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PSYCHIATRIC BRAIN COLLECTION IN MACEDONIA: GENERAL LESSONS FOR SCIENTIFIC COLLABORATION AMONG COUNTRIES OF DIFFERING WEALTH

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Abstract

Macedonia is a small country, and the current state has been independent for only 22 years. Medical research, which requires an extensive infrastructure, has been limited. We describe our experience in developing Macedonian research through a mutually beneficial collaboration between institutions in Macedonia and the United States.

Keywords

brain collection; international collaboration; Macedonia; USA

The European Union is engaged in major efforts to include countries with “formerly centrally planned economies” in research collaborations. In this Viewpoint, we attempt to draw on our experience to identify strategies for the success of such ventures, and to identify the benefits that may be obtained.

In 1996, we began a collaboration between the Department of Neuroscience (since renamed, “Molecular Imaging and Neuropathology”) at New York State Psychiatric Institute (part of the Department of Psychiatry at Columbia University), and the Institute for Forensic Medicine (part of the School of Medicine, Ss. Cyril & Methodius University) in Skopje, Republic of Macedonia. The subject of this collaboration was the neuropathology of schizophrenia. Autopsy specimens and clinical information were to be collected in Macedonia, and neuropathological studies to be performed in New York. The logic behind

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this collaboration was that Macedonia had a high autopsy rate and a group of well-educated physicians who had state support for their salaries but few additional resources to support research and little experience in obtaining such resources. NYSPI and Columbia University, on the other hand, had abundant resources for brain research, but only a few autopsies of psychiatric cases, performed in scattered locations by busy pathologists with little time to spare for lengthy brain-collection protocols. The eventual goals were: (1) A smoothly-functioning system to collect autopsy specimens and clinical information in an optimal manner for psychiatric research. (2) Development of the research culture in some departments of the School of Medicine in Macedonia to the level that would be expected of an institution in North America or Western Europe.

One of the authors of this article (GR) had come to Columbia to do research in neuropathology, which by chance took place partly in the laboratory of another (AJD), a neuropathologist who saw a need for an ongoing source of psychiatric autopsy brains. The visitor was well acquainted, in Skopje, with the other co-author (AD), Director of the Institute for Forensic Medicine, who saw the need for his Institute and its staff to become seriously engaged in medical research, and the director of the chronic care psychiatric hospital in Skopje, who shared this view. With a $5,000 institutional pilot grant (**Frontier Fund** for Psychiatric Research of the Department of Psychiatry at Columbia University) we visited the School of Medicine in Skopje and gave lectures about our research. A psychiatrist from the chronic care psychiatric hospital in Skopje visited Columbia for three months of training and reliability testing in standardized retrospective psychiatric diagnosis with the modified Diagnostic Evaluation After Death [1]. The Director of the psychiatric hospital instructed his staff to refer autopsies to the Institute for Forensic Medicine in Skopje. Several brains were collected in formalin, and the clinical diagnostic reviews were performed. Further modest funding, obtained the following year from the Fogarty Foundation through the US/Macedonian Joint Fund for Science and Technology, allowed additional travel and small amounts of supplies. Of equal importance, this represented success in an open peer-review process with joint American and Macedonian participation, thereby demonstrating to aspiring Macedonian researchers that promising science could compete successfully with the local academic hierarchy. Furthermore, the Macedonians were well aware of the budget, and they were impressed that all of the funds were used for expenses of the project, in contrast to their previous impressions that foreign funds went mostly to the foreign investigators, with small payoffs to Macedonian directors. With these funds, several more Macedonian psychiatrists were trained in New York and in Skopje in the Modified Diagnostic Evaluation After Death (mDEAD) and in psychological autopsy interviews [2], and the scope of the project was expanded to include suicide and mood disorders. The Macedonian pathologists were taught how to collect frozen specimens, and several visited Columbia to observe how the specimens were being used. Two Macedonian psychiatrists visited for several months to help develop a new chart review instrument [3]. A Macedonian psychiatrist and pathologist who had visited in this process were hired to work on an ongoing project at Columbia. (Both subsequently received independent grants at Columbia.) Eventually, in 2002, funding was received from the National Institute for Mental Health (NIMH) to fund the collaboration on both continents so that it could supply material for several research studies at the School of Medicine in Skopje, Columbia and other

institutions. This finally allowed us to begin payments for the time of the psychiatrists and pathologists who were working in Macedonia. That one could be supported through competitive research was an important realization in a country with inadequate salaries and high unemployment, even among physicians.

Shortly after we received NIMH funding for the collaboration, several other Macedonian directors offered to join our project if their institutes could be paid, a common attitude among directors emerging from centrally planned economies. They were surprised to learn that all of our funds were already committed to the existing participants, and that we could only help them to apply for funding after they had produced results that would form the basis of such an application. This was a paradigm shift in a country where experts and directors had previously received foreign funds for the promise of reversing their country's lack of progress. Instead of being rewarded for backwardness, they were now being told that they would have to prove that they could deliver, like the rest of the world, and that we believed that they were capable of doing this. The EU has adopted the same attitude, and now expects Macedonian scientists to apply competitively for the same grants as other European scientists. This is to the benefit of Macedonian science, since the Macedonian government sees that the only way to recoup its contribution to EU research funds is through scientific excellence. The Ministry of Science has become very encouraging of our projects.

The collaboration now collects approximately 25–75 brains per year, with a median post mortem interval of 13 hours. Sliced tissue is frozen in 1,1,1,2-tetrafluoroethane (R-134a). Other slices are fixed for 5 days in formalin and then transferred to buffer to preserve immunoreactivity. With immediate access to fresh tissue, we have been able to develop a new procedure for Golgi staining of neurons, with uniformity and reliability unprecedented in human specimens. The majority of psychological autopsies are completed within days of death. The tissue and clinical data have been used in 39 funded research projects in the US, Canada and Macedonia.

To establish an international scientific resource, we had first to overcome a sense of colonialism. The Macedonian participants felt that they were supporting our research, rather than developping their own. However, by visiting Columbia, they came to understand that they did not yet have the infrastructure or expertise to employ contemporary research procedures in Macedonia. During their visits, they also identified certain procedures, such as immunohistochemistry, that they could bring back to Macedonia and begin to use. The collaboration also expanded their access to the scientific literature and to consultation with recognized experts, which provided tangible benefits as well as alleviating a sense of isolation.

We also fought the colonial characterization with publicity. We took pains to meet with journalists and government officials, including the first two presidents of Macedonia, to explain the scientific importance of the project and our hopes that it would help build Macedonian research. We brought the head of our department to Macedonia, where he lectured at the Academy of Sciences and Arts, met with academic and government leaders, and admired the scenery. We never requested financial contributions from Macedonian

sources, and we always made it clear that we appreciated the value of the Macedonian labour and facilities that were available to the project.

The second problem that we encountered was the absence of an institutional tradition of research and collaboration. The forensic pathologists were reluctant to share information with the psychiatrists, whom they considered outsiders, so psychological autopsies were missed on many of the early cases. This difficulty was overcome only slowly. We repeatedly explained the need for cooperation, and that the tissue was useless without clinical information. Over several years, our insistence took root, while the forensic pathologists also developed personal relationships with the psychiatrists that facilitated communication. Although the School of Medicine had an ethics committee, there was no requirement of advance approval of research protocols, so there was a natural reluctance to submit proposals for review. We had to insist on its necessity and to explain its value as protection against spurious charges of impropriety (which are not uncommon in the Macedonian press). When it became appropriate, the ethics committees in the School of Medicine and the Macedonian Academy of Sciences and Arts were registered with the US Office of Human Research Protection, and all participating institutions filed Federalwide Assurances.

Administrative problems in Macedonia might have been insurmountable without the personal attention of one of the authors (GR) during visits to Macedonia. The greatest difficulty was to obtain permission to take the tissue out of Macedonia (by contrast, permission to bring it into the US was obtained with a single request to the Centers for Disease Control). Although the specimens were taken as checked baggage on commercial flights, it was necessary, in addition to obtaining permits from the Ministry of Health, to employ an expediter who would accompany the traveling researcher to the airport and formally export the tissue.

One advantage that we gain from working in Macedonia is the time and enthusiasm that our collaborators bring to the work. Another is a relative absence of “red tape”: frivolous lawsuits are nearly impossible, and privacy protections, while required, are less burdensome than in countries that can afford more regulation. In return, we have introduced our Macedonian colleagues to current standards for scientific conduct, including rigorous IRB protocols and grant administration. We have impressed them with the extensive commitments of time and resources that are needed for biomedical research, and with the intense alliance that can result from scientific collaboration. The material has engendered joint publications originating in both countries, and Macedonia has become increasingly integrated into the mainstream of neuroscience research. Aside from grants supporting the collection of brains, the Fogarty Foundation and NIMH have funded two grants for neurobiological research in Macedonia, establishing facilities for electron microscopy, stereology, and proteomics that we hope to develop into international resources The Macedonian government has recognized the importance to the country of scientific research, and in the past three years has spent tens of millions of euros on scientific equipment.

Similar programmes could be established in other Balkan countries. Bulgaria, Albania, Serbia, and Croatia present many of the same advantages as Macedonia. With the benefit of our Macedonian experience, there are certain things that we would do differently:

1. Intensify early, on-site training and supervision in laboratory procedures.
2. Make an early investment in equipment so that portions of the research can be conducted locally.
3. The local principal investigator should not be the director of the collaborating institution, but rather a senior member of that institution, who is free to advocate for the project.
4. It is very important to maintain independent contacts with all of the participating institutions, in order to avoid establishing or reinforcing a local hierarchy in which inter-institutional jealousies inhibit cooperation.

When institutions from developed and less developed countries collaborate, there is a danger of falling into stereotyped roles that inhibit productivity, with each side complaining about the other. Any successful collaboration has to be seen as valuable by all of the participants. Through a frank exchange of ideas, each participant will realize that the others value what he or she gives, and each participant understands the value of what is received.

A decade ago, a member of the Macedonian Academy of Sciences asked what should be done to improve the School of Medicine. When told that all the faculty should be required to be first author on at least two peer-reviewed research papers in international journals, the academician, with a very respectable publication record of his own, replied that, unfortunately, this was unrealistic. This has already changed. Since we started collaborating, and mainly in the last two years, the junior faculty of the Institute for Forensic Medicine, independent of their work with us, has produced five peer-reviewed research reports [4–8] and two peer-reviewed case reports [9–10] in international journals.

LITERATURE

1. Keilp JG, Waniek C, Goldman RG, Zemishlany Z, Alexander GE, Gibbon M, Wu A, Susser E, Prohovnik I. Reliability of post-mortem chart diagnoses of schizophrenia and dementia. Schizophrenia Research. 1995; 17:221–228. [PubMed: 8562497]
2. Kelly TM, Mann JJ. Validity of DSM-III-R diagnosis by psychological autopsy: a comparison with clinician ante-mortem diagnosis. Acta Psychiatrica Scandinavica. 1996; 94:337–343. [PubMed: 9124080]
3. Ortakov V, Mancevski B, Keilp J, Oppenheim S, Dwork AJ. Application of cognitive scales to medical records of schizophrenia inpatients. Schizophrenia Research. 1999; 35:131–140. [PubMed: 9988850]
4. Jakovski Z, Nikolova K, Furac I, Masic M, Janeska B, Kubat M. Allele frequencies for 15 STR loci in a population from the Republic of Macedonia. Int J Legal Med. 2006; 120:53–55. [PubMed: 16088410]
5. Jakovski Z, Nikolova K, Jankova-Ajanovska R, Marjanovic D, Pojskic N, Janeska B. Genetic data for 17 Y-chromosomal STR loci in Macedonians in the Republic of Macedonia. Forensic Sci Int Genet. 2011; 5:e108–111. [PubMed: 21549657]
6. Jakovski Z, Nikolova K, Jankova-Ajanovska R, Janeska B, Pojskic N, Marjanovic D. Allele frequencies of the new European Standard Set (ESS) loci plus SE33 locus in a population from the Republic of Macedonia. Forensic Sci Int Genet. 2012; 6:e90–92. [PubMed: 21802383]
7. Davceva N, Janevska V, Ilievski B, Spasevska L, Popeska Z. Dilemmas concerning the diffuse axonal injury as a clinicopathological entity in forensic medical practice. J Forensic Leg Med. 2012; 19:413–418. [PubMed: 22920765]

8. Davceva N, Janevska V, Ilievski B, Petrushevska G, Popeska Z. The occurrence of acute subdural haematoma and diffuse axonal injury as two typical acceleration injuries. J Forensic Leg Med. 2012; 19:480–484. [PubMed: 23084313]
9. Jakovski Z, Jankova R, Nikolova K, Spasevska L, Jovanovic R, Janeska B. Forensic DNA expertise of incest in early period of pregnancy. J Forensic Leg Med. 2011; 18:34–37. [PubMed: 21216379]
10. Stankov A, Jakovski Z, Pavlovski G, Muric N, Dwork AJ, Cakar Z. Air gun injury with deadly after-math-case report. Leg Med (Tokyo). 2013; 15:35–37. [PubMed: 23017978]