THE USE OF HEPARIN IN THROMBOSIS*

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THE discovery of heparin in Howell's laboratory, in 1916, and his demonstration that it was a natural anticoagulant of blood, raised hopes that it might also be a preventive of thrombosis. Unfortunately the early experiments on animals and the clinical use of the drug as a preventive of clotting in blood transfusions were discouraging, owing to the toxic symptoms produced. In 1929, however, one of us (C. H. B.) initiated research on the purification of heparin, in the Connaught Laboratories, and Charles and Scott[1] succeeded in preparing it in the form of a crystalline, barium salt, which was 100 times more potent than the original crude material and completely free of toxic properties. This success revived our interest in the possible clinical value of the drug and encouraged us to study, both upon animals and patients, its influence on those pathologic conditions which are based upon thrombosis.

That heparin has a profound influence in preventing thrombosis has been amply demonstrated by a long series of experiments upon animals, begun in the Department of Surgery, in 1932, and reported elsewhere,[2] in which it was shown that the thrombosis, which normally results from mechanical (Fig. 1) and chemical injuries to veins, could be prevented in a high percentage of cases by its intravenous administration. This suggested that, if it could be given safely to patients, it might be used as a prophylactic in those conditions which lead to postoperative pulmonary embolism, and as an adjuvant in those operations upon blood vessels in which the outcome has been so doubtful, because of the tendency of thrombosis to occur at the site of the operation.

Experimental Investigation.—The early experiments on toxicity were done on dogs, using heparin of a potency of 15 units per mg. In these animals, when the clotting time had been prolonged to half an hour, muscular weakness and vomiting developed, and when larger doses were given the animals died of profuse intestinal hemorrhage. The postmortem examinations disclosed multiple hemorrhages in all the organs and beneath all serous surfaces. These results led to the efforts to purify heparin and ultimately to the preparation of an extract with a potency of 250 units per mg. This preparation produced no toxic effects on animals even when the clotting time was prolonged to four hours. This encouraged further experimental study.

Arterial Anastomosis.—While great improvement has been made in the results of operations on the blood vessels by the development of special technic, there still remains a high percentage of cases in which operations on arteries and veins fail because of thrombosis at the line of suture. In the

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hope that heparin might improve the results, a series of experiments was performed in which the axillary, femoral and carotid arteries in dogs were sectioned and then sutured with fine silk. In 50 such experiments, in which regional heparinization was used, the arteries remained patent in 40, or 80 per cent; whereas, when no heparin was used, only 18, or 35 per cent, re-

FIG. 1 FIG. 2

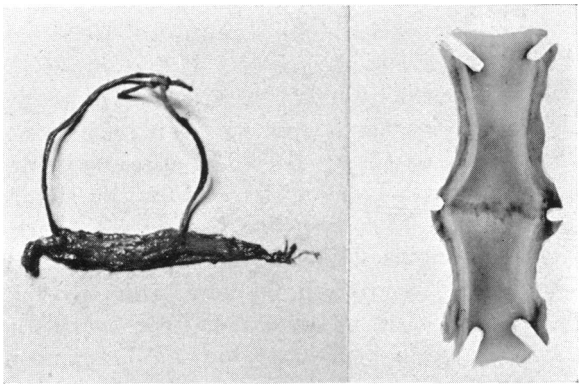


FIG. 1.—Illustrating method of inserting the suture before crushing the vein.
FIG. 2.—Anastomosis of artery recovered one year later.

mained patent. It was shown in these experiments that, if the lumen could be kept patent for 72 hours, the suture lines were healed and there was no longer a tendency to thrombosis or clotting at this site (Fig. 2). Specimens recovered a year afterward showed only a slight scar.

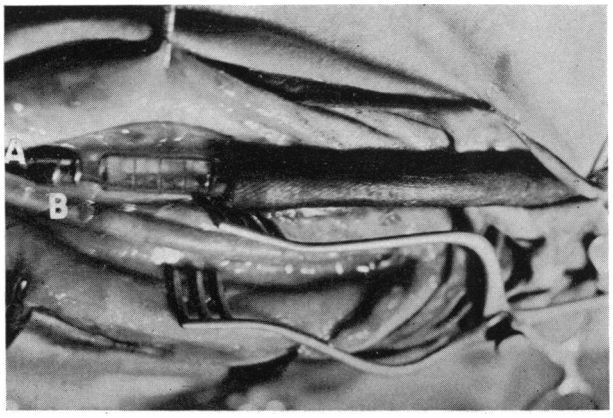


FIG. 3.—Regional heparinization: (A) Showing needle in lumen of artery. (B) Proximal to suture line.

Venous Grafts.—In an earlier report the different methods of administering heparin were described, and suffice it to say here that the term "regional heparinization" has been coined to describe the injection of sufficient heparin into an artery proximal to a suture line (Fig. 3) to affect the clotting time locally in that vessel and in the blood returning from that extremity, but not

to change the clotting time of the whole blood stream. "General heparinization," on the other hand, is a term employed to denote that the clotting time of the blood in all parts of the body has been increased, and this has been effected by a continuous intravenous injection.

To study the effect of regional heparinization, segments of carotid artery varying from one to three and one-half inches in length were excised, and a similar length of external jugular vein, removed from the same animal, was anastomosed at both ends to take the place of the segment of artery removed. The veins stood the pressure satisfactorily and, with regional heparinization, the lumen was kept patent in 70 per cent of 25 such cases (Figs. 4, 5, and 6). Further research is in progress on this subject which will be detailed in a subsequent communication.

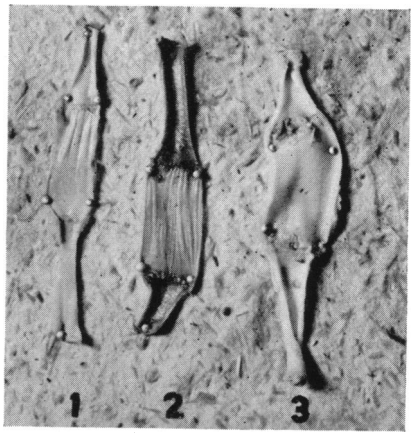


FIG. 4.—Venous grafts: (1) Recovered 48 hours after grafting. (2) Recovered eight hours after grafting. (3) Recovered eight days after grafting.

Peripheral Embolism.—Our experience with embolectomy[6] is now sufficiently great to show that while this operation is useful in trained hands in early cases, it is of no value where the embolus has been lodged for more

FIG. 5

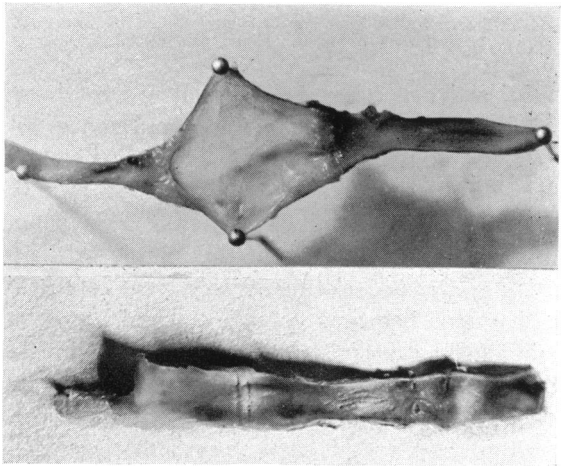


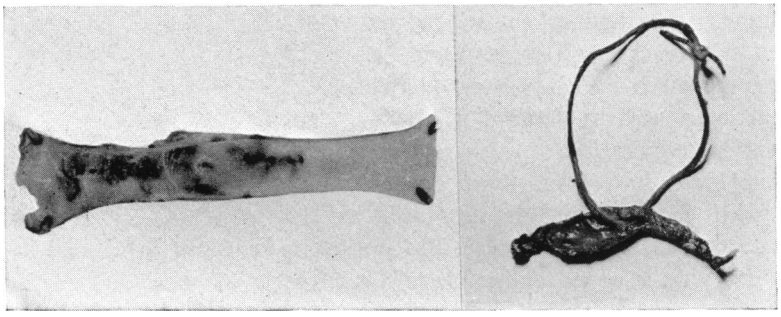
FIG. 6

FIG. 5.—Suture line and graft patent three weeks later.
FIG. 6.—Showing change in wall of vein graft after six months.

than 12 to 15 hours. In these, the damage to the intima is such that after the removal of the embolus a thrombus quickly occludes the artery again and so spoils the operation. To study this, a series of experiments was per-

formed on dogs in which the femoral and carotid arteries were opened by linear incisions and plugs of sterilized foreign body and blood clot placed at bifurcations. The incisions in the vessels were closed and the plug left in situ for from 24 to 72 hours. The lumina of the vessels were than cleared through an incision at another spot. In nine controls treated in this way, all the vessels rapidly became occluded again by a thrombus. In eight others, after similar treatment and with either regional or general heparinization, thrombosis did not occur and the vessels all remained patent (Fig. 7A).

Splenectomy.—To investigate the effect of heparin in the portal circulation, in a control group of eight dogs, the spleen was removed and the splenic vein injured by crushing it over a linen suture lying in its lumen. Ten days later the veins were removed and in all the controls these were occluded. In eight other animals, a similar operation was carried out, with similar



A B

FIG. 7.—(A) Shows artery three months after embolectomy. Suture lines healed. (B) Shows lumen of splenic vein clear.

injury to the vein, and general heparinization was continued for 72 hours. Seven days following this, the veins were removed and in all the lumen was patent (Fig. 7B). While there was satisfactory evidence that heparin would prevent thrombosis in the peripheral circulation, it was not known what effect it would have in the portal circulation. This would appear to be evidence that this substance will prevent thrombosis in the portal system.

Transplantation of Organs.—Without very great care in technic, Carrell's transplantation of organs has been carried out and the circulation has been restored and maintained successfully for many months with the aid of heparin. Using our technic, control cases failed when heparin was not used.

Administration of Heparin to Human Beings.—With the knowledge that heparin was nontoxic and would prevent thrombosis and clotting in blood vessels in animals, it was decided to carry the experiment further and try it on clinical cases in the wards of the hospital.

Published reports[2] describe the first efforts at giving heparin to patients in the Toronto General Hospital and contain descriptions of methods of giving it and the effects obtained by the different methods.

To determine if heparin was toxic, it was administered intravenously to

several patients but it was disappointing to find that about half of them showed toxic effects in the form of headache, nausea, vomiting, faintness, pallor, chills, rapid pulse and a fairly marked fall in blood pressure. Its further use had to be abandoned, therefore, until a still purer preparation could be produced. This was finally accomplished by Charles and Scott[1] when the crystalline barium salt was isolated; and since then no toxic effects on patients have been observed. As a result of its intravenous administration, the blood clotting time can be maintained for as long as 40 days at a level three or four times the normal, and it is possible to administer it to the average patient on the wards without the anxiety that formerly attended its use.

Before it could be considered safe to use heparin in the wards, one had to be assured that its administration would not have a cumulative effect, and to have some idea of how long a time would elapse after stopping the injection before the clotting time would return to normal. It was important to know this as there was always the possibility of a hemorrhage occurring during the administration of the drug. This matter was studied in both animals and patients, and it has been shown that when the administration of the drug is stopped it rapidly disappears from the blood. In patients whose clotting time has been raised to 20 minutes, the effect has completely disappeared in an hour and even when the clotting time was raised to an hour and a half there was a return to normal in an hour and 20 minutes. This knowledge was comforting in one patient, who had been heparinized for four weeks because of phlebitis and who developed symptoms of reactivation of an old duodenal ulcer and a hemorrhage. With the discontinuance of the heparin the bleeding ceased and patient recovered.

Negative Phase.—Neither in the experimental animals nor in human beings, when the effect of heparin has worn off, has there been any demonstrable change in the blood. The clotting time does not become shorter than the normal time; the sedimentation rate, van den Bergh reaction, prothrombin index, platelet and red and white blood counts do not change. In none of the cases that have received heparin clinically, has there been any evidence of late or residual effects such as recurrent thrombosis or embolism after the clotting time returned to normal.

Arterial Anastomosis and Venous Grafts.—Thus far, we have not had an opportunity to employ this operative procedure in the hospital but hope to try it when a suitable patient appears. Not infrequently, surgeons are confronted with a situation where a tumor involves an important artery, and in which the artery must be ligated off to allow removal of the tumor. The choice lies between leaving at least part of the tumor or tying the vessel, and in certain instances, as in the case of the internal carotid, this is accompanied by very grave risks. It is proposed under such conditions to remove a segment of the artery, to reconstruct it with a venous or arterial graft, and then to heparinize the patient. It is hoped also in aneurysms, arteriovenous fistulae, and probably in some other diseases of arteries that, after resecting

the affected area, the main trunks can be reconstructed and the circulation restored.

Peripheral Embolism.—Our clinical experience with heparin in this disease has not been great, as the number of cases admitted to the surgical wards is small, but in the few we have had, the results have been impressive. In none has amputation been necessary and in several the peripheral pulse

FIG. 8 FIG. 9

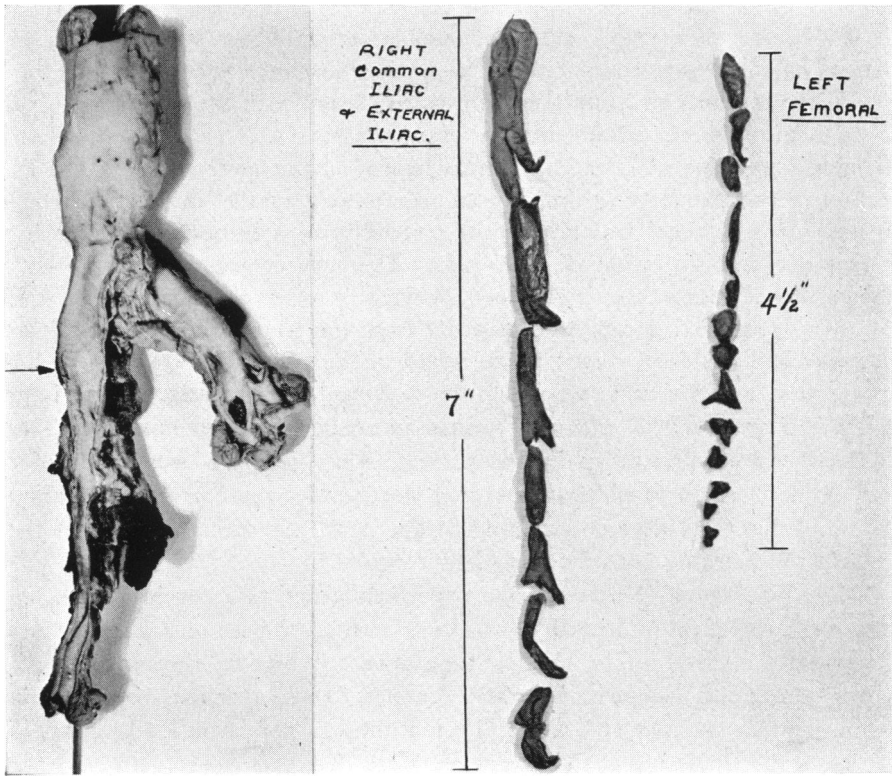


FIG. 8.—Aorta, iliac and femoral vessels patent; suture line at arrow healed.
FIG. 9.—Emboli removed.

beyond the occlusion returned and persisted. Such observations, however, are not conclusive, as it is always possible that the recovery occurred through the development of the collateral circulation. However, in one very unfavorable case, a subsequent autopsy enabled us to examine the arteries and to see that a complete restoration of the circulation had taken place. This was a patient who was operated upon 25 hours after the first appearance of symptoms for embolism involving both common iliac and femoral arteries. The emboli were removed but they did not slip out as easily as in earlier cases because of some stickiness of the intima. Before the arterial clamps were removed from the arteries these were filled with a heparin solution. When the clamps were removed, the circulation returned quickly to both feet. From

then on, the patient's blood clotting time was kept above 20 minutes for two weeks, and then the heparin was discontinued. The circulation remained normal and there were no ill effects apart from a moderate sized hematoma in the abdominal incision, which caused no special trouble. However, in the left foot, even though the palpable pulsations in the anterior and posterior tibial arteries remained normal, there was some residual anesthesia and loss of motion. These were nearly complete at first but showed daily improvement, so that at the end of the second week the foot was well on the way to recovery. This was interesting, because of the fact that the circulation was restored and maintained in a leg and foot that had been cut off from nourishment for a sufficient length of time to cause some of the tissues to

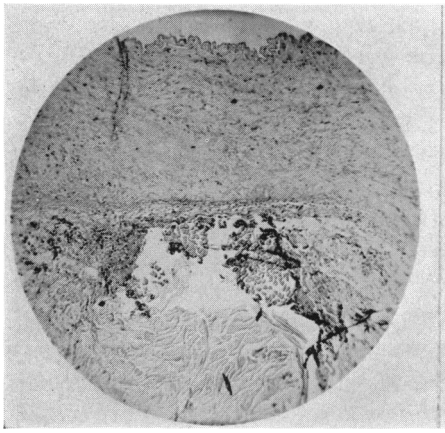


FIG. 10.—Photomicrograph of the suture line in wall of iliac vessel (×25).

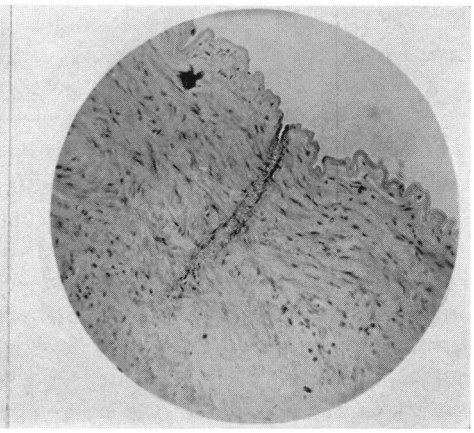


FIG. 11.—Photomicrograph showing the intima headed; no thrombosis (×100).

be seriously damaged. On the fifteenth day postoperative, the patient died of other lesions. The aorta, iliac and femoral arteries were recovered (Figs. 8 and 9). The vessels were all perfectly clear, with not the slightest sign of thrombosis or blood clot, either on the areas from which the emboli were removed or at the incisions. The latter were healed so perfectly that they could not be found on the intimal surface, except after a very careful search (Figs. 10 and 11).

In four other cases of embolism, embolectomy was carried out successfully, and by employing heparin the vessels remained clear, and palpable pulsations in the peripheral arteries were restored and maintained.

This is a field where, from experimental evidence as well as from the results in a few clinical cases, it would appear probable that heparin can be of great assistance. Also, it might be worth while giving heparin in cases of embolism which are seen too late to have the embolus removed, in the hope that heparin will prevent extension of the thrombus and clot, and in this way assist the other measures used in restoring collateral circulation.

Splenectomy.—Based on the experimental evidence, five patients in the Toronto General Hospital have been treated with heparin following splenec-

tomy. Three were in cases of familial jaundice, which made uneventful recoveries after operation, and are well now, more than one year later. In the other two, the spleen was removed to facilitate the operation of complete gastrectomy. One case is alive and well, the other died of general peritonitis. At autopsy, the systemic and portal vessels were examined and the pathologist reported no generalized thrombosis and fewer and less extensive thrombi than are usual in the stumps of the splenic and other vessels that have been ligated in the operative field. While these cases had no complications from thrombosis, it will be necessary to observe the effect of heparin on many more before conclusions can be drawn.

Postoperative Pulmonary Embolism.—To date, 335 patients at the Toronto General Hospital have been given heparin. Except in the first nine cases, the 500 unit per mg. preparation has been employed, and with this there have been no toxic effects observed. The injection was given in each case in a superficial vein through an ordinary steel needle which stayed at the same spot in the same vein for periods varying from three to eight days without thrombophlebitis developing in a single vein. There has been no evidence of phlebitis or thrombosis with embolism developing during, or following, the administration of heparin in any of these cases.

In this group, there were 315 cases which received heparin postoperatively. These operations included all those performed in general and orthopedic surgery. While the incidence of pulmonary embolism is about one in 400 operations, yet, when minor procedures such as transfusion, excisions of cysts and lipomata, *etc.*, are eliminated, and some special groups of more major operations are considered, the figures are quite different. For example, in the Toronto General Hospital, 2.2 per cent of all operations of partial and complete gastrectomy died of pulmonary embolism; of resection of colon, 3 per cent; of abdominoperineal resection of rectum, 6 per cent; of fractured neck of femur, 4.3 per cent; and of prostatectomy, 7.5 per cent, died of pulmonary embolism.

The group of 315 postoperative cases receiving heparin includes many of these types of operation and in none has there been evidence of pulmonary embolism or thrombophlebitis.

Pulmonary Embolism.—Seven cases of pulmonary embolism with infarcts varying in number from one to six in each case, arising from thrombophlebitis of the legs, were treated with heparin. All the cases showed rapid clinical improvement within 24 hours and had less pain in the legs and chest. Although several of the cases had recurring embolisms of serious proportions every few days, before the intravenous injection of heparin was started, no further embolisms, with one possible but not proven exception, occurred after the treatment was started.

While the group of cases is too small to draw conclusions from, still it offers some hope that this method of treatment may be useful in such cases.

Phlebitis.—Twenty-eight cases of spontaneous thrombophlebitis, including several cases of phlebitis migrans, have been treated with heparin. There

has been no evidence of embolism in any of these and the clinical signs and symptoms, pain, swelling, tenderness and fever, appeared to show more rapid improvement than in a control group.

The Time Heparin Is Started in Postoperative Cases.—From the experimental[2] and clinical experience, it has been proven, fairly conclusively, that heparin will not dissolve a blood clot or a thrombus, either in vivo or in vitro. From this evidence, it may be assumed that if the bleeding has been stopped at the time of operation, heparin will not start a hemorrhage. To obtain hemostasis, as in all good surgical technic, all the larger and medium sized vessels should be tied off, or sealed with a cautery, and the small vessels will look after themselves and will not be the source of a hematoma. It is possible, however, that vessels which do not bleed when the patient is in shock may bleed with a rising blood pressure. If such a vessel is bleeding, heparin will certainly allow it to bleed more than it would do otherwise.

For these reasons heparin is not administered for from four to 24 hours following operations, to allow the normal processes which control bleeding to operate. If there is any doubt about oozing or bleeding, the patient is not given heparin.

Hematoma Following Administration of Heparin.—With the above mentioned precautions, only four cases developed hematomata postoperatively, while under the influence of heparin. The hemorrhage stopped when heparin was discontinued and all the patients recovered.

Method of Administration.—As there are no toxic effects, the patients in the wards have received general heparinization. The ordinary intravenous drip is used, and to the salt solution sufficient heparin is added to increase the clotting time of the patient to about 15 minutes. Usually, heparin is added in the proportion of 10 units of heparin to 1 cc. of saline; in the average patient this should run at about 25 to 30 drops per minute. The rate, however, is adjusted, according to the effect on the clotting time, and this is estimated every few hours until the correct rate of injection can be determined. Further details on this aspect of the subject have appeared in a recent publication.[3]

The Time Heparin Is Discontinued.—The time thrombosis begins following operations is purely a matter of conjecture at present, but if stasis, changes in the composition of the blood and eddying play a part, the patient under anesthesia, with a lowered blood pressure, in shock, and in cramped positions on the operating table or in bed, is under ideal conditions for the initiation of the process. The methods of combating these conditions, as described by many writers, do a great deal in decreasing the incidence of embolism, and it is hoped that the remaining difficulties may be overcome by the use of heparin.

The injection is discontinued when the patient has regained normal activity, *i.e.,* when the factors thought to contribute to the production of thrombosis have ceased to act. This time has been reached when shock has passed and the blood pressure and circulation are normal; the incision has healed

and is not painful, so that deep respirations are possible; the patient feels well and energetic and moves about actively in bed and can do exercises; distention is gone; the appetite has returned and the gastro-intestinal and urinary functions have returned to normal; the chest is clear and the temperature and pulse are normal.

Selection of Cases.—It is hoped that the method of investigation, used by Bancroft and his coworkers,[4] will help in selecting those cases which are most likely to develop thrombosis. It is hoped that in these cases heparin, in appropriate amounts, may prevent the formation of a thrombus and thereby prevent embolism. Before starting treatment, the blood clotting time, prothrombin index, platelet count, bleeding time and the other ordinary blood analyses must be ascertained.

Complications Resulting from Giving Heparin.—As there are no toxic effects, and hemorrhage need not occur if the proper precautions are taken, heparin may be given, in appropriate amounts, in any postoperative case. If, however, there is active hemorrhage, heparin should not be given.

Indications for the Use of Heparin.—(1) *Postoperative Cases.*—A patient, in whom active thrombosis is detected either following an operation, or during an illness, or who has had a pulmonary embolism, is probably in grave danger, and, in the light of our present knowledge, would probably benefit from the administration of heparin. Until the methods of detecting those cases likely to develop thrombosis are perfected, the group of postoperative cases likely to develop this complication should be treated. As this investigation is still in the experimental stage, further indications and limitations may be discovered.

(2) *Phlebitis, Embolism, Operations on Blood Vessels.*—While our clinical experiences with the use of heparin are limited in these types of cases, the experimental evidence, especially in operations upon blood vessels, gives very strong support in favor of its value. In suturing of vessels, repair of aneurysms and arteriovenous fistulae, heparin may be of great assistance in obtaining good results.

(3) *Blood Transfusion.*—In blood transfusion, heparin can be employed quite satisfactorily instead of citrate. To prevent coagulation, the donor may be heparinized, as Hedenius[5] has shown, or heparin may be added to the blood as it is removed from the donor. It is useful also in removing blood for the ordinary laboratory tests where citrate or oxalate is commonly used.

(4) *Coronary Thrombosis and Cerebrovascular Thrombosis.*—Other possible fields in which heparin might be useful, but which have not been explored, are coronary thrombosis and cerebrovascular thrombosis. While the administration of heparin could not remove the thrombus already present, it might prevent extension of the process. Extension, in both diseases, may be manifested in some cases by recurrent attacks or extension of the lesion within a few hours or days. It might have a useful rôle, also, in lateral and cavernous sinus thrombosis and in progressive thrombosis on heart valves.

CONCLUSIONS

(1) Heparin in its purified form is nontoxic, both experimentally and in human beings.

(2) In lesions where intravascular clotting is a problem, heparin may be useful.

(3) Experimentally, heparin will prevent thrombosis in blood vessels; clinical results thus far obtained do not contradict this conclusion.

(4) As all this work is in the experimental stage, final conclusions cannot as yet be drawn.

We wish to take this opportunity to acknowledge the assistance of Mr. L. B. Jaques, Dr. T. S. Perrett, Dr. R. Wilkinson and Dr. R. McKenzie. The financial assistance of the Banting Research Foundation in making grants at various times to the assistants is also gratefully acknowledged. The heparin used in the earlier stages of this work was supplied without charge by the Connaught Laboratories.

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DISCUSSION.—DR. FREDERIC W. BANCROFT (New York, N. Y.): I am impressed with the marvelous work that has been done by Doctor Gallie and his group in the use of heparin as an anticoagulant. There is no doubt that anticoagulants are an adjuvant in the treatment of thrombosis and embolism.

In discussing thrombosis and embolism, the physical factors of trauma, venous stasis, dehydration and infection enter into every case, and the blood clotting factors of the individual are a secondary cause. Therefore, one must focus one's attention upon preventing the physical factors. Nevertheless, it is obvious that some patients are more susceptible to thrombosis and embolism than are others, and it is this type of case that we must guard against. Doctor Homans has very truly said that the prevention of thrombosis and embolism is gunning for the hundredth case. The criticism has been brought against Doctor Stanley-Brown's and my previous reports of our prophylactic therapy for thrombosis and embolism, that we had not given analyses of the types of cases that we have treated that might be susceptible to embolism; so I should like to just briefly review 1,646 consecutive cases which we had studied by means of the plasma clotting index and the fibrinogen test which we presented to this Society a year ago, and which we have treated by the prophylactic regimen we described. We have included in this list the types of cases we felt were susceptible to thrombosis and embolism. As you have

seen by the figures presented by Doctor Gallie's group, these varied from 2 to 6 per cent in the Toronto Hospital series, before they had started the use of heparin.

In the analysis of our cases, about 14 per cent showed high blood clotting indices, and all of the accidents reported were in this group. It so happens, however, that the four deaths from embolism were cases in which we had had the blood clotting factors but had not put on prophylactic treatment. In the series that we had placed on prophylactic treatment, no accident occurred. This may sound strange, but where one has continued the study of cases for a number of years, every now and then the analysis of the blood clotting factors will be overlooked in the study of a patient and, therefore, if he has a high clotting index, prophylactic therapy may not be instituted. In one of our cases, for instance, of phlebitis, the patient was a young woman, age 21, who had had an appendicectomy and freeing of adhesions about the ascending colon. It was noted on her fifth postoperative day that her clotting factors were high, and this was again noted on the ninth day, but she seemed to be doing so well that she was not given sodium thiosulphate or placed on a diet. On the eleventh postoperative day she developed phlebitis in her left femoral vein.

The following tables I believe are self-explanatory:

PERCENTAGE OF THROMBI AND EMBOLI ACCORDING TO DISEASES† TESTED CASES*

Fifth Avenue Hospital Series

Diseases	No. of Cases	Phlebitis	Percentage	Emboli	Percentage
Appendices	398	1 Phlebitis	0.2	1 Embolus, nonfatal 1 Embolus, fatal	0.5
Herniae	199	1 Phlebitis	0.5	1 Embolus, fatal	0.5
Gallbladders	142	1 Phlebitis	0.7	1 Coronary thrombosis, fatal	0.7
Hysterectomies for fibroids	121	1 Phlebitis	0.8	0	
Stomach resections for ulcer or Ca.	43	1 Phlebitis	2.0	0	
Adhesions	25	1 Phlebitis	4.0	0	
Perineal plastics	87	1 Phlebitis	1.0	0	
Salpingectomy, oophorectomy	110	0		0	
D & C, for bleeding	102	0		0	
Thyroids	37	0		0	
Breast lesions	29	0		0	
Urologic	86	0		0	
Gastrectomy for Ca. of esophagus	15	0		0	
Hemorrhoids	40	0		0	
Fistulae	20	0		0	
Colon and rectum, resections	29	0		0	
Infections	63	0		0	
Miscellaneous: Fractures, Varicose veins, Tumors, Tuberculosis, Pelvic peritonitis	100	0		0	

Presbyterian Hospital Series

920 cases tested
12 per cent showed high indices
Only 46 per cent of these received prophylactic treatment
No accidents in treated group
Nine accidents in untreated group
Two of these unrecognized as only fibrinogen was high
Control service had 12 accidents

New York Hospital Series

575 cases tested
13 per cent showed high indices
Only 49 per cent of high were treated
Treated group: One treated case had a nonfatal pulmonary infarction on the fourteenth day
Untreated group: One fatal embolism. One nonfatal embolism
Control service: Two emboli

† All accidents occurred in the high index group but had not received prophylactic treatment.

* 12 to 14 per cent of tested cases showed high indices.

The summary of the above 1,646 cases shows that there were three fatal accidents from embolism and one nonfatal, or approximately .02 per cent. There were six cases of phlebitis, or approximately .04 per cent. The tabulation of the results at the New York Hospital and at the Cornell Clinic shows the results of their treatment, but which we have not analyzed fully, as yet, as to the series of cases.

Our prophylactic regimen on a patient showing high clotting factors is to give intravenously for several days 10 cc. of a 10 per cent solution of sodium thiosulphate, to increase fluids by mouth, and to restrict the fats and carbohydrates in the diet.

On analyzing the results of the work of Doctors Murray and Best with heparin, and ours with sodium thiosulphate, I feel that we are not as far apart as one might believe. It is very possible that sodium thiosulphate has a definite effect in helping the liver liberate heparin, as we know that sulphur compounds can do this. We have of course no proof of this theory.

Diet, we feel, is very definitely a factor. A high protein, high fat diet does increase the percentage of people who are subject to embolus, and a diet low in proteins and fats will diminish the clotting factors, as we have been able to show in both dogs and humans.

Finally, in summarizing the advantages of Doctor Murray's and Doctor Best's treatment, they have been able to perform arterial suture and embolectomy by employing a method that will open up an entirely new field in surgery, and the future will show what a great advance this is. They have also been able to show very much better results than we have in the treatment of thrombosis and embolism after the initiation of the disease. We have been able to abort cases of early phlebitis, but we have had very few good results after it has existed for over 48 hours. Doctor Murray has shown us where they have had cures of phlebitis after it has persisted for a considerable period of time.

The disadvantage, it seems to me, of their procedure is that heparin has a very short duration of action, and, therefore, a continuous intravenous administration has to be kept up from 72 to 120 hours. At present, the average expense per patient amounts to about $80, which does not entirely

include the discomfort to the patient and the increased nursing cost in giving a continuous intravenous administration over this long period.

During the period since 1928 that we have been studying thrombosis and embolism, we have made blood determinations on over 8,000 cases and are convinced that our tests are, in general, an accurate analysis of the clotting tendencies of an individual. We have had only one case of multiple embolism, which was operated upon in another hospital, and which had low clotting factors. With this exception all of the accidents we have examined are in the high blood clotting group. It is true that 12 per cent of postoperative cases show high clotting factors and that only about 1 per cent of the 12 per cent demonstrate an accident. Nevertheless, a large percentage of these cases run a higher elevation of temperature than is normal and may be potential thrombosis or embolism cases.

We believe, therefore, that an analysis of the clotting factors gives us the group in which accidents are apt to occur and that at the present time it is much cheaper to treat these cases prophylactically by sodium thiosulphate than it is with heparin.

We believe that after thrombosis or embolism has occurred, the employment of heparin is far superior to sodium thiosulphate.

It is interesting to note that a number of medical groups have been treating coronary thrombosis by sodium thiosulphate and that the physicians who have been carrying out this procedure feel that their cases have done much better than they did by other methods of treatment. It is too early to place any definite reliance on this procedure. The cases of coronary thrombosis that we have studied have all had high clotting factors.

DR. HOWARD LILIENTHAL (New York, N. Y.): The only reason that I am discussing this paper is that I asked Doctor Gallie if I might do so. Had I known just what the paper was going to be, I never would have been so forward. I was interested, not so much in heparin, as in the general object which was attained by this group. This is a tremendous advance. Synthetic heparin will be the next step in progress.

I am particularly interested in this question from the standpoint of therapy by means of leeches and their hirudin, which accomplishes the same result. I remember when leeches were used for bloodletting from inflamed regions, to great advantage. But I think the treatment would have done more good, if, after the leech had filled himself full of blood and dropped off, the leech-bite had not been permitted to bleed but had been stopped so as to leave the hirudine in the patient. In all probability the good that the leeches did was to get rid of a certain amount of the local thrombosis which occurred in the infected tissue.

The French have been using leeches for a long time. In the memoirs of the French Academy of Medicine, for March, 1923, there are papers which are of interest. It has been suggested that there was danger of producing embolism from thrombophlebitic veins by using leeches. I do not believe that this is likely to happen.

I have used leeches for a long time, and I have obtained absolutely amazing results. I had two cases of saphenous phlebitis, first one side and then the other, following prostatectomy, the thrombophlebitis extending into the femoral vein. The patient, years ago, had had the same type of infection and had been in bed for nearly six months. This time, he was out of bed three days after I had treated him by means of leeches. Then, about ten days later, the same condition appeared in the other leg, and leeches were again employed with the same result. The man has remained well for the past eight months.

A friend of mine, a doctor in New York, had thrombophlebitis recently in the left leg. I suggested leeches and his doctor said, "Oh, that won't do any good," and he advised continuing only bed rest. I met the doctor at a medical meeting only three or four days ago, looking perfectly well, and I said, "Too bad you didn't use leeches." "Oh," he said, "I did use leeches and I was out of bed and well in two weeks." If he had used heparin, he probably would have recovered just as quickly and, of course, heparin has the advantage over hirudine in that it has now been made available, whereas, hirudine still has not been supplied commercially.

Dr. Arthur Master, not long ago, read a paper on coronary thrombosis in which he showed that this disease is very common—more so than most surgeons are apt to believe—after operations of any kind. I believe that here heparin would be valuable. This was hinted at in today's communication, and I think the treatment ought to be used as a routine.

There is only one other point that I want to make. I was talking with Dr. Carl Koller, the discoverer of the anesthetic value of cocaine, and I mentioned this action of leeches, not at the time knowing about heparin. "Oh," he said, "that's fine; I'm going to use it in the next case of central retinal embolism that I get." I believe that if it is used immediately, it may save the sight of the eye.

Of course, heparin is not yet generally obtainable, but it soon will be. In the meantime, I certainly would recommend, in any case of angina where the disease is supposed to be due to thrombosis, that leeches should be applied. You can use as many as ten or 15. They do not need to be put on near the heart.

Dr. Mont R. Reid (Cincinnati, Ohio): I rise only to confirm the great value in the use of heparin in experimental work and also to answer the question I know must have occurred to Doctors Gallie and Murray as to how one could keep our experimental arteriovenous fistulae open and make any worthwhile studies.

The observations we made upon fistulae between the aorta and vena cava would have been absolutely impossible without the use of heparin. As it was, we could prevent any clotting at all in that type of fistulae for four or five hours, or longer, if we had wanted to continue the experiments.