# EXHIBIT 9

# TO THE SUPPLEMENTAL DECLARATION OF MICHELLE M. UMBERGER IN SUPPORT OF SUMMARY JUDGMENT OF UNENFORCEABILITY OF THE PATENTS-IN-SUIT DUE TO INEQUITABLE CONDUCT

B. BACKGROUND AND SIGNIFICANCE:

CRITICAL EVALUATION OF EXISTING KNOWLEDGE. 2 percent of the entire population will have an intracranial aneurysm; such an intracranial aneurysm will rupture in less than one percent of the population, and will be the cause of death in 0.5 percent. Twenty-five thousand intracranial aneurysms rupture every year in North America (Weir 1985) leading to bleeding into sub-arachnoid space or into cerebral tissue. The primary purpose of treatment for ruptured intracranial aneurysms is to prevent rebleeding that in most cases would be catastrophic. When studying the recent and past history of treatment of intracranial aneurysms, one can trace three independent trends, namely the extravascular, the endovascular, and the extra-endovascular approach.

Extravascular Approach. Microsurgical treatment of aneurysms, preserving the parent artery, is currently the treatment of choice for most intracranial saccular aneurysms. The methods of surgical treatment include: a metallic surgical clip placed at the aneurysm neck, a suture ligation of the neck, or wrapping the entire aneurysm. All these procedures are performed without entering the interior of the aneurysm (extravascular treatment). In order to reach the aneurysm, general anesthesia, craniotomy, brain retraction and manipulation, arachnoid dissection around the neck of the aneurysm, are required. When considering surgical treatment of saccular intracranial aneurysms, mortality is 4%-8%, while morbidity is 18%-20% (Ljunggren 1985). As long as timing of surgical intervention after sub-arachnoid hemorrhage is concerned, an early intervention carries higher mortality and morbidity rates while a delayed intervention carries risks of rebleeding, with higher mortality and morbidity. Because of all the risks associated with the surgical approach, other methods of treatment have been proposed.

Endovascular Approach. At present time it is possible, without either general anesthesia or craniotomy, to enter the interior of an aneurysm by an endovascular approach. Recently developed microcatheters are able to navigate into the cerebral arteries and enter an aneurysm. The intravascular approach has the special advantage of avoiding intracranial operative procedures. When a balloon is mounted on the tip of a microcatheter, it is possible to introduce, inflate, and detach it into the aneurysm, thereby occluding the aneurysmal sac and neck with preservation of the parent artery. Romodanov and Shcheglov (1982) reported their experience on endovascular balloon embolization of 93 anterior circulation aneurysms; Higashida and Hieshima (1986) reported their similar experience on 25 cases of both anterior and posterior circulation aneurysms. In both series a solidifying polymer was used to fill the balloon

before detachment. Romodanov reports one case of aneurysm rupture during the embolization, while Higashida had no aneurysm rupture in 25 embolized cases. The same authors report one case each of balloon rupture with subsequent leakage of the solidifying substance: both patients died. Rupture or the premature detachment of the balloon led to neurological complications in four more cases (two cases each). Endovascular balloon embolization of saccular aneurysms is an attractive method in cases in which the surgical approach is difficult, but it is obvious that the inflation of a balloon into an aneurysm carries some risks of aneurysm rupture owing both to possible overdistention or deformation of portions of the sac and to the traction produced while detaching the balloon. If an aneurysm ruptures during a classic surgical intervention, the surgeon can manage this occurrence, while little can be done if an aneurysm ruptures during a balloon embolization. The ideal embolizing agent should adapt itself to the irregular shape of the aneurysm. On the contrary, in balloon embolization, the aneurysmal wall must adapt itself to the shape of the balloon. Furthermore, balloon embolization is not always possible. The diameter of the deflated balloon may be too large to pass through the intracerebral arteries. This is often the case when there is cerebral vasospasm, a frequent complication in cases of ruptured intracranial aneurysm. So, as is true with surgery, it is necessary to wait for the vasospasm to resolve, thus introducing the risk of rebleeding.

Extra-Intravascular Approach. The aneurysm is surgically exposed or stereotaxically reached with a probe. Its wall is then perforated and various techniques are used to occlude the interior of the aneurysm and thereby render it incapable of rebleeding. The methods suggested are: a) electric thrombosis, b) IBCA embolization, and c) ferromagnetic thrombosis.

a) Electric Thrombosis. This technique is based on the fact that while blood cells, red blood cells, platelets and fibrinogen are negatively charged at the normal pH of blood. If a positively charged electrode is positioned in the blood stream, it will attract these blood components and thus promote thrombosis (see Preliminary Studies). Mullan (1974) published his experience on 61 cases of stereotaxic electric thrombosis or intracranial saccular aneurysms. He was able to introduce stereotaxically very fine copper-plated steel needles across the neck of the aneurysms. Thrombosis was initiated by the passage of a direct current for five minutes through each needle. Mullan stated that "the results indicate that the technique in selected cases is comparable to, but not necessarily superior to standard surgical methods". This technique has not become very popular because: the aneurysm has to be punctured, extensive equipment is required, a burr hole is required, and it is necessary to go through

the cerebral tissue to reach the aneurysm with the probe.

b) IBCA embolization. Isobutyl-cyanoacrylate (IBCA) is a liquid adhesive which polymerizes rapidly on contact with blood to form a firm mass. Zanetti (1972) and Debrun (1984) performed experimental studies on IBCA embolization of surgically created aneurysms in dogs. Both authors injected IBCA in the aneurysm by puncturing its sac with a small needle. To avoid the spillage of IBCA into the parent artery during IBCA injection, Zanetti momentarily reduced or interrupted the flow into the parent artery, while Debrun inflated a balloon into the parent artery at the level of the neck of the aneurysm before injecting IBCA into the aneurysm. Despite this, injection of IBCA into saccular aneurysms has not become a clinical method of treatment owing to the risk of spillage of IBCA from the neck of the aneurysm with consequent occlusion of the parent artery.

c) Ferromagnetic Thrombosis. In past years some authors tried to treat intracranial aneurysms by stereotactic placement of a magnetic probe against the sac of the aneurysm followed by injection into the aneurysm of iron microspheres by puncturing its walls with a small needle. The aim was to create an intraaneurysmal thrombus by the attraction of iron microspheres to the extravascular magnet. Nevertheless the fragmentation of the metallic thrombus, once the probe was removed, was a significant problem. In 1980, Alksne published his experience with 22 consecutive cases of anterior communicating artery aneurysms treated by stereotaxic iron-acrylic occlusion; he suspended the iron powder in methyl-methacrylate to prevent fragmentation. This technique has not become very popular for the same reasons as electric thrombosis and IBCA embolization.

GAPS. As long as their size is concerned, saccular cerebral aneurysms can be subdivided in four groups: small (less than 6 mm in diameter), medium-sized (6-15 mm), large 15-25 mm) and giant (more than 25 mm in diameter). Small and medium sized aneurysms account for over 80% of intracerebral saccular aneurysms. At present time, even with the risks and disadvantages above described, balloon embolization is the only possible treatment of medium-sized saccular cerebral aneurysms (volume ranging from 0.1 to 1.76 cc) via endovascular approach. In fact, balloon embolization is not suitable for the treatment of small saccular cerebral aneurysms (volume ranging from 0.004 to 0.1 cc) as the inflation of a balloon into their sac carries unacceptable risks of rupturing the aneurysms (Romodanov 1982). Furthermore, balloon embolization is not suitable for treatment of aneurysms in the acute face after aneurysm rupture (Ramodanov 1982). Surgery is therefore the only possible treatment for

small saccular cerebral aneurysms, and for medium sized saccular aneurysms in the acute phase, at present. This project is intended to fill in gaps described above by providing thrombosis and consequent occlusion of small saccular aneurysms via endovascular approach, even in the acute posthemorrhagic phase.

SIGNIFICANCE. Assuming that it will be possible, with this research, to produce by electrothrombosis a permanent thrombosis of sac and neck of experimentally created small saccular aneurysms preserving the parent artery and with no distal embolization, then the knowledge gained will serve as a scientific basis for treatment, even in the acute posthemorrhagic phase, of small and medium sized intracranial saccular aneurysms via endovascular approach thus avoiding the hazards of current surgical techniques (i.e. avoiding general anesthesia, craniotomy, brain retraction and manipulation, arachnoid dissection, etc.).

The hypothesis is that electrothrombosis can be an alternative method to occlude saccular intracranial aneurysms when surgery and/or balloon embolization are too risky. In order to prove this hypothesis, we propose to perform an animal experimentation. If the research is successful, i.e., if in 100% of cases it will be possible to occlude the sac and neck of the experimental aneurysms, preserving the parent artery and with no untoward distal embolization, then it will be possible to apply the technique in the clinical setting.

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C. PRELIMINARY STUDIES:

Electrothrombosis is the production of endovascular thrombi artificially induced by an endovascular positively charged metallic electrode.

There are some metals that have a high dissociation constant of positively charged metallic ions (Fe++, Cu++, Be++). Some researchers, during the past century introduced such metals in the blood stream in order to obtain a thrombus. Velpeau in 1831 and Phillips, in 1832, were the first to introduce needles into the lumen of a vessel, through its wall, withdrawing the needles after a thrombus had formed. They did not apply any electric current to the needles, obviously. The same authors suggested that the introduction of metals with high dissociation constant of positively charged ions might be useful in the treatment of aneurysms. Moore in 1864 was the first to introduce a permanent wire into the sac of an aortic aneurysm to produce a intraaneurysmal thrombus.

The first to apply a positive electric current, passing it through needles, temporarily introduced into an aneurysmal sac, was Cineselli in 1847; his aim was to enhance the formation of a clot by the passage of an electric current. Blakemore (1938; 1951) had good results in the treatment of aortic aneurysms with "wiring and electrothermic coagulation." Lintou (1951; 1952) reported his similar experience concerning the intrasaccular wiring of abdominal and thoracic aortic aneurysms. Werner (1941) was the first to treat an intracranial aneurysm by electrothermic coagulation. Until that time, it was not yet clear why an intravascular electrode should produce a thrombus around itself. Afterwards, other researchers have shown the reason for this.

In 1952, Bigelow demonstrated that washed platelets migrate to the positive pole of an electrophoretic cell. In 1924, Abramson had already demonstrated that the same happens to white blood cells. In 1953, Sawyer showed that the passage of direct electric current through citrated or heparinized blood led to precipitation of blood elements around the positively charged electrode (anode); the elements precipitated were found to be almost exclusively RBC, WBC, platelets and fibrinogen.
Furthermore, Sawyer (1953) demonstrated that the inner surface (intima) of the intact vessel wall has a constant negative charge (ranged from -3 to -15 mV) relative to the adventitia. Owing to this conditions, the blood elements above mentioned are constantly repelled from the inner wall of the normal vessels: this prevents the formation of intravascular thrombi. If the vessel wall is

injured, then an immediate reversion of the polarity takes place (Sawier 1953) so that the intima becomes positively charged, relatively to the adventitia, and attracts the corpuscolate elements of blood: this phenomenon undoubtedly plays an important role in the thrombo-coagulation of blood.

Several in vitro and in vivo experiments have been done to study the electrothrombotic phenomenon. Also several applications of the electrothrombosis in the human beings have been performed.

IN VITRO STUDIES:

In 1953, Sawier utilized citrated of heparinized blood of dogs to produce in-vitro clotting by electrothrombosis. The procedure was done as follows: several 30cc samples of blood were drawn from one dog either heparinized with 1cc of heparin for each 5cc of blood or citrated with 40 mg. of sodium citrate/cc of blood. Aliquot of this blood were placed in Kahn tubes. A pair of platinum electrodes of known weight separate by lucite rings inserted into the tubes was used to pass an electric current through the blood. Constant currents from 0.2 mA to about 10 mA were passed between the electrodes for approximately 30 minutes. The electrode pairs were then removed from the remaining blood in the tube and all unprecipitated blood elements were carefully blotted and removed from the electrodes. The electrodes and precipitated blood elements were then carefully weighed and the net weight of the precipitated blood elements was calculated. The results of this study indicated that with currents up to 3 mA, the amount of thrombus precipitated on the positive electrode was directly proportional to the COULOMBS (mA x min.) which had been passed between the electrodes; it was also stated that during the passage of current, no change of the pH of blood occurred. The blood elements precipitated on the positive electrode consisted of platelet, red blood cells, white blood cells and fibrinogen.

In 1977, Thompson showed that electrothrombosis is effective even in blood rendered thrombocytopenic with ristocetin. He performed in vitro experiments both in citrated blood and in citrated thrombocytopenic blood of dogs. He utilized a 15 mA direct electric current applied for 20 minutes to stainless steel electrodes (mean diameter 0.9 mm.) With this experiment he assessed that it is possible to produce thrombus in both normal and thrombocytopenic blood, with the only difference that the weight of the former is higher than that of the latter.

In 1978, Miller performed in vitro experiments in citrated blood of dogs. He utilized a 5-10 mA direct electric current to produce thrombi on the positively charged electrode in 10-15 minutes. Two different kinds of metals were tested as constituents of the electrodes: stainless steel and platinum. It was possible to determine that platinum produces thrombi 3-4 times larger than stainless steel. Furthermore, Miller observed that during the passage of current, the stainless steel electrodes dissolve because of electrolysis while platinum electrodes don't. He also stated that there is no difference in the dimension of the clot if the diameter of the platinum electrode is changed (whether the diameter is 0.9 mm or 0.25 mm, the dimension of the clot is the same) and that the dimension of the clot is directly proportional to the time of current application.

In 1978, Piton tested various metals in saline. He tested silver, copper, platinum and stainless steel electrodes (all of them having a 0.6 mm in diameter) applying a 10 mA direct electric current. He was able to assess that the silver electrode undergoes electrolysis in 22 minutes, the stainless steel electrode in 12 minutes, the copper electrode soon is affected by oxidation while platinum is not electrolyzed.

Reviewing the above summarized in vitro experiments, it is possible to say that:

1) Utilizing a direct electric current, a thrombus will precipitate on the positive electrode (anode),

2) The weight of thrombus is directly proportional to the COULOMBS (mA x minutes), and,

3) Platinum produces the largest clots and it is not affected by electrolysis.

IN VIVO STUDIES

In 1953, Sawier performed a series of experiments on dogs to determine if the passage of a direct electric current between an endovascular endoaortic positively charged platinum electrode and a negatively charged external electrode closely approximated the adventitia of the aorta would precipitate a thrombus inside the artery. The result was that a complete thrombosis of the aorta took place when applying a 2 mA current for 84 minutes. The artificially precipitated thrombus is histologically similar to thrombi produced

spontaneously in injured blood vessels.

Salazar (1961) was able to produce a complete coronary thrombosis in dogs applying a very small endovascular electric current (0.5 mA - 3V) for 2 hours, into the coronary arteries.

Araki (1965) studied electrically induced thrombosis by the use of both internal (positive) and external (negative) electrodes. He utilized a 3mA direct electric current for one hour. A thrombus could be constantly produced in as high a proportion as 90.9% in the carotid artery of dogs. The electrically induced thrombi were mural first, and then rapidly grow into completely occluding thrombi. No tendency towards spontaneous dissolution was observed in the electrically produced thrombi. Thrombus formation was markedly inhibited when the carotid artery was infused with heparin.

Thompson (1977) produced, by electrothrombosis, a permanent occlusion of the splenic artery in dogs (angiographic follow-up = 4 months). No distal embolization was observed. During these experiments Thompson applied to the endovascular stainless steel electrode, a 15 mA positive direct electric current for 15-20 minutes.

Piton (1978) used rabbits to produce electrothrombosis of the aorta, of the femoral artery and of the common carotid artery. A 10mA - 9V electric current was applied to the platinum or stainless steel endovascular electrode (anode). It was possible to show thrombosis in every case; furthermore, placement of the endovascular electrode without passage of current did not cause any arterial obstruction.

All these authors verified that the thrombosis actually occurred by both serial angiograms and histologic examinations.

HUMAN APPLICATION

As long as electrothrombosis of human cerebral saccular aneurysms is concerned, Mullan (1963-1964-1969-1974) was the first to treat a large number of patients. His technique consists of stereotaxic insertion through a burr hole of very fine copper-plated steel needles (0.2 mm in diameter) across the neck of an aneurysm at 1.0 mm intervals. A positive direct current (0.5 - 1mA for five or more minutes) is passed through each needle. Serial angiograms are taken every thirty minutes until satisfactory thrombosis is achieved.

Results: In a series of 61 patients, there were four operative deaths directly attributed to the procedure. in eight patients occlusion was incomplete: all of these eight patients died between one and sixty-six days later of recurrent hemorrhage. In 49 patients a satisfactory total occlusion of the aneurysm was achieved. In most of the patients, later angiograms were performed. In all of these, complete obliteration of the aneurysm persisted. Mullan concluded that stereotaxic copper electric thrombosis offers a comparable but not superior risk factor as compared to conservative management (until the time is right for standard craniotomy) plus surgical clipping. This technique has the disadvantages of requiring more complicated operative equipment and in being unsuitable for either aneurysms with branches overlaying the aneurysmal neck or patients with established cerebral vasospasm.

Araki (1965) was able to treat an anterior communicating aneurysm by electrothrombosis. At open craniotomy, with a temporary clip on the right anterior cerebral artery, he manually introduced a platinum needle (0.2 mm in diameter) into the aneurysm. Then a 3 mA positive direct current was passed for one minute. This procedure was repeated nine times, from different angles to the aneurysmal sac. Postoperative angiography showed obliteration of two thirds of the aneurysm.

PRINCIPAL INVESTIGATOR'S FINDINGS

Starting from September 1980 until June 1983, the Principal Investigator has performed in vitro and in vivo experiments in the field of electrothrombosis.

In vitro experiments: many experiments have been performed: 1) to confirm that a positively charged electrode introduced into the blood produces a thrombus; 2) to check whether copper or stainless steel is more idoneous in producing thrombosis (platinum was not used); 3) to asses which is the best current/time ratio in order to produce artificial thrombi.

The experimental apparatus included: a) a stainless steel bowl, 7 cm. in diameter and 5 cm. in height, filled with heparinized arterial blood; b) an electric pump for blood circulation; c) a silastic 3mm. inner diameter tube simulating vessels; d) a thermostatic 37° bath in which most of the silastic tube is introduced; e) a direct current generator; f) various kinds of stainless steel and copper wires having a 0.1-0.2-0.3 diameter; g) a water manometer to check the pressure inside the circuit. In synthesis the experiment is a model of blood circulation at 37° and at 60 cm $H_2O$ pressure. The stainless steel bowl

represents the negative electrode and is connected to the negative pole of the current generator. The positive electrode (anode) is introduced into the lumen of the silastic tube for about 5 millimeters. While the blood was actually flowing into the system, a positive 10mA direct current was applied to the anode for 10-15 minutes in order to obtain a thrombus around the tip of the "endovascular" electrode. At the end of the procedure, the system was emptied of blood and filled with saline so that it was possible to see the thrombus precipitated around the anode (the silastic is transparent).

The in vitro studies confirmed that it is possible to obtain a thrombus around the anode; stainless steel appeared to be better than copper; the best current/time ratio appeared to be 10mA for 10 minutes.

In vivo experiments: as soon as in vitro experiments were finished, the principal investigator performed a series of in vivo experiments. Artificial aneurysms had been created by the principal investigator with microsurgical technique. An autogenous jugular vein pouch was grated on the common carotid artery of fifteen anesthetized rabbits, thus producing a saccular aneurysm. Via transfemoral approach, a polyethylene 3F microcatheter was positioned on the neck of the aneurysm. Through the microcatheter, the tip of a stainless steel wire (0.1 mm. in diameter) was positioned in the sac of the aneurysm. Then an artificial intraaneurysmal thrombus was obtained applying to the proximal wire a slight positive direct electric current (10 mA). In ten cases it was possible to obtain an intraaneurysmal thrombus. In three cases, only partial thrombosis was achieved. In two cases the electrode perforated the aneurysm with subsequent hemorrhage. At that time, because of both, the stiffness of the microcatheter and the rudimentary wire, most of procedures were complicated by either carotic spasm or carotid stenosis at aneurysmal neck. Summarizing the in vivo experiments (Guerrisi-Guglielmi, 1983) it was possible to state that, "from the analysis of first results, we can infer that electrothrombotic method appears to be effective in aneurysm occlusion, even though it will need further experimental studies in order both to improve the technique by making it precise and safe, and to seek more suitable materials for this purpose." It is also very important to notice that at the end of most procedures, the tip of the stainless steel wire detached within the clotted aneurysm by electrolysis. As already mentioned, the same phenomenon was observed during the in vitro experiments.

Beginning on February 1989, the principal investigator has performed another series of in vivo experiments in the field of electrothrombosis via endovascular

approach. A total of 24 swines were operated to create as many saccular aneurysms on the common carotid artery. At the begining of this study three animals died of postsurgical hemorrhage (one day after surgery); six died of aneurysmal rupture four days after surgery; four animals had their aneurysm damaged by the primitive materials utilized to produce endoaneurysmal electrothrombosis; two aneurysms occluded sponteneously. In the last nine cases, due to both technical improvements in the surgical technique and dramatic technical improvements in the materials utilized to embolize the aneurysms, it was possible to create as many aneurysms and to successfully embolize them by electrothrombosis, Fig. 1a-b (Appendix). The surgical, as well as the embolization techniques will be described in detail in section D: Experimental Design and Methods.