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Title: Plato's Cave: shadows or reality? What are future diagnostic targets for human rabies?

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Abstract: Early laboratory diagnostic of rabies is a critical component of not only patient's prognosis and choices about possible therapeutic interventions but also about decisions regarding risk assessment and prophylaxis of contacts. Since Zinke's demonstration of transmission of rabies through saliva in 1804 and Negri's discovery of eosinophilic inclusion bodies in 1903, rabies laboratory diagnostics have focused on the detection of either rabies virus and its antigen (DFA, MIT), antibodies (RFFIT, IFA, FAVN) and later also on its RNA (PCR) as primary diagnostic targets. However, given unique pathobiology of solely neuronal spread of rabies virus and its ability to initially avoid the immune system, these markers cannot be detected earlier than few days before disease symptoms onset. Two major questions raising from differences between medicine and individual patient care and public health and population preventive care influence current directions in rabies laboratory diagnostics. On one hand, modern rapid high-through output technologies are being developed to detect single viral particle or its nucleic acids. On the other hand, simple, low tech, field suitable laboratory methods with high specificity and sensitivity are critically needed to be implemented in canine rabies-endemic countries in decentralized fashion to promote rapid laboratory based PEP decision-making process. Second, largely neglected issue, is the identification and selection of proper diagnostic targets to confirm rabies infection in the incubation and in early morbidity periods. Since antigen and RNAs, most often used markers, are currently not detectable during incubation period, their detection during morbidity period only confirms clinical diagnosis in a patient presenting with symptomatic encephalitis. What is the future of human rabies laboratory diagnostics? What progress was made in past 40 years? Should we continue to enhance techniques to detect real culprit (viral components) or should we focus more on earlier detectable traces of virus presence (sets of small-molecule metabolites or single nanoparticles i.e. shadows)? Past and current rabies laboratory diagnostic techniques for rabies will be reviewed herein and potential novel approaches, their benefits and disadvantages as well as applications will be discussed in an interactive format.