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Concerning the relation of the coagulation time of the blood to thrombosis in phlebitis.

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The etiological factors or conditions concerned in the production of thrombosis may be briefly summarized as :

- (1) Those due to central or peripheral slowing of the blood stream.
- (2) Those associated with lesions in the walls of the blood vessels.
- (3) Alterations in the blood itself, such as tend to favor coagulation.

In actual cases, it appears without exception that two or more of these factors are associated in the production of thrombosis. Although the etiological agents mentioned above are generally accepted as the correct interpretation of thrombosis, it must be remembered that experimentally, as well as clinically, very discordant results are reported as to the causation of thrombosis, notably such as occurs in clinical phlebitis. Until more certain data are secured in regard to the process, but little can be expected in the way of successful prophylactic treatment or in the certain prognosis of those instances in which this lesion is to be feared.

The object of this brief study has been an attempt to show to what extent increased and decreased coagulability of the blood, artificially induced, may play a part in the production of thrombosis, or, expressed, in other words, whether in conditions productive of phlebitis, thrombosis is more likely to occur when the coagulation time of the blood has been lowered artificially or less apt to take place when analogous artificial means have been employed to prolong the coagulation time of the blood.

Our experiments have been conducted on a series of young and healthy rabbits, one third of which have had their coagulation time reduced by daily administration of 2 gms. of calcium lactate, an equal number of animals whose coagulation time has been arti-

ficially lengthened by daily dosage of 2 gms. of citric acid and one third used as control animals. The drugs were introduced into the stomach by tube feeding and it was found possible, with this dosage to reduce the coagulation time of the blood in the calcium lactate animals one half and to lengthen it in the citric acid animals about one third. Corroborating work already well authenticated, the maximum effect of these drugs takes place about two hours after their administration, and probably entirely passes away within twelve hours, especially with the rapidly excreted calcium salts. In our animals the drugs were continued in daily doses throughout the experiment, since it was found that effects were quite as apt to occur several days after the initial injury as immediately on its infliction, thus more closely approximating the conditions as they occur in man.

When autopsies were to be performed the animals were chloroformed and while the heart action was still vigorous a carotid artery was opened and the animal suspended so that the blood was very generally emptied from all the vessels of the body, and post-mortem clot or fibrin could not become confused with the true thrombi. We believe this to be an important step in the technic.

Our experiments may be grouped in two series: Series I comprises local injuries produced in and around the ear veins. Nine experiments of this character were performed. Series II includes attempts to produce vascular lesions predisposing to phlebitis and thrombosis by intravenous injections of various irritants. Five sets of experiments.

Series I; Experiment a.—A segment (3 cm.) of the distended marginal vein was isolated by compression between two artery clamps and the intervening vein distended with blood was intermittently compressed with toothed forceps for five minutes when minute hemorrhagic extravasations along the course of the trunk were demonstrable. The isolating clamps were then removed and the circulation allowed to become reestablished. The resulting perivenous inflammation was slight and no thrombosis followed either in the calcium citric acid or control animals.

Experiment b.—Clamping the marginal vein with ordinary paper clips, cutting off at the time the anastomosing circulation, for thirty minutes, was followed by immediate reestablishment of the normal blood flow in all animals without subsequent results.

Experiment c. — A 2 c.m. segment of the marginal vein was clamped and isolated with paper clips for twelve hours, the anastomosing circulation being meanwhile prevented. Immediately on the removal of the clips the circulation was reëstablished in all animals, the absence of thrombosis in these experiments being like the results of the experiments reported by Baumgarten and his student Rizor who was able to compress the vein for an even greater length of time without resulting thrombosis. After three days considerable inflammatory reaction developed about the site of some of the clamps, this being most marked in the calcium lactate animal, where finally a small segment of the vein became thrombosed. The inflammatory reaction was less marked in the control animal and there was still less reaction in the citric acid rabbit, thrombosis being absent in both. From these experiments one may conclude that mere stagnation of the venous blood produced no marked tendency toward thrombosis in the ear veins but that inflammatory lesions, with consequent phlebitis are more extensive in the case of the calcium animal and thrombosis may occur at the immediate point of injury of the vessel walls.

Experiment d. — A quantity of 24-hour growth of virulent pneumococci in bouillon was injected about the ear vein, the injection being continued to such a point as to cause compression anæmia of the desired segment of the vein. The circulation was shortly reëstablished and the amount of subsequent inflammatory reaction was slight. No thrombosis occurred in any of the animals. Our results in this experiment are therefore quite unlike those of Von Talke where, however, the coagulation of the blood was not altered, for Von Talke claims to have regularly produced thrombosis in this way.

Experiment e. — Five minims of 5 per cent. AgNO_3 were injected into the perivenous connective tissue of the ear. Immediate permanent thrombosis of the adjacent vessels followed. No difference in extent or degree existed between the three animals. This experiment was repeated using 1 per cent. solutions of AgNO_3 . Slight perivascular inflammation without thrombosis resulted and was of about equal severity in all the animals.

Experiment f. — Three drops of pure turpentine was injected between the branches of the median ear vein. This was followed

within twelve hours by edema and an active inflammatory exudation with thrombosis of the involved vein in all three animals. The thrombosis was notably more extensive and resolution most delayed in the animal which had received the calcium lactate, less so in the control and least of all in the rabbit which had been poisoned with citric acid.

The same relations as regards severity and occurrences of lesions followed when 50 per cent. turpentine in inert oil was employed in the experiment except that the resulting inflammation and subsequent thrombosis was longer delayed.

Series II. *Experiment a.* — Fine comminuted sterile pumice was injected into the marginal ear vein in an attempt to see if the resulting thrombosis following probable embolism of the terminal arterioles would be more extensive in those animals which had received the calcium salt and less so in that which had received citric acid. All three animals recovered perfectly from the operation and later autopsies showed no lesion whatsoever which could be attributed to this injection.

Experiment b. — Fifteen minims of sterile cod liver oil was injected into the marginal ear veins of the three animals. None of them showed symptoms and later post mortems showed no lesions attributable to the experiment.

Experiment c. — Two minims of a pure 24 hour culture of virulent typhoid bacilli were introduced through the marginal vein. No symptoms of illness followed and these animals were subsequently utilized in experiment *d.* These results are exactly contrary to those of Jakowski who in similar experiments in guinea pigs and rabbits obtained almost constant thrombosis, but without the associated employment of calcium or citric acid.

Experiment d. — Fifteen minims of a suspension of a 36 hour broth culture of virulent typhoid bacilli in an equal bulk of sterile cod liver oil were introduced through the marginal vein. This was done in the expectation that embolism caused by the oil would be likely to afford sites for the growth of the bacilli and probable resulting thrombosis as described in the experiments of Jakowski. All the animals became seriously sick and on post mortem examination multiple serous petechiae, general parenchymatous degeneration, lymphadenitis and frequent infarctions

were found, but no general or isolated thrombosis. These lesions were notably most extensive in the calcium lactate animal and least so in the citric acid, but when the experiment was repeated under similar conditions, exactly opposite results followed, which leads us to believe that chance was really the controlling factor in determining these changes.

Positive results have been obtained in but a single set of experiments ; those were where turpentine was injected.

In so far as the results of this preliminary study go, one is led to the conclusion that thrombosis is most readily induced where active inflammatory lesions exist in the blood vessels probably associated in most instances with secondary degenerative changes. Purely mechanical lesions are much less apt to be productive of conditions favorable to thrombosis as a sequence of phlebitis.

Marked artificial increase or decrease in the coagulation time of the blood by the use of calcium lactate or citric acid, does not render animals abnormally prone to thrombosis incited by changes other than inflammatory.

Where true phlebitis exists, thrombosis is apt to be more extensive and less readily resolved, when the coagulation time of the blood has been shortened by the use of calcium lactate, and it is less extensive and more quickly absorbed where the coagulation time has been increased by the administration of citric acid.

Experiments as yet incomplete, appear to suggest that the rapidity or slowing of the general circulatory flow has but little bearing on the relative production of thrombosis in phlebitis, much less than clinical and anatomical observations have generally led us to think. We have also been led to suspect that the presence or absence of anastomoses of abundant degree is largely concerned as a factor in determining the location and extent of thrombosis in phlebitis.