HEMOSTASIS IN NEUROSURGERY

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"The confidence gradually acquired from masterfulness in controlling hemorrhage gives to the surgeon the calm which is so essential for clear thinking and orderly procedure at the operating table." Halsted

INTRODUCTION

The purposes of this article are two: first to list and evaluate the several devices employed by neurosurgery in the control of hemorrhage and, second, to show how neurosurgery has been led inevitably to utilize the clotting functions of blood itself as an aid to hemostasis and to interpret the more recent innovations by reference to those functions. In discussing the whole range of the hemostatic procedures of neurosurgery, a larger purpose is also thereby served, namely, to acquaint general surgery, and its other sub-branches, with the details of modern hemostasis without ligature. For it is a curious and inviting thought that the feature that most aptly distinguishes neurosurgery as a specialty is the control of hemorrhage without the use of the ligature. The delicate and pulpy nature of the central nervous system, the fineness and indispensability of its structures, the close confinement of the avenues of approach, and the relative depth at which work is done, all combine to make hemostasis with the ligature virtually an impossibility. It has fallen upon neurosurgery, therefore, to devise methods of bleeding control that are workable under the peculiar circumstances of its several fields of activity, with the result that an impressive catalogue of methods has grown up during the three-score years by which neurosurgery counts its age, each one in turn resulting in a drop in the mortality rates, a strengthening of surgical courage, and a shortening of the time consumed by an operation.

It is a mistake, however, to presume that the principle of hemostasis without ligature is modern in origin. On the contrary we have but reverted to the practices of the ancients and in a sense have regressed from the pinnacle to which, after a long struggle, surgery rose when in 1876 Lister introduced the chromicized catgut suture and Halsted in 1879 turned the use of that ligature into a delicate and discriminative procedure by inventing the modern hemostat. One of the "musts" of any surgeon's library is the attractive little book, The History of Hemostasis, by Samuel C. Harvey (1929), which acquaints us with the story of the control of bleeding from the earliest recorded medical times until the turn of the present century. It will be found there that many of the methods described in this paper are but refinements of practices employed during that incredibly long journey by which our scientific ancestors progressed toward the final adoption of the principle of ligation of vessels.
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This study is concerned only with methods for accomplishing permanent hemostasis, not with the temporary control of bleeding during the course of an operation.

HEMOSTATIC METHODS

1. BONE WAX

It is altogether fitting that the introduction of bone wax to surgery should have been accomplished in a laboratory experiment by Victor Horsley while he was preparing for his career in neurosurgery (1885), prior to his appointment at Queen Square, prior even to the first of those ten initial intracranial operations\(^{30}\) by which he established both his fame and the essential hopefulness of brain surgery. A little note in the *British Medical Journal* for 1892,\(^ {31}\) written in response to an inquiry, recalls the event. Some technique of Magendie had given him the idea, and he tried modelling wax worked soft in the fingers on the free bleeding cut surface of the cranial bones in dogs. As such a proceeding instantly arrested the bleeding, he attempted to make an antiseptic compound for operations on man, which, however, was not satisfactory. He then enlisted the aid of a Mr. P. W. Squire to make experiments so as to arrive nearly at the tenacity of modelling wax, and in this he succeeded with the following formula: beeswax, 7 parts; almond oil, 1 part; salicylic acid, 1 per cent. Horsley added that it is nearly always sterilized by boiling before use, and kept in covered stoppered bottles.

2. THE CUSHING CLIP

"The thought has doubtless occurred to many that much time and trouble would be saved in major operations could there be devised some form of haemostatic clamp, the mere placement of which would leave a fine, knotted ligature on the bleeding point so as to obviate the alternatives which we now possess, either of leaving a pendent instrument or taking the time necessary for ligation."

Thus wrote Cushing\(^ {11}\) in 1911, by way of introducing the tiny implantable metal clip that has come to bear his name. Improvements there have been in manipulation of sutures and ligatures, including a simple form of the Singer sewing machine, but thus far nothing has appeared that produces a knotted ligature without digital effort, and the Cushing clip meanwhile has been put to an increasing number of uses "in operations during which vessels are necessarily divided at depths easily reached by a clamp but in positions awkward for ligation," and it now does real service in the thoracic and retroperitoneal spaces, in addition to its primary domain of the brain and spinal cord. Whereas, however, the metal clip had formerly to be used upon vessels of all sizes, and consequently in large numbers, it is now possible to coagulate the smaller vessels with the electric cautery and reserve the use of the clip to the occasional larger artery or vein, with consequent reduction of the numbers of implanted metallic "ligatures" and a noticeable improvement in the radiographs taken subsequent to operation, if not for any demonstrable physiological gain. Further inroads upon the use of the metal clip are
imminent with the opportunity to halt bleeding from veins by the application of an absorbable matrix soaked in thrombin, so that the clip may soon be reserved for occlusion of small to medium-sized arteries, notably the middle meningeal and the several confluents and branches of the circle of Willis, not excluding the intracranial portion of the internal carotid.\textsuperscript{16} General surgeons, and those of the other specialties, would do well to study the possibilities of the metallic ligature in connection with similar situations in their work.

The original Cushing clip was hand-wrought by an ingenious method. The silver wire was wrapped tightly about a rod which bore sharp flutings, and grooves in its opposite sides. The several turns of the wire were hammered against the flutings to produce transverse ridges, and individual clips were then cut apart by means of scissors sliding along the grooves. Thus the clips bore a fine ridging which helped prevent them from slipping off after being squeezed shut upon the vessels. Clips are now fabricated by a tool which cuts, shapes, and embosses them at a single operation, but in other respects the original invention stands fundamentally unchanged in the newer models: a rack for storage of the prepared clips; and a carrier with grooved nosepiece and a spring-and-ratchet handle, to serve them up to the surgeon’s use. A recent innovation has been the substitution of inert tantalum for the more erodable silver wire, a refinement of some importance. A possible further addition of value would be the production by instrument makers of an alternate size, one moderately larger than the present standard to bring within its scope vessels that cannot be fully secured by the present clips yet are not too large to be held safely within the jaws of a cramped wire.

3. ELECTROCOAGULATION

Cautery with the hot iron was used to some extent in Hippocratic times and it became the paramount tool of the surgeon, to the point that it replaced the knife, in the degraded medicine of the middle ages—“any one could apply the cautery, practically no one the ligature,” remarks Harvey. Selective use of the cautery to sear an artery and promote tight coagulation of its edges was recommended by Albusasis (11th century). It was the achievement of Paré (1552) to make clear the great advantage of the ligature over the cautery, yet surgeons were loath to relinquish a practice that derived authoritative support from Hippocrates and Galen, and about which had grown up a huge ritual, so that two hundred years later the cautery was still in spotty use. Ultimately it died out to await rejuvenation in the guise of electrosurgery.

The discovery by d’Arsonval (1891)\textsuperscript{1} that electrical currents of high frequency alternation are devoid of the physiological stimulation (muscle twitching and pain) long known to be associated with the low frequencies used in power transmission, set the stage for the twin fields of medical diathermy and electrosurgery, as these branches came to be called. The basic effect employed by both is that of heating. In diathermy the heating energy
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is diffused over a large area and the resulting rise of tissue temperature is slight and within physiological limits. In electrosurgery the current, and consequently the heat, is focussed at the end of a sharp-pointed or other small terminal electrode, causing necrobiotic effects varying from slight dehydration (desiccation) up to the point of boiling and coagulating the tissue proteins in their own juices, or of outright charring. Extraordinary tissue temperatures are sometimes reached in electrosurgery; it was shown by Doyen\(^7\) that the spark from an electrode held a short distance away from the tissue produces temperatures in the carbonized area as high as 1,100°F. (heated iron as used in medieval times turns to light yellow at 400°, purple at 550°, dull red at 1,000° and cherry red at 1,600°F.). When, however, the electrode is placed in direct contact with the tissue the concentrated heating effect of the arc is lost, and tissue temperatures, as measured by Doyen, confirmed subsequently by Ward and West,\(^4\) and again by Huntton\(^9\) appear to lie in the zone 150°F. to 180°F. Electrosurgery then, when used correctly, can be held down to the range of simple protein coagulation, although few of us lay claim to completely avoiding the "popping" that occurs when steam is generated or the charring at still higher temperatures from the spark discharge.

In view of the critical dependence of neurosurgery upon methods of hemostasis that do not involve implacing and tying a ligature, it is difficult now to explain the long delay of that specialty to investigate and adopt what has become the number one device in the list. The d'Arsonval apparatus was used for destruction of skin lesions by Rivière\(^3\) as early as 1900, and Doyen\(^7\) in 1907 supplied the important improvement of a large indifferent "ground" plate. By altering the design of the circuit, W. L. Clark\(^8\) in 1910 obtained what proved microscopically to be tissue dehydration, and for this mild type of electrosurgery he proposed the term desiccation. Clark also added considerably to the power and quality of the instrument by installing multiple spark gaps in the place of the single gap then in vogue. Meanwhile Lee deForest, in 1908, using his newly invented 3-electrode thermionic valve, had supplied the first radio tube high frequency apparatus capable of furnishing a cutting current, with which Neil and Steinberger, experimenting on dogs, "made fine, clean incisions with little bleeding."\(^10\) That this was not an isolated example of the use of electrosurgery in the role of the scalpel, is revealed by two reports issued in Europe in 1910\(^14,20\) describing electrical methods of cutting tissue. Finally, the tuned frequency of the circuit was increased from the 500,000 cycles common to the diathermy apparatus, to the more effective 2,000,000 to 3,000,000 cycles of electrosurgery not, as Cushing\(^12\) remarks, by Bovie in 1926, but by Doyen in 1907–1908.\(^17\) Thus the essential features of electrosurgery as we know it today were all at hand by the end of the year 1910, including the choice between the multiple spark gap machine and the vacuum tube oscillator, the determination of the most suitable frequency, and a knowledge of the effect of electrical heating upon tissues, including the terms fulguration, coagulation,
desiccation or dehydration and cutting current. It is true of course that one could scarcely thumb through a catalogue and order a "Burdick" or a "Bovie" but the experimentive surgeon of the day could and did find equipment builders who produced passable models for his use. It is a matter of record that electrosurgery was early extended from the lesions of the skin to intranormal surgical fields, being adapted to hemorrhoids in 1907, the tumors of the bladder in 1910 and by its outstanding advocate, W. L. Clark, to a large variety of applications, including the breast, cervix, tongue and throat, being found especially useful in the highly vascular structure of the angiomata.

Thus it is scarcely creditable to neurosurgical acumen that it was not until 1926 that the accidental proximity of an electrophysicist working in a cancer hospital on one side of Van Dyke Street in Boston, and a pioneer neurosurgeon on the other, brought about the long awaited trial of electrosurgery in what was to be its most perfect application, hemostasis in the field of brain surgery. We owe deep gratitude to Cushing for the energy with which he adopted this idea once it came to mind.*

When I first had the good fortune to see this [electrosurgical] loop being used bloodlessly to scoop out bits of tissue from a malignant tumour for purposes of biopsy, I foresaw that a new tool had been put into our hands to facilitate the piecemeal removal of at least some of the heretofore inaccessible intracranial tumours. He proceeded to try out electrosurgery first upon cranial tumors, then upon neoplasms of the intracranial chamber. With its help, he succeeded in doing at a single stage what previously had required two or three separate operative procedures, and so taken was he with the result that he made one case (an olfactory groove meningioma) the subject of his MacEwen Memorial Lecture delivered in Glasgow in 1927. Next year he reported (with Bovie) on the use of electrosurgery in some five hundred odd operations, and mentioned details of technique, especially the importance of applying the cautery precisely upon the bleeding vessel (which would have pleased Albucasis), according to the maneuver introduced earlier by Ward of grasping the vessel walls between the points of the dissecting forceps (or a hemostat) and conducting the current from a contact made upon the handle. He foretold the gradual recession of the silver clip from its paramount position in neuro-

* The following anecdote has come by letter from Dr. S. C. Harvey: "John Morton and I were attending a session of the American Medical Association in Atlantic City in June, 1925 and were watching a demonstration of the use of a desiccating and cutting diathermy machine on a big block of beef, such as is regrettably unobtainable these days! Dr. Cushing came along, stopped to speak to us, and in a purely jocular fashion, one of us, I am not sure which, said, "Here's something you ought to use on the brain!" Not that we had any idea it was applicable there, but I think with the mischievous purpose of stirring Cushing up at the thought of employing such a gross and disgusting procedure as was evidenced in the demonstration. We did not get the reaction we expected from him. He seemed rather thoughtful, and we separated after a time, with no further thought about the incident. He apparently returned to Boston, and being aware that they were trying out Clark's method of removing malignancies at the Huntington, established contact there. Bovie of course was the physicist, and was working at the time on improving the high frequency apparatus and was in the process of developing a better machine than had been manufactured before. It may have been that Cushing had this in the works before he went to Atlantic City, but he gave no evidence of it at the time, and I cite it as evidence —scarcely necessary —of his alertness and aggressiveness in picking up a new idea."
surgery, since, "though for the control of the larger vessels clips cannot be wholly superseded, they are used less and less frequently and the current more and more for hemostasis."

Thereupon electrosurgery spread throughout the specialty, receiving notice from Sachs\textsuperscript{29} and, with certain warnings, from Dandy.\textsuperscript{19} It is eminently useful in disposing of veins, especially the free-lying veins that bridge the subdural space between the brain and the dural sinuses. Small arteries also can be treated with dispatch, although with some electrocautery fails unless assisted by a clip. Many surgeons sear a pathway into bloodlessness before incising the cortex. A few minor improvements in equipment have appeared: the attachment of the conducting wire to a terminal on the (metal) suction tip\textsuperscript{29} proves to be a convenience when surgical teams are shorthanded; and the introduction of forceps with mutually insulated points facilitates concentration of the current flow upon the tissue held between them (theoretically a refinement upon Ward's suggestion; in practice, somewhat cumbersome). Both spark gap machines and those based upon the vacuum tube are purchasable, and superb results are possible with either class of equipment if the operator will but learn how to get the most from it.

4. STYPTICS

The styptic (having the power of contracting organic tissue; that which arrests hemorrhage; astringent.—\textit{Oxford English Dictionary}) was never a hemostatic of good choice in surgery. Invariably it was a substitute, an improvisation, which succeeded or not according to luck as well as the skill and patience of the surgeon. It comes down to us from antiquity, having received mention from Galen and the medieval chroniclers, who left rules for implanting the alum, the copper sulfate button, or the ferric chloride granules against the vessels of the amputation stump.

While the styptic is intended to be localized at the point of bleeding, in practice its caustic action includes the neighboring tissue, be that muscle, fat, mucous membrane or what not, and the ultimate control of hemorrhage depends upon a lifeless eschar which covers and confines the bleeding vessel. The precipitation of proteins caused by the action of the chemical is not that highly specialized crystallization of fibrinogen into fibrin by which nature coagulates blood, but an indiscriminate amorphous destruction of all protein elements. As a hemostat, the resulting eschar is poor in quality and unreliable. Except to complete the list of agents employed by neurosurgery, the styptic could be put aside as unworthy of mention in the face of its modern rivals of the biochemical series. In times past, however, neurosurgeons have often deliberately impressed powerful caustics to the task of hemostasis. For example, it was Cushing's habit in later years to have at hand on the instrument tray a basin of Zenker's solution \textit{(corrosive sublimate 5 parts, potassium bichromate 2.3 parts, sodium sulfate 1 part, water q.s. 100)}, partly for destruction of neoplastic remnants following tumor extirpation, but partly also to use in daubing upon bleeding spots that failed to re-
respond to other treatment. This practice he began while doing the trans-sphenoidal operations upon adenomata of the pituitary (the thrombin-soaked patch was not yet born), and found it useful also after evisceration of acoustic neurinomata.* I had a brief moment of glory upon my first day of service at the Brigham Hospital when by accident I upset the entire contents of this basin into the wound.

DISCUSSION OF THE FACTORS INVOLVED IN THE BLOOD CLOTTING MECHANISM AND THEIR UTILIZATION IN SURGICAL HEMOSTASIS

Before continuing to the remaining sections of this review, it will be helpful to examine briefly the physiology of the coagulation of the blood.†

Fibrin, the end result of the biochemical action by which blood clots, is the meshwork that springs into existence to trap and freeze the corpuscles and prevent their further flow. All of the constituents of fibrin are present in normally flowing blood. The trigger that releases these constituents, the chemical forces that drive them into the chain of combinations resulting in the clot, and the true nature of the constituents themselves, have formed the waters of an immense sea of investigation which as yet are by no means thoroughly fathomed. Surgeons, and in particular neurosurgeons, have followed the charting of these waters with avid interest, hoping that by some magic there would appear a device to ease the task of blood stopping and so shorten their labors, and it is important to observe that from the earliest days of neurosurgery one or another segment of the blood clotting mechanism has been employed, with varying degrees of success, in the hemostasis of capillary ooze and venous bleeding. To understand the action of these hemostatic aids one needs to familiarize himself once again with the equations representing the coagulation of the blood, which were introduced forty years ago and are still considered correct.

I. Prothrombin + Ca++ + thromboplastin = thrombin.

II. Fibrinogen + thrombin = fibrin.

It will be noted that four parent substances are involved, each of which deserves brief discussion. Prothrombin, the precursor or mother substance of thrombin, is a constituent of plasma as well as of lymph, and is distinctly an extracellular substance. Its presence in the blood depends upon a normally functioning liver and upon an ample supply of vitamin K, so that a hemorrhagic diathesis can be expected in disorders involving obstructive jaundice, biliary fistula or liver damage. Calcium is indispensable to the coagulation process, and the simple displacement of calcium by a citrate or an oxalate prevents the reaction from taking place. Thromboplastin is the trigger that discharges the mechanism. In contrast to prothrombin, it is an intracellular substance, and this physical separation of the two serves to hold the coagulation process in check until by injury, or by some artificial stimulus, their

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* Letter from S. C. Harvey.
† Condensed in large part from A. J. Quick: The Hemorrhagic Diseases and the Physiology of Hemostasis.
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chemical combination takes place. In the circulating blood, thromboplastin is carried almost exclusively by the platelets, to be released when they agglutinate; the disease hemophilia is based upon a deficiency of platelet thromboplastin or a disorder of platelet behavior which tremendously hampers the supply of this essential element. Thromboplastin is also found, intracellularly, in most other tissues of the body, notable amounts being present in the brain and the lung.

The successful combination of these three elements, prothrombin, calcium and thromboplastin, leads to the formation of an intermediary product, thrombin. It remains now to combine thrombin with fibrinogen to form fibrin, the end product of the clot. Fibrinogen, a plasma protein, possesses one unique characteristic that differentiates it sharply from its two companion proteins, serum albumin and serum globulin; it is converted by the action of thrombin from a colloidal sol to a gel which microscopically shows a crystal-line-like structure. This ready conversion to an insoluble compound makes it an ideal hemostatic agent in nature. By good fortune, too, the supply of fibrinogen is rarely if ever at fault, and the amount in the blood is at least five times greater than is needed for the effective control of hemorrhage.

From this very brief examination of the coagulation process it becomes apparent that the strategic point of attack, for purposes of surgical hemostasis, is the addition of an active prepared thrombin to the flowing blood at the point of its emission. Two good reasons dictate this choice rather than any other. First, the occasional defects of the clotting mechanism lie almost exclusively in the preliminary steps by which thrombin is formed, and such defects (hemophilia, jaundice, etc.) are thus circumvented if the first reaction is by-passed. Second, the reaction between thrombin and fibrinogen is the last step in the process, and it goes forward with considerably more force and speed than does the reaction to an artificial stimulus applied to the initial stages. Only recently, however, has this choice become evident or, indeed, practical, and neurosurgical progress in biochemical hemostasis, as one might designate this tool, was long concerned with substances containing thromboplastin, with end products which bear traces of the primary factors, or with rough-textured substances tending to agglutinate the platelets. The story begins with the simplest form of hemostasis, natural clotting, and takes up in succession the methods by which the natural process can be speeded up.

5. PATIENCE AND PRESSURE

One of the basic ingredients of neurosurgery is patience, or at least so it has been until very recent times, and in the era of the 6, 7, and 8 hour operations for brain tumors a great deal of the time spent, while the surgeon and his weary team shifted collectively from one foot to the other, was consumed in fact by a succession of experiments in the normal clotting time of blood. Five to 8 minutes is the average space of time for a good clot to form, and if the clot attaches itself with sufficient firmness, and provided that the
after-coming pressure is not too great, the flow of blood is effectively checked by nature.

A small increase in the magnitude of the hemorrhage alters the situation. Then the volume of flow or the backing-up of pressure washes away the precipitating clots as fast as they form, leaving nothing to plug the rent in the vessel. But natural clotting will bring even these hemorrhages under control if a little pressure is applied to hold the vessel walls together and give the clot time to solidify and adhere before it is called upon to assume the responsibilities of a hemostatic, and such temporary compression of vessels during thrombus formation is probably the oldest method known in the control of hemorrhage.\(^{27}\) Moreover, it is thoroughly practical in many situations today, especially if the compression can be maintained without attention from the surgeon who goes about other phases of the operation while awaiting the formation of the clot. A suggestion made by Grey,\(^{24}\) which has been revived and put to highly effective use by Poppen,\(^{47}\) is the laying down of a piece of rubber tissue (gutta-percha) against the bleeding vessel before applying the cotton pledget. This is done to prevent adherence of the clot to the material, since ordinarily the smooth rubber surface can be peeled away without disturbing the clot.

6. ABSORBABLE PACKS

It is but a short step from the temporary pressure which results in a permanent clot to the use of a soluble or absorbable pack which can be left in place to await later resolution by the body. One such substance, oxidized cellulose, was introduced recently by Yackel and Kenyon\(^{68}\) of the Eastman Research Laboratories and is supplied (thus far, only for research purposes) by Parke, Davis & Company. It is prepared from ordinary gauze sponges or cotton pledges by the action of nitrogen dioxide, which converts certain of the hydroxyl radicals of cellulose to carboxyl groups, thus making the material soluble at the alkalinity present in tissue juices, while maintaining the original texture of the substance. Actually the cellulose in the form of cotton or gauze is converted into a solid organic acid with maintenance of its original structure and having a tensile strength of about two-thirds that of the original fabric. This product, because of its carboxyl content or acidic nature, is slightly hemostatic (in the manner of a styptic).

Because of its acidity (about pH 4.0) oxidized cellulose inactivates thrombin. This characteristic was not sufficiently understood during the early surgical investigation of the material. The error is apparent in the report by Putnam,\(^{48}\) and accounts probably for the wide discrepancy in the clotting effectiveness of the same thrombins when tested in vitro upon fibrin foam and oxidized cellulose, as reported by Bering.\(^{4}\) It was not until Seegers and Doub\(^{66}\) (May, 1944) measured this inactivation experimentally, and showed the rate at which it proceeds, that the process was made clear. They supplied instructions for neutralizing oxidized cellulose at the operating table by dipping it in a 1 per cent solution of sodium bicarbonate, and this procedure was followed by Uihlein, Clagett and Osterberg,\(^{60}\) whose re-
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The use of hot water irrigations for hemostasis is a matter of such common knowledge that it has proved difficult to trace the practice back to its point of innovation. For our purposes it may be said to begin with a paper read by the obstetrician Milne Murray45 before the Edinburgh Obstetrical Society in the year 1886. At that time strong rivalries had developed between the advocates of cold irrigations and those of hot, both sides admitting that cold irrigations cause spasm of blood vessels and allaying of hemorrhage, but with one school maintaining that warmth of all degrees dilates vessels and promotes hemorrhage while the other, admitting readily the undesired effect of a bath of tepid water on an incised and bleeding wound, insisted that a stream of hot water directed on a bleeding surface, such as that exposed during an operation for vesico-vaginal fistula or for repair of the perineum, at once arrests hemorrhage by stimulating contraction of blood vessels. Murray put the proposition to the test in a well-executed experiment upon the uterine vascular network of rabbits, and two of his experiments deserve recounting here.

In the first one, water at 40°F. was directed upon the vascular mesometrium stretching from the vagina to the cornua of the uterus on one side, while water at 115°F. was similarly directed upon the other. Four minutes was the duration of irrigation. Soon after the commencement of the stream, both sides became pale—almost white. At the end of four minutes the side receiving the cold water showed signs of returning vascularity, whereas that receiving the hot was still perfectly anemic. Four minutes later the cold side was bright red, the hot side was still white. Eight minutes after, the cold side was an intense scarlet, the blood vessels standing out in spiral lines all over the tissue, while the hot side had assumed the appearance it had before the experiment. Half an hour later the conditions were still the same.

This showed clearly, said Murray, that while contraction follows at once in...
both cases, the contraction induced by the cold water is succeeded by an intense reaction, whereas the vessels constricted by hot water regain their ordinary tone slowly, and without reactionary congestion.

The second experiment concerned hemostasis. A pregnant uterus was incised, and the edges of the wound caught by a pair of hooks so as to hold them apart, and permit bleeding to occur. The blood escaped freely. A small stream of water at 123°F. was allowed to flow on the wound, when the bleeding immediately ceased. Cold water was gradually added to the vessel containing the water, and the temperature slowly fell to 100°F. About one minute afterwards the bleeding recommenced, at first slowly, but as the temperature fell to 90° the blood escaped more rapidly. During the five or six minutes which were necessary to reduce the temperature to 50°F. the blood continued to flow as before. When 46°F. was reached the escape of blood became markedly less, and, a piece of ice being added, the temperature rapidly fell to 38°F., and then to 36°F., when the bleeding entirely ceased, the water running off colorless. In about two minutes thereafter, the stream of water still being kept up, the oozing again commenced. A morsel of ice laid on the wound was quickly dissolved, and washed away in the escaping blood, and it was evident that the cold had lost its influence. The experiment was concluded by dipping a sponge in water just hot enough to be barely tolerable to the hand (115° to 120°F.) and wrung out over the wound when bleeding ceased. The incision was then closed.

Now it so happened that a Dr. Horsley, who we may presume was the young Victor, then 28, was present in the audience, and arose at the conclusion of the paper to ask a question (to which he received no answer). Evidently he took to heart the lessons of this demonstration, for he referred to it in detail in his address “On the Technique of Operations on the Central Nervous System”\(^{32}\) in 1906, quoting Murray, whom I also quote:

> It is certain that water from 70°F. to 103° or 105°F. will invariably dilate blood vessels and promote the flow from open ones, but it is equally certain that water of temperatures from 110°F. to 120°F. will have just the opposite effect.

Horsley found this to be correct in practice, and stated that what we require is a temperature that stimulates contraction of small vessels without at the same time causing heat coagulation of the nervous tissue. He felt that the temperature should not exceed 115°F. nor fall below 110°F.

Cushing therefore appears to have been on weak ground when in 1911\(^{11}\) he advocated the use of solutions in the temperature range of 100° to 105°F. in his list of hemostatic aids but, so far as I am aware, he deviated little from this practice in later years, despite the tedious delays that often took place before tumor beds could be made dry.

Two questions remain to be discussed. Does an irrigation with hot water merely delay bleeding through temporary vasoconstriction, or does it produce permanent and true hemostasis? Second, what is the upper limit of temperature that can be safely employed without damaging nerve cells?

The answer to the first appears to be favorable to the hot irrigation. Howell\(^{35}\) states that “hot sponges or cloths applied to a wound hasten clotting, probably by accelerating the formation of thrombin and the chemical changes of clotting,” and Wiggers\(^{35}\) agrees that heat “tends to accelerate all chemical reactions concerned in coagulation.” Presumably,
then, hot irrigations promote both temporary vasoconstriction (of no little usefulness during the advance through tissue that is ultimately to be removed) and the coagulation of blood. Murray’s second experiment, however, contains a note of warning with respect to the ability of heat to coagulate, because upon cooling it may be found that a portion of the control was of the nature of vasoconstriction and therefore temporary. The surgeon is best advised to use heat for what it is worth, preferably not during the last 10 to 15 minutes that the full field is exposed, unless followed by some supplemental step, such as laying tissues back upon each other to maintain vascular pressure.

The second question can be answered in part, but not with full satisfaction. Dusser de Barenne and Zimmerman,13 using a carefully controlled heating element, charted the depths of destruction of the cerebral cortex in the monkey under the effect of temperatures ranging from 122°F. to 176°F., with exposure times of from ½ to 5 minutes. From this we learn that an exposure of ½ minute at a temperature of 122°F. resulted in death of nerve cells of the most superficial cortical layers. What degree of temperature the cortex (or indeed any structural part of the nervous system) can withstand without damage is not indicated, and it would be immensely valuable to neurosurgery if the Yale group would set up Dusser de Barenne’s apparatus and make that determination.

Evidence from another source is helpful here. The work of Pincus and Fischer,64 in a study of the thermal death point of cells grown in culture, indicates that a rise of 10°C. (18°F.) maintained for 30 minutes has no apparent effect and that a temperature of 13°C. (25.4°F.) above normal can be withstood for 2 or 3 minutes with growth inhibition but without death. Huntton26 concludes that an estimate of 11°C. above normal (for humans, this means a temperature of 118.6°F.) is quite conservative. Meanwhile therefore, until the problem is worked out specifically for the primate nervous system, it appears safe and reasonable to follow Horsley’s advice, and keep the irrigating fluids between 110° and 115°F.

8. THROMBOPLASTIN

It may well have been that the abundant presence of a phospholipid coagulant in the cells of the brain played a major role in setting brain surgery upon its feet, and that nature in a measure made up for what neurosurgery lacked in its early days. This possibility was recognized by Horsley after his first few operations (1886), when his alert mind borrowed a contemporary discovery of physiology. He wrote:29

No doubt one additional reason why the hemorrhagic oozing so soon stops in a brain-wound is that clotting is induced early by the presence of the lecithin protid compound which exists in quantity in the brain, and has been discovered by Dr. Wooldridge57 to play a very important part in the process of coagulation.

Thus began the interest of neurosurgeons in the physiology of hemostasis, and the adoption of its several processes to surgical use.
The next step was many years in coming, but it descended logically from awareness of the coagulating properties of bits of living tissue. Horsley on one side of the Atlantic, and Cushing on the other, independently and at about the same time (1909–11), began to apply small stamps of freshly-cut muscle to areas of capillary and venous bleeding, with gratifying results. Both men recognized that other kinds of tissue could be used, and tried bits of fascia among other things, but returned to muscle as superior to all. Horsley then went on to experimental studies of muscle implants, demonstrating that when held against torn vessels until bleeding stops, they possess to a satisfactory degree the property of adhesion, and measured this adhesiveness upon living divided arteries, finding that it withstood blood pressures of 60 to 80 mm. Hg. He examined the zone of adherence microscopically and observed blood platelets and fibrin fibrils within a few minutes of commencing the preparation. Finally, he demonstrated that muscle loses its hemostatic properties after boiling—all very sound work in the field of hemostasis.

The active principle of the tissues that promotes clotting was demonstrated by Howell (1912) to be another phospholipid, cephalin, not lecithin as reported by Wooldridge. He showed it to be thromboplastic in nature, similar in properties and action to the corresponding substance carried by the platelets of the blood. Since that time preparations of thromboplastin of one sort or another have been available and Cushing, in an experiment unreported but well-remembered (1929–30), employed cephalin to halt the oozing from brain or dura by applying it on thin sheets of cotton, only to rediscover that any clotting agent fails if the vehicle upon which it is applied must be removed. At the present time, preparations of thromboplatin, extracted from lung or from brain, are marketed by several concerns, but their clinical usefulness is directed to the standard laboratory test for estimating the prothrombin concentration of the blood. Thromboplatin in all its forms, including the muscle implant, is rapidly being superseded by a much more active agent of hemostasis, thrombin, applied with an absorbable vehicle.

9. THROMBIN

"The action of thrombin in converting soluble fibrinogen into insoluble fibrin can be considered the most fundamental reaction in the coagulation of the blood." This sentence from Quick tersely expresses the importance of the material upon which hopes are now pinned in the search for a rapid stimulus to blood coagulation in the operative field.

Thrombin has not yet been prepared in pure form. The relative purity was advanced by slow stages following the preparation available to Schmidt (who gave it its name) in the 1890's, until Mellanby in 1933 produced a material with a potency of from 60 to 100 Iowa units per mg. Further

* Defined (1938) in these terms: 1 unit of thrombin is that amount which will clot 1 cc. of a standard fibrinogen solution in 15 seconds.
purification was not far distant. In 1938 a group (Seegers, Brinkhous, Smith and Warner)\textsuperscript{34} at the University of Iowa succeeded in preparing from beef plasma a dried thrombin with a potency in the neighborhood of 300 to 500 units per mg., roughly 5 times stronger than Mellanby’s product. When dissolved as a 1 per cent solution, 1 cc. of this material clotted 1 cc. of blood within 2 seconds. Here then, was a hemostatic substance of remarkable power. Its effectiveness was determined in animal studies\textsuperscript{57} by applying the thrombin to bleeding surfaces with an atomizing spray. Two conclusions were reached: the material was non-toxic when so used; and it was reasonably effective in controlling ooze. The evidence of this preliminary report was then strengthened by studies\textsuperscript{63} in which the toxicity experiments were extended to include intramuscular and intraperitoneal injections (6,000 units, in the rat) with no untoward effects and, sterility problems having been overcome meanwhile, trials were reported in 21 human cases. Successful hemostasis was accomplished in a case of mastoidectomy, in the donor area of a skin graft, and in the tooth sockets of hemophiliac patients still bleeding 24 hours after extraction. By 1940 the potency of their preparation was doubled\textsuperscript{53} and it moved upward another notch in 1942,\textsuperscript{66} by which time 1 mg. represented better than 1,500 units and contained less than 10 per cent of inert material. Extensive clinical experiences using this relatively pure product (thereafter marketed by Parke, Davis & Company) were reported by the Iowa investigators for 225 cases,\textsuperscript{59} again through the use of a spray or wash or of the dried powder itself, but without employing a vehicle or tampon. Notable results were obtained, although secure hemostasis did not always follow because of the tendency for the clotted blood to float away under the force of aftercoming hemorrhage. Important findings were: the compatibility of thrombin with the sulfonamide group of drugs; the absence of local irritation; and the lack of sensitization in patients in whom the preparation was used repeatedly. In none of the cases was there evidence of intravascular thrombus formation. Beef thrombin, then, appeared to be not only a highly active clotting agent for human blood but, upon the evidence at hand, harmless in application.

Meanwhile, thrombin prepared from rabbit plasma had been tested on small experimental human wounds,\textsuperscript{43} where it too served successfully to control bleeding.

A third source of thrombin was soon to be exploited. In a discussion of the physical chemistry of the plasma proteins, Cohn (1941)\textsuperscript{7} suggested that human albumin could be prepared by the procedures then applied to obtain bovine albumin, and should prove useful for a number of therapeutic purposes, particularly in the treatment of shock due to acute loss of blood. No suggestion was ever more ripe for the times. The bloody holocaust of Pearl Harbor and the ensuing declarations of war both east and west set in motion a huge program of human blood donations for the benefit of the soldiers of this nation. Part of this blood was converted to plasma and part taken down to the albumin fraction. There resulted a large supply of left-over materials,
from which two substances pertinent to this review, thrombin and fibrin foam, were manufactured. The thrombin was of a considerably lower order of potency than that prepared by Seegers, with activity of 10 to 20 units per mg., yet this potency sufficed for clinical use.\textsuperscript{19} The experimental and clinical experiences with this substance will be recited in the ensuing section on fibrin and other absorbable carriers of thrombin.

The parallel success of the thrombins prepared from three different species of animals was not unexpected to biochemists, since it had been shown by Quick\textsuperscript{48} that thrombins obtained from various mammalian bloods appear to be identical, but they differ from bird thrombin and also from amphibian thrombin. Thrombin therefore appears to possess group rather than species specificity.

A word may be added as to the antigenicity of thrombin. Thrombin is protein in nature, and the unremoved impurities of the preparations likewise probably are proteins. It is possible theoretically to sensitize an animal of one species to the thrombin prepared from another, and this in fact has been successfully accomplished by Beatrice Seegal (personal communication) in guinea pigs and in rabbits. On the other hand, it can be stated that the use of a dissimilar thrombin (bovine) in clinical hemostasis has not brought indications of sensitization, and that there is considerable evidence to show that it will not do so. The case for this will be discussed in a forthcoming paper, together with the introduction of new data.\textsuperscript{41}

One further aspect should be mentioned. The injection of thrombin into the blood stream is a dangerous procedure, apt to result in embolus formation, but the danger, to considerable degree, is a quantitative affair. One hundred units have been injected into a 285 gm. rat with no obvious disturbance,\textsuperscript{63} and Seegal managed with care to instill 140 to 200 units into guinea pigs without evoking fatality from intravascular clotting. Transpose now the situation to clinical surgery, substitute a 70,000 gm. human being, and apply thrombin only to extravascular areas toward which blood is flowing out of veins or arteries. The likelihood of transport into the vascular system is remote, and the danger, should it occur, small. Here, too, positive experimental evidence exists to show that intravascular clotting does not occur, and that a venous channel remains patent beneath a rent repaired by a thrombin-soaked absorbable matrix, even though thrice performed. This experiment also will be related in a subsequent report.\textsuperscript{42}

10. FIBRIN AND OTHER ABSORBABLE CARRIERS OF THROMBIN

The control of capillary ooze, and of bleeding from vessels scarcely larger than capillaries, has been one of the most vexing problems in the collection of insolubles that tumbled from that Pandora's box called neurosurgery. This type of hemorrhage, of so little consequence in most surgical localities, is both a supreme nuisance to the neurosurgeon and a risk to the life of his patient. Another type of hemorrhage of peculiar import is the flow from tiny but accessible arteries that lie upon structures too indispensable
to risk damaging by ligation, clip or cautery. Still a third type is the ominous gush from larger veins—the superior sagittal sinus in its posterior third, for example—the total occlusion of which means disaster to the patient. These examples have one thing in common: they bespeak the need for a substance with which to patch the bleeding area, just as one patches a tire, together with the means to vulcanize that material in place.

Cushing and his team of investigators in the Laboratory for Surgical Research began a hunt for such a substance 30-odd years ago. He teed off with the conjecture (1911) that:—"fibrin from whipped blood might be so prepared that it could be immediately plastered on bleeding surfaces, just as cotton is now used, and thus obviate the necessity for any subsequent replacement."11 He was thinking evidently of improving on his practice of the day of saving well-solidified blood clots for implantation against bleeding points, but it is altogether probable that those clots retained traces of the uncombined primary factors of coagulation, especially thromboplastin and thrombin, which supplied an action quite apart from any influence of the fibrinous clot itself. However that may be, one of the assistant resident surgeons, Ernest Grey, was instructed "to find an absorbable material which might be used for this purpose," and succeeded, as reported (1915) in "Fibrin as a Haemostatic in Cerebral Surgery."24 Grey used sheep’s fibrin (as well as human blood) because it was readily procurable from the local Wassermann laboratory; washed it; soaked out the red cells; and sterilized it, apparently by autoclaving. Then he tested its effectiveness in halting bleeding, and found it to control hemorrhage better than wet cotton because "while fibrin probably exerts no appreciable chemical influence on the process of coagulation it appears to possess some mechanical property favorable to the formation of a firm clot." That mechanical property obviously is the rough texture which hastens agglutination of platelets and so starts the natural process of clotting upon its way. Grey recognized that "clotting may perhaps be hastened by dipping the piece of fibrin into a solution such as the Kocher-Fonio coagulen," but it was impossible to use that substance because it was not sterile and there was no way known of sterilizing it. It was used experimentally, however, for Harvey wrote:25,26

The methods which have been used to combat these forms of hemorrhage [capillary ooze and venous bleeding] are of two types. Kephalin and the Kocher-Fonio coagulen are examples of the one type which depends upon chemical means to decrease the coagulation time of the blood. One objection holds true for all these substances. To apply solutions of this nature, some form of tampon is necessary, and in the removal of the latter, the clots are dragged from the hemorrhagic areas leading to secondary bleeding.

Thus did these surgeons of the first world war clearly visualize the problem, the solution of which was to rank high in the scientific achievements of the second. Harvey improved upon Grey’s fibrin preparation by converting it to paper and plasticizing the protein with heat. If, to be sure, the fibrin of Grey and Harvey, unassisted by any active clotting agent, failed to survive in its intended role as a hemostatic (Cushing gave it a clinical trial),25 its
sponsors had nonetheless performed a valued service by studying the reaction of tissues to the implanted material, and by comparing both the reaction and the absorption rate with similar factors connected with muscle implants. Fibrin was tolerated better by the body than muscle, and it disappeared earlier.

Fibrin then dropped temporarily from sight. Attention reverted to solutions and powders that coagulated blood upon their admixture. The later remarkable improvements in preparations of thrombin made that substance, by itself, a passably-good seal for bleeding areas. Still, the right combination of a patch and a vulcanizer did not appear.

a) *Fibrin Foam.* In 1944, Ingraham and Bailey\(^3^7\) reported upon the successful use of a matrix of fibrin to carry a solution of thrombin to the site of hemorrhage, and to hold it there while clotting took place. The fibrin, prepared by E. A. Bering, Jr.,\(^4\) was made as spongy and porous as possible so as to multiply the surface area upon which active clotting could occur. This sponginess proved valuable also in another direction. If the matrix was squeezed out before application (or sucked dry of its excess solution of thrombin through a cotton pledget immediately after implantation) it tended to take blood into itself by swelling, as is the habit of a sponge, thus insuring a thick substantial clot rather than a film at the surface. Adhesiveness was gained by the direct precipitation of fibrin, aided (probably) by the gluing effect of the blood platelets which sprouted to life at the moment of the clotting reaction.

Surgical operations in monkeys, and in 95 patients, 18 of whom subsequently yielded up the tissue upon which it was implanted, either by autopsy or at reoperation, served as the proving ground. The results were gratifying: the hemostatic action of the fibrin-thrombin combination was found to be speedy and reliable in control of ooze and venous bleeding, and histological studies showed that the fibrin pledgets were rapidly absorbed and excited a minimal tissue reaction. Subsequent studies\(^2,3,8,39\) supplied anew the comparison of fibrin with muscle, and confirmed the conclusions reached by Harvey and Grey that, of the two, fibrin is tolerated better and absorbed more quickly. Additional comparisons were made with bone wax, with black silk sutures, and with oxidized cellulose. Meanwhile quick advantage was taken of the by-products accumulating from the program of blood fractionation in the production of serum albumin, and preparation of fibrin foam was begun in quantity for the armed forces. Woodhall\(^6\) has reported recently upon its use in 226 operations in rehabilitation neurosurgery, and no one reading the details of his report can fail but share to some degree his optimism for the method.

b) *Oxidized Cellulose:* See Section 6.

c) *Starch Sponge.* A third absorbable material, prepared from starch,\(^5\) deserves listing because with further improvements it may perhaps become a useful item. The specimens examined have been too friable and structureless for surgical handling.
d) *Gelatin Sponge.* In the writings of Bering, and of Ingraham and Bailey, great prominence was given to the fact that fibrin foam is derived from human and not from animal blood. Without entering upon the controversial questions implied in this stand, it can be pointed out that all parties interested in fibrin foam have been keenly aware of the fortuitousness of its existence, dependent as it has been upon the nation-wide program of human blood donations due to the war. Anticipating that either these donations, or the subsidiary program of conversion of blood to serum albumin, would one day cease to exist, two chemists, Correll and Wise, began well over a year ago the search for a substitute material. This they have found in gelatin.9

The choice of gelatin was inspired. Gelatin is a peculiar protein compound, rich in glycocoll, proline and arginine but poor or entirely deficient in the amino acids containing aromatic radicals upon which both the anaphylactic reaction and the precipitin reaction depend.68,64 Gelatin, therefore, is nontoxic, it fails to produce anaphylaxis, and it has lost all trace of its species identification. It is a "universal protein."

The next step was to produce a matrix satisfactory to the surgeon and absorbable by the body. In this they succeeded fully. The resulting sponge weighs but 9 mg. per cc., absorbs 50 times its weight of water and, what is more important, takes up 45 times its weight of blood. It can be produced in pieces of any size and shape. It is tough, cuts easily without fragmenting, and resists rough handling. When wet, it plasters to the irregularities of the surface upon which it is laid. Digestion studies with a standard pepsin solution have shown that digestion occurs in about 30 minutes, a value similar to that for fibrin foam. Absorption studies in rats revealed that disappearance was complete in 30 days while nodules of fibrin foam persisted beyond 50 days.

The future of the thrombin-absorbable matrix method of hemostasis therefore seems assured, notwithstanding the recent cancellation of the program for manufacture of serum albumin. Moreover, certain improvements have been gained in the new gelatin sponge, notably as regards efficiency and surgical handling. The material has been submitted to study in a number of investigations, and a report on one of these, its use in neurosurgery, as studied both in monkeys and humans, appears elsewhere in this journal.42

**CONCLUSION**

The progress of neurosurgery has been paced by the successive advances in the technique of its most difficult phase, hemostasis. In neurosurgery the use of the ligature, so indispensable to surgery in general, is rendered impracticable due to the nature of the nervous system and to the conditions that govern the surgical approaches to its contents. In this paper, ten substitute methods for obtaining hemostasis have been listed and evaluated, not only for the attention of neurosurgeons, but equally as a guide to general
surgeons and those of the other specialties, since many of these hemostatic aids have wide fields of application. Some of the methods, such as bone wax, the Cushing clip, the electrocautery and hot water, are old standbys with well-established reputations. Some indeed are obsolete, as with the styptic and the several forms of thromboplastin. Some are new and experimental, and can be reviewed only by giving critical regard to the evidence upon which they have been recommended.

No one of these methods suffices to bring an operation to a successful conclusion. The surgeon is well advised to have most of them at hand and, to a very considerable extent, his surgical skill can be measured by the versatility, the correctness and the confidence with which he brings them into play.

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