form the basis for later clinical statements. Since the cardiovascular system is closely linked to renal function, not least because of hormonal circuits such as the renin-angiotension-aldosterone system, Kuschinsky

¹¹⁸¹ KUSCHINSKY GUSTAV, Kreislauftherapie mit Adrenalinverwandten Mitteln in: *Klinische Wochenschrift* 17 (1938) pages 145–148

¹¹⁸² KUSCHINSKY GUSTAV / LÜLLMANN, H., Über die Wirkung von synthetischem Hypertensin auf Kammer- und Vorhofmuskulatur der Katze in: *Klinische Wochenschrift* 37 (1959) pages 928–931

¹¹⁸³ KUSCHINSKY GUSTAV / HÄRTFELDER, G. / MOSLER, K.H., Der Antagonismus verschiedener Sympatholytica gegenüber dem inhibitorischen Adrenalin- oder Noradrenalineffekt am elektrisch gereizten Meerschweinchenileum in: *Naunyn – Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie* 234 (1958) pages 91–101

¹¹⁸⁴ KUSCHINSKY GUSTAV / FÖRSTER, W. / LÜLLMANN, H., Über adrenolytische Wirkungen von d,l,1-(4-oxyphenyl)-1-oxy-2-n-butylamino-aethan in: *Naunyn - Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie* 210 (1950) pages 23–30

¹¹⁸⁵ KUSCHINSKY GUSTAV / EHMER, A. / JAHR, K. / LÜLLMANN, H. / REUTER, H. / WOLLERT, U., Progesteronbisguanylhydrazon als Vertreter einer neuen herzwirksamen Substanzgruppe in: *Naunyn - Schmiedebergs Arch* 247 (1964) page 342

¹¹⁸⁶ KUSCHINSKY GUSTAV / PORZIG, H. / SCHOLZ, H., Untersuchungen über Wechselwirkungen zwischen Digitoxigenin, Noradrenalin und Calcium unter Hypothermiebedingungen an isolierten Präparaten aus Säugetierherzen in: *Naunyn-Schmiedebergs Archiv für Pharmakologie und Experimentelle Pathologie* 261 (1968) pages 191–211

¹¹⁸⁷ KUSCHINSKY GUSTAV / REUTER, H., Über den Wirkungsmechanismus von Ajmalin, in: *Naunyn - Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie* 242 (1961) pages 17–23

¹¹⁸⁸ KUSCHINSKY GUSTAV / LINDMAR, R. / LÜLLMANN, H. / MUSCHOLL, E., Der Einfluß von Reserpin auf die Wirkung der „Neuro-Sympathomimetica“ in: *Naunyn - Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie* 240 (1960) pages 242–252

¹¹⁸⁹ KUSCHINSKY GUSTAV, Kreislauftherapie mit Adrenalinverwandten Mitteln in: *Klinische Wochenschrift* 17 (1938) pages 145–148

¹¹⁹⁰ KUSCHINSKY GUSTAV / OBERDISSE, K., Die Kreislaufwirkungen des Meta-Sympatols, in: *Archiv für experimentelle Pathologie und Pharmakologie* 162 (1931) pages 46–55

also devoted parts of his research activities to kidney function and its pharmaceutical modulation.

Within Kuschinsky's research, this relationship becomes also clear through the experimental setup, *“Im folgenden wurde untersucht, inwieweit verschiedene hypertonische Lösungen (sechsfach isotonische Lösungen von Natriumchlorid, Natriumsulfat, Glucose und Mannit) (...) pharmakologische Dosen von Theophyllin und Vasopression nach i.v. Injektion Veränderungen der Blutfülle der Nierenrinde und der Weite der Tubuli (...) Gefäßbild der Niere studiert. Zur Kontrolle der Kreislaufwirkungen der Injektion von hypertonen Lösungen sowie von Vasopression oder Theophyllin i.v. wurden Blutdruckversuche durchgeführt“*¹¹⁹¹, inter alia, but also through the direct conclusions of this experiment *„Die Blutgefäßreaktion in den Nierenschnitten dieser Tiere dürften vielleicht als Kreislaufveränderungen im Schockzustand aufgefaßt werden.“*¹¹⁹²

Further investigations on this topic also evaluate the pharmacological effects of several pharmaceutical or other physiologically relevant compounds such as theophylline¹¹⁹³, atropine¹¹⁹⁴, barbiturates¹¹⁹⁵ etc., subject to several types of administration, e.g. intravenously, orally, or in an intraperitoneal manner at the same time. The involvement of Kuschinsky in renal research is also reflected in a research proposal *“Behandlung von Nierenkrankheiten”* from 1944 to the German Research Foundation¹¹⁹⁶ or investigations with experimentally induced inflammation of micro-capillaries of the kidney tissue, more precisely in the glomerulus¹¹⁹⁷, which can occur in humans due to chronic underlying diseases such as diabetes mellitus or other autoimmune diseases leading to cell-mediated tissue damage or are directly caused by autoantibodies. The clinical overlap can be seen on the attempt to treat those conditions with a licensed medical substance *Calcium Sandoz*, intramuscularly administered

¹¹⁹¹ KUSCHINSKY GUSTAV / VORHERR, H., Gefäß- und Tubulusweite der Niere bei osmotischer und Wasserdiurese und nach Theophyllinjektionen, in: Naunyn - Schmiedebergs Archive für experimentelle Pathologie und Pharmakologie 238 (1960) pages 281–291

¹¹⁹² Ibidem

¹¹⁹³ Ibidem

¹¹⁹⁴ KUSCHINSKY GUSTAV, Diurese, Filtration und Sekretion der Niere unter dem Einfluß verschiedener Pharmaka, in: Naunyn - Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie 204 (1947) pages 718–737

¹¹⁹⁵ KUSCHINSKY GUSTAV, JUNGBLUT, P. / VORHERR, H. / CULLMANN, B., Die Wirkung von Thiopental-Natrium und Pentobarbital-Natrium auf die Nierengefäße von Mäusen in: Naunyn - Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie 231 (1957) pages 473–478

¹¹⁹⁶ KUSCHINSKY GUSTAV, Bundesarchiv Berlin- Lichterfelde, Bestandssignatur R 73 / Archivsignatur 12537, Sonderdrucke / Berichte, Aktennummer S 4891-5380(1720/10)-III/45

¹¹⁹⁷ KUSCHINSKY GUSTAV, Über die Behandlung der experimentellen Glomerulonephritis mit Calcium in: Klinische Wochenschrift 24 (1947) pages 531–532

calcium gluconate which is then examined in terms of its potential to reduced letality and pathological increase in blood pressure in those laboratory animals used.¹¹⁹⁸

Further examples for clinical implications drawn from Kuschinsky's cardiovascular research are represented by his recommendations on the rational use of medicines within this context for human use. Herein, the use of substances such as adrenaline is assessed critically and limited to specific indications instead of a unreserved continual or even wide-ranging use “*Bei akuter Kreislaufinsuffizienz insbesondere bei Beteiligung des Herzens an der Insuffizienz , ist das Sympatol in Einzelinjektionen zu geben (...) Für leichte Hypotonien kann Sympatol oder Ephedrin usw. Auch per os gegeben werden Dabei wird die allgemeine körperlich und psychisch (...) günstig auswirkende Sympathicusreizung besonders des Sympatols zu berücksichtigen sein*“¹¹⁹⁹ Within these considerations, aspects such as loss of efficiency¹²⁰⁰ and enlivening effects for humans use that exceed immediate therapeutic purposes are reflected as well as an optimization of physical capabilities with already marketed drugs such as *Kombetin-Böhringer* or *Purostrophan* were investigated: „*Wie die Versuche zeigen, wäre es auch bei normalen Menschen günstig, für die Herzleistung vor schweren körperlichen Anstrengungen Digitalissubstanzen zu geben*“¹²⁰¹ Further references to Kuschinsky's interest and arising expertise within this field become evident at early stages of his academic career already, as on a survey lecture given in Shanghai on January 12th 1935. In this pharmacological overview Kuschinsky does critically deal with all back then current categories of cardiac and vasoactive drugs, here again giving concrete, research based advice for drug use , minding safety and aspects of effectiveness “*Das Natrium nitrosum ist in seiner Wirkung nicht immer gleichmäßig . Neben Amylnitrit , als sehr schnell aber sehr flüchtiges Mittel , ist besonders Nitroglycerin zu nennen , dessen Wirkung viel anhaltender ist.*“¹²⁰²

4.3.2. Research on hormonal processes

Another main area of Kuschinsky's research referred to hormonal processes and chemically related structures as well as both their physiological and pharmacological effects. Naturally

¹¹⁹⁸ Ibidem

¹¹⁹⁹ KUSCHINSKY GUSTAV, Kreislauftherapie mit Adrenalinverwandten Mitteln in: *Klinische Wochenschrift* 17 (1938) pages 145–148

¹²⁰⁰ KUSCHINSKY GUSTAV, Über die Stellung des Sympatols in der Adrenalinreihe in: *Naunyn-Schmiedeberg's Archiv für experimentelle Pathologie und Pharmakologie* 157 (1930) pages 114-115

¹²⁰¹ KUSCHINSKY GUSTAV, Die Verhütung von Erschöpfungszuständen des Herzens durch Digitalissubstanzen. In: *Klinische Wochenschrift* 24 (1947) pages 502–503

¹²⁰² KUSCHINSKY GUSTAV, Personalakte Kuschinsky (UK K 442) von 1932- 1940, Nr. 1a, therein Kuschinsky G. (1935) Zur Pharmakologie des Kreislaufs , Vortrag gehalten auf der 52. Sitzung der Medizinisch Naturwissenschaftlichen Gesellschaft, Shanghai 12.1. 1935

there was a certain thematic overlap with his cardiovascular research interest as he also investigated their actions on heart¹²⁰³, and kidney function.

In a joint research project with his colleagues Lüllmann and Jahr, while already presiding over the Pharmacological Chair at the University of Mainz, Prof. Kuschinsky investigates potential cardiac and hormonal effects of a derivative of progesterone. Herein focus was not only put on relevant electrolyte balances but also comprises the assessment of parameters such as toxicity as seen on lethal and tolerable doses “*Bei i.v. Injektion hing die Toxizität von der Injektionsgeschwindigkeit ab. Wurde die Substanz in 0,2 ml /20 g Maus innerhalb von 30 sec. injiziert, starben alle Tiere nach der Dosis 2,52 mg/kg, während die Dosis von 2.50 mg/kg von allen Mäusen überlebt wurde*“¹²⁰⁴ or other pharmacological influences on other tissues in the gastrointestinal tract. Investigations on immediate hormonal effects and chronopharmacological aspects of thyroid hormones, particularly with regards to electrolyte shifts were investigated in animal models, and compared to findings from the available literature. This served Kuschinsky and his colleagues to understand and to correlate their own pre-clinical findings to previous human experiments, performed by others, both in healthy and diseased test subjects “*Nach Staffuuth soll bei Thyreotoxikose im gesamten Körper ein erhöhter K- Austausch stattfinden (...) bei hyperthyreotischen Patienten einen verminderten K- Umsatz fanden. (...) Gleiche Veränderungen des ⁴³Kalium- Umsatzes (...) wenn sie euthyreoten Versuchspersonen T3 verabreichten*“¹²⁰⁵

Further basic research regarding acute or intermediate- term impacts on hormone balances included drug induced effects, as seen on the organic mercurial diuretic substance *Novasurol*, generating new hypotheses on its mode of action.¹²⁰⁶

Thematic intersections of naturally occurring peptide hormones of varying chemical structure were assessed in terms of their abilities to influence blood pressure¹²⁰⁷, diuresis¹²⁰⁸ and also

¹²⁰³ KUSCHINSKY GUSTAV, Über die Wirkung von embryonalem Herzextrakt auf Herz und Nebennierenhypertrophie im Schwimmversuch in: Naunyn - Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie 205 (1948) pages 424–428

¹²⁰⁴ KUSCHINSKY GUSTAV / EHMER, A. / JAHR, K./ LÜLLMANN, H. / REUTER, H. / WOLLERT, U., Über die Herzglykosid-artige Wirkung von Progesteronbisguanylhydrazon (Progesteronbiguazon) in: Naunyn-Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie 248 (1964) pages 521–539

¹²⁰⁵ KUSCHINSKY GUSTAV / KLAUS, W. / REUTER, H., Akute Trijodthyroninwirkungen auf den Kalium-Umsatz von Meerschweinchenvorhöfen in: Naunyn-schmiedebergs Archiv für Experimentelle Pathologie und Pharmakologie 245(4) (1963) pages 500–509

¹²⁰⁶ KUSCHINSKY GUSTAV, Über den Einfluß des Wassers und des Novasurols auf den Hormongehalt des Hypophysenhinterlappens, in: Archiv für experimentelle Pathologie und Pharmakologie 192 (1939) pages 536–543

¹²⁰⁷ KUSCHINSKY GUSTAV, Über die diuretische Wirkung von Hinterlappen-Präparaten und Ihre Beziehung zur antidiuretischen Wirkung des Vasopressins in: Klinische Wochenschrift 18 (1939) pages 207–208

uterine musculature with implications for medical use such as in perinatology, of which one research project had been supported financially by the German Research Foundation in 1939.¹²⁰⁹ Other, fundamental research projects with potential implications for reproductive health, investigated both in male and female study animals dealt with aspects of safety and the degree of efficiency with the pharmaceutical products marketed by Bayer.^{1210,1211}

Those hormonal investigations carried on after the Second World War, where besides a fundamental understanding in terms of the mode of action of those hormones, also their side effects were screened within human experiments. This led to a detection of various side effects, such as vertigo, increase in blood pressure and erythema on the upper part of the body after subcutaneous injection, being indicative for short term effects.¹²¹²

Further post-war research with female sex hormones *Oestradiolbenzoat*, provided by Schering A.G. had primarily methodological implications, assessing hormonal effects on muscular tissue, to enable future research via electrophysiological experimentations.¹²¹³ Kuschinsky's great interest and expertise within hormone – related questions does also become apparent in early contentual reviews, incorporating the back then up to date questions within this research area “*Man sah, daß Extrakte imstande sind die Schilddrüse morphologisch zu verändern wie bei der Basedow'schen Krankheit, daß also morphologische Beziehungen zwischen HVL und Schilddrüse bestehen*”¹²¹⁴ and engaging in peer to peer discussions about endocrinological disorders such as acromegaly at his time in Shanghai. Other of his expert statements in a

¹²⁰⁸ KUSCHINSKY GUSTAV / BRUNNER, H. / PETERS, G., Der Einfluß von Oxytocin auf die renale Wasser- und Salzausscheidung der Ratte in: Naunyn - Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie 228 (1956) pages 457–473

¹²⁰⁹ KUSCHINSKY GUSTAV, Über den Gehalt des Harnes an Hinterlappenähnlichen Wirkstoffen in: Klinische Wochenschrift 18 Jahrgang Nr. 7 (1939) pages 251f

¹²¹⁰ KUSCHINSKY GUSTAV, Über die Wirkung luteinisierender Substanz auf die Funktion der lipoidhaltigen Zellen des Ovariums in: Archiv für experimentelle Pathologie und Pharmakologie 179 (1935) pages 717–721

¹²¹¹ KUSCHINSKY GUSTAV, Über die Wirkung luteinisierender Substanz auf den Hoden in: Archiv für experimentelle Pathologie und Pharmakologie 179 (1935) pages 722–725

¹²¹² KUSCHINSKY GUSTAV / BRUNNER, H. / MÜNCHOW, O. / PETERS, G., Der Einfluß von natürlichem und synthetischem Oxytocin auf endogene Kreatinin-Clearance, Salzausscheidung und Säureausscheidungsfähigkeit der Ratte und auf die Diurese des Menschen in: Naunyn - Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie 230 (1957) pages 80–89

¹²¹³ KUSCHINSKY GUSTAV / HÄRTFELDER, G. / MOSLER, K.H., Über pharmakologische Wirkungen an elektrisch gereizten glatten Muskeln in: Naunyn - Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie 234 (1958) pages 66–78

¹²¹⁴ KUSCHINSKY GUSTAV, Personalakte Kuschinsky (UK K 442) von 1932- 1940, Nr.71, therein Kuschinsky G. (1933) Ueber Hypophysenvorderlappen- Hormone, Vortrag gehalten auf der 43. Sitzung der Medizinisch Naturwissenschaftlichen Gesellschaft, Shanghai 25.11.1933

overview format also include hormonal effects, and do incorporate their potential interactions with other substances such as vitamins, while also referring to his own research findings.¹²¹⁵

Not least because of entries in his personal file, stating hormones as one of his major research interest¹²¹⁶, and subsequent financial support “*Sachbeihilfe in Höhe von 1000 RM*”¹²¹⁷ of public authorities for projects aiming at exploring hormonal functions “*Untersuchungen über die Wirkungsmechanismen von Hypophysenhormonen und Pharmaka bei der Harnbildung*”¹²¹⁸ this area can be identified as a major one within Kuschinsky’s work.

4.3.3. Pharmaceutical- Medicinal Chemistry

The field of Pharmaceutical and Medicinal Chemistry can be understood as a discipline of pharmaceutical sciences with the aim of understanding structural conditions of pharmacological targets and the identification and creation of pharmaceutical compounds which can address these targets to create a intended effect. This frequently involves several analytical methodologies such as HPLC, IR- spectroscopy, massspectrometry or NMR spectroscopy or methods of clinical chemistry such as analysis of serum or urine samples.

A definition suggested by Ghosh states that “*Pharmaceutical Chemistry is the “chemistry of drugs” which uses the general laws of chemistry to study drugs (...) study of physical and chemical properties of drugs, their preparation, chemical composition, nature, behaviour, structure and influence on an organism*”¹²¹⁹

Kuschinsky’s research did indeed imply the assessment of chemical physical properties of drugs or potential new pharmaceutical compounds, at times also contributions to their synthesis or research on chemical profiling of molecules. The use of both qualitative and quantitative methods for analysing them, led to a subsequent categorization of the several modes of action with regards to specific body organs.¹²²⁰

Examples of his publications which explicitly deal with the analysis of various, heterogenous chemical substances, such as hydrazone, pyridine oder phenylethylamine derivates etc, pertain

¹²¹⁵ KUSCHINSKY GUSTAV, Kuschinsky "Wichtige neue Arzneimittel" in: Deutsche Medizinische Wochenschrift Nr.27/28“ (1943)

¹²¹⁶ KUSCHINSKY GUSTAV, Personal file Kuschinsky in the University Archive Mainz “Der Verwaltungs-Direktor bei der Friedrichs- Wilhelms Universität zu Berlin, Personalakten des Oberassistenten Dr Gustav Kuschinsky, angefangen 1.11.1931- 31.03.1940“ pages 2 and 31

¹²¹⁷ KUSCHINSKY GUSTAV, Bundesarchiv Berlin- Lichterfelde, Bestandssignatur R 73 / Archivsignatur 12537, Sonderdrucke / Berichte / Sachbeihilfen vom 12. Mai 1942 / Kur 4/16/4

¹²¹⁸ Ibidem

¹²¹⁹ GHOSH JAYASHREE, A textbook of pharmaceutical chemistry in: S. Chand Publishing (2003)

¹²²⁰ KUSCHINSKY GUSTAV / LÜLLMANN H., Kurzes Lehrbuch der Pharmakologie und Toxikologie in: Thieme Verlag 11. neubearbeitete Auflage (1982)

mainly to the cardiovascular field^{1221,1222}, but also include other areas of therapeutic interest such as the one of sedative drugs¹²²³.

Methodological considerations which display the nature of PMC content are shown on both the synthesis of the new type of therapeutic agent “Progesteronbisguanylhydrazon”¹²²⁴ and its quality control, the hormonal basic structure. The pharmaceutical quality needed for use in human is validated by infrared absorption spectra, of this compound and its reference progesterone. “*Das Hydrochlorid zeigt eine Bande bei 273 $m\mu$, $\epsilon = 3,10 \times 10^4$. Sie deutet Substitution am C-Atom 3 des Progesteron durch den Guanylhydrazinrest an (β -ungesättigtes Keton). Eine schwächere Bande bei 233 $m\mu$ $\epsilon = 2,02 \times 10^4$ weist auf die Substitution am C₂₀ des Progesteron.*”¹²²⁵ By doing so not only the identity validation of the chemical structure of the synthesized product is assured, but also its chemical purity is monitored, both two essential steps within drug development and manufacturing.

The consistent striving for understanding structure- efficiency relationships and physico-chemical properties of drugs, displays a central theme of Kuschinsky’s research, as seen on detailed considerations with regards to drug design. This can be demonstrated on positive inotropic agents in which the specific chemical conditions are being examined, such as required chain length of carbon atoms within the entire molecule, “*Das Wirkungsmaximum lag bei einem Abstand zwischen dem Guanylhydrazon- Resten von 9- 10 Atomen.*”¹²²⁶

This in effect also involved further implications on a orbital model level, as mesomeric effects were considered by Kuschinsky and his colleagues as well, aiming at explaining the necessary preconditions for chemical reactivity and thus ultimately therapeutic response “*Die von uns für eine Herzglykosid Wirkung geforderten, isolierten elektronen- dichten Stellen sind*

¹²²¹ KUSCHINSKY GUSTAV / LÜLLMANN, H. / MUTSCHLER, E. / WOLLERT, U., Beziehungen zwischen der Struktur von Bisguanylhydrazonen und der Art ihrer Herzwirksamkeit in: Naunyn - Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie 251 (1965) pages 153–154

¹²²² KUSCHINSKY GUSTAV / EHMER, A. / JAHR, K. / LÜLLMANN, H. / REUTER, H. / WOLLERT, U., Progesteronbisguanylhydrazon als Vertreter einer neuen herzwirksamen Substanzgruppe in: Naunyn - Schmiedebergs Arch 247 (1964) page 342

¹²²³ KUSCHINSKY GUSTAV / KRAUTWALD, A. / RIEDEL, H., Über die sedative Wirkung von Pyridinderivaten, in: Archiv für experimentelle Pathologie und Pharmakologie 193 (1939) pages 219–230

¹²²⁴ KUSCHINSKY GUSTAV / EHMER, A. / JAHR, K. / LÜLLMANN, H. / REUTER, H. / WOLLERT, U., Über die herzglykosid-artige Wirkung von Progesteronbisguanylhydrazon (Progesteronbiguazon) in: Naunyn-Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie 248 (1964) pages 521–539

¹²²⁵ Ibidem

¹²²⁶ KUSCHINSKY GUSTAV / EHMER, A. / JAHR, K. / LÜLLMANN, H. / MUTSCHLER, E. / WOLLERT, U., Über die Wirkung einfacher Bisguanylhydrazone auf Herzgewebe in: Naunyn - Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie 247 (1964) page 343

*in diesem Molekül infolge der Teilnahme der Pi- Elektronen an der Resonanz beider Benzolringe nicht genügend stark ausgeprägt*¹²²⁷

These considerations were often made with the back then newly designed molecules, assessing their efficiency in dependence of several modifications of chemical substituents^{1228,1229} at times also in a 360 degree view both on pharmacokinetic and – pharmacodynamic properties, testing the potential drug candidate for future indications. Here, the enzymatic degradation of the compound and other aspects of metabolism were considered, as well as searching for active metabolites of the drugs applied.¹²³⁰

The (re)-discovery of clinically promising pharmaceutical compounds from natural products, especially their structural optimization or analytical preparation to obtain the required pure substances does also represent an aspiration of pharmaceutical chemistry, while showing links to pharmaceutical biology in this sense. Kuschinsky declared himself in favour of differentiation and analysis of single components within herbal extract and at times synthetic optimization of those standardised components to benefit therapeutic use, also incorporating aspects of appropriate storage¹²³¹, altogether categories of chemical analytics and thus Pharmaceutical Chemistry.

4.4. Cross case comparison with Prof. Starckenstein and Prof. Wiechowski

4.4.1. Areas of scientific research and contribution to modern pharmacology

Prof. Kuschinsky's areas of scientific interest and research differed in terms of scope and specialisation to his predecessors at the German University, but also with regards to the methodology used within his later publications.

Prof. Starckenstein engaged in a range of rather comprehensive toxicological questions that did not only, in contrast to Kuschinsky assess merely toxicological parameters or aspects of detoxification, but in fact dealt with wider issues of both chronic and toxicity including occupational intoxications and forensic medicine. By contrast Kuschinsky frequently limited

¹²²⁷ Ibidem

¹²²⁸ KUSCHINSKY GUSTAV, EHMER, A. / JAHR, K. / LÜLLMANN, H. / REUTER, H. / WOLLERT, U., Progesteronbisguanylhydrazon als Vertreter einer neuen herzwirksamen Substanzgruppe in: Naunyn - Schmiedebergs Arch 247 (1964) page 342

¹²²⁹ KUSCHINSKY GUSTAV / LÜLLMANN, H. / MUTSCHLER, E. / WOLLERT, U., BEZIEHUNGEN ZWISCHEN DER Struktur von Bisguanylhydrazonen und der Art ihrer Herzwirksamkeit in: Naunyn - Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie 251 (1965) pages 153–154

¹²³⁰ KUSCHINSKY GUSTAV / KRAUTWALD, A. / RIEDEL, H., Über die sedative Wirkung von Pyridinderivaten, in: Archiv für experimentelle Pathologie und Pharmakologie 193 (1939) pages 219–230

¹²³¹ KUSCHINSKY GUSTAV, Gesamtdroge oder Reinsubstanz ? in: Deutsche Medizinische Wochenschrift Nummer 37 (1939)

his experimentations to test the tolerability and level of toxicity as determined e.g. via median lethal doses or cardiac toxicity, particularly in animal models as one part of holistic investigations of drug actions.^{1232,1233}

There are few publications dealing with toxicological questions directly, instead there is primary evidence about Kuschinsky's research addressing the pharmacotherapy of intoxications with substances containing mercury⁴²¹ or pharmacotherapeutic treatment of experimentally induced intoxications to mimic pathophysiological inflammation and here again to investigate subsequent options for pharmacotherapeutic treatment in animal experimentations.¹²³⁴

Whereas biological research can be seen as one relevant field in both Starckenstein's and Wiechowski's work, also holding professorships in each case and investigating phyto-pharmaceutical and – pharmacological questions in a detailed manner, this does not hold to be true with Kuschinsky, as he has neither been Professor for Pharmacognosy, nor publishing in this field in a comparable manner. Publications which do use phytochemicals such as flavonoids *Rutin* or other naturally occurring substances such as alkaloids *Chinine* or *Ajmalin* do neither focus on biogenesis of those substances in the plants per se, neither do they involve microscopic or chemically analytic nor prepatative experimentations, but do instead focus on pharmaco- physiological effects.^{1235,1236,1237}

Compared to his two colleagues, Kuschinsky's pharmacological research has been more specialised as seen on his focus on cardiovascular issues and hormonal questions, whereas, especially Starckensteins research encompassed wider fields of pharmacological research, ranging from inflammatory, infectious, analgesic, sedative- hypnotic ones to the evaluation of alternative procedures such as balneotherapy etc.

¹²³² KUSCHINSKY GUSTAV / HÄRTFELDER, G. / MOSLER, K.H., Über pharmakologische Wirkungen an elektrisch gereizten glatten Muskeln in: Naunyn - Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie 234 (1958) pages 66–78

¹²³³ KUSCHINSKY GUSTAV / OBERDISSE, K., Die Kreislaufwirkungen des Meta-Sympatols, in: Archiv f. experimentelle Pathologie und Pharmakologie 162 (1931) pages 46–55

¹²³⁴ KUSCHINSKY GUSTAV, Über die Behandlung der experimentellen Glomerulonephritis mit Calcium in: Klinische Wochenschrift 24 (1947) pages 531–532

¹²³⁵ KUSCHINSKY GUSTAV, Über Gefäßabdichtung durch Rutin in: Klinische Wochenschrift 27 (1949) page 317

¹²³⁶ KUSCHINSKY GUSTAV / REUTER, H., Über den Wirkungsmechanismus von Ajmalin, in: Naunyn - Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie 242 (1961) pages 17–23

¹²³⁷ KUSCHINSKY GUSTAV / LÜLLMANN, H. / MOSLER, K.H., Über den Einfluß von Chinin, Papaverin und Temperaturherabsetzung auf die mechanische und elektrische Aktivität des isolierten Uterus der Ratte in: Naunyn-Schmiedebergs Archiv für Experimentelle Pathologie und Pharmakologie 237 (1959) pages 495–506

A certain extent of thematic resemblances can be seen in Wiechowski's interest in metabolic research processes, as documented on his broad biochemical research which he brought into a context of renal excretion processes with uric acid and its metabolites in certain species. Kuschinsky did likewise engage in several research questions targeting a holistic understanding particularly on cardio-renal function, frequently in a hormone driven context, whereas Starkenstein rather investigated drug influences on organ functions depending on the context of the wider-ranging scope of his pharmacological research, without particular focus besides the actual compound being investigated.

Also methodologically, both in terms of individual methods applied per experiment, but also in terms of methodological considerations both Wiechowski und Kuschinsky display a certain extent of similarities, incorporating these own considerations into their research more explicitly. Although methodological, mathematical- statistical considerations naturally played a part within the work of all three scientists, Kuschinsky and Wiechowski especially dedicated several parts of their publications for displaying and explaining both their modification of methods or gave recommendations on the optimal approach to conducting those experiments.

Compared to his two colleagues, Kuschinsky's use of a refined electrophysiological approach to isolated organs is much greater, which also has to be seen as a phenomenon of time, as instrumental- analytical possibilities and development forged ahead, allowing to provide more detailed and thus quantitative effects of pharmaceuticals. Never the less, also Starkenstein and Wiechowski investigated drug actions, particularly on organ levels, by the use of other back then more restricted analytical methods. Electrophysiology, still today is a valuable method both in a clinical and experimental setting, to explore disease mechanisms and thus to pathophysiology by understanding symptoms of diseases and also to identify possible pharmacological targets.¹²³⁸

Remarkably, as those technical prerequisites had not been available yet, Starkenstein and Wiechowski already used methods including physiological parameters such as heart rate, blood pressure etc. in combination with a preceding chemical-structural analysis of the investigated compound to gain an initial hypothesis of a mode of action of a specific drug.

Whereas drug combinations and their actions, such as in the case of Veramon, or other drug interactions had been a distinct field of interest within Starkenstein's research, Kuschinsky

¹²³⁸ LAU DENNIS H., Opportunities and challenges of current electrophysiology research: a plea to establish 'translational electrophysiology' curricula, in: EP Europace, Volume 17, Issue 5 (2015) pages 825-833

also considered those aspects of pharmacotherapy at least in some of his basic research driven publications, e.g. with respect to calcium- dependent concentrations in the myocardium.^{1239,1240} In Wiechowski's case there is evidence that he did, with regards to clinical application in the context of gastrointestinal or infectious complaints, deal with drug interactions with aliments or beverages and thus optimal intake *“Sie darf nur in Wasser und auf leeren Magen gereicht werden, Wein Tee und andere Getränke als Suspensionsmittel sind unzulässig”*¹²⁴¹

Whereas Wiechowski's basic research shows clinical links to future therapeutic use and also had direct clinical implications, such as in the case of medicinal charcoal, Starkeinstein's efforts for public health had been more distinct. This was the case, both in the sense of aspirations towards a more evidence based medicine than the one prevailing at those times but also via linking systematization and guideline like strategies of therapeutic interventions to pharmaeconomic value of individual preparations, alongside with educational efforts of the entire wider health care professions. As a contrast to both his colleagues, Prof. Kuschinsky did not engage in public health topics in this respect, although there is some secondary evidence that he obtained financial support from some organisations and institutes affiliated with the National Socialist regime to investigate the risks of smoking and tobacco use and thereby, at least theoretically, cancer prevention. *“A number of scientists from outside the University of Jena contributed to research at the Institute. In addition to Günther Just, other scientists such as the Director of the Institute for Racial Hygiene at the German University in Prague, Professor Karl Thurns and the pharmacologist, Professor Gustav Kuschinsky, also from Prague, conducted research in collaboration with the Institute and received financial support from the Institute.”*¹²⁴²

According to another secondary sources this so- called *“Karl Astel's Institute for Tobacco Research (was) established in 1941 at Jena University by a 100 000 Reichsmarks grant from*

¹²³⁹ KUSCHINSKY GUSTAV / PORZIG, H./ SCHOLZ, H., Untersuchungen über Wechselwirkungen zwischen Digitoxigenin, Noradrenalin und Calcium unter Hypothermiebedingungen an isolierten Präparaten aus Säugetierherzen in: Naunyn-Schmiedebergs Archiv für Pharmakologie und Experimentelle Pathologie 261 (1968) 191–211

¹²⁴⁰ KUSCHINSKY GUSTAV / PORZIG, H. / SCHOLZ, H., Über Wechselwirkungen zwischen Digitoxigenin, Noradrenalin und Calcium am Myokard in: Naunyn-Schmiedebergs Archiv für Pharmakologie und Experimentelle Pathologie 260 (1968) pages 188–189

¹²⁴¹ WIECHOWSKI WILHELM, Ueber Adsorptionstherapie in: Medizinische Wochenzeitschrift Nr.34 (1921) page 1470f

¹²⁴² ZIMMERMANN SUSANNE / EGGER M. / HOSSFELD U., Commentary: Pioneering research into smoking and health in Nazi Germany— The ‘Wissenschaftliches Institut zur Erforschung der Tabakgefahren’ in: Jena, International Journal of Epidemiology, Volume 30, Issue 1 (2001)

Hitler's Reich Chancellery »¹²⁴³ assessed the mutagenic dangers for reproductive health, addressing questions of *racial hygiene*¹²⁴⁴ According to this source Kuschinsky also received financial support “total of 17444 RM (in 1943) (...) from Astel's Institute”¹²⁴⁵ for a series of animal experiments to examine potential health risks imposed by tobacco use or intake.

First hand publications¹²⁴⁶ or supervised dissertations¹²⁴⁷ before 1945 on this topic and other ones pertain to research on the central nervous system and do also deal with performance enhancing effects and research questions “*Untersuchungen über die Wirkung von Nikotin auf psychische und physische Leistungen des Menschen*”¹²⁴⁸ or “*Untersuchungen über die zentralerregende Wirkung des Theophyllins*”¹²⁴⁹

Kuschinsky's own research on nicotine and methamphetamine *Pervitin* in 1943 clearly deals with assessing possible synergistic effects of both stimulating drugs, which particularly in the case of the phenylethylamine did pursue interests of fighting symptoms of fatigue aiming to strengthen the operational capability for a certain amount of time. Eventhough his and his colleague's research is limited to animal experimentation, it clearly generates knowledge about its rational use, which then implicitly delivers initial conclusions for later human use “*Wenn wir die absoluten Dosen Nicotin und Pervitin vergleichen, so können wir feststellen, daß wir bei der Ratte 5-7 mal so viel Pervitin benötigen, um dieselben erregenden Wirkungen zu erzeugen wie mit Nicotin.*“¹²⁵⁰

In this regard one must say that Kuschinsky's contribution's to public health issues in the years before 1945 did not at all times address direct patient's or society's medical needs in terms of curing disease or mitigating pathological conditions, but instead, at least within parts of his research also did aim at optimization of physical performance¹²⁵¹ or at times also at assessing the potential of pharmacological interventions to use it exhaustively.^{1252,1253} This in

¹²⁴³ PROCTOR ROBERT N., Commentary: Schairer and Schöniger's forgotten tobacco epidemiology and the Nazi quest for racial purity in: *International Journal of Epidemiology*, Volume 30, Issue 1 (2001)

¹²⁴⁴ Ibidem

¹²⁴⁵ Ibidem

¹²⁴⁶ KUSCHINSKY GUSTAV / HOTOVY, R., Über die Zentral Erregende Wirkung des Nicotins in: *Klinische Wochenschrift* 22 (1943) pages 649–650

¹²⁴⁷ KUSCHINSKY GUSTAV, Universitätsarchiv Mainz Personalakte Kuschinsky im Universitätsarchiv Mainz, Ges 131 / S64/11 page 5 and page 5(6)

¹²⁴⁸ Ibidem

¹²⁴⁹ Ibidem

¹²⁵⁰ KUSCHINSKY GUSTAV / HOTOVY, R., Über die Zentral Erregende Wirkung des Nicotins in: *Klinische Wochenschrift* 22 (1943) pages 649–650

¹²⁵¹ Ibidem

¹²⁵² KUSCHINSKY GUSTAV, Die Verhütung von Erschöpfungszuständen des Herzens durch Digitalissubstanzen. In: *Klinische Wochenschrift* 24 (1947) pages 502–503

fact, does stand in strong contrast to both Starckenstein's and Wiechowski's research aims and experiments, which both with either their basic research or extended research interests primarily addressed medical problems or research questions without such implications. In comparison with those two, Kuschinsky's overall research focus and interest seems to be rather focused on substances that, particularly in case of hormones influence growth^{1254,1255}, metabolism^{1256,1257} and reproduction^{1258,1259} or in case of cardioactive substances also physiological fitness and capacity.

Whereas a basic interest in those research fields and questions also alongside with pharmacotherapeutic interventions does naturally also concern public health issues, the transgression of research questions that exceed beneficial therapy and do not primarily promote well-being on many levels, does in fact not meet up to date definitions of public health. Kuschinsky's research has to be seen ambiguously in this respect, as he on the one hand contributed to both physiological and pharmacological basic research and thus innovate therapies such as Starckenstein and Wiechowski did, but by contrast to his colleagues did also engage in research that shows- in parts- aspects of doping, on the other hand.

4.4.2. Extent of contribution to modern clinical trials and Phase I-IV studies

Kuschinsky's contribution to drug development, as reflected on specific research stages, is primarily manifested in extensive preclinical research, as he either dealt with the identification and pharmacological evaluation of hormonal, cardioactive drugs or those with effects on haematological or renal parameters. By doing so aspects of pathophysiology and physiology were addressed, which together with in- vivo experiments on laboratory animals helped to gain information about efficacy and safety. In contrast to Wiechowski and Starckenstein, factors such as mutagenicity were examined "*Prevention-oriented cancer research*" (...)

¹²⁵³ KUSCHINSKY GUSTAV, Über die Wirkung von embryonalem Herzextrakt auf Herz und Nebennierenhypertrophie im Schwimmversuch in: Naunyn - Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie 205 (1948) pages 424–428

¹²⁵⁴ KUSCHINSKY GUSTAV, Über den Einfluss verschiedener Temperaturen auf die Sekretion des thyreotropen Hormons in : Archiv für experimentelle Pathologie und Pharmakologie 1935 Vol.179 (1935) pp.726-737

¹²⁵⁵ KUSCHINSKY GUSTAV, Personalakte Kuschinsky (UK K 442) von 1932- 1940, Nr.71, therein Kuschinsky G. (1933) Ueber Hypophysenvorderlappen- Hormone, Vortrag gehalten auf der 43. Sitzung der Medizinisch Naturwissenschaftlichen Gesellschaft, Shanghai 25.11.1933

¹²⁵⁶ KUSCHINSKY GUSTAV, Über die diuretische Wirkung von Hinterlappen-Präparaten und Ihre Beziehung zur antidiuretischen Wirkung des Vasopressins in: Klinische Wochenschrift 18 (1939) pages 207–208

¹²⁵⁷ KUSCHINSKY GUSTAV, Über den Gehalt des Harnes an Hinterlappenähnlichen Wirkstoffen in: Klinische Wochenschrift 18 Jahrgang Nr. 7 (1939) pages 251f.

¹²⁵⁸ KUSCHINSKY GUSTAV, Über die Wirkung luteinisierender Substanz auf die Funktion der lipoidhaltigen Zellen des Ovariums in: Archiv für experimentelle Pathologie und Pharmakologie 179 (1935) pages 717–721

¹²⁵⁹ KUSCHINSKY GUSTAV, Über die Wirkung luteinisierender Substanz auf den Hoden in: Archiv für experimentelle Pathologie und Pharmakologie 179 (1935) pages 722–725

“whether nicotine was a mutagen”¹²⁶⁰, then again less focus was put on the identification of basic chemical- pharmaceutical characteristics, such as solubility, chemical stability etc. with the exception of synthesis and chemical optimization of drugs. One reason behind this could be that Kuschinsky often dealt with substances that had previously been marketed by pharmaceutical companies. Therefore these basic characteristic had been known at this time already, as they usually represent a requirement within the approval dossiers, in the course of the authorisation process.

Both pharmacokinetic and pharmacodynamic variables had been investigated thoroughly by Kuschinsky with respect to the identification of possible mode of actions of drugs^{1261,1262,1263}, the assessment of structure- effect- relationships^{1264,1265,1266}, dose- response- relationships^{1267,1268,1269} but also issues regarding the antagonization of drugs¹²⁷⁰, specific effects on organ-level¹²⁷¹ or the comparison of potency between several drugs¹²⁷². With regards to pharmacokinetics, frequently parameters of elimination^{1273,1274}, as measured by the

¹²⁶⁰ PROCTOR ROBERT N., Commentary: Schairer and Schöniger's forgotten tobacco epidemiology and the Nazi quest for racial purity in: International Journal of Epidemiology, Volume 30, Issue 1, (2001)

¹²⁶¹ KUSCHINSKY GUSTAV / LANGECKER H., Über die Wirkung des Atropins auf die Nierenfunktion in: Naunyn-Schmiedeberg's Archives of Pharmacology 208(1) (1949) pages 35-36

¹²⁶² KUSCHINSKY GUSTAV / REUTER, H., Über den Wirkungsmechanismus von Ajmalin, in: Naunyn - Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie 242 (1961) pages 17–23

¹²⁶³ HATTINGBERG, M. / KUSCHINSKY, G. / RAHN, K.H., Der Einfluß von Pharmaka auf Calciumgehalt und 45 Calciumaustausch der glatten Muskulatur der Taenia Coli vom Meerschweinchen.253(4) (1966) pp. 438–443

¹²⁶⁴ KUSCHINSKY GUSTAV, Über die Bedeutung von Sulphydrylgruppen für Prozesse am Aktomyosin in: Die Naturwissenschaften Heft 18 Jahrgang 38 (1950)

¹²⁶⁵ KUSCHINSKY GUSTAV / EHMER, A. / JAHR, K. / LÜLLMANN, H. / MUTSCHLER, E. / WOLLERT, U., Über die Wirkung einfacher Bisguanilhydrazone auf Herzgewebe in: Naunyn - Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie 247 (1964) page 343

¹²⁶⁶ KUSCHINSKY GUSTAV / OBERDISSE, K., Die Kreislaufwirkungen des Meta-Sympatols. , in: Archiv f. experimentelle Pathologie und Pharmakologie 162 (1931) page 46–55

¹²⁶⁷ KUSCHINSKY GUSTAV / LINDMAR, R. / LÜLLMANN, H. / MUSCHOLL, E. / Der Einfluß von Reserpin auf die Wirkung der „Neuro-Sympathomimetica“ in: Naunyn - Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie 240 (1960) pages 242–252

¹²⁶⁸ KUSCHINSKY GUSTAV / FÖRSTER, W. / LÜLLMANN, H., Über adrenolytische Wirkungen von d,1,1-(4-oxyphenyl)-1-oxy-2-n-butylamino-aethan in : Naunyn - Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie 210 (1950) pages 23–30

¹²⁶⁹ KUSCHINSKY GUSTAV / HÄRTFELDER, G. / MOSLER, K.H., Über pharmakologische Wirkungen an elektrisch gereizten glatten Muskeln in: Naunyn - Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie 234 (1958) pages 66–78

¹²⁷⁰ KUSCHINSKY GUSTAV / LÜLLMANN, H., Über die Beziehungen der Barium-Ionen zum Acetylcholin in: Klinische Wochenschrift 28 (1950) pages 137–138

¹²⁷¹ KUSCHINSKY GUSTAV / JUNGBLUT, P., Eine Methode zur Beurteilung des Nierengefäßtonus bei Mäusen in : Naunyn - Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie 225 (1955) pages 533–540

¹²⁷² KUSCHINSKY GUSTAV / LÜLLMANN, H. / MOSLER, K.H., Über den Einfluß von Chinin, Papaverin und Temperaturherabsetzung auf die mechanische und elektrische Aktivität des isolierten Uterus der Ratte in: Naunyn-Schmiedebergs Archiv für Experimentelle Pathologie und Pharmakologie 237 (1959) pages 495–506“

¹²⁷³ KUSCHINSKY GUSTAV / HOFMANN, P. / MUTSCHLER, E. / WOLLERT, U., Die Verteilung von Progesteron- und Dodecandion-2,11-bisguanilhydrazon im Meerschweinchenorganismus in: Naunyn-Schmiedebergs Archiv für experimentelle Pharmakologie und Experimentelle Pathologie 257 (1967) pages 288–289

renal clearance¹²⁷⁵ for instance, but also distributive processes within the organism have been examined via concentration measurements in the serum and the affinity to plasmaproteins¹²⁷⁶ or cellular components such as erythrocytes.¹²⁷⁷

The majority of those experiments involved laboratory animals and as in both Wiechowski's and Starckenstein's case also a variety of tests on isolated organs or pulverized organic powders, depending on the research question. Naturally, in all three cases physio- pharmaco- and toxicological issues, were addressed. With regards to ethical considerations within those experiments Kuschinsky also displayed , just like Starckenstein and Wiechowski , a diligent and considerate approach to the treatment of those animals to reduce discomfort^{1278,1279,1280} or to minimize the necessary amount of killing of laboratory animals where necessary.¹²⁸¹

Within those in- vivo experiments, e.g. involving renal procedures, Kuschinsky took preventive measures to limit the risk of possible subsequent infections “*Postoperativ erhielten die Tiere 10-20000 IE Depotpenicillin i.m.*”¹²⁸² but also took care of analgesia¹²⁸³ and provided anaesthesia¹²⁸⁴ from the outset aswell “*Die Kanninchen erhielten zur Narkose*

¹²⁷⁴ KUSCHINSKY GUSTAV / KRAUTWALD, A. / RIEDEL, H., Über die sedative Wirkung von Pyridinderivaten, in: Archiv für experimentelle Pathologie und Pharmakologie 193 (1939) pages 219–230

¹²⁷⁵ KUSCHINSKY GUSTAV / BRUNNER, H. / MÜNCHOW, O. / PETERS, G., Der Einfluß von natürlichem und synthetischem Oxytocin auf endogene Kreatinin-Clearance, Salzausscheidung und Säureausscheidungsfähigkeit der Ratte und auf die Diurese des Menschen in: Naunyn - Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie 230 (1957) pages 80–89

¹²⁷⁶ KUSCHINSKY GUSTAV / SCHMITTEL, K. / HOFMANN, P. / MUTSCHLER, E. / WOLLERT, U., Über die Eiweißbindung von Bisguanylhydrazonen in: Naunyn-Schmiedebergs Arch. Pharmak. u. Exp. Path. 257 (1967) pages 328

¹²⁷⁷ KUSCHINSKY GUSTAV / KRAUTWALD, A. / RIEDEL, H., Über die sedative Wirkung von Pyridinderivaten, in: Archiv für experimentelle Pathologie und Pharmakologie 193 (1939) pages 219–230

¹²⁷⁸ KUSCHINSKY GUSTAV / MUSCHOLL, E., Die Behandlung der experimentellen Quecksilbervergiftung mit 2,3 Dimercaptopropionsäure, in: Naunyn - Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie 223 (1954) pages 408–419

¹²⁷⁹ KUSCHINSKY GUSTAV / JUNGBLUT, P., Eine Methode zur Beurteilung des Nierengefäßtonus bei Mäusen in: Naunyn - Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie 225 (1955) pages 533–540

¹²⁸⁰ KUSCHINSKY GUSTAV/ HOFMANN, P. / MUTSCHLER, E. / WOLLERT, U., Die Verteilung von Progesteron- und Dodecandion-2,11-bisguanylhydrazon im Meerschweinchenorganismus in : Naunyn-Schmiedebergs Archiv für experimentelle Pharmakologie und Experimentelle Pathologie 257(1967) page 288–289

¹²⁸¹ KUSCHINSKY GUSTAV / PORZIG, H. / SCHOLZ, H., Untersuchungen über Wechselwirkungen zwischen Digitoxigenin, Noradrenalin und Calcium unter Hypothermiebedingungen an isolierten Präparaten aus Säugetierherzen in : Naunyn-Schmiedebergs Archiv für Pharmakologie und Experimentelle Pathologie 261, (1968) page 191–211

¹²⁸² KUSCHINSKY GUSTAV/ JUNGBLUT, P., Eine Methode zur Beurteilung des Nierengefäßtonus bei Mäusen in: Naunyn - Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie 225 (1955) pages 533–540

¹²⁸³ KUSCHINSKY GUSTAV / MUSCHOLL, E., Die Behandlung der experimentellen Quecksilbervergiftung mit 2,3 Dimercaptopropionsäure, in: Naunyn - Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie 223 (1954) pages 408–419

¹²⁸⁴ KUSCHINSKY GUSTAV / HOFMANN, P. / MUTSCHLER, E. / WOLLERT, U., Die Verteilung von Progesteron- und Dodecandion-2,11-bisguanylhydrazon im Meerschweinchenorganismus in : Naunyn-Schmiedebergs Archiv für experimentelle Pharmakologie und Experimentelle Pathologie 257 (1967) pages 288–289

entweder 150- 200 mg Natrium phenyläthylbarbituric./kg. i.v. , die Hunde 20 mg Morphin hydrochlorid. und 1 g Urethan/kg. i.p.”¹²⁸⁵

Current ethical standards regarding animal welfare base on principles that had been officially introduced within the late 1950’s and early 1960’s and even date back from more than hundred years earlier. They frequently do imply principles of the so called 3R process, aiming at the “*reduction in the number of animals used to obtain information of given amount and precision*”¹²⁸⁶ as well as the “*decrease in the severity of inhumane procedures applied to those animals, which still have to be used*”¹²⁸⁷ or to entirely replace animal experimentation by other methods which do not involve living organisms.

Kuschinsky did not only aim at a minimization of pain and discomfort within the publications, taken into consideration here, but also showed a practical implementation of those guidelines. He did utilize organs of animals that had been killed in other, e.g. nutritional contexts for his research and thereby indirectly limited the number of needed laboratory animals for his research, e.g. “*Die Herzen wurden den Tieren im Schlachthof sofort nach dem Töten entnommen und in kalter Tyrodelösung (4 Grad Celsius) in das Laboratorium gebracht*”¹²⁸⁸

Besides preclinical experiments, there is evidence for Kuschinsky’s research using either human probands^{1289,1290} or specimens of human origin¹²⁹¹ at times as well. Within clinical experimentations involving ten human subjects for a two month period in 1956, a administration of increased subcutaneously administered dosages with a synthetically produced hormone was tested with regards to its side – effect profile.¹²⁹² Comparing this

¹²⁸⁵ KUSCHINSKY GUSTAV / MUSCHOLL, E., Die Behandlung der experimentellen Quecksilbervergiftung mit 2,3 Dimercaptopropionsäure, in: Naunyn - Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie 223 (1954) pages 408–419

¹²⁸⁶ HUBRECHT ROBERT / CARTER E., The 3Rs and Humane Experimental Technique: Implementing Change. Animals in : an open access journal from MDPI, 9(10),754. (2019)

¹²⁸⁷ Ibidem

¹²⁸⁸ KUSCHINSKY GUSTAV / PORZIG, H. / SCHOLZ, H., Untersuchungen über Wechselwirkungen zwischen Digitoxigenin, Noradrenalin und Calcium unter Hypothermiebedingungen an isolierten Präparaten aus Säugetierherzen in: Naunyn-Schmiedebergs Archiv für Pharmakologie und Experimentelle Pathologie 261, (1968) pages 191–211

¹²⁸⁹ KUSCHINSKY GUSTAV / BRUNNER, H. / MÜNCHOW, O. / PETERS, G., Der Einfluß von natürlichem und synthetischem Oxytocin auf endogene Kreatinin-Clearance, Salzausscheidung und Säureausscheidungsfähigkeit der Ratte und auf die Diurese des Menschen in: Naunyn - Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie 230 (1957) pages 80–89

¹²⁹⁰ KUSCHINSKY GUSTAV, Methoden zur Prüfung diuretisch wirkender Stoffe in: Naunyn - Schmiedebergs Archive für experimentelle Pathologie und Pharmakologie 238 (1960) pages 195–218

¹²⁹¹ KUSCHINSKY GUSTAV / SCHMITTEL, K. / HOFMANN, P. / MUTSCHLER, E. / WOLLERT, U., Über die Eiweißbindung von Bisguanlylhydrazonen in : Naunyn-Schmiedebergs Arch. Pharmak. u. Exp. Path. 257 (1967) page 328

¹²⁹² KUSCHINSKY GUSTAV / BRUNNER, H. / MÜNCHOW, O. / PETERS, G., Der Einfluß von natürlichem und synthetischem Oxytocin auf endogene Kreatinin-Clearance, Salzausscheidung und Säureausscheidungsfähigkeit 196

active treatment versus double blind placebo receiving test subjects, including healthy and young volunteers “(7 Männer und 3 Frauen) im Alter von 24 bis 36 Jahren”¹²⁹³ this study shows analogies to Phase 1 studies, the first- time application of a new type of drugs in humans.

Further investigations with human probands did comprise other minimally invasive therapies such as the administration of registered thiazid diuretics either as single doses or in concomitant use with glucocorticoids¹²⁹⁴, a combination which in therapeutic doses for the short amount of time used here, can also be considered as safe.

Besides this direct involvement, Kuschinsky also utilized body liquids for his research, which either involved albumin¹²⁹⁵ or urine samples¹²⁹⁶ for pharmacokinetic analysis, both to be obtained without considerable distress for the individuals. Not only the scientific justifiability both also the informed consent and research on healthy volunteers with safe and approved substances does speak in favour of high ethical standards within Kuschinsky’s experimentation both in animal and human experiments.

Kuschinsky’s contribution to an objective evaluation of drugs, as seen on his explicit recommendation for standardized methods and procedures is also reflected in a publication from 1955 “Über die Beurteilung der Wirkung neuer Arzneimittel”¹²⁹⁷ in which he advocates for placebo- controlled and side-effects capturing trials with healthy volunteers “Experimentelle Anordnung (...) Alternierende Behandlung (...) Hälfte der Patienten das Mittel erhält, die andere Hälfte ein in derselben Aufmachung zu verabreichendes Scheinmedikament.”¹²⁹⁸ Those clinical experiments should also be secured statistically and be based on methodologically sound preclinical experiments clarifying basic pharmacological facts such as the mode of action while also involving ancient and empirical knowledge where possible “Aber auch Digitalis, Salizylate, Coffein, Mutterkorn und Ipecacuanha (Emetin)

der Ratte und auf die Diurese des Menschen in : Naunyn - Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie 230 (1957) page 80–89

¹²⁹³ Ibidem

¹²⁹⁴ KUSCHINSKY GUSTAV, Methoden zur Prüfung diuretisch wirkender Stoffe in: Naunyn - Schmiedebergs Archive für experimentelle Pathologie und Pharmakologie 238 (1960) pages 195–218

¹²⁹⁵ KUSCHINSKY GUSTAV / SCHMITTEL, K. / HOFMANN, P. / MUTSCHLER, E. / WOLLERT, U., Über die Eiweißbindung von Bisguanlylhydrazonen in : Naunyn-Schmiedebergs Arch. Pharmak. u. Exp. Path. 257 (1967) pages 328

¹²⁹⁶ KUSCHINSKY GUSTAV / BRUNNER, H. / MÜNCHOW, O. / PETERS, G. / Der Einfluß von natürlichem und synthetischem Oxytocin auf endogene Kreatinin-Clearance, Salzausscheidung und Säureausscheidungsfähigkeit der Ratte und auf die Diurese des Menschen in: Naunyn - Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie 230 (1957) pages 80–89

¹²⁹⁷ KUSCHINSKY GUSTAV, Über die Beurteilung der Wirkung neuer Arzneimittel in : Deutsche Medizinische Wochenschrift Nr. 36 (1955) page 1287

¹²⁹⁸ Ibidem

sind verhältnismäßig leicht in ihren Wirkungen zu erkennen, so daß ihre Einbeziehung in den Arzneischatz der früheren Zeit leicht verstanden wird.“¹²⁹⁹ By contrast to both Starkenstein and Wiechowski, there was no evidence found that would document any involvement from Kuschinsky’s side in self- experiments, nor in detailed considerations regarding specific group of patients such as pediatric patients.^{1300,1301} However, there are analogies between Starkenstein’s ethical considerations about the medical profession and Kuschinsky’s reflection upon medical actions as well, which are both relevant for assessing their attitudes towards engagement with patients in treatment processes and thus within clinical settings. Starkenstein conceptualizes any “modern” medical practice being based on humanistic values such as "Ethik und Kultur"¹³⁰² or "Vernunft"¹³⁰³ and practically acknowledges that physicians might, either derive a diagnosis via extensive diagnostic tools, or at times also by virtue of their experience and practical knowledge more quickly, through precise questioning of the patient.¹³⁰⁴ Though Kuschinsky does not deal with those ethical questions in such detail, he also conforms with Starkenstein in the sense that, he acknowledges that there might be a certain sense of medical intuition as well: “blitzartiges Assoziieren der im Augenblick wesentlichen wissenschaftlichen Gedankengänge handelt (...) bei genauer , ruhiger Betrachtung als stichhaltig erweist”¹³⁰⁵

4.4.3. Relations to the pharmaceutical sector and pharmaceutical profession

Although all three scientists collaborated with the pharmaceutical sector throughout their careers, Kuschinsky’s research rather displays indirect touchpoints with pharmaceutical companies, as seen on the evaluation of mostly marketed drugs or simply by benefiting of the supply of their drugs.^{1306,1307,1308} In this respect he also contributed to the pharmacological

¹²⁹⁹ Ibidem

¹³⁰⁰ STARKENSTEIN EMIL, Die Entstehung der endogenen Harnsäureausscheidung als Grundlage für die Bemessung der Arzneimitteldosen im Kindesalter in: Archiv für experimentelle Pathologie und Pharmakologie (1937)

¹³⁰¹ WIECHOWSKI WILHELM / Klausner, E., Ueber die lokale Behandlung der Harnröhren gonorrhoe mit Silberglykosiden (Neoreargon) in: Deutsche Medizinische Wochenschrift (1925)

¹³⁰² STARKENSTEIN EMIL, Instinkt und Intuition in der Forschung, im Studium und im ärztlichen Berufe in: Einheitsbestrebungen in der Medizin (1933)

¹³⁰³ Ibidem

¹³⁰⁴ Ibidem

¹³⁰⁵ KUSCHINSKY GUSTAV, Über die Beurteilung der Wirkung neuer Arzneimittel in: Deutsche Medizinische Wochenschrift Nr. 36 (1955) page 1287

¹³⁰⁶ KUSCHINSKY GUSTAV / LINDMAR, R. / LÜLLMANN, H. / MUSCHOLL, E., Der Einfluß von Reserpin auf die Wirkung der „Neuro-Sympathomimetica“ in: Naunyn - Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie 240 (1960) pages 242–252

¹³⁰⁷ KUSCHINSKY GUSTAV / REUTER, H., Über den Wirkungsmechanismus von Ajmalin, in: Naunyn - Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie 242 (1961) pages 17–23

profiling of various substances and to their optimized or extended clinical use, however in comparison to both Starkenstein and Wiechowski, this did not lead to the launch of medications based on his previous research, as in the case of the latter ones.

The variety and amount of companies he engaged with professionally seems more extended compared to Starkenstein and Wiechowski, which could also be due to the fact that from the 1940's the "evolution of the pharmaceutical industry"¹³⁰⁹, as described by Marlerba et. al, experienced an enormous boost. This had been caused by factors such as further understanding in drugs mechanisms and pharmacological sciences, but also in advances in laboratory technologies and political opportunities, which for instance became noticeable through increased funding for research and development.¹³¹⁰ In this respect, all three scientists, and this applies all the more so for Starkenstein and Wiechowski, contributed to therapeutic innovation even before it became an agenda item within this industry context. Starkenstein's clear criticism of commercial interest and lobbying pressure without delivering truly innovative medications or Wiechowski's critique towards commercialised interests within the pharmaceutical profession can be seen as indicative for that gradual development. Even more so, both Starkenstein's and Wiechowski's research in terms of dermatology, endocrinology, antiinfective agents, sedative or analgesic drugs etc. did truly drive innovation in pharmacotherapeutic treatment at the time.

As previously described, Kuschinsky focused his research much more towards hormonal and cardiovascular research but herein clearly helped to further clinical development of drugs, which involved the chemical optimization of discovered molecules, as seen on his research with bisguanlyhydrazones, which represented a more efficient way of finding new drugs, based on the given scientific and technological progress. Eventhough Kuschinsky also uttered criticism with regards to commercially driven interests "*dieselbe Substanz (...)unter verschiedenen Namen verkauft*"¹³¹¹, his scepticism towards any alternative medicines, e.g. homeopathic products, seems to be particularly pronounced "*Sonst besteht die Gefahr (...) Suggestivwirkungen für pharmakologische Wirkungen hält.*"¹³¹²

¹³⁰⁸ KUSCHINSKY GUSTAV / HILLE, U. / SCHIMASSEK, H., Über Histamin als Mittler-Substanz bei der Wirkung von Adrenochrom auf die Blutungszeit in: Naunyn - Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie 215 (1952) pages 48–51

¹³⁰⁹ MALERBA FRANCO / ORSENGO L., The evolution of the pharmaceutical industry in : Business History, 57(5) (2015) page 664-687

¹³¹⁰ Ibidem

¹³¹¹ KUSCHINSKY GUSTAV, Über die Beurteilung der Wirkung neuer Arzneimittel in: Deutsche Medizinische Wochenschrift Nr. 36 (1955)

¹³¹² Ibidem

Though both Starckenstein and Wiechowski also clearly plead for an evidence based approach to drug utilization and research, both did not exclude either historical remedies or particularly natural medicines from their research a priori, making them the subjects of further investigations to a much broader extent.

In terms of the pharmaceutical profession as such, Kuschinsky adopted a rather moderate stance, as he indeed authored professional literature which had been repeatedly issued through the years^{1313,1314,1315} and also took part in educational events for pharmacists^{1316,1317}, but did not as enthusiastically engage in discussions about the development of the pharmaceutical profession as his other two colleagues. Based on the evidence it cannot clearly be said whether Kuschinsky's overall interest particularly in pharmaceutical concerns and fundamental pharmaceutical sciences did either decline, or had never been truly there in the first place. His initial interests though, as stated in his personal file display a certain overlap to those sciences, as seen on his given research interest in phytopharmaceutical research "*Chinesische Drogen*"¹³¹⁸ or suggested in his autobiographical recollections during his time in China.¹³¹⁹

4.4.4. Degree of socio-political and humanist interests

Whereas Kuschinsky's political involvement can be clearly documented on his party membership and also within other NS organizations, both Starckenstein's and Wiechowski's political activities had been either limited to higher education policies or are located within the social- democrat spectrum in Wiechowski's case. A common feature however between Wiechowski's and Kuschinsky's quite diametrically opposed party political activities is the limited duration of time of their memberships, indicating either an annoyance of political institutions and offices or changes in political circumstances.

¹³¹³ Scientia Pharmaceutica, Wissenschaftliches Organ der Österreichischen Apothekerschaft, Heft 2, 42. Jahrgang, in: Buchbesprechungen Kurs der Allgemeinen Pharmakologie und Toxikologie (1974)

¹³¹⁴ Scientia Pharmaceutica, Wissenschaftliches Organ der Österreichischen Apothekerschaft, Heft 1, 41. Jahrgang (1973)

¹³¹⁵ Scientia Pharmaceutica, Wissenschaftliches Organ der Österreichischen Apothekerschaft, (1974) Heft 3, 42. Jahrgang, Buchbesprechungen (1974) page 201

¹³¹⁶ Österreichische Apothekezeitung 17 Jahrgang, Folge 8, (1963), page 112

¹³¹⁷ Österreichische Apothekezeitung 17 Jahrgang, Folge 24, (1963), page 380

¹³¹⁸ KUSCHINSKY GUSTAV, Personal file Kuschinsky in the University Archive Mainz "Der Verwaltungsdirektor bei der Friedrichs- Wilhelms Universität zu Berlin, Personalakten des Oberassistenten Dr Gustav Kuschinsky, angefangen 1.11.1931- 31.03.1940" pages 2 and 31

¹³¹⁹ MANN GÜNTER / DUMONT F., Medizin in Mainz. Praxis und Wissenschaft, Entwicklungen und Erinnerungen in: 40 Jahre Medizinische Fakultät und Klinikum 1946-1986. Verlag: Mainz. Kirchheim (1986)

Based on the evidence used within this thesis, no further political activities could be identified in Kuschinsky's case after 1945 in a party political sense. How deficient those party membership information turns out to be, in trying to characterize their overall political stances and positions becomes evident in Starkenstein's case as well. He did not actively engage in party political activities, but can be regarded as an important intellectual figure within socio-political progresses of his time, especially in the case of his health policy activities and also emerging ideas about professional development within the healthcare sector. Interestingly, in contrast to his rather progressive professional ideas within the medical and healthcare sector, he is being described as rather conservative with regards to personal views and attitudes.

Both the spectrum and the extent of interests and reflections on humanist topics, particularly in Starkenstein's case differ considerably to Kuschinsky, who did indeed publish his memoirs and within the field of pharmaceutical history, but did neither display the same fascination for wider historical research, as Starkenstein did. Similarly, his personal dedication with religious topics and thereby the amount of available sources on this topic, sticks out to a greater extent as seen in Kuschinsky's biography. The latter one might have had certain personal religious convictions as suggested by a reported conversation from 1940 with a catholic priest at the German University " *mit Prof. Kuschinsky eine längere Aussprache, wobei wir u.a. auch auf das Verhältnis und die Bedeutung der Religion für das Völkerleben zu sprechen kamen. Ich hatte bei dieser Aussprache den Eindruck, daß Prof. Kuschinsky in dieser und in anderen Fragen durchaus nicht den radikalen Parteistandpunkt teilte (...)*"¹³²⁰ but did clearly not address metaphysical questions as Starkenstein did through his several publications. This does also concern his extensive linguistic and literary affinity, e.g. as seen on his recurring quotes of Goethe's opus.

As opposed to Wiechowski's at times energetic behaviour, particularly within discussions and interactions with colleagues and opponents both within the academic and political arena, Kuschinsky's behaviour must have been rather marked by moderation and quiet diplomacy, as suggested by several sources " *sehr lebenswürdiger und kluger Mensch (...) bemüht sich ehrlich*"³⁷⁵ over time: " *Dank (...) seines Taktes und seines bescheidenen, aber bestimmten Auftretens war mir Dr. Kuschinsky ein lieber Mitarbeiter.*"¹³²¹

¹³²⁰ KUSCHINSKY GUSTAV, Universitätsarchiv Mainz Personalakte Kuschinsky im Universitätsarchiv Mainz, Ges 131 / S64/11 page 6 (Sheet 1-14)

¹³²¹ KUSCHINSKY GUSTAV, Personal file Kuschinsky in the University Archive Mainz "Der Verwaltungsdirektor bei der Friedrichs- Wilhelms Universität zu Berlin, Personalakten des Oberassistenten Dr Gustav Kuschinsky, angefangen 1.11.1931- 31.03.1940" Page 8

These character traits also manifested themselves in his capabilities of purposeful socialising , particularly in a professional context, as seen in his successful establishment of scientific summit in Mainz or within other personal and professional occasions as described before (4.1.4. personal traits) “*Da ich gute Kontakte zu einem Apotheker hatte, konnte ich die Medikamente selbst überbringen.*”¹³²² Wiechowski, although apparently caring for his social environment both in personal and professional setting, did by contrast show aspects of social phobia, particularly towards the end of his life “*er vertraute sich niemandem an*”¹³²³, and in this respect was, at least temporarily much more withdrawn from social life.

A characteristic, all three pharmacologists had in common, besides their obvious affinity for pharmacological research can be seen in travelling and spending time abroad, here again, all three biographees often combined this with professional duties.

5. The three cases in the conceptual framework of victimization

5.1. Review of each case in reference to the initial working hypothesis

As described previously, the perpetrator- bystander- victim constellation can be applied during the years 1939- 1945 to the situation prevalent in Prague and also at the German University, as well as to other Nazi occupied regions, since all four prerequisites are met: “*perpetrator group (as) dominant entity within (...) region*”¹³²⁴, “*actual or contrived stress*”¹³²⁵ on victim group and general population , “*creation of an ideology*”¹³²⁶ and “*constellation only exists (...) during genocidal action*”.¹³²⁷

In the proper meaning of the word, Prof. Wiechowski cannot be assigned to either one group , either victim, bystander or perpetrator since his life ended before the corresponding time in 1928 and he did therefore not actually experience this specific political situation. It could therefore be argued that Wiechowski´s case displays a “normal”, that is a apolitical research driven academic biography, without any points of contact with nationalistic policies, which based on the sighted documents is however not entirely accurate.

¹³²² MANN GÜNTER / DUMONT F., Medizin in Mainz. Praxis und Wissenschaft, Entwicklungen und Erinnerungen in: 40 Jahre Medizinische Fakultät und Klinikum 1946-1986. Verlag: Mainz. Kirchheim, (1986) page 242

¹³²³ STARKENSTEIN EMIL, family archives c.o. Dr. W. van Emde Boas, Netherland, „Wilhelm Wiechowski – Sein letztes Lebensjahr von Ilse Kaiser 1929“

¹³²⁴ EHRENREICH ROBERT M. / COLE TIM, The Perpetrator-Bystander-Victim Constellation: Rethinking Genocidal Relationships in: Human Organization; Oklahoma City Vol. 64, Iss. 3, (2005) pages 213-224

¹³²⁵ Ibidem

¹³²⁶ Ibidem

¹³²⁷ Ibidem

Incorporating the miscellaneous socio-political dynamics leading to the rise of the National Socialist dictatorship in various European countries, one also needs to consider nationalist ideologies, which had been emerging since the late 19th century. Wiechowski was clearly affected to some extent by these movements and choose to actively deal with them, which despite of his premature death does provide some indications about his opposed positions towards them. Alongside with his pro- pacifist and pro -feminist attitudes which had been influenced by his familial background, Wiechowski can be considered a person clearly opposed to those nationalist movements, which according to Hartung gradually accumulated to an ideology that then subsequently paved the way for radical nationalism and early stages of Nazism: *“Wenn mithin festzuhalten ist, daß Anfang der 80er Jahre völkische, antisemitische und rassistische Tendenzen miteinander zu verschmelzen begannen, so kann man doch für diesen Zeitpunkt noch nicht von voller gegenseitiger Integration und von einer präfaschistischen “Weltanschauung“ sprechen. Diese Stufe wurde erst nach 1900 erreicht“*.¹³²⁸

Besides his generally rather liberal and modern views on education and women’s rights, particularly his membership in the Social Democratic Party alongside with his demand for national autonomy, displays his opposed stances to hegemonial claims of one nation.

His moderate political beliefs and also his moral courage are further manifested in his resistance towards those nationalistic trends e.g. in higher education policies within the hostilities against the Jewish university rector Prof. Steinherz or in his critical attitude towards military misuse of science. In this respect, Wiechowski has to be seen in clear opposition towards any extreme nationalist trends *“seiner Gesinnung nach nichts weniger als ein Demokrat beschrieben”*¹³²⁹, which is also reflected in his long- lasting friendships with a variety of artists and writers and particularly with his mentee Emil Starckenstein.

His broad scientific but also artistic interests paired with his multi- faceted character, that could either display productive and altruistic social involvement but also reverse to impulsiveness in discussions as well as social seclusion at the same time, characterise Wiechowski’s idiosyncaries and thereby special aspects within his overall biography.

Prof. Starckenstein did clearly experience the direct effects of both uprising nationalism and the detrimental effects of a ultimate fascist dictatorship, that incorporated racism, extreme

¹³²⁸ PUSCHNER UWE / SCHMITZ W. & ULBRICHT / JUSTUS H., Handbuch zur völkischen Bewegung 1871-1918 in Walter de Gruyter (2012) page 28

¹³²⁹ SPIRO KARL, Erinnerung an Wilhelm Wiechowski in: Die Medizinische Welt – ärztliche Wochenschrift Nr. 6 (1929)

nationalism and systematically organised genocidal actions. According to Ehrenreich's and Cole's suggestions one should explore victimised individuals under the aspects of "*how they responded during the perpetrators' seizure of power (...) how they reacted to the instigation and implementation of the destruction process ; and what forms of resistance they offered*"¹³³⁰

Another factor given attention to within the suggested model are "*survival strategies*" of the victim group, being defined as "*a subset of society that is classifiable on the basis of some socially constructed distinction (...) used as a foundation for the creation of an ideology*"¹³³¹

Due to the mere fact that Starkenstein was of Jewish descent, he had already been assigned to an, already by definition, victimized and stigmatised group within the National Socialist ideology and then also factually experienced this victimization on various personal and professional levels. As described before this victimization did lead to his forced migration after 1939, leading to the detention and his assassination in the KZ Mauthausen and abduction of his son Walter, who vanished most likely had been murdered as well. Further levels of his and his family's victimization have to be seen in the psychological distress of the surviving family members, who first of all had to deal with their father's and son's or respectively brother's death and displacement and loss of their sense of home and social connections, due to their forced exodus. In addition, financial distress, and regime imposed obstacles to continue their academic studies have also to be mentioned, since they were the future basis to care for themselves for both children.

In this sense Starkenstein's case clearly meets the author's definition of those victim's being "*totally powerless to alter this decision making process, and their actual belief systems or worldviews are entirely superfluous to the process*"¹³³²

One survival strategy such as escape from this unalterable condition following the professional victimization and personal distress, particularly due to the expulsion from the Pharmacological Chair in Prague under German occupation, can be seen in the escape to the Netherlands. Although, Starkenstein had not been a member of official political parties, his humanist body of thought, as transported via his many publications or speeches in public, often in an academic context, have definitely to be seen as a form of reaction to nationalist tendencies and thus a form of resistance as well. Starkenstein's work within the field of the history of medicine, did contentually often deal with Jewish culture and its contribution to the

¹³³⁰ EHRENREICH ROBERT M / COLE T., The Perpetrator-Bystander-Victim Constellation: Rethinking Genocidal Relationships in: Human Organization; Oklahoma City Vol. 64, Iss. 3, :213-224. (2005) page 218

¹³³¹ Ibidem, pages 218 ff

¹³³² Ibidem, page 217

development of medicine^{1333,1334,1335}, while acknowledging the positive multiethnic and multicultural collaboration in these efforts “*Wie aus diesen wenigen Beispielen hervorgeht stand Rom hinsichtlich seiner Medizin fast ganz unter dem Einfluss griechischer Ärzte , die griechische Medizin, die wie wir gesehen haben , ebenso den Osten wie den Westen beherrschte , wurde dann durch den Islam abgelöst,; als Vermittler zwischen Christentum und Islam scheinen auf dem Gebiete der Heilkunde im besonderen die Juden eine gewisse Rolle gespielt zu haben.*“¹³³⁶

Furthermore, Starkenstein’s historical reviews also unmasked antisemitic stereotypes as well as discrimination of Jewish people in the past¹³³⁷, while at the same time advocated for human handling of migration and especially integration of eastern European Jews to central Europe¹³³⁸, which clearly was opposed to National Socialist interests and political agendas. His declared belief in individual responsibility and decisions of conscience, combined with humanist or religious ideals “*Dort wo ehrliche und aufrichtige Liebe das Handeln beherrscht , wird sie auch den richtigen Weg nicht verfehlen lassen*“¹³³⁹, were also non-compliant with a fascist worldview.

Starkenstein’s reactions to the advancement of National Socialist troupes were naturally very limited (line C’ within the model) as they represented a form of “*intellectual resistance*” which did start long before he had been forced to leave Prague and his “*Escape and Hiding*”¹³⁴⁰ in the Netherlands in order to try to flee the “*universe of the destruction process*”¹³⁴¹. As described by Ehrenreich and Cole “*a person in hiding is still at grave risk of being recognized or betrayed, however , and thus re- inserted into the universe of the destruction process*”¹³⁴², which unfortunately also applies in Starkenstein’s case, which had

¹³³³ STARKENSTEIN EMIL, Kräuterbücher Eine Quelle für Medizin-, Natur-, Kunst-, und Kulturgeschichte (1928)

¹³³⁴ STARKENSTEIN EMIL, Die Juden in der Medizin des Mittelalters in: Selbstwehr zum 1. Weltkongress jüdischer Ärzte in Tel- Aviv Nr. 175a Archiv Box 3, Archive (Starkenstein Nr 152- 215) no year detectable on publication

¹³³⁵ STARKENSTEIN EMIL, Musa ben Maimun, der Arzt des Mittelalters Nr. 175 Archiv Box 3, Archive, no year detectable on publication

¹³³⁶ STARKENSTEIN EMIL, Kräuterbücher Eine Quelle für Medizin-, Natur-, Kunst-, und Kulturgeschichte (1928)

¹³³⁷ STARKENSTEIN EMIL, Juden- Namen in: Der B’Nai B’Irth Monatsblätter der Grossloge für den Cechoslovakischen Staat (1925)

¹³³⁸ STARKENSTEIN EMIL, Hygienische und sanitäre Verhältnisse Polens in: Archiv für soziale Hygiene und Demographie (1917)

¹³³⁹ STARKENSTEIN EMIL, Krombholz- Feier : Gedenkrede für Julius Vinzenz Krombholz, Medizinische Fakultät der Deutschen Universität in Prag und Verein deutscher Ärzte in Prag in: Medizinische Klinik (1933)

¹³⁴⁰ EHRENREICH ROBERT M / COLE T., The Perpetrator-Bystander-Victim Constellation: Rethinking Genocidal Relationships in: Human Organization; Oklahoma City Vol. 64, Iss. 3, :213-224.(2005) here page 220

¹³⁴¹ Ibidem

¹³⁴² Ibidem

been arrested in his Dutch exile and subsequently abducted to the concentration camp Mauthausen.

In Kuschinsky's case, by clear contrast to his predecessor one's, he actually did have a greater freedom to choose his actions and thereby to act as either member of the resistance, bystander or perpetrator within the Nazi occupied political constellation. This is already due to the fact that within the National Socialist thinking he had not been classified as an outsider to the ideologically defined national community "*deutschblütiger Abstammung*"¹³⁴³, but as a part of it instead.

In order to meet the criteria of the perpetrator group, the "*level of active participation*"¹³⁴⁴ is defined as a decisive aspect, as well as the "*willingness to be actively involved in the official or unofficial organisations that lead, conduct, or support the actual murder of the victim group*" ... "*motivated by opportunism, ideology, inertia (...) or some combination thereof.*"¹³⁴⁵ Based on the sources available and used within this thesis, Prof. Kuschinsky, did not actively engage in elements of genocide, neither within his research activities or political actions, nor in any other social or personal situations, known to the author.

Within his pharmacological and all other research activities, also interests of the regime, such as performance enhancing effects etc. played a certain role indeed, however no indications of unethical experimentations, neither in animals or humans were found. In addition to that, Kuschinsky's research can only be regarded as little to moderately useful to the destruction process itself, since a lot of experiments did not have an application oriented use and were in fact of a broad fundamental nature or at times aimed at therapeutic research.

In terms of politics, Kuschinsky did indeed obtain membership in various NS organisations, such as the NSDAP in 1937 or the *NS Dozentenbund* 1938 etc. but at the same time did not actively participate in party politics or propaganda, nor did he take part in military service¹³⁴⁶. His rather passive behaviour in terms of supporting the nationalist agenda, is also backed up by his solidarization with marginalised groups at a small scale level. Instead of full-heartedly agreeing with the National Socialist agenda, Kuschinsky's rather showed a two sided profile,

¹³⁴³ KUSCHINSKY GUSTAV, Personal file Kuschinsky in the University Archive Mainz "Der Verwaltungsdirektor bei der Friedrichs- Wilhelms Universität zu Berlin, Personalakten des Oberassistenten Dr Gustav Kuschinsky, angefangen 1.11.1931- 31.03.1940" page 44/46f/49

¹³⁴⁴ EHRENREICH ROBERT M. / COLE T., The Perpetrator-Bystander-Victim Constellation: Rethinking Genocidal Relationships in: Human Organization; Oklahoma City Vol. 64, Iss. 3 (2005) pages 213-224

¹³⁴⁵ Ibidem, page 217

¹³⁴⁶ KUSCHINSKY GUSTAV, Universitätsarchiv Mainz Personalakte Kuschinsky im Universitätsarchiv Mainz, Ges 131 / S64/11 page 11/17 (12)

driven by his research ambitions and opportunism pertaining to his career. Being a beneficiary of the subsequent integration into the Nazi political and academic system, he was supported both financially and regarding his professional development.

This does rather meet the criteria of a bystander, *“People will be constantly changing their positions within the spectrum depending on a wide range of temporal and regional variables, including the policies being implemented by the perpetrator group”*¹³⁴⁷, as Kuschinsky’s behaviour does in fact show dynamic and contrary elements over time.

Within Ehrenreich’s and Cole’s model, Kuschinsky is placed on the left hand side of the triangle, but does not really exceed its midpoint, symbolizing *“inaction and acquiescence”*¹³⁴⁸ with regards to the destruction process. Naturally he also does not reach the bottom of the left hand side *“rescue or resistance”*¹³⁴⁹ since he remained a part of the ethnic group defined by the perpetrators, and did not manage to distance himself clearly, albeit his efforts to support certain victimized individuals on a small scale level.

5.2 Final considerations

In line with previous research¹³⁵⁰, referring to the persecution and victimization of Jewish scholars and also the beneficial treatment of so called *“Aryan”* scientists, this dissertation adds three biographees that had been affected to variable extent by fascist ideology. As described by Löffelholz, *“even in a small professional community such as pharmacologists, the whole spectrum of persecution was evident, ranging from forced careers in exile to extermination in a concentration camp”*¹³⁵¹, which definitely applies to Starkenstein as well as the *“loss of research support”*¹³⁵² following his academic expulsion by the Nazi regime. As also demonstrated within this article, other victimized pharmacologists either committed suicide, or had to give up their academic career in exile *“George Pietrkowski (...) immigrated to Italy (..) and settled down as a general practitioner”*¹³⁵³, displaying their truly limited opportunities to shape their fate, which is also backed up by the research findings in this dissertation.

¹³⁴⁷ EHRENREICH ROBERT M. / COLE T., The Perpetrator-Bystander-Victim Constellation: Rethinking Genocidal Relationships in: *Human Organization*; Oklahoma City Vol. 64, Iss. 3 (2005) pages 213-224

¹³⁴⁸ Ibidem

¹³⁴⁹ Ibidem

¹³⁵⁰ LÖFFELHOLZ KONRAD, The persecution of pharmacologists in Nazi Germany and Austria in: *Naunyn-Schmied Arch Pharmacol* 383 (2011) pages 217–225

¹³⁵¹ Ibidem, page 217

¹³⁵² Ibidem, page 219

¹³⁵³ Ibidem

As shown in the case of Kuschinsky, by contrast, non- victimized scholars usually had a greater scope of decision making compared to “*non- Aryans*” which did not only encompass opportunism but also could involve certain levels of compunction, as also described in the case of Otto Kraye.¹³⁵⁴

Ideological influences on science, have been demonstrated to be rather restrictive with regards to the overall research spectrum and investigated scientific fields e.g. in Löffelholz’s research. This can also be sensed in the case of Kuschinsky’s rather specialised research interests, compared to Starkenstein’s or Wiechowski’s much broader ones through various subjects and topics, not only in pharmacology.

¹³⁵⁴ Ibidem, pages 219 / 222 / 224

III. Glossary, source references and further appendices

6.1 Glossary

Secondary plant constituents	Chemically heterogenous group originating from secondary plant metabolism with large health effects in humans, e.g. antioxidative ones in the case of flavonoids
Qualitative pharmaceutical analysis	Analytical methods to determine the identity of a drug or other chemical substances like ionic compounds, often based on previous chemical separation processes and subsequent specific detection of ions or functional groups.
Quantitative pharmaceutical analysis	Analytical methods in consideration of chemical proportions in order to determine the exact content of chemical substances. This can be done by volumetric or gravimetric methods for example
Stereochemistry	The precise three- dimensional description of molecules including their chemical constitution and configuration
Chemical constitution	The basic structure of a molecule as defined by the type of chemical bonds as well as their overall amount, e.g. double bounds.
Chemical configuration	The spatial arrangement of molecular groups
Straub preparation of the heart	Experimental set up to investigate humoral and drug induced effects on the isolated heart
Purine metabolism	Biochemical processes involving the heterocyclic compound purine, which can either be sythetised by the human body or be absorbed by nutrition
Pharmakokinetics	Physiological processes a drug undergoes in the human or animal body, characterized by adsorption, distribution, metabolism and elimination in a time dependent manner.
Pharmacodynamics	Effects, as seen on physiological or immunological effects a drug evokes within the human body. Usually stimulating or inhibitory effects take place on pharmacological targets, such as receptors or enzymes
Compartment (human body)	Hypothetical distribution areas within pharmacokinetic calculations in order to estimate dosing intervals
Phase I- reaction	First partial step of the biotransformation of drugs, primarily marked by oxidative and reductive processes with the help of enzymes

Phase II- reactions	Subsequent chemical steps that serve hydrophilization and thus elimination
Bioavailability	Pharmacological parameter that characterizes the systemically available proportion of a drug
Bolus alba	Aluminium silicate with the molecular formula $Al_4[(OH)_8Si_4O_{10}]$ of its main component, used as a pharmaceutical excipient
Pharmacognosy	A subfield of Pharmaceutical Biology that deals with the microscopic analysis of biogenic substances, such as plants in order to identify new potential drugs for therapeutic use.
Phytotherapy	Therapeutic use of plant components such as leaves, rhizome, blossom within medicinal teas, oil, distillates etc, either based on research or traditional herbal books.
Colloid osmotic pressure	Osmotic pressure within vessels caused by proteins with essential functions for the maintenance of the overall plasma volume
Drug targets	Usually protein based target structures within the human or animal body e.g. ion channels, enzymes or G protein coupled receptors
Clinical pharmacotherapy	Application based science dealing with the efficacy, safety and applicability of drugs, including clinical and observational trials
Vestibular organs	Organs of equilibrium within the human body
Balneology	Therapeutic use of baths, spas to increase physiological and psychological well-being
Ionic bond	Chemical bond caused by electrostatic attraction of positively and negatively charged ions.
Astringent	Externally applied drugs that support tissue repair and have in situ anti-inflammatory effects based on their surface effects
Antiphlogistic drug	A class of drugs that reduces systemic inflammation
Antiseptic substances	Substances that are applied locally to prevent a spread of infection, usually with a broad spectrum of activity
“Me- too- drugs”	Usually a drug with similar chemical structure but no superiority in clinical outcomes
Pharmaceutical Quality	Clearly defined standards of drugs or their preparations in accordance with official pharmacopeia, especially with regards to identity, content, purity of them
Roborantia	Obsolete expression for tonics, vitalizing drugs

IUPAC nomenclatur	Rules for the systematical designation of chemical structures as suggested by the International Union for Pure and Applied Chemistry
Evidence based use	Therapeutic decisions based on the current state of research
Structure effect relationship	Chemical interactions of drugs via specific chemical groups causing biological and thus pharmacological effects
Cardiomyopathy	Pathological changes within the heart muscle due to reasons such as coronary heart disease leading to cardiac conduction disorders and possibly heart hypertrophy
Scientific reproducibility	Scientific standard ensuring that similar results are obtained if an experiment is repeated under the same circumstances to ensure objectivity of results
Medulla oblongata	Part of the central nervous system in charge of various vital functions such as respiration and reflexes
Ozonisation	Chemical reaction in which oxygen is taken up via intermediate stages to double bonds of carbon
Acetylation	Chemical reaction in which within functional groups hydrogen is substituted via an acetyl group
Optical activity	Chemical property of certain substances with the capability to alter the direction of polarised light with relevant implications for drug efficacy and safety
i.v.- route	Direct administration of a drug into venous blood vessels, with a 100 % bioavailability per definition
s.c.- administration	Administration of drugs into subcutaneous fat tissue resulting in a depot effect
Parasympatholytic effects	Drugs that can inhibit the effects of the neurotransmitter acetylcholine leading to physiological effects such as reduction of intestinal activity
Biological control circuit	Physiological control processes in which blood pressure, hormonal balance, respiration etc. are regulated
Glukokinines	A variety of substances of herbal origin that are capable to decrease blood sugar levels.
Tyrode solution	Standard solution used within many laboratory experiments in which a physiological composition of electrolytes is required
Auricular fibrillation	Tachycardic arrhythmia, due to pathophysiological innervation of the atrium

Cardiac analeptics	Stimulating agents targeting cardiac activity such as caffeine
Taxonomy	Hierarchical order within biology
Intraperitoneal injection	Rare parenteral application into the peritoneal cavity usually within animal experiments
Microdose	Off- label use to mitigate side effects while maintaining certain principal or desired effects, at times also misused
Randomized trial	Procedure to allocate study subjects by pure chance to either placebo or control group etc. in order to reduce bias within the trial and striving for comparability of groups
Real world condition	Reverse condition to those found within controlled clinical trials, especially in terms of co- morbidities, biological gender, or specific situations such as pregnancy
Risk- benefit assessment	Part of the pharmaceutical admission procedure taking into account physical and psychological risks which should ususally not outdo the therapeutic benefit
Off- label use	Act of using a licenced drug for another indication, in another dosage or dosing interval etc. than approved by regulatory authorities
Biocompatibility	Tolerability of drugs or specific substances with human tissue, organ systems or bodily fluids

6.2. Register of sources used within this thesis and body of literature

6.2.1. Archival Sources

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6.3 Transcript qualitative interview with Prof. van Emde Boas on May 9th 2021

(The informal introduction as well as any form of onomatopoeia or filler words or summary comments have been removed from the transcript, otherwise the interview is displayed ad verbatim)

Patrick Zawadzki: Thank you very much for taking the time again... If it's okay let's start with the topic guide.. we have divided this into two parts ... so the first part would pertain to your grandfather's, Prof. Starkenstein's contribution to modern pharmacology and modern pharmacology is defined as an evidence based pharmacology and also based on objective proof... and the second part would pertain to his personality and personal life. To begin, could you please introduce yourself- what's your background, what's your name – that would be fine.

Prof. Dr. van Emde Boas: My name is Walter van Emde- Boas, the grandson of Starkenstein, my mother Magda Starkenstein came to the Netherlands slightly after the fact... her father already had to leave following the annexation of Bohemia and Moravia ... and he was expelled from the University... My mother remained in Prague for a couple of months because her brother, Starkenstein's son Walter was arrested later on ... (he) came free and she stayed in Prague as long as she could in order to see him safe... getting away... which eventually he managed to get to Poland .. then later on he went to the Ukraine and that's where everything ends. My mother had a contact in Amsterdam, actually she was planning to continue her travel to New Zealand. Starkenstein was in Amsterdam but had hoped to be able to travel to the US... neither of which plans eventually succeeded.... My mother married a dutch psychiatrist (named) van Emde Boas , so that's my link to Starkenstein. I am a neurologist by training, clinical neurophysiologist, physician with a speciality in epilepsy and epilepsy surgery and diagnosis (...) I am married and I have children, I share Starkenstein's interests in books an history of medicine .. we will probably get to that later on.

Patrick Zawadzki: Thank you very much, (...) I want to establish a link to your grandfather a little bit, and after having read some publications ... not all of course, (...) the first notion that you have from his publications and what you know from your grandfather's research ... how would you classify his research in terms of breadth and variety of topics?

Prof. Dr. van Emde Boas: Well let's say ...I think in answering these questions ... part of what I would say is second hand in the sense that I have read relatively few of his papers but I know from my mother and more recently from for example this symposium in 2014 in Prague that he did not only publish a lot about very varied areas .. the main topics were iron, opiates, of course there was the pain killer Veramon, his work on sea sickness but apart from that he had a very wide interest in Judaica, in History of Medicine, in old books in botany... I knew that .. (...) I knew from my mother and my grandmother when she was still alive that one of his already quite early elements of work was the combination of pharmaka in order to have optimal synergy and as few side effects as possible ... and only later on I learned that in that he was probably one of the very first ... some of the people in the Prague symposium told me that had he lived he might have been Nobel (prize) material ... I don't know , I can't judge that. So my impression is that, again from the stories of my mother that his "Lehrbuch" which was published early before the war and for that reason was suppressed by the Germans and afterwards was never published in English although there was a translation made and there

was a contract for an American publication that never came about ... His work was quite important but I could not judge that for myself.

Patrick Zawadzki: Do you have any idea about his relation to other health care professions such as pharmacists in particular?

Prof. Dr. van Emde Boas: He had a lot of correspondence with people all over the world not just pharmacists but also most specifically medical historical things and also of course jewish interest he was quite active ... so there is still a lot of correspondence available which has to be worked out at some time or another ... I guess there is a number of dissertations there once the material gets to be analysed... there is not only the writing of medical historical papers, essays on Judaism, but I have a manuscript of a novel, which was never finished and never published, he really was an exceptional man in the way how he managed to do all this but he certainly had a lot of contacts. There is correspondence where the Nobel committee asks him to give his opinion .. actually he promoted the Prize of Otto Loewi ... Loewi thanks him for that later on.

Patrick Zawadzki: How do you think his wide interests in literature and art etc. might have affected his upbringing of your mother , or how do you think it could have been influenced (by those interests)? She has become an art historian if I am not mistaken?

Prof. Dr. van Emde Boas: Well certainly the atmosphere at the home of Starkenstein was not an easy one, he was quite stern, and in any way he was not much of a family man in the sense that he did a lot of work ... but certainly there was an interest in art, in travel in music, in opera etc. he included the children from very early on and he absolutely supported the idea that not just his son but also my mother would go to university ... a choice of her own to make that art history .. but he certainly supported that .. he was keen on education, I know from one of the early friends of my mother in school period, she died now ... she lived in London for many years... but she told us that whenever she visited, actually she was in the class with Magda's brother, my uncle... during lunchtime or evening they would visit the Starkenstein house, she was afraid of my grandfather because he was always examining. But another important glimpse about he also thought about education ... his children were still born in Austria- Hungary, my uncle was born in 1915 my mother was born in 1917, in 1918 the Czech Republic became independent and also the children were raised in a german speaking jewish intellectual (household) my grandfather insisted that they also learned Czech, because they should speak Czech in the Czech Republic. So they went to German school, after school they had to go to Czech lessons and to pass exams in both languages.

Patrick Zawadzki: What would you say, how would Starkenstein see himself ... Bohemian ... Austrian ... Czech ... as a Jew.... as a conservative or liberal Jewish person... maybe all of that?

Prof. Dr. van Emde Boas: Certainly a combination of it. Given the fact that he was born in Bohemia and lived in Czechoslovakia ... apart from the War years that he spent in Radom, Poland as an Officer in the Austrian- Hungarian army. But he felt Czech, he felt certainly very Jewish but actually in his early years he considered becoming a rabbi... later on he decided to follow the steps of his grandfather and father and do medicine. He followed the Jewish tradition, he was overall quite liberal, considering liberal or orthodox jewish (faith), he was not so liberal in his general political views ... he was rather old- fashioned, both his children were, already during their student days quite left oriented, certainly Starkenstein did not like

that very much. I know that according to the papers, he was accused of communist sympathies but that was bloody nonsense- he never was. (...) As far as this left thing is (concerned) it is Kafka... Die Verleumdung.

Patrick Zawadzki: Speaking about the Nazi regime....your grandfather had been expelled from University, simply because of the fascist ideology and had been replaced by Gustav Kuschinsky (and of course that had been a very negative impact on his life) ... Has your mother ever spoken with you about this or how your grandfather has felt about this .. how it has affected his academic career ... his personal life?

Prof. Dr. van Emde Boas: Well it has affected his personal life in a very extensive way , he had to move to the Netherlands , hoping to get away to the States, but that never succeeded. There is correspondence already from the pre- war years (...) with John Forton in Yale, and there was a controversy about e.g. the fact that Starkenstein was receiving money from Schering and at that time the US academies frowned upon this type of financing and my grandfather had to explain that in Europe there was no finance at all in the universities unless this type of income. He felt very offended by the fact that he had to leave University, that his students suddenly were anti, just because he was Jewish and just because the fascist took over. It took my mother quite a while to convince him to leave Prague because despite the fact that he had been expelled from the university , he could not imagine that something really bad could happen because of his position, because of the role he had played before ...as many Jews, intellectuals at that time were fooling themselves

Patrick Zawadzki: Speaking about the two points that you mentioned, his really successful collaboration, not only academically with many other intellectuals but also with the pharmaceutical sector with the three medications (...) “Vermaon”, “Ferrostabil” and “Vasano” , it abruptly ended in those years and also due to political reasons and this is another aspect (...) what I am wondering is how did he try to reinvent himself and to regain his life both professionally and personally after starting all new in the Netherlands- do you know anything about this?

Prof. Dr. van Emde Boas: Yes, I know a little bit, of course he had to leave quite acutely without true preparations ... at that time luckily he was still allowed to take his stuff with him through the help of Ernst Laqueur with whom he had correspondence and knew quite well, Laqueur was a professor of Pharmacology in Amsterdam and was working with the pharmaceutical company in Oss on hormones and Laqueur arranged an introduction for Starkenstein in the Amsterdam Chininefabriek at that time with Jan Kok, who later became a Professor of Pharmacology in Amsterdam, he was working there and they secured the position for him there ... actually parts of his library were stored there over the war and survived for that reason because that part of the library which was in his home in Amstelveen was stolen later on.

Patrick Zawadzki: Do you have any idea by whom it was stolen?

Prof. Dr. van Emde Boas: The Germans. When you had to leave your home , there was a organisation, perfectly done ... people who were paid by the Germans who would take the stuff... actually I had the mail somewhere from someone who had been investigating the robbery of the Germans of intellectual material ... there had been cases with books, Judaica... with notes on it ... Starkenstein library.... That's gone... part of it... the literature library, notably all German works were not in the house in Amstelveen, but were with my mother in

their house in Amsterdam and they are now with me, his medical historical collections , some of the books happened to be already in Yale at that time of his movement because of an exhibition that John Forton was organising at that time together with Henry Sigerist , a well known medical historian and the idea was to (her) father to go there and to give lectures etc. But that never materialised with those books were in the Staates, the books which were kind of hidden because they were in the library in the Chininefabriek and they survived after the war... were sold by my grandmother who needed money to a nephew who had a scientific antique book and journal shop in New York, Brooklyn and they were mostly sold as a big collection of notably books on medical plants etc. to the Brooklyn Zoo Library.

Patrick Zawadzki: He had a very big interest in the so called “Kräuterbücher” and using knowledge of the past...

Prof. Dr. van Emde Boas: Yes, there are almost a hundred of them in the Bronx library ... very well kept ... you might contact... she is now retired but one of the librarians there Mary Long was working on Starkenstein for a long time.... She was in this symposium in 2014 also. I do have a full list of his collection at that time but many of the books have been disposed of course. Well the reprint collection that was left in the Chininefabriek, went to Olomouc and now it is in Prague. I had a few old medical books which are from his library, but most of it is dispersed.

Patrick Zawadzki: Your greatfather at some point was not able to find refuge in the U.S., do you think it was at that time too late to escape Europe (Germany or Austria) because of the occupation or what was the problem, what do you think?

Prof. Dr. van Emde Boas: Well at the time that he came to the Netherlands , first you had problems of getting visa and by the time that did or did not succeed, the Germans were here and its was (the) end of the story.

Patrick Zawadzki: Do you have any knowledge (about) political activism on any level of your grandmother or your grandfather – this could also be intellectual resistance of course ?

Prof. Dr. van Emde Boas: Neither. My grandmother was completely apolitical and grandfather did not take part in ... as far as I am aware... and my mother never mentioned anything of it that he was really active in politics .. I already told he was in favour of the Czech Republic, he was certainly supportive of Beneš and his government ... but he was not actively participating in politics other than the activites in university where of course he was in all kinds of commissions etc. This idea that he was left and that he had communist leanings or even activities , which was in the official accusation from the Germans and which is relevant, because he was not arrested as a Jew during the Nazi year later on ... he was arrested in 1941 on criminal charges ... we never really got to know the true story .. but the idea is and that was also supported by for example by Prof. Raskova from the Phrmacological Department that at that time Starkenstein left, Kuschinsky took over, there was a lady in the department who was very much antagonistic to him, very jealous , had hoped to get a better position, that she did not get...

Patrick Zawadzki: What was her name... do you happen to know her name?

Prof. Dr. van Emde Boas: I do not know her name. I think Šimůnek will know the story and may know the name.

Patrick Zawadzki: But she was a researcher, too... probably?

Prof. Dr. van Emde Boas: Yes. And then there again, there is no proof ... nothing ever came out, so maybe people will not be very eager to tell this name because it is hearsay. According to my mother this is a true story, that she (that researcher) actually alerted the Germans to do something about Starkenstein is that while... in Amsterdam he started to publish again from the Quininefabriek. she found this reason to act. This is the story and from that ... as I said he was arrested not as a Jew but on criminal charges, was actually moved not directly to one of the camps but went from Amsterdam ... not the jail but the house...that's where you put people before they go to jail (preliminary arrest) and then he went into the jail in Scheveningen from there he went to Kleve from there he was moved ... yet another... I think Prague then Theresienstadt and eventually Mauthausen.

Patrick Zawadzki: That has been quite a horrible journey. Speaking about other things, which might not be true... the death certificate which was issued by the Nazi Regime ...

Prof. Dr. van Emde Boas: No, No..... Herzversagen, Darmkatharr, were the most common things ... we do not know the details ... he was still corresponding for some time... we still have letters from Kleve, one from Theresienstadt, not from Mauthausen I think ... I was born on August 1942, so a couple of months before his death ... he was still aware of my birth .. he answered in a letter congratulating my mother with that... but otherwise we do not know exactly what has happened. There are a few, probably fantastic stories ... what's the word... like the late books at the end of the bible the Apocrypha... one story which my mother told me .. we don't know if it is true... is that... of course he was to step back in time .. during the First World war he was running an infectious diseases department in Radom where he had many people with Fleckenfieber, Thyphus, so he was quite an expert on that ... and according to my mother there is a story that Because the Germans actually had a lot of problems with Fleckenfieber, Thyphus in their camps, just after he had been murderer or parished or whatever... people came looking for Starkenstein to Mauthausen because they needed him – don't know if it is true... Then there was this story from some other sources that ... never really documented that he died during experiments that he was killed by phenol injections.... We don't know.

Patrick Zawadzki: With you being a physician, maybe you could also comment on that – I personally think it is very unlikely that somebody who was a middle aged man and relatively healthy, nobody knew of any precondition, then suddenly dies...

Prof. Dr. van Emde Boas: No indication of any heart condition whatsoever.... He didn't smoke he didn't drink ...

Patrick Zawadzki: ... and also he published quite a lot before that alleged coronary heart disease ... he (probably) would not have been able to publish so much and to be so active... You were also speaking about your mother's brother Walter I guess... Could you please tell me what happened to him ... what were the circumstances?

Prof. Dr. van Emde Boas: He was arrested ... actually he was also studying medicine ... he published a few things actually already in the student years amongst others also in Medical History. He was even more than my mother active in left-oriented student organisations ... and the night that the Germans came to Prague ... he was arrested right away. He was set free a couple of weeks after that and at that time Starkenstein and his wife had already left for the

Netherlands on instigation of my mother because the trip to the Netherlands had been planned before the annexation... he was already driven out the university... left it earlier. And then Walter together with some friends tried to escape to Poland .. they didn't make it .. he was back in Prague again... then the second time they did manage to get to Poland .. he continued to finish his studies in Warsaw as far as I know, maybe in another city I would have to check ... I think it was Warsaw , then when Poland was invaded he went East ... and what we know is that he went to the Ukraine ... that he actually worked there..... he wanted to become a surgeon ... but never got to do a speciality training. As far as we know, but even there the documentation is very limited... he married a Ukrainian woman and whether or not she was in part responsible for him being picked up, eventually ...or whether he is just one of the many, many Jews that perished in whatever way in the Ukraine... we don't know. The story ends, we have a letter from a solicitor from Prague who claims that he still has correspondence from Walter from one of the camps, but we've never seen it ... my mother has done a lot of work first... directly after the war, but yet again in the years afterwards, and the last time after the "Wende" when the Russian archives became available to the Red Cross... but we have never been able to get together the story.

Patrick Zawadzki: ... so in other words you are also the last surviving family member (in direct line) of Starkenstein ?

Prof. Dr. van Emde Boas: ... my brother... I have a younger brother.

Patrick Zawadzki: I was wondering whether Prof. Kuschinsky (or parts of his family) did ever reach out to you (in order) to discuss the situation or maybe even try to apologize ?

Prof. Dr. van Emde Boas: Not that I am aware of ... my mother never mentioned him ... and this may be very stupid but I never realized that Kuschinsky was the one who took over ... I am still of the generation who had Kuschinsky's Lehrbuch ... I did medical training starting in 1961.. and of course his Pharmacology book... and it was Thieme ... and I never realized he was in Prague.

Patrick Zawadzki: ... A certain amount of time... he was in Mainz after the war... the he had to leave for obvious reasons as well in 1945 . How would you like your grandfather to be remembered on various levels , I mean academically, personally .. concretely... practically- do you have any ideas?

Prof. Dr. van Emde Boas: Well, if let's say there would be a revival of Starkenstein with a recognition primarily of course of his importance for Pharmacology and the international career he would have had, had the textbook really been published ... I am sure if the war had not been there , there would have been an English and probably French edition which would have gone to many editions. And if it is true that his work on combining medication was so important .. I did not even know that ... that would be very nice. I think that also he could be remembered as a rather renaissance type of person with great interest in history, literature, medical history. His interest in Goethe probably would have resulted in more publications in that direction – I have published some but not much. He was also interested in art, but there, I think he was not really knowledgeable , we inherited a couple of paintings which most of them were not what they... what he thought he was buying ... they were good but not that good. And as a member of the family, what I understood from my mother, he was very influential in his presence ... but he was not easy

Patrick Zawadzki: ... in which respect would you say ?

Prof. Dr. van Emde Boas: He was stern, he was demanding and although he certainly would be there if he would take the children on trips , involve them in travel .. much of his travel was in part professional...but there he would take them. My mother was with Starkenstein at the “Physiologenkongress” in Moskau in 1936 where for the first time there was simultaneous translation, which was very impressive to her and although she studied art history and worked as a art critic until the very end , most of her work and certainly her income came from being an interpreter... She was very good at that , speaking six languages. She was always very impressed by this first experience with this type of translation in Moskau.

Patrick Zawadzki: I know particularly about Chinese publications that has been translated into at least four or five languages...Italian, Spanish , Russian... so there was quite a distribution of your grandfather’s knowledge still at his lifetime. My last question would be: Do you know anything about the relationship of Prof. Wiechowski and your grandfather... maybe because they worked together, obviously in Prague for some time. What I have read in the publications is that there was mutual respect and admiration and so on and I feel that the difference from the “handing over” from Wiechowski and your grandfather (happened) in a manner of linking their research. So your grandfather really also took up quite a lot of the ideas and kept on researching and kept on refining ... Do you know anything about their relationship both professionally and personally?

Prof. Dr. van Emde Boas: Well I know that, of course Wiechowski was Head of the Department where Starkenstein came in rather young and had the opportunity to work and grow and that Wiechowski actually was not only the boss but I also think a friend of the family. But I do not know much about that. Certainly my grandfather always mentioned the name with respect, gratitude.

Patrick Zawadzki: Well thank you so much, we got through the entire topic guide – thank you it has been really interesting indeed and valuable , because a lot of the information you have given me , I certainly did not know so detailed before and you could also confirm quite a lot – so I really appreciate it very much and I am really delighted that you took the time and to be meeting you of course.

Prof. Dr. van Emde Boas: It’s my pleasure and it’s interesting to see that people are still interested in Starkenstein and working on him.