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Ethical Guidelines for rTMS Research

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Repetitive transcranial magnetic stimulation (rTMS) uses high frequency magnetic pulses to deliver electrical energy across the scalp and skull, permitting stimulation of the brain through the intact skull. In addition to being a valuable tool for basic research in neurophysiology, rTMS has promising therapeutic uses for the treatment of such conditions as depression, obsessive compulsive disorder, and epilepsy. However, the occurrence of seizures in some normal volunteers during rTMS has raised ethical and safety questions about this research.

In June 1996 an international conference was held in Bethesda, Maryland, to consider safety issues in the conduct of research involving the use of rTMS. What follows is an overview of rTMS research, a report of issues raised at this conference, and our own conclusions regarding the ethical guidelines that must be applied to future research involving this promising new biomedical technology.

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Background of rTMS Research

Transcranial magnetic stimulation (TMS) is a technique introduced in 1985[1] that uses the principle of inductance to get electrical energy across the scalp and skull in order to produce changes in neural activity in the brain. It involves – placing a small coil of wire on the scalp and passing a very brief and powerful current through it. This produces a magnetic field that passes unimpeded through the tissues of the head. The magnetic field, in turn, induces a much weaker electrical current in the brain that is capable of activating nerve cells in the cerebral cortex. If the primary motor area of the cortex is stimulated, twitches and easily recordable electrical activity are produced in muscles of the other side of the body.

A few years prior to the development of TMS by Barker and colleagues, others had devised a means of activating the brain through the scalp with electrical rather than magnetic pulses. This represented an important technological advance. Prior to this, brain stimulation required the removal of part of the skull, which restricted human investigations to patients who were being operated upon for other reasons. However, electrical transcranial stimulation can be painful and this has severely limited its use. TMS, on the other hand, is much less uncomfortable and has been widely applied in clinical and, to some extent, basic neurophysiology. Early on it was used successfully as a tool to evaluate the physiological state of the motor pathways in the spinal cord in diseases such as multiple sclerosis by measuring the time that it took for neural activity generated in the cortex by a single magnetic stimulus to produce a measurable response in a muscle.[2] TMS is widely used for clinical purposes, particularly in Europe.

Specialized stimulating coils that produce a focal magnetic field have permitted TMS to be used to map the representation of the body in the motor cortex, much as it was done on the exposed brain by the pioneers of brain mapping such as Wilder Penfield earlier in the century.[3] The combination of this mapping technique with MRI scanning has allowed the precise localization of the motor cortex on images of individual subjects' brains.[4] In addition to mapping, the production of muscle responses, TMS is widely used as a probe in physiological studies of the motor cortex and spinal cord. TMS can provide a measure of the functional state of the brain and has helped to elucidate the basis of simple motor behaviors. In 1988, Arnold Starr[5] found that the size of the electrical response or motor-evoked potential (MEP) produced in a muscle by stimulation of the primary motor cortex was increased if the stimulus was given in the 1/4 second or so before the subject was able to move the muscle in response to the "go" signal in a reaction time task. This was evidence of a gradual process taking place in the motor cortex during the reaction time that began be-

fore conscious perception of the "go" signal and culminated in movement. This process was found to be slowed in patients with Parkinson disease, who have trouble initiating movement.[6]

Later, it was found that TMS can also be used to alter the functional state of the brain in order to influence behavior. For example, a single stimulus to the motor cortex, given while a subject was preparing to move in response to a "go" signal could have dramatic effects on the reaction time, accelerating or delaying the movement depending on the intensity of the stimulation.[7,8] In Parkinson disease patients, the abnormally slow reaction time and retarded increase in excitability of the motor cortex prior to movement could be corrected by the application of a single TMS pulse.[6]

Conventional (single-pulse) magnetic stimulators are capable of producing one pulse every 1-3 seconds and overheat rapidly when required to do so for more than a few minutes. However, in 1988 a new type of stimulator was introduced that was able to produce trains of pulses at frequencies of up to 60 per second (although it was only fully effective at up to about 25 per second). This type of stimulation, repetitive transcranial magnetic stimulation (rTMS) has remarkable effects and has opened a new field of research in human neurophysiology.

Current Research Areas

The first demonstration that rTMS was not simply another electrophysiological tool came in 1990 when Alvaro Pascual-Leone and his colleagues found that rTMS applied over the area of the left frontal lobe which controlled the motor production of speech could cause transient muteness, or speech arrest.[9] It became clear that rTMS was able to produce sustained interruptions of organized activity in specific areas of the cortex, which would allow neurophysiologists to map the locations of cognitive and perceptual functions. This has been done successfully for various forms of memory,[10,11] the ability to name objects,[12] the ability to learn motor patterns,[13] and visual perception.[14]

In addition to producing disruptions, rTMS can produce facilitating effects on behavior. For example, continuous rTMS of the motor cortex with an intensity just below the threshold for producing muscle responses improves reaction time and other parameters of motor performance in Parkinson disease patients.[6] In unmedicated patients, this effect persists for hours and can bring speed of hand movement and gait up to medicated levels.[15] Here, rTMS appears to be replacing neural excitation of the motor cortex by other brain areas that is deficient in Parkinson disease. Although rTMS itself is not practical as therapy because of the bulkiness of the equipment, this work has pointed the way toward a promising new form of treatment for Parkinson disease. Recent work has shown that treatment of the motor cortex with low frequency rTMS produces relatively long-lasting depression of MEPs to test TMS pulses.[16,17] This is interpreted as indicating an increase in inhibitory neural activity. This is a potentially useful effect in epilepsy, which is a failure of inhibition in the cortex. Treatment with electrical pulses has been used to block the generation of seizures in animals[18] and may be able to decrease the frequency of epileptic events in humans as well.

Repetitive transcranial magnetic stimulation delivered to the prefrontal area of the cortex has effects on mood in normal individuals.[19,20] Subjects show a small but significant tendency to rate their mood as being better after stimulation of the right prefrontal area and worse after stimulation of the same area on the left. Building on this work, Pascual-Leone et al. and George et al. have also demonstrated that daily treatment with rTMS to the left prefrontal area causes clinical improvement in patients with severe depression.[21,22] Repetitive transcranial magnetic stimulation is currently being tested for therapeutic effects in other psychiatric conditions, such as obsessive-compulsive disorder, with encouraging preliminary results.[23] This recent work has resulted in considerable attention from clinicians in psychiatry and neurology and the lay public to what had been an exciting, but little known, area of neuroscience.

Basis for Concerns: Adverse Events

In addition to its beneficial effects, rTMS has significant risks. Transcranial magnetic stimulation with conventional single-pulse stimulators has produced epileptic seizures in several patients with predisposing brain lesions such as strokes.[24-26] At least one of these patients also went on to develop epilepsy, presumably as a result of the underlying lesion. There is an additional report of a patient with amyotrophic lateral sclerosis and no known history of seizure or any other brain disorder who had a secondarily generalized seizure with single-pulse TMS.[27] To date, rTMS has caused seizures in five normal volunteers and one depressed subject. The first occurred in a young woman participating in an early study of the safety of rTMS conducted at the National Institute of Neurological Disorders and Stroke (NINDS) before the limits of safety for the intensity, frequency, and duration for trains of rTMS were known.[28] Three seizures occurred subsequently in the same laboratory. The next two were caused by trains that were within published safety guidelines,[28] but that were delivered with very short intervals between trains.[29] Following these two events another secondarily generalized seizure occurred at the NINDS. The set of parameter values used was on the edge of the area thought to be safe and after this event the NINDS safety table was revised.

We have also observed a seizure in a woman with severe depression who was participating in a treatment trial of rTMS. She had received rTMS to the prefrontal area several times without mishap. The seizure occurred after the subject, without the knowledge of the investigators, began taking psychi-

atric medications that lowered the seizure threshold. There is one other report of a seizure caused by rTMS in a healthy man.[30] None of these subjects suffered lasting physical sequelae. Most had electroencephalograms that, while predictably abnormal immediately after the seizure, normalized within one or two days. Two subjects had neuropsychological testing before and after the seizures.[28,29] These initially showed mild recall deficits, which disappeared within 24 hours. However, the first subject developed some degree of anxiety about the possibility of a recurrent seizure. She reported becoming acutely anxious whenever she experienced any sort of muscular cramping or discomfort in the right arm, thinking it might be the onset of another seizure. Having been told by the EEG technologist that the photic activation procedure accompanying the electroencephalogram after the seizure could provoke epileptic activity, she actively avoided flashing lights, believing that they would cause another seizure. There is no evidence to suggest that a single provoked seizure or even a series of induced seizures, as in electroconvulsive therapy (ECT) for depression, makes another seizure more likely in an otherwise healthy individual.[31]

Despite the efforts of several investigators[32,33] to develop TMS and rTMS as diagnostic and localizing tools for the study of epileptic areas of the cortex, seizures in epileptic subjects have been surprisingly rare. This is probably due to the fact that most subjects have remained on their antiepileptic medications during these studies. Only one seizure is reported with single-pulse TMS in an epileptic patient.[34] With rTMS a seizure was produced in an epileptic subject who was being stimulated on the side of the brain opposite to the epileptic focus.[35] Perhaps the greatest experience in this area belongs to Tassinari and coworkers at the University of Bologna who, having administered rTMS to over 60 patients with various types of epilepsy, have observed seizures that appeared to be induced by rTMS in two patients (out of 10) with progressive myoclonus epilepsy and one (out of four) with epilepsia partialis continua.[36] Other investigators[37] used high stimulation intensities and frequencies in an attempt to activate seizure foci in 10 unmedicated patients and not only failed to produce seizures, but caused significant, if transient, reductions in epileptiform electroencephalographic activity.

While seizure is the most obvious and acutely serious of the risks of rTMS, other adverse effects are possible. Several studies have examined transient effects of rTMS on cognitive, perceptual, and motor functions after focal stimulation, but few have looked for longer-lasting, unintended effects in these areas. In the first study of the safety of rTMS,[28] Pascual-Leone et al. screened for various types of deficits before and up to two hours after maximum intensity stimulation at a range of frequencies delivered to several scalp locations in 9 normal subjects. No significant effects of stimulation were found on the results of any of these tests except in one subject who had a generalized seizure (see above). However, there were trends toward shortening of motor reaction time and improved short-term verbal memory in the subjects who received the greatest number of stimuli and the highest stimulation frequencies. The effect on recall was most pronounced in those subjects who had received the most stimulation. In a subsequent safety study,[16] we found significant increases in finger tapping frequency, but, as in the earlier study, the only cognitive finding of note was a trend toward enhanced verbal recall.

In another study at the NINDS aimed at examining the effect of rTMS on a language task, in which subjects received unprecedented intensities and amounts of stimulation, there was a significant decrease in short-term memory scores when subjects were tested within an hour after the experiment.[38] Unfortunately, these subjects were not reexamined, so the time course of their recovery is not known. Other sources of harm range from the simple and avoidable, e.g., possible hearing loss from the noise generated by the stimulating coil, to the highly speculative but potentially sinister, such as the shaping of brain pathways[39] and maps[40] by repeated activation with rTMS in a kind of artificially imposed learning known as long-term potentiation.

Basic Ethical Considerations

The reported occurrence of seizures in 9 research subjects during the 7 years of rTMS research lends urgency to the task of developing ethical guidelines for the future conduct of rTMS studies.

Requirements for Ethical Research. Such guidelines must be governed by three ethical and legal requirements applying to all research on human subjects.[41] First, there is the requirement for informed consent. This means that the subject's choice must be free and voluntary and based on the provision of all relevant information. Subjects must be informed of "any reasonably foreseeable risks or discomforts" (45 CFR 46.116(9)(2)). Because of the relative newness of rTMS, subjects should also be told that rTMS may involve risks to the subject which are currently unforeseeable (45 CFR 46.116(b)(1)). Second, there is the requirement that risks to the subject be "reasonable in relation to the anticipated benefits" (whether for the subject or in terms of the generalizable knowledge that may result) (45 CFR 46.111(a)(2)). This requirement of a favorable balance of benefit to risk imposes a responsibility of independent assessment on investigators and IRBs. Although current regulations privilege the autonomy of research subjects in determining whether they are willing to accept the balance of risks to benefits in a protocol,[42] their judgments must nevertheless be deemed "reasonable" in the eyes of the investigator and the review board. Third, there is the requirement of justice in the distribution of the burdens and benefits of research. This requirement is violated when research is conducted on

categories of patients rendered vulnerable by economic, social, or physical conditions or who are likely to bear only the burdens of research and not its benefits.

Suitable Categories of Subjects. Against this background, it is possible to identify those classes of patient-volunteers who, in view of the known and unknown risks, might be suitable subjects for rTMS research. One broad group of admissible research subjects are individuals suffering from neurological or psychiatric disorders for whom rTMS might provide significant clinical benefit. Both the risk-benefit and justice requirements of human subjects research support the appropriateness of this patient category, which includes adult patients with progressive myoclonus epilepsy and children with juvenile myoclonus epilepsy. These individuals must already deal with the physical and psychosocial risks of seizure on a recurrent basis as well as risks associated with high dosages of anticonvulsive medication. Slow rTMS might point the way to a new means of seizure control for these individuals and other forms of rTMS might provide a way of testing new seizure medications. Patients with refractory depression also fit into this class of suitable research subjects. Electroconvulsive therapy (ECT) is a therapeutic alternative for these patients (or has already been tried without success). The seizure risk of ECT is 100% and there are additional risks not present for rTMS, including use of a general anesthetic, memory loss, cardiac arrest, broken teeth, reactions to drugs, and so on. The risk of seizure and its attendant complications with current or foreseen TMS regimens is therefore on a far lower scale of magnitude than this existing alternative therapy. Additional categories of patients might be identified among individuals suffering refractory obsessive-compulsive disorder and other seriously disabling psychiatric conditions for whom there is evidence that rTMS might provide direct benefit.

Outside of the category of patient-volunteers for whom rTMS might provide clinical benefit, an additional category of suitable research subjects are patients with disorders that might not be treated by rTMS but which rTMS might help us better understand. Parkinson disease patients fit into this category. Although research suggests that rTMS can have the short-lived effect of reducing Parkinson symptoms, the primary benefit here lies in an improved understanding of the processes leading to this disease. It is this link between rTMS and Parkinson research that makes this patient class suitable, not the fact that Parkinson disease patients already face substantial independent psychosocial risks that mitigate the impact of seizure events. Ordinarily, on grounds of justice, subjects' existing suffering and vulnerability is an argument *against* their inclusion in additionally risky research. In this case, this argument is overridden by the unfairness of denying these patients an opportunity to contribute, whether for themselves or others, to the future treatment or cure of a disease from which they suffer.

Normal Volunteers. Identifying the category of suitable patient-subjects raises the question whether normal volunteers should be allowed to participate in rTMS research. Some might argue against permitting this, since rTMS does not now appear to have the magnitude of scientific or clinical benefit that warrants imposing on healthy individuals the immediate and long-term risks associated with even a single seizure event. Although there is no evidence suggesting that rTMS-induced seizures will recur in a nonepileptic individual, studies in animals have shown permanent physiological changes in the brain, lowering the threshold of excitability (a phenomenon known as "kindling"[43]). It cannot be said, with sufficient confidence, therefore, that a normal volunteer will not have another seizure as a result of the first one, nor can it be said that a subject potentially susceptible to seizures will not be pushed over the edge by repeated rTMS excitation. Quite apart from the reality of further seizure risk, there is risk of a subject's continued anxiety about seizure recurrence. There is also a possiblity that the subject may experience insurance and employment discrimination.

Although these risks raise a formidable barrier to the use of normal volunteers in rTMS research, we do not believe they altogether rule it out. Repetitive transcranial magnetic stimulation promises significant benefits in terms of scientific understanding of normal and abnormal brain functioning and clinical treatment for psychiatric and neurological disorders. We believe that *fully informed normal volunteers should be permitted to participate in rTMS research when it is likely to produce generalizable knowledge of vital importance for the understanding of human neurophysiology or the amelioration of disease conditions.* In such cases, research may go forward in conformity to the recommended guidelines listed below and subject to a further safety factor indicated in guideline 7.

The governing phrase in this recommendation is that research be "likely to produce generalizable knowledge of vital importance." This phrase is adapted from current federal regulations governing research in which more than minimal risk is presented by interventions or procedures that do not hold out the prospect of direct benefit to the child-subject (45 CFR 46.406). Our application of this language to rTMS research on adult subjects expresses our belief that research posing significant neurological risks for normal subjects for whom the protocol promises no direct medical benefits must be of compelling scientific or therapeutic potential. This standard permits rTMS research that points the way to significant therapeutic advances and/or that strengthens (or weakens) significant hypotheses about brain function.

One example of such research is the use of rTMS to determine differences in the lateralization of mood response in depressed and normal subjects. Such studies have major implications for our understanding of normal mood and depression. Another example is a study using rTMS in the visual areas of the

brains of blind subjects to disrupt braille reading. Such a study may help confirm earlier PET scan results indicating that supposedly specialized areas of the brain can take over functions in a completely different sensory domain.

Recommended Guidelines

To assist IRBs and researchers, we propose the following guidelines for the conduct of all rTMS research. Guidelines 1-9 apply to the assessment of individual protocols. Guideline 10 applies to the rTMS research community as a whole, to manufacturers of rTMS equipment, and to funding agencies sponsoring this research.

It goes without saying that all the usual requirements of valid scientific investigation should be established before IRB review. This includes data from appropriate safety studies in animal models. In the case of rTMS this requirement remains in force even though for specific applications of rTMS in humans there might be significant limitations on the use of animal models. Differing brain volumes and configurations, different ratios between stimulation coil size and head size, and the need for patient self-reporting will often render animal models, including primates, inappropriate. Nevertheless, the burden rests on researchers to show why animal models cannot be used in specific rTMS experiments.

(1) *Researchers must demonstrate that they are using the lowest risk form of TMS suitable for the research.* Evidence suggests that seizure risk is greatest in the use of high frequency rTMS with brief intertrain intervals. Because lower frequency rTMS and even nonrepetitive TMS may be equally suitable for inducing the desired effect in some circumstances, researchers should proceed from low risk to higher risk modalities. The burden of proof rests on them to justify each increment of risk.

(2) *Researchers must adhere to well-developed exclusion criteria.* Adverse events have occurred in subjects with family histories of epilepsy or who were taking medication that lowered their seizure threshold. The research community is responsible for developing, disseminating, and applying exclusion criteria based on this and other information. Because seizures in a woman can endanger a child she is carrying, consideration must also be given to the standards to be applied to fertile women in rTMS research, including such matters as appropriate means of reporting pregnancy status and preventing conception.

(3) *Researchers are responsible for insuring full and informed consent on the part of research subjects.* This includes discussion of the history and consequences of adverse outcomes. Subjects must be made aware of the possible psychosocial risks of seizure, including risks to employment and insurability. Subjects must be reminded frequently that they are permitted to withdraw from research at any time. Only evidence of full and voluntary consent and procedures to guarantee it can justify the use in rTMS research of students or colleagues whose careers may depend on the researcher.

(4) *Researchers must be well trained and experienced in the use of rTMS and research should only take place in clinical settings equipped for seizure control.* Researchers must be familiar with the warning signs of seizure and at least one on-site member of the research team must be a medical doctor able to predict, forestall, and treat seizures.

(5) *There must be continuous monitoring of subjects during rTMS research.* Appropriate use of EMG and EEG must accompany all rTMS studies. Efforts must be made to develop ways of ensuring continuous monitoring even when stimulation makes the placement of electrodes difficult.

(6) *Research must be conducted within the best multidimensional limits of safety for the intensity, frequency, and duration for trains of rTMS.* It is the responsibility of the rTMS research community to develop evidence-based safety limits for the conduct of rTMS research. These safety limits must be constantly reviewed and updated with reference to reports of adverse events. (See below, guideline 10.)

(7) *When normal volunteers and other individuals not likely to receive direct medical benefit from the research are involved, additional margins of safety must be imposed on research.* These safety margins would be created by lower intensities, frequencies, and durations of stimulation than those identified as safe by previous experience with rTMS. The research community is responsible for developing and applying quantitative standards for safety in studies on the various subject groups. Additional safety margins should be proportionate to the perceived value of the research. Studies likely to produce less valuable generalizable knowledge require a larger additional margin of safety than studies of greater value. Presuming the full and informed consent of subjects, studies pointing the way to significant therapeutic advances and/or that test significant hypotheses about brain function may approach more closely to established safety limits.

(8) *There must be* objective *assessment of patient condition following rTMS.* Apart from those instances where adverse events have occurred there have been no reports to date of significant or enduring side effects of rTMS. However, such side effects cannot be ruled out, including possible cognitive alterations or impairments. Where cognitive effects are involved, it is not sufficient for investigators to rely on subjects' reports of their mental state, since the ability to assess one's condition may be impaired. Objective assessment of patient condition by competent clinicians is required on a continuing basis (as per guideline 9).

(9) *There must be clinical assessment of subjects at regular intervals following research until there is a reasonable certainty that the subject has not been harmed.* The longer term risks of rTMS are unknown. At higher levels of stimulation, enduring neurological and histological changes are a possibility, leading to alterations of seizure threshold or cognitive

changes in subjects. Provision must be made in all protocols for continuing contact with subjects and the maintenance of a record of subject reports and assessment. No time limit should be placed on this responsibility. IRBs can determine whether this requirement may be waived for some very low risk rTMS research.

(10) *The rTMS research community is responsible for developing and maintaining an international registry for adverse outcomes and, in the longer term, a database of rTMS research.* Such a registry should be up-to-date and immediately available to researchers throughout the world. Internet access is strongly recommended. Institutional review boards must see to it that researchers have utilized this registry in developing their exclusion criteria and safety parameters. In the absence of full information about the total number of protocols and subjects involved, however, reports of adverse outcomes alone are not an accurate measure of risk. For this reason it has been argued that what is needed is a full database of rTMS research. Such a database would certainly be of great value, and should be developed, even on a pilot basis. The research community, including manufacturers of rTMS equipment and funding agencies, should assist in the development of this resource. However, delays in funding and establishing such a database should not impede the immediate development of an adverse outcomes registry, since this registry can help investigators identify newly discovered risk factors of which they should be aware.

Larger Ethical Issues

Because of the promise and dangers of rTMS, society as a whole has a stake in the future directions taken by this new biomedical technology. This suggests two additional areas of concern and responsibility for the rTMS research community. One has to do with the immediate risks of abuse of this technology. We have noted that rTMS has been shown to have both positive and negative effects on mood.[19,20] Because of its noninvasive nature and seeming harmlessness at low intensities of stimulation, irresponsible researchers or others inside or outside the laboratory may be tempted to use rTMS for unauthorized research or recreational purposes. Researchers and manufacturers must work together now to prevent this by developing adequate laboratory security procedures and, when necessary, by working with governments or regulators to prevent this equipment from falling into inappropriate hands. In the laboratory, use of rTMS by researchers on themselves must be subject to IRB review in accordance with the guidelines for all rTMS research.

A second area of concern is the unknown and speculative longer-term risks and benefits associated with society's future development and employment of this technology. Repetitive transcranial magnetic stimulation holds out the prospect of a powerful new, noninvasive way of monitoring or influencing brain states. Many of the issues raised a generation ago by the work of José Delgado and others in connection with the direct electrical stimulation of the brain remain relevant and may even be accentuated by the development of rTMS. In the area of genetics, the research community has taken a proactive stance by helping develop various federally funded programs devoted to studying the ethical, legal, and social implications of the Human Genome Project. Although it is probably too soon to initiate an effort of this magnitude in the case of rTMS, longer-term and larger social implications should be on everyone's mind. An effort should be made on an ongoing basis to include discussion of these issues in conferences and publications dealing with ethical issues raised by rTMS.

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CALENDAR & ANNOUNCEMENTS

JUNE 26-27 A conference, Mammalian Cloning: Implications for Science and Society, will be held in Washington, D.C. Dr. Ian Wilmut will deliver the keynote address. For information: Bioconferences International, 2 Madison Ave., Larchmont, NY 10538; (800) 5-BIOCON, (914) 834-3100 within N.Y. State; (914) 834-4329 fax.

AUGUST 4-8 The Department of Medical History and Ethics at the University of Washington School of Medicine will offer its annual Summer Seminar in Health Care Ethics. For information: Marilyn J. Barnard, Medical History and Ethics, Box 357120, School of Medicine, University of Washington, Seattle, WA 98195-7120; (206) 616-1864; (206) 685-7515 fax; mbarnard@u.washington.edu.

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