

**Stroke in the Computer or Pie in the Sky: The Need for Advanced  
Computing and Information Technology in the Search for the Effective  
Treatment of Brain Disorders**

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*“A Nintendo for doctors”*

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**What’s New – if ?...**

A perfunctory literature search using MEDLINE reveals that, between the years 1990 and 2000, cerebral ischemia was the subject of 2237 full review papers, and brain injury was addressed by 1651. There were 292 reviews of neuroprotection. Interestingly, the concluding remarks of almost all abstracts (typically indicating the author’s own vision for the future) show distress rather than optimism. The statements that the future studies *must* (Doppenberg et al., 1997), or *should* (Doppenberg and Bullock, 1997), be *desirable* (Lee et al., 1999), and *will focus on* (Vannicci et al., 1999), or *will foster* (Maiese, 1998), the discovery of the definitive treatment, the pursuit of which is *incumbent on scientists* (Fisher and Takano, 1995) are supported by the exclamations of *the search continues* (Dobkin, 1997) and the decisive statements that *developments ... continue to reinforce the need* (Koroshetz and Moskowitz, 1996). All that clearly shows one thing: despite all the progress, the Golden Fleece — the definitive treatment of stroke and traumatic brain injury — eludes us as much today as it did ten years ago.

There is absolutely no doubt that a number of clear pathways involved in the damaging processes elicited by the arrest of cerebral circulation or mechanical injury to the brain emerged from the intensive research conducted during the last 20 years. There is an agreement on excitotoxic damage (Nava-Ocampo et al., 2000; Myseros and Bullock, 1995; Hovda et al., 1995). Few doubt that the massive accumulation of  $\text{Ca}^{2+}$  within neuronal cytoplasm plays a critical triggering role (Hossman, 1999; Lipton, 1999; Lee et al., 1999; Pashen and Doutheil, 1999) inducing a series of cascading events that affect multiple systems. Involvement of altered protein synthesis, arachidonic acid cascades (Lipton, 1999), free radical cascades (Schubert et al., 2000); the release of and the damage caused by the inflammatory mediators (Stanimirovic and Satoh, 2000; Stoll et al., 1998) are also critically involved. An increasing number of publications describe the significant role of the genetical foundations of neurons in glia in the processes involved in both death and recovery (Liu, 2001; Martin, 2001, Sun and Cheng, 1999). The list of the damaging factors is already very substantial; and while some of the involved processes are well defined, others are still not understood. Despite the massive amount of information at our hands, the effective clinical treatment of stroke and brain injury in human patients needs yet to be found.

There is no doubt that the inadequacies of the animal models of human cerebral ischemia and brain injury may have an adverse impact on the degree of success in the discovery of clinically useful forms of treatment of stroke, brain injury, and many other cerebral pathologies. Unquestionably, a lot still remains to be learned. On the other hand, it is equally likely that the sufficient information required for the definitive characterization of

the most promising therapeutic strategies is already at hand. It is not the amount of additional knowledge that we still need in order to reach the conclusive therapeutic end; rather, it is sorting and organizing the already existing data that must be attempted. There is a likelihood that the sheer volume of the available data is simply too much for individual scientists or groups to deal with. The existing data are too fragmented, and the relationships among individual elements of the “great puzzle” too obscure for clear identification. In short, the problem facing all aspects of neurosciences, both basic and clinical, is not that of inadequate knowledge but that of *Datapocalypse* (Davis, 1998), where too much is as dangerous as too little.

The amount of biomedical data available to the medical community is in a rapid exponential growth (Beeman et al., 1997). Between 1980 and 1990, cerebral ischemia appeared on the list of key words in 9695 papers. However, between 1990 and 2000, a very conservative estimate showed well over 16,000 papers with ischemia as either the main topic or subtopic. Clearly, the problem of systematic data cataloging, assignment, rejection of duplicates — and of the final integration into a coherent picture of violent and destructive events that start from a rather trivial wedging of a blood clot in one of the cerebral arteries — represents a magnificent challenge. Data mining combined with advanced modeling and simulation are probably the only approaches that offer a feasible chance of constructing a dynamic and true picture of brain and other pathologies (ubitz, 2001a).

## **Models: All Good for Science, None for the Clinic...**

According to the *Concise Oxford Dictionary of English* (1982), a *model* is a “representation in three dimensions of existing or proposed structure, etc. esp. on a smaller scale (working model); simplified description of system etc. to assist calculations and predictions.” *Webster’s New Riverside University Dictionary of English* (1988) expands the concept and adds “**2.** A preliminary pattern serving as the plan from which an item not yet constructed will be produced. **3.** A tentative description of a theory or system that accounts for all of its known properties.

Seen in their most restrictive context, none of these definitions fit what is collectively described in the literature as *models* of the wide range of brain injury forms encountered in the clinical setting. None of the current models work on a smaller scale because pathologies of the rat and the human appear to be very similar, and our understanding of either may be quite muddled at times. Neither is there any noticeable simplicity in the processes that accompany ligation of the middle cerebral artery in a rat or mouse as opposed to its obstruction by a thrombus in humans. A cell exposed to anoxic conditions in a cell culture can hardly be viewed as a *plan* for the reconstruction of the processes involved in traumatic brain injury. And despite the massive accumulation of new data, we are still very far from a “tentative description that accounts for all known properties” of most (if not all) forms of brain pathology.

Considering these limitations, it becomes apparent that the linguistic definitions of a model will apply only when used in the strict context of the human brain and its pathologies that physicians confront following a major car accident or a cerebrovascular incident. It is also in this context that the debate on the utility of the currently used models of brain injury is conducted.

While the “validity of rodent brain-ischemia models is self-evident” (Ginsberg, 1996), and many experimental therapies are quite effective, there is practically no demonstrable effect of these studies on clinical outcomes (Lanier, 1999; DeKayser et al., 1999; Pinard et al., 1999). Moreover, the art of modeling pathological processes in the brain has not progressed much during the past ten years. The excellent review of Ginsberg and Busto published in 1989 was as good and valid then as the more recent ones (Ginsberg, 1996; Cenci et al., 2002). What changed dramatically is not the nature of the models but the range of the analytical tools and techniques that now assist in the discovery, analysis, and understanding of the processes evoked by our modeling efforts. Until quite recently, the existence of many of these processes was entirely unsuspected (e.g., Pantoni 2002; Phan et al., 2002; Sharp et al., 2002).

The currently used tools in stroke/brain injury research are based on cell and cell culture methods, isolated tissue (e.g., brain slices), and surgical/pharmacological manipulation of animals intended to produce conditions similar to those observed clinically. As with all experimental approaches to human disease, methods used in the studies of stroke and

brain injury have demonstrable limitations (Choi, 1990; Hunter et al., 1995; DeGraba and Pettigrew, 2000).

Studies of single cells and cell cultures were essential for the current understanding of the molecular basis of the processes that characterize cerebral disorders. Dramatic progress in the development of available techniques (Unsicker, 1982; O'Reilly et al., 1992; Wood, 1992; Gould, 1994; Cohen and Wilkin, 1995; Jiang Gu, 1995; Maines, 1996; Xenbase: 2000 NIH Report) resulted in the explosive growth of the available data concerning practically every aspect of neuron and glia function. In addition, the data derived from the studies using non-neural/glia cells offer additional insights since many of the intracellular processes in these cells are indistinguishable from those found in either neurons or glia.

Brain tissue slices constitute an equally important and useful tool in the studies of electrophysiological events (Rabinovici et al., 2000; Artemenko et al., 2000; Tokunaga et al., 1998; Shinno et al., 1997) and neurochemical events (DeAlba et al., 1999; Siniscalchi et al., 1999; Calo et al., 1997) that accompany brain ischemia (Moro et al., 2000; Arriba et al., 1999; Newman, 1998). Coronal slices through the regions containing the hippocampus are particularly popular in those experiments because the characteristic and easily discernible structures of the brain in this area allow very precise placement of the electrodes, punching tools, etc. The convenience of the slice preparation is offset by its short lifespan, rapidly developing hypoxia within the central mass of the slice, and the absence of circulatory phenomena. It is therefore difficult to predict with absolute

certainty whether the observed results are normal, a combination of normal and artefactual, or purely artefactual. Thus, while slices represent a comparatively simple tool capable of generating very important data, the results of experiments on neuroprotection obtained in the brain slice preparation may require further validation in animal models. The latter difficulty is bypassed, at least in part, through the use of *ex-vivo* slices, where ischemia and its treatment are induced and initiated in the intact animal. Typically, the brain is removed and sliced following restoration of the blood flow (Artemenko et al., 2000; De Alba et al., 1999; Schurr et al., 1995).

Induction of traumatic brain injury or different forms of cerebral ischemia in animals is by far the most common method of modeling these disorders in humans (Feuerstein and Wang, 2000; Laurer and McIntosh, 1999; Adelson, 1999; Painter, 1995; Ohnishi and Ohnishi, 1995). Many different species have been used in these experiments (Hossman, 1998); but rodent models (rat, mouse, gerbil) are preferable for a variety of technical, economical, and, recently, ethical reasons (Ginsberg, 2000). A wide variety of techniques is used to induce brain ischemia, with the approaches as simple as strangulation (Siemkowicz and Hansen, 1978) or decapitation (Abe et al., 1983) in global ischemia, and as complex as permanent occlusion of the middle cerebral artery (MCAO; Tamura et al., 1981). In order to model the conditions of human stroke with greater accuracy, models of transient MCAO using intraluminal filament, microclips, or potent vasoconstrictors have been subsequently introduced (Mhairi and Macrae, 1992). Transgenic and knockout mice represent the latest and probably the most exciting advent in modeling human brain injury and stroke (Hara, 1999; Chan et al., 1995). Genetically

altered animals allow direct investigation of specific mechanisms whose involvement in the generation of brain damage was postulated on the basis of less direct studies using cell-, tissue-, and the classical animal-based models. The ability to modify expression of specific proteins (Hata et al., 1999; Sheng et al., 1999; Takagi et al., 1999; Weisbrodt-Lefkowitz et al., 1988; Kondo et al., 1997; Hara et al., 1997; Friedlander et al., 1997; Kondo et al., 1996; Bruce et al., 1996) allows determination of their importance in the overall process of pathological changes and serves, at the same time, as a highly specific pointer at the future targets for therapeutic interventions.

### **Enter Computers. Do THEY Make Sense?**

Rapid progress in computational and visualization technologies resulted in the explosion of modeling and simulation in virtually every walk of life. Surprisingly, despite highly promising results of the initial work, simulation and modeling of the brain has not gained the popularity one might assume it would deserve (Raggia et al., 1997; Lansner and Liljenstrom, 1994). Several reasons may explain the reluctance in accepting the heady blend of very advanced computing, simulation, visualization, and information technologies in the studies of stroke and brain injury. The most prominent of these is also the simplest: the level of the required knowledge is seemingly daunting, resulting in a widespread belief that the modeling techniques required for such studies vastly exceed the average technical sophistication of many active biomedical investigators. While this is not necessarily true, the persistent *communication gap* that still separates computer and medical scientists unquestionably prevents a meaningful exchange of ideas and cross-

insemination (Bower and Koch, 1992). Furthermore, the underlying doubts within the biomedical community that meaningful simulation-based models of systems as complex as the brain can be ever attained (Beeman et al., 1997) add to the reluctance with which computer-based simulation finds acceptance. Finally, and — in objective terms — most importantly, the costs of simulation using the most widely accepted object-based approach may be very high, and the equipment needs exceed the capacity of the majority of biomedical research centers (Howell et al., 1999; Eichler West et al., 1999). Even at the laboratories equipped with the necessary hardware, the practical execution of a simulation session may require very creative approaches in order to provide the necessary materiel support (Eichler West et al., 1999).

The subjective and objective difficulties notwithstanding, substantial results have been already obtained in simulation/modeling of cytotoxic and vascular events in ischemia (Kocher et al., 2000), pathogenic mechanisms in stroke (Ruppin et al., 1999; Goodall et al., 1997), calcium-related physiology (Coomber, 1998; Kim et al., 1998), blood flow dynamics (Piechnik et al., 1998), and spreading depression in focal ischemia (Revett et al., 1998). Very importantly, computational models of cognitive deficits following brain damage that are currently developed (Mayall, 1998; Christensen et al., 1998) and will provide a natural extension of the model-based studies of cerebral pathology. The creation of the GENESIS simulator-based database (part of the Human Brain Project; Beeman et al., 1997) and several other neural simulation programs (De Schutter, 1993) indicates that the field of simulation rapidly gains strength as an important research tool.

## **Medical Nintendo or the Birth of a Sledgehammer?**

Despite massive international scientific effort supported by equally massive expenditure of resources amounting to billions of dollars in research funds, the therapy that will effectively ameliorate the consequences of brain injury simply does not exist. Regrettably, practically all agents that were promising at the experimental stage failed when tested in the clinical environment. The only clinically viable treatment with rTPA agents (recombinant Transgenic Plasminogen Activator) is highly restrictive and produces only moderate results.

While the tempo of the intensity of current research devoted to brain pathology increases, the resulting data base expands even more rapidly. Consequently, it is progressively more and more difficult to perform an effective process of data reduction converting a sea of widely dispersed findings into a coherent, dynamic, and representative entity useful in the development of meaningful clinical therapies.

The inherent complexities of the involved processes and their ill-defined spatial and temporal relations make the process of conventional analysis of brain injury an essentially impossible task. Processing limitations of the human brain result in all such analyses being exceedingly simplistic and uni- or at best two-dimensional. The “computing power” of the human brain, as significant as it is, is insufficient to grasp and analyze the multidimensional reality of all systemic interactions that take place as parallel or near-parallel processes — characterized in turn by complex networks of individual and

often multilayered interdependencies of function, time, space, and pathology. For this reason, innovative uses of high-level simulation and modeling permit systematic reorganization of the currently chaotic knowledge database — opening a path out of the current maze of often disjointed facts, whose mere presence increases the complexity of the maze.

The few already existing studies (Ruppín and Reggio, 2001; Ruppín et al., 1999; Hudetz et al., 1993) clearly demonstrate that simulation and modeling of the brain based on advanced computational methods may represent the most direct form of approximating the real nature of the pathological processes in the brain. There is no doubt that these studies represent the very modest beginnings. Equally, there is no doubt that the continuous integration of new data emerging from laboratories worldwide is essential for the ongoing process of refining and improving the model and transforming it — similar to the models in chemistry and physics — into a powerful and flexible tool assisting in the understanding of the pathology of cerebral diseases, their pharmacological treatment, and clinical management (von Lubitz et al., 2000a)

### **How? The Agent and a Federation of Agents**

Formal models of complex physiological and metabolic processes are conventionally modeled using coupled differential equations (Bauer, 1978; Ghista, 1971; Hyndman, 1987; Mojtahedzadeh, 1992; Fell, 1997; Cardiovascular System Dynamics Society, 2000). While this approach is appropriate for monolithic systems, it has serious

shortcomings for systems with many interacting components such as the brain. In the latter systems, the monolithic models quickly become cumbersome to construct, debug, and maintain. Furthermore, small differences in parameter values in different components of a system (represented by a single “lumped” parameter in a monolithic model) may lead to divergent trajectories of system components due to the nonlinearity of the underlying dynamics.

Current approaches to brain modeling are based either on the concepts of linear relations resulting in very inaccurate *toy* models used in high school education (van der Valk, 1997) or, similar to other organs and their functions, on object-based programming that may be suitable for modeling complex systems that are adequately described by differential equations. The best example of such an approach that uses brain constituent as a subject is a very functional model of the Purkinje cell (West et al., 1999). However, as indicated in the preceding paragraph, in ultracomplex systems such as the brain, the variation in a number of *lumped constants* (of which Sokoloff’s lumped constant in cerebral blood flow equations is probably among the best known) may result in the ever-increasing deviation of the model from reality. Naturally, oscillations of this type will render the entire model completely useless as a mirror and a predictor of the behavior of its living counterpart.

Agent-based modeling (ABM) represents a new and powerful alternative to object-based modeling, where each entity in the system is represented by a separate computational process. Importantly, there is now a substantial amount of experience in practical

implementation of either class of models that led to a deep understanding of the relative strengths and weaknesses of these alternative modeling methods (Parunak, 1998; Parunak et al., 1998.) Although agent-based modeling has not been tested in the context of medical applications, its advent represents one of the most exciting avenues for simulation and modeling of complex biological systems under both normal and pathologically altered conditions.

The slightly cryptical notion of a *software agent* is, essentially, quite simple and represents a software component that extends the classic notion of a software object. In practical terms, while an object includes code and persistent state information (what it is and what it does), it also must be invoked externally in order to execute (in a biological system, only a highly specific and unique external event will set it into action). An agent, on the other hand, has not only the code and the persistent state but also its own thread of control and initiative. It actively monitors its environment and autonomously takes action based on its observations. Thus, agents represent the natural model for many naturally occurring systems (in the present context entities such as receptors, blood vessels, event cascades, etc.), and are increasingly used to implement engineered systems as well (Parunak, 1997)

In general, agent-based models have been hitherto applied to discrete systems; but these methods have been extended to modeling the behavior of continuous space (Parunak, 2000) — an approach with some formal similarities to finite-element modeling (Cook, 1981). The Swarm agent simulation system (Burkhardt, 1994; Langton, 1997) has proven

to be the most effective platform for the construction and execution of agent-based models with large numbers of relatively simple agents. As such, it appears to be one of the most suitable conceptual approaches to modeling medically relevant systems as well. At higher levels of simulation and modeling, one may envision agent federations. Each federate may represent a much larger entity capable of interaction with other federates, or it may exist as an individual and independent entity consisting of its own interacting agent (e.g., stroke patient and the treating physician, stroke patient and the medical treatment unit, etc.) The possibilities are quite endless, and the depth of simulation analysis offered by such systems is unprecedented.

In agent-based modeling, each agent is represented by its own independent computational element. Each element is endowed with a *will* — i.e., the ability to sample the environment and respond to it in an appropriate manner. Most importantly, there is no scale to the agent: a receptor subunit may be an agent as much as a treating physician. Thus, a very large number of agents can represent a multidimensional system in which spatial and temporal determinants play as important a role as the functional characteristics of the involved elements as, for example, in the penumbra zone of a focally injured brain.

Agent-based modeling offers the additional advantage of integrating the computational model of physiology with the already visual rendition of the modeled processes, either in a fully immersive (CAVE) or semi-immersive virtual reality system (e.g., ImmersaDesk systems; von Lubitz et al., 2000b, Beier et al., 2001.) Consequently, the combination of

the two currently separate techniques permits creation of highly flexible and interactive environments essential for experimentation, testing hypotheses, etc. In practical use, agent-based models that control and operate visual interfaces — the latter capable of responding to interactive manipulation — represent a substantial leap forward in the ability of an investigator to observe and manipulate a very large number of processes taking place within the brain (von Lubitz et al., 2000a.) The new level of manipulation that such a model would offer (e.g., deactivation or activation of metabolic pathways, activating receptors or enzymes, etc.) permits direct observation of the cumulative effect of these interactions and represents a highly efficient means for extremely rapid and convenient hypothesis testing. Unquestionably, the model would not obviate the need for animal testing. Nonetheless, the computer-based approach would offer a route that is more direct and, ultimately, much cheaper. Highly preliminary work in which “simple” simulation tools (METI Human Patient Simulator with differential equation-based pharmacology and physiology modeling) were used to predict the level of adenosine infusion needed by a post-stroke patient in order to maintain neuroprotective level without adenosine-mediated side effects (von Lubitz et al., 2001b) indicated the potential for saving \$ 250,000 in direct costs and approximately 12 months’ reduction in laboratory time compared to a similar study performed using classical investigational techniques.

### **Can it be Done?**

The concept of computer-based modeling of brain pathology appears as far-fetched science fiction. Yet, the first steps in computer-based modeling of pathological processes

have been made by Entelos, Inc. (Menlo Park, CA., [www.entelos.com](http://www.entelos.com)), who developed and commercialized highly efficient models of diabetes, rheumatoid arthritis, and obesity that were used in developing predictions in clinical trials of drugs against asthma, refuting existing hypotheses, etc. Theoretical development of an agent/VR/Human Patient Simulator-based model of burns has been conducted by a group of investigators from the University of Michigan and ERIM (Ann Arbor, MI) as a part of the IMERSME concept (Interactive Medical Education/Research Simulation and Modeling Environment/ Virtual Interactive Burns Environment) (von Lubitz et al., 2001a; Beier et al., 2001).

The important attribute of IMERSME and VIBE (von Lubitz et al., 2001a; Beier et al., 2001) is their compatibility with the Web-based E-world, i.e., as the public domain Web-based tools available to any investigator anywhere on the globe. Finally, the inherent plasticity of agent-based modeling allows fusion of the agent-based models with the already existing Human Patient Simulator technology and their integration with virtual environments. In the latter context, the “model suite” may be employed in training of clinical personnel giving them direct, visual insight into the nature of the pathological phenomena in the brain (or elsewhere), the proposed pharmaceutical treatment they may affect, how will they be affected, indicate possible pitfalls, and help in the execution of management patterns.

Contrary to the current approach proposed by the Virtual Human Initiative ([www.ornl.gov](http://www.ornl.gov)) based on the molecule-to-organism concept that requires massive

technical and financial resources to succeed, both Entleos Inc. and the UoM/ERIM groups base their solutions on the concept of reverse engineering (called by Entelos a *top-down* approach.) The latter method is based on the long-established engineering tradition of building a functional device by dismantling another — whose function is known — into increasingly smaller components and defining their role in the overall function of the complete unit. The determination of the importance of the unknown components is made vastly simpler by the virtue of the fact that the components with a known function predict that of the unknown. The entire process is similar to assembling a jigsaw puzzle in which the nature of the ultimate object is already known and a number of pieces are already in place, facilitating the correct placement of others. The latter predict the placement of new pieces, and the reconstruction of the ultimate object becomes both easier and significantly faster than a *de novo* construction. Probably the most celebrated event in the history of reverse engineering is the construction of the Russian TU-4 (Bull) bomber which, with the exception of engines, is an exact copy of the U.S. B-29 airplane. The development of the American machine took several years. The Russian aircraft started its test flights in just two years! Today, with the support of computing technologies, the involved process of reverse engineering the airplane would be reduced to significantly less. A recent article (Khachaturian, 2002) proposes the same approach in building models of Alzheimer's disease and suggests their subsequent use in the process of discovery of drugs aimed at the treatment of this disease.

## **Should it be done — and if so, how?**

The complexities of the suggested modeling effort cannot be underestimated. Neither can its scientific and, ultimately, economic importance. Stroke is one of the leading causes of morbidity and mortality and is associated with an enormous economic burden. The *economy of stroke* is encumbered even further by the rapidly rising costs of new drug development. Finally, increasing restrictions on the experimental use of animals, already felt in Europe, will undoubtedly affect the U.S. as well. The combined effects of the last two factors may have a catastrophic impact on the effective development of new drugs and the cost of treatment. Hence, simulation and modeling will become the only viable alternative. Yet, in order for the alternative not to become extremely expensive when it is developed as a *last-ditch defense* against the inevitable, the initial steps must be made as soon as possible. Consequently, it is imperative that at least a few initial modeling centers be created and adequately funded. The centers, together with the rest of the stroke/brain injury community, will face the following challenges:

- Using the existing body of knowledge to develop a functional Web-embedded, agent-based (or even more advanced) model of brain pathology that is both scalable and upgradable and capable of incorporating future data from all existing (i.e., molecular/cell/organ/animal) and future (e.g., nanobot, Drexler, 1992) testing platforms, with access based on flexible and scalable protocols (e.g., SIP) .

- To develop data transfer and storage standards (similar to DoD's HLA standard) permitting all investigators to interact with the model, test their experimental data, test their hypotheses, fit new data into the existing model, and allow interaction of the brain pathology model with the Virtual Human Initiative ([www.onrl.gov](http://www.onrl.gov)).
- To develop principles of model- and simulation-based, rapid, rational development of new drugs and other forms of therapeutic interventions.
- To develop sophisticated virtual reality visualization/interaction systems permitting intuitive interaction with the agent-based model, and allowing execution of experiments in the synthetic environment in basic and applied (treatment) aspects of stroke/brain injury. The model should also allow training of scientists, physicians, and subordinate medical personnel (e.g., nurses, paramedics) in the relevant aspects of these disorders.

In summary, effective utilization of advanced computational methods, virtual reality, and information technology has the potential of drastically changing the process of scientific discovery. Consequent improvement in the understanding of the exceedingly complex cerebral pathology will also reduce the lengthy process of discovery and testing of the clinically effective drugs. Many of the time-consuming test stages currently conducted either as elaborate animal or clinical trials will be done using synthetic models, decreasing the bench-to-bottle interval. The ultimate consequence will be the reduction

of mortality and morbidity associated with brain injury and the reduced cost of their treatment. and subsequent rehabilitation.

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