bonate in the stones of the dog has similarities to that between calcium bilirubinate and cholesterol in human calculi. There is the same tendency in both instances for a nucleus of the pigment material to be overlaid with another substance.

The observations here reported show that infection is not the essential factor in cholelithiasis. That it frequently plays the determining rôle is equally certain.[2] This it would seem to do by damaging the duct wall with result in desquamation,—which the sterile canula did in our experiments,—and by lessening the ability of the bile channels to rid themselves of the cell débris. The débris induces, or furthers, the direct deposition of solids, and may catch and retain potential nuclei for stone formation, in the shape of pigment particles from higher up in the biliary system, which would under ordinary circumstances be voided with the bile.

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The paradoxical shortening of blood coagulation after intravenous administration of sodium citrate.

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Sodium citrate, when administered intravenously in large doses (0.5 grams for dog or cat, 3.0 to 6.0 grams for man), produces a pronounced and progressive shortening in coagulation time of the blood which usually reaches its maximum within one hour and may persist for many hours. As a rule, the coagulation time slowly returns to normal within twenty-four hours.

This action of sodium citrate upon the coagulation of the blood *in vivo* is exactly opposite to what occurs *in vitro*. We

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[2] Gilbert, A., et Fournier, L., *Sc. et mém. de la Soc. de Biol.*, 1897, iv, 10 Ser., 936; Mignot, R., *Arch. gen. de Med.*, 1898, i, 129.

believe that it is dependent upon some effect on the blood platelets, which are not directly destroyed by the citrate but are damaged by contact with it and are then removed from the circulation by the spleen where they are destroyed and their thromboplastic contents gradually liberated into the circulating blood. This theory is based upon the following observations:

1. In the test tube, sodium citrate does not destroy the platelets, but it effects them so that they are actually preserved and therefore more easily counted.

2. Within a few minutes after the intravenous injection of sodium citrate the blood platelets often begin to diminish in number, the maximum reduction being usually observed after ten to fifteen minutes and the number as a rule returning to normal within half to one hour. The greatest reduction in blood platelets was observed in cats, in two of which 85 per cent. and 90 per cent. of the platelets disappeared from the circulating blood within ten and fifteen minutes respectively, and the count again reached normal a half hour after the injection.

3. Increasing amounts of free thromboplastic substance (cytozyme) probably derived from platelets begin to appear in the blood stream as the coagulation time becomes shortened.

4. No changes in the content of the blood in the other factors concerned in coagulation, such as calcium, fibrinogen or antithrombin, are demonstrable.

5. The increase in the thromboplastic agent cytozyme and the shortening in coagulation time of the blood do not occur simultaneous with the numerical change in the platelets, but follow it. The maximum shortening in coagulation time occurs some time after the numbers of platelets have again returned to normal, and persists for hours.

6. The characteristic shortening of coagulation time after intravenous injection of sodium citrate does not occur in animals (ducks) in whose blood few or no platelets occur. In fact, if sufficient citrate is administered, the opposite effect is accomplished in such animals and the coagulation time becomes markedly prolonged.

7. The shortening of coagulation time after intravenous injection of sodium citrate likewise fails to occur in human beings suffering from hemorrhagic blood diseases, in whose

blood there is also a pronounced numerical deficiency in blood platelets. In purpura hemorrhagica, in which such a reduction in the number of platelets is regularly present, the injection of sodium citrate may be followed by almost complete disappearance of platelets from the circulating blood. In both these diseases and in congenital hemophilia, in which there is presumed to be some deficiency in the quality of blood platelets, the injection of sodium citrate is followed by a prolongation in the coagulation time, a further diminution of the blood platelets and by a marked increase in the bleeding tendency.

8. The characteristic shortening of coagulation time does follow intravenous administration of sodium citrate in cases of obstructive jaundice, in which, although the coagulation time is prolonged and there is a bleeding tendency; the blood platelets in this condition are normal in number and unaffected.

Sufficient evidence has therefore been presented to indicate that the shortening of coagulation time after injection of sodium citrate in normal individuals or animals is due to some influence on the blood platelets. That this is not a direct destruction is indicated by the test tube experiment and by the fact that the maximum shortening of coagulation time does not occur simultaneous with the maximum reduction in platelets, but follows at some time between ten minutes to one hour later.

This sequence suggests that the platelets after contact with the citrate are damaged and removed from the circulation by some organ, there destroyed and their thromboplastic contents gradually liberated into the blood stream. The removal and destruction of damaged blood platelets is probably one of the functions of the spleen, especially in view of the rôle which it is presumed to play in the thrombopenia of purpura hemorrhagica.

Based upon these observations the *slow* intravenous injection of large doses of sodium citrate up to five grams has been successfully employed in arresting internal hemorrhages due to gastric ulcer, typhoid fever, pulmonary tuberculosis, etc., and also as a pre-operative prophylactic measure in obstructive jaundice. In hemorrhagic blood diseases for reasons detailed above, its use is strictly contraindicated.