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Abstract of Habilitation Thesis

Interface Medicine

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The present habilitation thesis entitled „Interface Medicine” reviews the author’s most important scientific, professional, and academic achievements after being awarded the PhD title (2007), as well as the perspectives for future scientific and professional development. The thesis includes four main parts.

The first part is devoted to the analysis of the main directions of research pursued to date, indicating the original results achieved in my personal studies, the main objectives of which revolve around the aim of integrating the various domains of or related to medical practice, including the various medical and surgical specialties, conventional and traditional medicine, statistics and medicine, informatics and medicine, psychology and medicine, such that the main areas of my interest are: nephro-neurology (the impact of kidney dysfunction on the evolution of stroke patients), neuro-cardiology (cardiac changes in stroke), nephro-cardiology (cardiorenal syndromes, the interplay between cardiovascular and kidney disease), sepsis and its relationship with kidney dysfunction and liver-biliary disorders, the usefulness of phytotherapy in internal diseases. Correspondingly, this first section is divided into several subsections with suggestive titles.

The subsection “Heart-kidney interface” includes original research regarding the cardiovascular changes in hemodialysis dependent chronic kidney disease patients, particularly the diastolic dysfunction of the left ventricle and cardiovascular calcifications.

In the paper „Determinants of left ventricular diastolic dysfunction in hemodialysis patients” [**Dorin Dragoș**, Delia Timofte, Dorin Ionescu, Andra-Elena Balcangiu-Stroescu, Maria Iuliana Ghenu, Ileana Adela Vacaroiu, Maria Mirabela Manea. *J Nephrothol.* 2023;12(2): e18393] we were able to demonstrate that, in hemodialysis patients, the diastolic dysfunction of the left ventricle is positively correlated with inflammation and oxidative stress markers and with the severity of aortic calcification and that its association with valvular and peripheral arterial calcifications / atherosclerosis is largely mediated by its association with degenerative aortic stenosis. We therefore concluded that therapeutic strategies should be designed to prevent or slow the course of left ventricular diastolic dysfunction in order to positively influence the cardiovascular and general outcomes of hemodialysis patients.

In another study [published as „Cardiovascular Calcifications Are Correlated with Inflammation in Hemodialysis Patients”. **Dorin Dragoș**, Delia Timofte, Mihai-Teodor Georgescu, Maria-Mirabela Manea, Ileana Adela Vacaroiu, Dorin Ionescu, Andra-Elena Balcangiu-Stroescu. *Medicina (Kaunas)* 2023;59(10):1801. IF 2023: 2,948] we reached the conclusion that, in CKD patients (particularly in those on hemodialysis), the imaging markers of atherosclerosis (valvular and arterial calcifications as detected by ultrasound and radiology) are positively correlated with inflammation markers and risk of death and negatively correlated with nutrition status.

The subsection “Brain-kidney interface” includes the results of a study performed on stroke patients who underwent thrombolysis [„Risk factors for the outcome after thrombolysis in acute ischemic stroke—the prominent role of kidney dysfunction: A retrospective cohort observational study”. **Dorin Dragoș**, Maria Mirabela Manea, Ana-Maria Dobri, Iulia-Cosmina Stoican, Iulia-Ioana Enache, Maria Iuliana Ghenu, Sorin Tuta. *Medicine (Baltimore).* 2023; 102(43): e35688. IF 2022-2023: 1,817] that reached the conclusion that kidney dysfunction is the main determinant of the outcome of thrombolysed stroke patients after exhaustively exploring the relationship between various neurological scores and outcome parameters. To our knowledge, no other study has attempted to explore such a large spectrum of outcome markers in thrombolysed stroke patients, and no other study has clearly highlighted the importance of kidney dysfunction in the outcome of these patients.

This result is bound to have a significant impact on practice: guidelines regarding thrombolysis in acute ischemic stroke patients may need to be altered so that neurologists carefully consider the potential for a poor outcome in stroke patients with renal dysfunction when deciding whether to administer the thrombolytic agent.

The subsection “Brain-heart interface” includes several studies regarding the cardiac consequences of stroke.

One of these studies [„Insular involvement in acute ischemic stroke is associated with increased risk for myocardial injury and in-hospital death”. M. M. Manea, D. Dragoș, I. Olaru, A.M. Dobri, L. Nistorec, C. Popa, S. Tuta. Poster presentation of the 5th Congress of the European Academy of Neurology, Oslo, Norvegia Jun 29-Jul 02, 2019. Abstract în European Journal of Neurology Volume 26, Special Issue Supplement 1, pag 752 EPO3017. IF: 4,516] reached the conclusion that in-hospital death is significantly correlated with high troponin T ($p=0.02$) and CK-MB ($p=0.03$) levels in the fourth day after an insular acute cerebrovascular event, indicating that a high level of myocardial injury markers in an acute ischemic insular stroke is, at least partially, explained by a neurogenic mechanism and is associated with an increased risk of death in the short term.

In another study [„Cardiac Arrhythmias and In-Hospital Mortality in 63 Cases of Ischemic Stroke Involving the Insula”. M.M. Manea, D. Dragos, C. Popa, S. Tuta. Presented at Europe Stroke Organisation Conference May 16, 2018. Abstract în European Stroke Journal 2018;3(1S): 514; IF 2018 = 1,095], we demonstrated that insular involvement was not a risk factor for death, nor were insular lateralization or atrial fibrillation. Although we showed that ST segment depression accompanied insular injury during stroke, we also demonstrated that insular infarction did not predict electrocardiographic anomalies that might have prognostic implications during the in-hospital stay after a stroke.

We have also demonstrated that left ventricular diastolic dysfunction may be a predictor for the occurrence of nonvalvular atrial fibrillation and could serve as a selection criterion for instituting prolonged electrocardiographic monitorization in stroke patients [„Association between echocardiographic diastolic function parameters and future nonvalvular atrial fibrillation in ischemic stroke patients”. M.M. Manea, A.M. Dobri, D. Dragos, C. Popa, S. Tuta. Poster, 5th European Stroke Organisation Conference 2019. Abstract în European Stroke Journal 2019; 4(1S): 150–778, pag. 5169, IF 2019 = 1,169].

While investigating left ventricular systolic dysfunction, we reached the conclusion that its prevalence is similar in ischemic stroke patients and in controls matched for age, sex, and atrial fibrillation prevalence (which is at odds with the conclusions of previous studies), although in the subgroups free of atrial fibrillation the prevalence of left ventricular systolic dysfunction is indeed higher in ischemic stroke patients than in controls [„Is Acute Ischemic Stroke Really Associated with Left Ventricular Systolic Dysfunction? A Case-Control Study”. Mirabela M Manea, **Dorin Dragoș**, Sorin Tuță. Neurology India 2022;70:596-9. doi: 10.4103/0028-3886.344651. IF 2022: 2,117].

The subsection “Kidney-immune system interface” includes a study regarding the influence kidney dysfunction may have on presepsin level in acute sepsis patients [„The cutoff value of presepsin for diagnosing sepsis increases with kidney dysfunction, a cross-sectional observational study”. Dorin Dragoș, Maria Iuliana Ghenu, Delia Timofte, Andra-Elena Balcangiu-Stroescu, Dorin Ionescu, Maria Mirabela Manea. Medicine (Baltimore) 2023; 102(1): e32620; IF 2022-2023: 1,817]. To our knowledge, this is the first study attempting to establish thresholds for significant increases in presepsin level adapted to the various degrees of KD as reflected by the only reliable and readily

available marker in acute/emergency settings, which is serum creatinine. Our conclusion was that the higher the severity of kidney dysfunction, the higher the expected level of presepsin, therefore the higher the cutoff point for significant increase in presepsin.

The subsection “Psychology-medicine interface” is dedicated to a career-long preoccupation with psychosomatic medicine, that started with my doctoral thesis „Phytotherapy as an adjunct in the psychotherapy of ailments with a functional component”, in which I introduced the term “psychocausal” and from which a series of articles derived describing psychological profiles associated with various internal diseases. Subsequently, I initiated an online survey attempting to gather more solid evidence to this respect, which resulted in the publication of several other articles describing the psychological profiles associated with functional digestive disorders and with gallstones disease.

Another career-long preoccupation makes the subject of the subsection “Conventional medicine-phytotherapy interface”, which lead to the publication of several review articles and to some statistical studies demonstrating that phytochemical taste may be more relevant than chemical class for the prediction of the ethnopharmacological activities [„Taste of phytochemicals: a better predictor for ethnopharmacological activities of medicinal plants than the phytochemical class?”. Dragos D, Gilca M. *J Ethnopharmacol.* 2018;220:129-146. IF 2018: 3,414], that the anti-inflammatory and anti-cancer activities of plant-derived compounds are more strongly associated with their taste than with their chemical class, that bitter phytochemicals have a higher probability of exerting anti-inflammatory activity [„Phytochemicals and Inflammation: Is Bitter Better?” Dorin Dragoș, Madalina Petran, Teodora-Cristiana Gradinaru, Marilena Gilca. *Plants (Basel)* 2022;11(21):2991. IF 2022: 4,658] as well as anti-cancer activity, while sweet taste is negatively correlated with both anti-inflammatory and anti-cancer activities, hence the hypothesis that bitter taste receptor agonists and sweet taste receptor antagonists may have a beneficial effect in slowing down the progression of inflammation to cancer [„Relevance of Phytochemical Taste for Anti-Cancer Activity: A Statistical Inquiry”. Teodora-Cristiana Grădinaru, Marilena Gilca, Adelina Vlad, Dorin Dragoș. *International Journal of Molecular Sciences* 2023;24(22):16227. IF 2023: 6,208].

The interest for phytotherapy is reflected also in an experiment on the anti-bacterial effects of essential oils demonstrating that oregano essential oil and thyme essential oil (in this order) have the highest efficacy against *Escherichia coli* and *Klebsiella pneumoniae* clinical strains [„Antibacterial Activity of Clove, Oregano, Thyme, Eucalyptus, and Tea Tree Essential Oils against *Escherichia coli* and *Klebsiella pneumoniae* strains”. Anda Baicus, Flavio Cesare Mattuzzi, Ana Maria Paraschiv, Rares-Sebastian Dinu, Maria Carina Dumitrescu, Andrei Alexandru Marinescu, Dorin Ionescu, Dorin Dragoș. *Revista Română de Medicină de Laborator (Romanian Journal of Laboratory Medicine)* 2022; 30(3): 327 – 338; IF 1,027].

The subsection “Medicine-informatics interface” is about the employment of informatics in helping the advancement of medical knowledge even without performing actual experiments and relies on my knowledge of programming languages to write/ build and manage documents and databases (Visual Basic for Applications), to perform statistical computations (R language for statistical computing and graphics, Python), to build and manage web pages (HTML, PHP, JavaScript). The most ambitious and time-consuming project was an on-line database (<https://plantmoleculartastedb.org/>) including more than 1500 taste active phytochemicals – on this occasion I put to value my ability to assimilate new skills, particularly in the field of information technology, by learning as a self-taught PHP programming language up to the level of being able to

write the software code underpinning this database [„PlantMolecularTasteDB: a database of taste active phytochemicals”. Teodora-Cristiana Gradinaru, Madalina Petran, Dorin Dragos, Marilena Gilca. *Frontiers in Pharmacology* 2021; 12].

Finally, the subsection “Medicine-statistics interface” points out my knowledge in medical statistics, that allowed me to perform myself the statistical calculations starting with my first active participation in a medical congress (the 4th National Congress of Cardiology, Bucharest oct. 1991) while I was a student at the beginning of the 4th year. Ever since, I have continued to perform the statistical calculations for all the papers I have authored. I have also earned by competition two medical statistics projects (Mobility Projects for Researchers): „Intro to Bayesian Statistics” (2018 Competition - PN-III-P1-1.1-MC-2018-2057) and „Big Data in Health research” (2019 competition - PN-III-P1-1.1-MC-2019-1689).

The second part of my habilitation thesis is about my professional training and achievements. My postgraduate training included several courses in clinical pharmacology, phytotherapy, and medical statistics. My professional training also included the participation in interdisciplinary teams in collaboration with the biochemistry, microbiology, and neurology disciplines, as well as initiating and coordinating projects in which younger collaborators (medical students and residents) were involved.

The third part of my habilitation thesis is dedicated to my academic achievements. Since 1995, I have been a member of the academic staff at the Faculty of Medicine of Carol Davila University of Medicine and Pharmacy, Bucharest. My academic achievements include: teaching activities (lectures and practical activities in medical semiology, nephrology, phytotherapy, applied physiology), writing numerous books and book chapters, participation in two students’ congresses in the evaluation and selection of the papers to be presented. The international recognition of my research activity is reflected by number of Web of Science citations per paper (total of 252, 234 without self-citation, an average of 6.81 per article), an H index of 10, the publication of 36 scientific articles included in the ISI Web of Science Core Collection (I have the position of first, corresponding, or last author for 23 among these). I have also published 41 articles in journals indexed in international databases (BDI) and 2 other articles in CNCSIS indexed journals. I have obtained several national and international awards for posters, articles, and published books.

I have performed reviews for 46 journals, most of them ISI indexed journals. I am a member of the editorial board of one BDI indexed international journal, associate editor for two ISI indexed international journals, and guest editor for one BDI indexed journal and one ISI indexed international journal.

I was a member of the organizer committees of three international conferences (New Trends on Sensing-Monitoring-Telediagnosis for Life Sciences – NT SMT-LS 2017, NT SMT-LS 2018, NT SMT-LS 2020). I had the quality of invited speaker in 19 national and international conferences. I was invited many times to speak in radio, television, and health festivals about various medical subjects. I am a member of 4 national and international professional societies.

The fourth part of my habilitation thesis includes the strategies envisaged for my future professional and scientific development and the main research directions. A particular area of my future research will be to continue the studies initiated in recent years that focus on interaction between and interdependence of various fields of medicine (nephrology, cardiology, neurology, gastroenterology, phytotherapy). Among the projects I intend to pursue: an enlargement of the study regarding the influence of kidney dysfunction on the outcome of stroke patients in general and in

particular of those subjected to a thrombolysis procedure, the interdependence of heart failure and kidney dysfunction and its influence on the outcome of the patients presenting in acute settings with the decompensation of both organs, the anterograde and retrograde impact of heart failure on liver function and structure, the cardiac changes in liver diseases including fatty liver and liver cirrhosis, the alteration of liver-biliary function in sepsis. I also intend to perform studies regarding the psychological features of patients with irritable bowel syndrome, as well as of patients with urinary tract infections. In cooperation with colleagues from Biochemistry discipline, I will continue to maintain and extend database with taste active phytochemicals (<https://plantmoleculartastedb.org/>), with the perspective of adding new pharmacodynamic activities (beside anti-inflammatory and anti-cancer; analgesic is next) and investigating their relationship with taste.

I will work towards increasing the number of active young scientists (doctoral and undergraduate students) involved in research projects and for attaining excellence in our professional activities. It is my belief that supporting the creativity of young researchers (doctoral, master, or undergraduate students) and maintaining our collaboration with high expertise colleagues from Romania and abroad is the key towards success, high scientific performance, innovation, and great discoveries.

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