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TRANSPLANTATION OF PERIPHERAL NERVES. Presented by PROF. G. CARL HUBER, Ann Arbor, Mich.

The data to be presented have been gathered in the course of experimental work carried on in conjunction with the Division of Head Surgery of the Office of the Surgeon-General and extend over a period of somewhat more than one year. During this period Lieut.-Col. Dean D. Lewis, Majors J. F. Corbett and Byron Stookey, and Capt. T. Roberg have in succession received assignment to the department of anatomy, University of Michigan, where this work has been carried on. To their initiative and untiring and hearty cooperation, the progress of the work and the results attained owe much.

In the prosecution of the experimental operative work strict asepsis was followed. So far as possible, the surgical technic was that of modern aseptic surgery. In practically all of the experimental operations union was by primary intention.

Owing to the difficulty of obtaining catgut sutures of suitable size and quality for uniting resected nerves, we were early in our work led to adopt a silk suture and as technic developed, Triple 0, Corticelli silk thread, unraveled so as to obtain three fine threads, became the standard suture in nerve repair. Before use, the sterilized threads were thoroughly waxed with sterile wax; this facilitating greatly the application of the suture. In practically all of our experiments of nerve transplantation the silk suture was passed through the nerve trunk and nerve transplant. The passing of a silk suture through a nerve trunk and transplant is innocuous, the silk suture becoming early encapsulated in a thin layer of connective tissue which does not materially interfere with the downgrowth of central neuraxes.

The tissues obtained from the animals operated on have for the greater part been stained after the pyridin-silver method, and for many of the experiments were sectioned at close intervals, in cross and longitudinal sections, for the length of the nerve operated on. This method gives a differential staining for the neuraxes, especially desirable in a study of the regenerative processes of peripheral nerves.

Regarding nerve regeneration, we maintain that regeneration of a degenerated portion of a peripheral nerve is through downgrowth of new neuraxes derived from the central nondegenerated portion of said nerve, the peripheral degenerated portion taking no immediate part in the regeneration of the neuraxes.

In the earlier stages of this experimental work, and in association with Lieut.-Col. Dean D. Lewis, the question of injecting absolute alcohol into a living nerve, and related problems, was dealt with in four series of experimental observations. Though not coming immediately within the scope of

the question under consideration, they have a bearing on certain of the experiments to be considered. In one of these series the use of absolute alcohol to obviate the formation of amputation neuroma was tested.

Series No. 1.—Sciatic of Rabbits.—Thirty-three experiments; respective animals under observation for periods varying from two to 157 days. The sciatic of rabbits was exposed and injected in about the middle of the leg with about 0.5 c.c. of absolute alcohol, in two or three point injections. The sciatic was then cut from 3 to 5 mm. distal to the point of injection and from 1 to 1.5 cm. of the distal sciatic stump resected. The wound was then closed. The operated animals were killed at intervals and it was observed that this simple procedure obviated the formation of amputation neuroma.

Series No. 2, a Control Series.—In this series it was ascertained that amputation neuromas form after every section of a peripheral nerve, even though the section be made under strict asepsis, with immediate closure of the wound and with wound healing by primary intention. In central nerve stumps injected with absolute alcohol, exposed and examined at stated intervals, it was noted that such central stumps terminate in a fine tapering end with no appreciable enlargement. From four to five weeks after section and alcohol injection, fine, newly formed neuraxes penetrate these tapering ends and may even grow beyond, but these down-growing neuraxes do not present the tangle and excessive proliferation of new nerve fibers noted in an amputation neuroma and there is primarily no proliferation of sheath cells. For use in human surgery it is recommended that from 1 to 2 c.c. of absolute alcohol be injected into the distal end of the nerve stump, from 1 to 2 cm. central to the cut end of the nerve. It is suggested, especially for the larger nerves, that a series of point injections be made, perhaps in two or three tiers, so that all parts of the nerve be reached with absolute alcohol. This method can be recommended as a simple and efficient method for preventing the formation of amputation neuroma.

Series Nos. 3 and 4.—In a further series the behavior of a living nerve injected in course with absolute alcohol or acetone, and without cutting the nerve, was experimentally studied. The injection of absolute alcohol into a living nerve causes fragmentation of neuraxes and myelin in the field coming under the immediate influence of the absolute alcohol. This fragmentation differs from that of Wallerian degeneration and is not accompanied by a primary proliferation of sheath cells. In due time, regeneration by the down-growth of central neuraxes follows. In cases of severe causalgia, in which section of the nerve is contemplated, injection of absolute alcohol without nerve section should be considered.

The great majority of our experiments have dealt with the question of bridging nerve defects of such extent that the severed nerve ends, after the necessary repair and resection, cannot be brought end to end, without undue tension, by process of simple suture. In this connection the question more immediately under discussion, namely, nerve transplantation, received especial consideration. In the series of experiments listed, the following nomenclature is used: A segment of nerve used to bridge a defect in a peripheral nerve, taken from another nerve of the same individual, is designated an *auto-nerve-transplant;* a segment of nerve taken from another individual, but of the same species, is designated a *homo-nerve-transplant;* a segment of nerve taken from another individual and of a different species is designated a *hetero-nerve-transplant.* Collateral questions, such as the use of certain membranous structures for purposes of sheathing a nerve-transplant and suture lines; the

question of the use of tubular sutures in nerve repair and of nerve suture under undue tension, subjected to experimental test, are not reported on at this time.

Experimental observations warrant the conclusion that bridging nerve defects by means of nerve transplants is a legitimate operation and one to be recommended in cases where there is loss of nerve substance of such extent that ordinary suture cannot be made without undue tension.

The experimental observations dealing with nerve transplantation and related questions are here considered under the following series:

Series No. 5. Auto-Nerve-Transplants.—Sciatic of dogs. Seventeen experiments, with respective animals under observation for periods varying from eleven to 382 days.

In these experiments the sciatic nerve was exposed and resected to the extent of from 2.5 to 3 cm. The resultant defect was bridged by means of a segment or several segments of nerve taken from one of the sensory cutaneous branches of the same dog. In our experiments the transplant was taken from the cutaneous radial branch. Since in surgical practice in dealing with the repair of the larger nerves, the resection of a normal nerve of approximately the same size for purposes of obtaining an auto-nerve-transplant is not justified, it has been the procedure to use for an auto-nerve-transplant a segment of one of the cutaneous nerves of much smaller size than the nerve to be bridged. The resultant difference in the size of the nerve to be bridged and the transplant has mitigated against obtaining optimum results. It occurred to us that this difference in size of transplant and nerve to be bridged might in a measure be overcome by making use of several segments of a smaller nerve to bridge a defect in a larger nerve. This procedure we designate a cable-auto-nerve-transplant. In eight experiments out of the seventeen of this series this method was tested by taking four segments of the cutaneous radial nerves to bridge a defect in the sciatic. These segments were sutured separately or in groups of two, both centrally and distally, between the resected ends of the sciatic. In the remaining nine experiments of this series the defect in the resected sciatic was bridged by using, respectively, one segment of the cutaneous radial, five experiments; two segments, three experiments; three segments, one experiment.

The observations made on these experiments may be summarized by stating that the "cable auto-nerve-transplant" presents a method for bridging nerve defects which gives every promise of favorable results. Within a few days after the operation the several segments of nerve transplanted become surrounded by connective tissue, so as to form an epineural sheath, binding them together in one nerve trunk in which the funicular arrangement of the several nerve segments transplanted is fully maintained. Downgrowing neuraxes coming from the central stump penetrate and pass through the several funiculi to reach the distal segment which in time becomes penetrated by new neuraxes. These experiments have been carried on for a time of sufficient length to obtain new motor nerve endings in the calf and plantar muscles and evidence of sensory regeneration. It is admitted that this operation is tedious, requires care and some skill and necessitates the making of a second wound. However, the experimental results justify its recommendation. In surgical practice the cutaneous radial and the cutaneous portion of the musculo-cutaneous of the arm, the lesser sciatic, and especially the sural of the leg may at convenience be selected as the nerves from which segments for a cable auto-nerve-transplant may be taken.

Series No. 6. Homo-Nerve-Transplants.—Sciatic of rabbits: seven experiments, with respective animals under observation for periods varying from eight to eighty-three days.

In these experiments a segment from the sciatic of one rabbit was used to bridge a defect in the sciatic of another rabbit experimentally resected. These experiments show that a fresh homo-nerve-transplant may be employed to bridge a nerve defect with every promise of success. Since chance alone would permit this operation in surgical practice other experiments dealing with homo-nerve-transplants were devised and will be considered in this report.

Series No. 7. Hetero-Nerve-Transplants.—Sciatic of rabbits: thirty-nine experiments. In sixteen of these the two sciatics of half grown guinea-pigs were used to bridge a defect in the sciatic of grown rabbits; in twenty experiments one of the sciatics of a full grown guinea-pig was used to bridge a defect in the sciatic of a full grown rabbit; in three experiments one of the major nerves of a dog was transplanted to a sciatic of a rabbit. The respective animals were under observation for periods varying from three to over 300 days.

The question of the possibility of using hetero-nerve-transplants is of academic and practical interest. The ease with which fresh, normal nerves may be obtained as hetero-nerve-transplants warrants the interest taken by surgeons in experiments dealing with hetero-nerve-transplants. Opinions current in literature are not unanimous as concerns experimental observations on hetero-nerve-transplantation. Our own results may be summarized in this brief abstract in the statement that neurotization of the distal stump through a hetero-nerve-transplant is experimentally possible. However, the results obtainable are not as certain and not as favorable as when auto-nerve-transplants or homo-nerve-transplants are used, and the resultant distal regeneration not as complete. Therefore, this procedure cannot be recommended as an operation of choice in surgical practice.

The following series of experiments deals with the use of degenerated auto-nerve-transplants, homo-nerve-transplants and hetero-nerve-transplants. Every nerve transplanted undergoes degeneration. Whether nerves degenerated before transplantation would prove more favorable for downgrowth of central neuraxes than nerve transplants taken from fresh, normal nerves which would undergo degeneration after transplantation, seemed worthy of experimental test.

Series No. 8. Degenerated Auto-Nerve-Transplants.—Sciatic of dogs: three experiments; respective animals under observation for periods varying from 127 to 416 days.

In this series of experiments the sciatic nerve was cut and the wound closed. About twenty days later the cut sciatic was again exposed and a segment of the degenerated distal stump transplanted to the resected ulnar of the same dog. The experiments of this series are too few to warrant drawing definite conclusions. The statement seems justified that regeneration of the distal stump of a resected nerve through a degenerated auto-nerve-transplant is possible, but that such regeneration is not more favorable nor more rapid than when a nondegenerated auto-nerve-transplant is used.

Series No. 9. Degenerated Homo-Nerve-Transplants.—Sciatic of dogs: five experiments; respective animals under observation for periods varying from seventeen to 328 days.

For this series the sciatic nerve of a number of dogs was cut and the wound closed. Some twenty to thirty days later the cut sciatic was again exposed and a segment taken from the degenerated distal stump and transplanted to bridge

a defect in a resected sciatic of another dog. The observations made on these experiments warrant the general conclusion that regeneration of the distal stump of a resected nerve may be obtained through a degenerated homo-nerve-transplant. The possibility of using a degenerated nerve as a homo-nerve-transplant in surgical practice is warranted by these observations.

Series No. 10. Degenerated Hetero-Nerve-Transplants.—Sciatic of rabbits: eighteen experiments; respective animals under observation for periods varying from three to 244 days.

For these experiments one of the major peripheral nerves of a dog was cut and allowed to degenerate for periods varying in the respective experiments from about twenty to thirty days. A segment of the degenerated nerve was then transplanted to the resected sciatic of a rabbit. The syncytial, nucleated strands found within the sheaths of degenerated peripheral nerves, having undergone Wallerian degeneration, may be regarded as simulating embryonic tissue. Such tissue, it was argued, should prove more favorable for downgrowth of central neuraxes than would be the nondegenerated nerve fibers of a hetero-nerve-transplant. The observations made on this series of experiments do not bear out this assumption. It was observed that the degenerated hetero-nerve-transplant undergoes a secondary degeneration. In certain of the experiments downgrowth of the central neuraxes through and on the degenerated hetero-nerve-transplant was obtained. However, the results, even in the experimental observations, were so uncertain that the adoption of this procedure in surgical practice is not warranted.

The following series of experiments was devised to test the possibility of storing homo-nerve-transplants for a period of several weeks before use. The possibility of obtaining human nerves under aseptic precaution, from amputated limbs, and storing them until operative procedure demands their use, would obviate the difficulty experienced in surgical practice of obtaining fresh human nerves on demand.

Series No. 11. Homo-Nerve Transplants Stored in Petrolatum.—Sciatic of rabbits: eight experiments; respective animals under observation for periods varying from sixty-six to 155 days.

Dujarier and Francois (*Bull. et mém. Soc. de chir. de Par.* **44**: : January, 1918), in a series of twenty-four cases reported the use of homo-nerve-transplants stored in petrolatum before use in operative procedure. They recommend that the nerves be removed from amputation stumps under aseptic precautions, and placed at once in warmed, sterile petrolatum and then kept at nearly 0 C. temperature. Nerves were thus kept for several weeks. Before use, the petrolatum was again warmed, the nerve removed and washed in warm sterile serum. Twenty-four cases were operated on and reported before sufficient time had elapsed to enable determining the ultimate results. It is reported that in all cases but one the healing of the wound was by primary intention.

At the time our experiments were undertaken we were unable to find any experimental observations on this method. In our experiments the method suggested by the French observers was followed as closely as the brief account descriptive of the method permitted. The sciatics of full grown rabbits were removed under asepsis, placed at once in sterile petrolatum contained in tubes warmed to the melting point of the petrolatum. The tubes were then placed in a small ice chest kept at constant temperature of 3 C. In the several experiments, after periods varying from four to thirteen days, the nerves thus treated were used to bridge defects of about 3 cm. lengths, caused

by resection of the sciatics of rabbits. The results of these experiments are gratifying. Functional return was noted in the experiments of longer duration. Time has not permitted a histologic study of the tissue removed. In the experiments of shorter duration a microscopic study of the transplant shows abundant down growth of central neuraxes through the transplant. The experimental observations warrant the statement that this method, as suggested by the French observers, deserves consideration in surgical practice.

Series No. 12. Homo-Nerve-Transplants Stored in Liquid Petrolatum.—Sciatic of rabbits: forty experiments; respective animals under observation for periods varying from one hour to 229 days. (To date, certain of the animals are still under observation.)

Under the method of storing nerves in petrolatum (Series No. 11) it is necessary to warm the petrolatum to the melting point before the nerve segment can be placed therein, likewise when the nerve segments are removed therefrom. To obtain sterile serum is not always easy. For these reasons we have devised a simple method which consists in storing nerves in liquid petrolatum. We have used Squibb's liquid petrolatum. This is a clear, bland fluid. The required quantity was placed in large tube-vials, corked with cotton plugs, then autoclaved on successive days. After cooling to room temperature, the tubes with liquid petrolatum were placed in the ice chest and cooled to 3 C. The sciatics of full-grown rabbits were removed with asepsis, placed in the cooled and sterile liquid petrolatum and kept at 3 C. Nerve segments thus stored in liquid petrolatum were used in the several experiments after storage of from four to thirty-nine days, as nerve transplants to bridge defects of approximately 3 cm. length in the sciatic of rabbits. For each experiment the tube containing the nerve transplant was taken from the ice chest just before the operation, and when required, the nerve transplant was taken from the liquid petrolatum, and this allowed to drain off by holding the nerve segment suspended from one end by means of forceps. Sutures were then placed near each end of the nerve segment and the ends cut by means of sharp scissors to within about 2 mm. of the sutures. The nerve segment was then sutured to the two ends of the resected sciatic. Nerves stored in this manner even for a period of thirty-nine days, retain their color and consistency remarkably well. The experimental animals of this series of longer duration, six months and over, have not as yet been killed and examined. The experiments completed and fully studied warrant the conclusion that neuraxes derived from the central end will grow through a homo-nerve-transplant, having a length of 3.5 cm., and stored in liquid petrolatum for a period of somewhat over five weeks, quite as well as through a freshly removed homo-nerve-transplant. Very satisfactory neurotization of the degenerated distal segment has been obtained through a homo-nerve-transplant stored in liquid petrolatum, having a length of somewhat over 3 cm., 100 days after the operation. Experimental observations warrant the statement that the use of human nerves obtained from amputated members and stored in liquid petrolatum as here directed, for the purpose of bridging nerve defects, deserves serious consideration as a surgical procedure.

Series No. 13. Homo-Nerve-Transplants Stored in Sterile 50 Per Cent. Alcohol.—Sciatic of rabbits: eighteen experiments, with respective animals under observation for periods varying from two to 151 days. (Certain animals of this series are still under observation.)

Nageotte (*Bull. et mém Soc. de chir. de Par.* **44**: 1918) has recommended the use of nerve transplants stored in 50 per cent. alcohol. For this series

the sciatics of full-grown rabbits were removed under asepsis and placed at once in 50 per cent. alcohol contained in wide-mouthed glass-stoppered bottles. In the 50 per cent. alcohol the nerve segments were stored for periods varying in the several experiments from seven to twenty-nine days. Just before use as a nerve transplant the nerve segment was taken from the 50 per cent. alcohol and placed in a dish containing sterile normal salt solution in which they remained from fifteen to twenty minutes. When taken from the 50 per cent. alcohol the nerve segments are quite hard, though not brittle. After a short stay in the normal salt solution they again become quite pliable. The nerve segments were taken from the normal salt, sutures placed, the ends freshened by cutting with sharp scissors about 2 mm. from the suture lines and the operation completed by transplanting the nerve segment into a defect caused by resection of the sciatic of a rabbit. Time has not permitted conclusive observations on this series. The observations made thus far indicate clearly that downgrowing neuraxes coming from the central stump penetrate readily a homo-nerve-transplant having a length of 3 cm. and stored in 50 per cent. alcohol for nearly four weeks, and thus guide the downgrowing neuraxes to the degenerated distal stump.

In this series of experiments of homo-nerve-transplants stored in petrolatum, liquid petrolatum, or 50 per cent. alcohol, the observations indicate that the nerve segments thus stored do not retain a latent viability. The sheath cells of the transplants show no evidence of proliferation and appear not to have a biologic significance. The neurolemma sheaths of the transplanted nerve fibers are well preserved and through these the downgrowing neuraxes of the central stump find ready paths and thus reach the distal stump. Therefore, it seemed desirable to test the behavior and the value of hetero-nerve-transplants stored in liquid petrolatum and 50 per cent. alcohol and for this purpose the following series of experiments were undertaken.

Series No. 14. Hetero-Nerve-Transplants Stored in Liquid Petrolatum.—Sciatic of rabbits: six experiments, respective animals under observation for periods varying from five to 117 days. (Certain of the animals of this series are still under observation.)

For this series certain of the major nerves removed from dogs under strict asepsis were stored in liquid petrolatum, as described under series No. 12, for periods varying from eleven to twenty-five days, and then used as nerve transplants to bridge defects in the sciatic of rabbits caused by resection. None of the longer time experiments of this series have thus far been studied histologically. Therefore, no conclusions as to the value of this method can at the present time be drawn.

Series No. 15. Hetero-Nerve-Transplants Stored in 50 Per Cent. Alcohol.—Sciatic of rabbits: three experiments, respective animals under observation for periods varying from sixty-four to 117 days. (Two of the animals are still under observation.)

For this series certain of the major nerves of dogs were removed and stored in 50 per cent. alcohol as described in Series No. 13. They were then used to bridge defects in the sciatic of rabbits. Two of the animals of this series are still under observation; the other experiment was terminated by death of the animal too soon after operation to admit of drawing definite conclusions.

References are frequently made in surgical literature to the use of certain membranous structures employed as sheaths which are wrapped about nerve transplants or suture lines. Concerning the necessity or value of such sheaths

there is no unanimity of opinion. The following series of experiments was undertaken to test their value. It should be stated that it is here recognized that the clean, surgically aseptic, operative wounds in animal experiments, made through normal tissue, do not simulate the operative wounds in surgical practice in many cases of secondary nerve suture, made in the presence of abundance of cicatricial tissue. However, it was hoped that certain general principles might be ascertained to serve as guides in surgical practice.

Series No. 16. Auto-Nerve-Transplant with Nerve Transplant and the Suture Lines Wrapped in Several Layers of Cargile Membrane.—Sciatic of dogs, thirteen experiments, with respective animals under observation for periods varying from twenty hours to 359 days.

In these experiments we made use of Cargile membrane prepared by Johnson & Johnson. The left sciatic and the right ulnar nerves of respective dogs were exposed and a segment of the right ulnar from 3 to 4 cm. long was transplanted to bridge a defect in the sciatic, caused by resection. After suturing the transplanted ulnar, the transplant and the sutures were surrounded by two or three layers of Cargile membrane, closely applied and wrapped about the nerve. The wound was then closed. Untreated Cargile membrane, as here used, it was found, was absorbed within a period of ten days; that is to say, before it could serve a purpose in preventing connective tissue formation in the immediate vicinity of the transplant and suture lines. Therefore, its value in surgical practice is seriously questioned.

The difficulty of obtaining Cargile membrane at the time these experiments were made led us to attempt resterilization of that portion of each membrane not used at any one operation. This was accomplished by placing the same in 70 per cent. alcohol in which they were stored, often for days. Before their use they were placed several hours in absolute alcohol and before use in operations taken from the absolute alcohol, spread out on dry sterile towels and allowed to dry. In five of the thirteen experiments of this series such alcoholized Cargile membranes were used to wrap the nerve transplant. It was found that this very simple method very materially alters the absorbability of the Cargile membrane as found in the market. In one experiment terminated nearly five months after the operation distinct evidence of the Cargile membrane was found. In another experiment terminated nearly seven weeks after the operation the alcoholized Cargile membrane was found to have been practically unaltered and remained closely wrapped about the nerve. There was evident no material increase of connective tissue about the alcoholized Cargile membrane thus used as a sheath.

The use of alcoholized Cargile membrane, prepared as above stated in double or triple layers, as a sheath for wrapping nerve transplant or suture lines after nerve suture, when such sheathing is deemed necessary, deserves consideration in surgical practice.

Series No. 17. Auto-Nerve-Transplant Wrapped in Auto-Fascial Sheath.—Sciatic of dogs, fifteen experiments, with respective animals under observation for periods varying from fourteen to 324 days.

In this series of experiments the left sciatic and right ulnar, or vice versa were exposed and a segment of the ulnar transplanted to the sciatic. After suturing the transplant in place this was wrapped in a piece of fascia recently taken from the same dog. The fascial membrane taken was removed and trimmed to such size that when applied it extended about 8 mm. beyond the central and distal suture lines of the transplant, and when wrapped about the nerve formed a closely fitting tube with edges overlapping about 5 mm.

Fine silk stay sutures and several half mattress sutures were placed to hold the sheath in position and complete the tube. The experiments of this series admit the general conclusion that an auto-fascial sheath is very slowly absorbed, evidence of its persistence having been observed three months after operation. However, even in the aseptic wounds made in normal tissue, where use could be made of the fascial planes for exposing the nerves, there is observed a distinct connective tissue proliferation about the fascial sheath, to such extent as to prejudice against this procedure in surgical practice, especially in operations where nerve repair is made through and in cicatricial tissue.

Series No. 18. Auto-Nerve-Transplant with Nerve Wrapped in a Formalinized Arterial Sheath.—Sciatic of dogs, eight experiments, with respective animals under observation for periods varying from six to 241 days.

In this series of experiments the left sciatic and right ulnar, or vice versa, were exposed and a segment of the ulnar transplanted to bridge a defect in the resected sciatic. After the transplant was sutured in place, this was surrounded by a sheath prepared from the wall of a formalinized artery. The carotid arteries of large dogs were removed and stretched over glass rods of suitable size. They were then fixed in 5 per cent. liquor formaldehydi for forty-eight hours; washed in water twenty-four hours; boiled in distilled water for twenty minutes; then stored in 70 per cent. alcohol in sterile, wide-mouthed, glass-stoppered bottles for from several days to several weeks, as necessity demanded. Before use, a segment of the fixed artery of required length was slipped from the glass rod, cut longitudinally along one side and placed in sterile normal salt solution for about thirty minutes. The arterial sheath thus prepared was then wrapped about the nerve transplant and allowed to extend over the suture lines about 5 mm. and fixed in place by central and distal stay sutures and several half mattress sutures, using fine silk. The experiments of this series admit of drawing the following general conclusion: that a formalinized arterial sheath, prepared as above stated, remains in place and without absorption for several months, and this without inciting material increase of connective tissue. It is more particularly the elastic tissue of the vessel wall that resists absorption. Since formalinized arterial sheaths are easily prepared and may be kept on hand in sterile condition in 70 per cent. alcohol, and are easily applied, this method deserves consideration in surgical practice, when sheathing of a transplant or suture line in nerve repair is deemed desirable.

Series No. 19. Auto-Nerve-Transplant with Completely Detached Auto-Fat Sheath.—Sciatic of dogs, two experiments; animals under observation, one, four days; the other, 324 days.

In this series the left sciatic and right ulnar were exposed and a segment of the ulnar transplanted to the sciatic. The nerve transplanted and the suture lines were then wrapped in a membrane of subcutaneous fat, taken from the same animal to one side of the sciatic wound. After removing the membrane of fat, which had an average thickness of about 5 mm., this was gently washed in sterile normal salt solution, so as to remove as far as possible the adherent blood, and was then wrapped about the nerve transplant and suture lines. The sheath was held in place by the use of several fine silk stay sutures. One of these experiments was terminated by the death of the animal four days after operation; in the other, the animal was killed 324 days after operation. In the latter experiment, regeneration of the distal segment was obtained. However, the region of the transplant was surrounded by a distinct layer of dense fibrous tissue occupying the region of the fat sheath and binding the trans-

plant to the subcutaneous tissue. Definite conclusions based on this single experiment hardly seem warranted. However, the result obtained argues against the use of a complete detached fat sheath, even when this is taken from the same animal, since the fat membrane is replaced by dense fibrous tissue.

Series No. 20. Tubular Suture by Use of Formalinized Artery.—Ulnar nerve of dogs, twelve experiments, respective animals under observation for periods varying from four to 298 days.

In this series we made use of the resected ulnars of certain of the experiments in Series Nos. 16 to 19, to test experimentally the value of an arterial tubular suture as recommended by Foramitti and since used in the Russo-Japanese war by Hashimoto. The formalinized arterial tubes were prepared as stated under Series No. 18, essentially as described by Foramitti. Before use, the formalinized carotid artery of a large dog was taken from the glass rod and a segment about 1 cm. longer than the defect in the nerve to be repaired was removed and placed for about one-half hour in sterile normal salt solution. A fine silk suture armed with a fine needle at each end was then passed through the central and distal stump of the resected ulnar, about from 2 to 3 mm. from the cut ends. The needles of each suture were then passed through the opposing sides of the formalinized arterial tube from 7 to 8 mm. from the respective ends of the tube and the ends of the resected nerve, central and distal, drawn into the lumen of the arterial tube and held in place by knotting the silk sutures over one side of the arterial tube. The wound was then closed by using the necessary fascial and skin sutures. In this series of experiments no nerve-transplant was inserted, the ends of the resected ulnar, from 4 to 5 cm. apart, were merely inserted into the ends of the arterial tube and kept in place by means of stay sutures.

In this series, as stated for series No. 18, it was found that the formalinized artery resists absorption for a period of at least three months. In certain of these experiments it was evident that one or the other of the ends of the nerve had been pulled out of the lumen of the arterial tube some time soon after the completion of the operation. In two of the experiments of more than three months' duration neurotization of the distal ulnar was obtained through downgrowing neuraxes of the central stump, conveyed to the distal stump through the lumen of the formalinized artery. This series confirms the possibility of obtaining regeneration of the distal degenerated end of a nerve, after loss of from 4 to 5 cm., through a tubular suture in case the tubular suture resists absorption for a period of sufficient length to admit of downgrowth of the central neuraxes to the extent of reaching the central end of the degenerated distal stump. However, the method cannot be recommended for adoption in surgical practice since other methods for bridging nerve defects offer greater assurance of success.

Series No. 21. Direct Suture of Nerves Under Tension.—Ulnar nerve of dogs, eleven experiments, respective animals under observation for periods varying from twenty-two to 324 days.

In this series use was made of the resected ulnar nerves of certain of the experiments in Series Nos. 16 to 19. A silk suture was passed through the central and distal stumps of the ulnar, resected to the extent of from 4 to 5 cm. and by applying tension and flexing the limb the resected nerve ends were brought to as close approximation as possible and sutured. In a number of these experiments the line of suture was wrapped with several layers of alcoholized Cargile membrane or a formalinized artery sheath was applied. In other experiments the wound was closed without sheathing the

suture line. Purposely, no endeavor was made to immobilize the limb. On opening the wounds in the several experiments at stated intervals, it was noted that in all but one experiment the suture had torn out either centrally or distally and that the nerve ends had separated for a distance about equal to that obtained before the tension sutures were applied. In the one experiment in which the suture did not appear to have been torn out, limited neurotization of the distal stump was obtained.

DISCUSSION

LIEUT.-COL. DEAN D. LEWIS: We are to be congratulated on having this paper presented at the present time when so many peripheral nerve injuries are being treated. There is one thing that I think has been definitely demonstrated; namely, that all regeneration takes place from the proximal stump. I also believe that it has been definitely proved that without protoplasmic bands no regeneration takes place. That is illustrated in section of the spinal cord or in section of the optic nerve.

I believe all peripheral nerve surgery should be taken care of in evacuation hospitals and that in all cases primary suture should be done. It is exceedingly interesting to study peripheral nerve injuries in the evacuation hospital, say fifteen hours after injury. In all the cases I have seen, either from high explosives or machine-gun bullets, the nerves immediately after section have been found contused. A machine-gun bullet may make a perfectly clean hole, but if one examines the peripheral nerves, one finds on each side of the defect for half an inch that all elements of the nerve are destroyed. So if an attempt is made to make suture, considerable approximation must be accomplished to get neurofibrilla in contact with neurofibrilla. In the musculospiral it is practically impossible to approximate these without flexion of the elbow, or in the sciatic without flexion of the knee to a right angle.

There has never been much opportunity to study these nerves that had primary suture. It is unfortunate that the primary sutures at the evacuation hospitals are so distributed in this country that it is impossible to make a study. At Fort Sheridan I have found only one case of extensive primary suture. Quite a number of the cases, in fact the majority of them, have had a separation of the nerve ends with a neuroma. They have had complete loss of function primarily, but they have gradually improved. Now, six or seven months after the injury, we find that this preliminary return of function has come to a stationary point. I operated on two cases this morning, which had improved rapidly for some time, but for the last three months had been stationary. In one of these cases, which was the sciatic, I found just a few adhesions. The only thing to do was to excise the neuroma and attempt a neurolysis and suture the healthy muscle above and below and wait for return of function. The second case I operated on this morning had what was theoretically a complete ulnar lesion and a partial median lesion. The ulnar had a very distinct lesion of the nerve with some of the funiculi destroyed and yet there were enough funiculi left to conduct the impulses through. The median was bound in scar tissue. It was merely an indication for neurolysis. There are very many cases with division of both nerves. The most serious are the lesions in the arm in which the median and ulnar are divided. It is surprising that an ulnar lesion alone is less frequent than an ulnar combined with a median. If you flex the forearm to get an end-to-end suture of the separated ends of the ulnar, it is difficult to handle the

median. It is much better to make an end-to-end suture of the median and to transplant in the ulnar than to sacrifice the ulnar by doing some other operation on the median.

There is no doubt that the ideal nerve repair is end-to-end suture and that it should be attempted in all cases. To resect the humerus in order to make an end-to-end suture of the median or the ulnar, in my opinion, should never be done.

In lesions of the sciatic of over 2½ inches' defect, one can flex the knee to a right angle and immobilize and close a defect of nearly 2½ inches. In the case of the ulnar just above the wrist-joint, it is practically impossible to close any defect by flexion of the wrist. In these cases an auto-transplant ought to be used. In most of these cases you can get an auto-transplant directly from the site of your operation. For instance, in the case of the median or ulnar, you can use the cutaneous branch. I think that is the operation of choice. In cases where you cannot well sacrifice the cutaneous nerve, I think a man is justified in using some form of tubulization, using either a formalinized artery or a fascial tube. A fascial tube has a distinct limitation in all these injury cases, because a fascial tube transplanted in the presence of scar tissue will become scar tissue. That is the fate of fascial tubes in all these wounds.

I think we have three things to take into consideration. First, primary end-to-end suture on those cases with small nodules in the nerve. Then linear section and auto-neurolysis with the idea of allowing the nerve to expand to allow the nerve axons to grow through. Second, combined with this, the operation in which one dissects off the scar tissue . Third, if one cannot bridge the defect, an auto-transplant should be used.

In all these nerve operations we must consider the after-treatment. There are some sad things happening in war surgery by over-emphasis of certain points. Thomas, years ago, said that all paralyzed muscles should be placed at rest. We heard for many years about the cocked-up splint for musculospiral paralysis. Now, some of these boys have worn the cocked-up splint for the cure of drop-wrist for so long that they have an ankylosis of the wrist. It is just as harmful to over-stretch healthy muscles as it is to maltreat paralyzed muscle. To make a primary suture is by no means to finish the case. The after-treatment is most important in the correction of the paralysis.

Another thing sometimes forgotten is that up to the present time we have not had the opportunity of studying the results of our operations on nerves. I do not believe we can say anything about the return of function in these cases, even in the musculospiral or popliteal, for at least seven months. It would be very unfortunate if any of these wounded men were discharged before the period has expired in which we can expect a regeneration, because if we are going to learn anything in the line of peripheral nerve surgery from this war, these men must be watched for at least two years before we can make definite statements in regard to operations on peripheral nerves.

MAJOR LEWIS J. POLLOCK said that statistics relative to the incidence of peripheral nerve lesions sustained in battle were not as yet available. Those obtained from reports of the American Expeditionary Forces were not reliable for the reason that many cases of peripheral nerve lesions were not referred to the neurologist. As a result a large number of patients suffering with severe wounds, or those requiring complicated dressings were not observed from the neurologic standpoint. As consultant to a number of base hospitals, Major Pollock had between thirty and fifty such cases referred to him during a

month from each of these hospitals. A survey made of the cases brought to his attention on Sept. 7, 1918, when the population of the hospital under investigation was 1,440, revealed forty cases, or a percentage of 2.77.

In the early part of November, 1918, the total figures submitted to the chief consultant in neuropsychiatry led him to believe that the percentage of peripheral nerve cases in the American army was 1.76. This did not approach the figures given by the French and British, which were nearly 6 per cent. At this time a bed to bed examination of all patients wounded in extremities was made and in four hospitals under Major Pollock's supervision it was found that of 2,130 cases examined, 332 had peripheral nerve lesions. The total population of these hospitals at the time was 7,050. The percentage of peripheral nerve lesions in the total population was 4.5. The percentage of peripheral nerve lesions in cases examined was 14.9.

Analyses of the types of lesions seen were inaccurate for similar reasons. The prominence of certain clinical symptoms in some injuries made it necessary to submit such a case to the neurologist, so that ulnar lesions were very frequently referred to the neurologist whereas median lesions were frequently overlooked. Internal popliteal lesions were rarely referred to the neurologic department.

The lack of standard nomenclature often contributed to the reports of internal popliteal lesions where a partial sciatic lesion was present.

The striking feature of the clinical picture of early nerve lesions was the large percentage of marked and rapid improvement. An analysis of the first 100 cases seen in Base Hospital No. 13 showed that after three months sixty-one cases had been discharged. Twenty of these cases had sufficiently recovered to be sent to convalescent and replacement camps. Thirty-nine cases remained in the hospital; twenty of these were manifestly partial lesions, and only five were so severe as definitely to indicate the necessity for surgical interference.

The actual percentage of recoverable cases of peripheral nerve lesions can only be ascertained when accurate statistics of the cases suffering with disability as the result of a peripheral nerve lesion may be compared to statistics of the occurrence of peripheral nerve lesions in battle. It might be mentioned that probably 10,000 peripheral nerve lesions were sustained in battle. Not very many more than 3,000 cases had been classified as peripheral nerve cases in the hospitals in the United States. Only one third of the cases observed in United States General Hospital No. 28, Fort Sheridan, Ill., would require operative interference and of these cases but the smaller proportion would require nerve suture.

DR. W. R. CUBBINS: I would like to ask the essayist the age of the animals that were used and if the transplants were put into nerves that were freshly sectioned or into nerves that had been traumatized.

DR. A. B. KANAVEL: I would like to ask one question: In the transplantation of tissue from one person to another is it not a good plan to test the cytolytic action of the serum of the donor on the serum of the recipient of the transplanted tissue? In man it may differ from that of the lower animals. In man we more often have a cytolysis that affects the cells of the transplant. Before I went to war I was engaged in the experimental investigation of transplantation and we had very great difficulty to obtain dogs in which we could show hemolysis.

As to the combined injury of the ulnar and median: When there was a defect in the ulnar that was difficult to bridge, I transplanted the ulnar to the

anterior surface of the joint thus, placing the nerve on the flexor instead of on the extensor surface. In that way I have been able to treat both lesions.

PROFESSOR HUBER (closing): In all these experiments except the first few in the treatment of neuroma, practically all the dogs that were used were 2 or 3 years old. I have only two experiments of secondary transplantation in which the neuroma was cut out and transplant put in. One of these happened to be a homo-degenerated nerve and the other was a homo-transplant. Personally, I feel that it makes no difference whether we are operating on fresh animals or not. I think in all this work we are simply gaining practice that can be applied to surgical technic. I think one could remove a neuroma not only once but several times, and the neuroma will reform and reform. I think the surgeons have had that experience with their methods in the past, and have found that neuromas reform after they have been removed. That means, of course, a new outgrowth from the stump. I cannot say how many times that will take place, but I know it will take place a number of times. I think as far as the neuromas are concerned that they will grow down from the stump after the primary injury. There is a little doubt as to how long after degeneration the nerve fibers will go down into the peripheral stump. I think Colonel Lewis collected statistics for a time, and I think he found that after the ninth month this occurred, but up to the ninth month it made very little difference as to the time that elapsed between the operation and the suture. After the ninth month there was a difference in the result, although, as I recall, there were successful cases in which the suture was done years later.

I feel that the transplant may be either an auto, hetero, or one of the homo sort in case of secondary suture if enough of the stump is removed to get above the neuroma into the healthy tissue. The neurons will grow just as they did primarily. If there is no transplant, there will be formed a new neuroma.

I am aware of the situation as far as human surgery is concerned with reference to hemolysis and the other condition that Dr. Kanavel speaks of. I do not think it is necessary to have a living transplant. I think stored transplants show that qualification. I was myself surprised to see neuraxes growing down in the transplant after it had been soaked in 50 per cent. alcohol, and still they grow down in a nerve that has been injected with absolute alcohol, as is done in cases of neuralgia. I suppose even Dr. Patrick has had cases of recurrence of the neuralgia after injections of alcohol.

DR. PATRICK: It *always* returns.

DR. HUBER: There is very good experimental evidence. I believe that the neuron sends out neuraxes which make use of the neurolemma sheaths as paths of least resistance and reach the peripheral stump in that way. I want to take this question with methods other than the silver staining. I think some time, if time permits, I shall study again nerve regeneration in the central nervous system and optic nerve. I am not quite certain whether the opinion of surgeons and experimenters in regard to regeneration in the central nervous system and in the optic nerve is correct, and whether after all there is not an attempt at regeneration. We have in the central nervous system and in the optic nerve no neurilemma sheaths. We have no paths of least resistance, no little tubes through which the axons can pass. We have neuroglia which is very quickly replaced by connective tissue. I believe one will be able to show that if the central root is cut and sutured, the neuraxes will pass up

into the cord so far as there are neurolemma sheaths, and then form a neuroma inside as soon as you get into the tissues of the central nervous system. I do not recall any very recent work. I do not recall any careful experimental work more recent than that of Ströbe, with the technic of whose work I am familiar. I used it in 1895, and since that time I think we have learned to stain neurons better than Ströbe stained them.

Surgeons who are familiar with the work of Foramitti in using formalinized artery tubes may know that these artery tubes, calves' arteries, were used by Hashimoto in the Russo-Japanese War, and used in the Balkan War extensively. We have used this method in perhaps six or eight cases, but we used with them an auto-transplant. These I have not reported on tonight. In a number of cases we bridged the gap in the ulna of 4, 4½ or 5 cm., by inserting the ends of the resected nerve into the lumen of the formalinized artery. In two of these cases the neuraxes reached the peripheral stump and there was observed regeneration of the peripheral stump, but not so good as when a transplant was used. It is a method that could be used. I feel I cannot state from personal experience that there is not the same amount of connective tissue formation following the use of a formalinized artery as with a fascial tube. The formalinized artery will remain in place and is not absorbed, at least for six months after implantation. The neurons pass down through the lumen of the tube and reach the peripheral nerve stump.

PHILADELPHIA PSYCHIATRIC SOCIETY

Regular Meeting, May 9, 1919

CHARLES S. POTTS, M.D., *President*

DRUG TOXEMIAS, THEIR NATURE, ETIOLOGY AND SYMPTOMATOLOGY. Presented by DR. JOSEPH C. DOANE.

Dr. Doane said that since March 1, 1915, when the Harrison law became effective, much misplaced sympathy had been lavished on the drug taker. Cheap sensationalists had seized on the subject of drug diseases to add to their own incomes, without any knowledge of the subject, or any desire to do good. The stage had also aided to disseminate misconceptions as to the nature of the disease, and such publicity had only added to the number of persons who needed only to know of a vice to become vicious.

The term "drug habit" was not descriptive, for the continuance of the use of a drug was not truly a habit. The physiologic action of the drug did not explain the etiology of drug disease. Symptoms of withdrawal yielded to the drug which brought about withdrawal pain and might partially explain drug abuse. Rather did it seem that drug addiction was but a symptom of some physical, moral or mental abnormality, and that moral and mental degeneracy were but the parents that begot the litter in which drug inebriety, sexual perversion and other social monstrosities were numbered.

Out of a series of 393 cases of drug disease studied at the Philadelphia General Hospital, 267 began the use of drugs on the advice or example of others so afflicted. It appeared, then, that drug disease was but an inevitable expression of some abnormal moral or mental trend, and that this particular form of expression was more or less accidental. Relief of pain, physicians'