normal approximately equal unity when the acid added is one other than CO_2. The HCO_3 ion would therefore appear to be freely diffusible into and out of the cell wall. The differing values of the ratio obtained by other observers, using different pressures of CO_2, suggest that the formation of carbhemoglobin has complicated the picture.

We have not yet further investigated the apparent dependence on the hematocrit value (or red cell content) of the pH at which $(Cl)_c/(Cl)_s = 1$. As already stated, this pH appears to vary directly with the hematocrit value. It would seem reasonable to suggest, however, other conditions being equal, that blood with high red cell content, *i. e.*, better buffered, would take up more CO_2 when saturated with alveolar air, and therefore result in a larger transference of Cl from plasma to red cells. This in turn would mean a more rapid rise in the $(Cl)_c$ curve and a correspondingly rapid fall in the $(Cl)_s$ curve, so that the crossing of the curves is shifted to left. Conversely, the pH at which $(Cl)_c/(Cl)_s = 1$ in anemic blood would be expected to shift to the right, *i. e.*, at a lower pH.

Summary. An investigation has been made of certain aspects of Van Slyke's laws concerning the distribution of ions between red cells and plasma at different pH values. When hydrochloric acid was used to bring about variations in blood pH, losses of CO_2 from plasma water and cell water were equal, so that the ratio $(HCO_3)_c/(HCO_3)_s$ remained unchanged and equal to unity at all pH values. The values of $(Cl)_c/(Cl)_s$ at different pH values did not parallel the values of $(HCO_3)_c/(HCO_3)_s$ but gradually rose to unity at values of pH which varied, the actual value appearing to depend upon and to vary with the red cell content of the blood.

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A New Method of Administering Heparin.*

LEO LOEWE, PHILIP ROSENBLATT AND MAX LEDERER. (Introduced by B. Kramer.)

From the Department of Laboratories, Jewish Hospital of Brooklyn, N.Y.

In the course of studies on experimental subacute bacterial endo-

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carditis, attempts were made to produce the disease in heparinized rabbits. The methods for heparinizing humans, namely, by continuous venoclysis or by repeated intravenous injections, were virtually impossible of adaptation for the rabbit. However, rabbits will develop and maintain a prolonged coagulation time over a protracted period with repeated subcutaneous injections of heparin, the average daily requirement being about 45 mg of commercial heparin† administered in fractional doses.[1]

In order to eliminate the disturbing abrupt rises, sharp peaks and unpredictable drops in coagulation time as well as the technical difficulties incidental to fractional daily dosage, a simpler means had to be devised for continuous heparinization by the subcutaneous route.

In view of the success obtained with pellet and capsule implantation of hormones,[2] similar experiments were pursued with heparin. Pellets containing 50 mg and glass capsules tightly packed with 100 mg of heparin were implanted under sterile precautions subcutaneously or subfascially through a small skin incision. While rabbits could be heparinized in this fashion, this approach had to be abandoned for the following reasons: The results with glass capsules were erratic. On some occasions a spectacular but shortlived effect was obtained; at other times, the results were negative and when the capsule was removed subsequently it was discovered that practically none of the heparin had been acted upon.

Additional shortcomings were: The necessity for instrumental procedure; the rapid absorption of pellets with resultant inordinately delayed coagulation time and subsequent precipitate drop; the presence at times of local hemorrhage and the obvious impracticability of sustaining heparin effects over prolonged periods.

To accomplish a slower and more equable absorption of heparin, the Pitkin menstruum, composed of gelatin, glacial acetic acid, glucose, and water in definite proportions was suggested as a vehicle. Ampuls containing varying amounts of heparin and vasoconstrictor elements in the Pitkin menstruum were prepared. All the ingredients apart from heparin were found to be inactive in control experiments.

The contents of the ampul are liquefied at 55°C, drawn up through a 1½ inch, 18 gage needle into a previously warmed sterile 2 cc syringe and immediately injected subcutaneously. The material congeals promptly following inoculation.

† The heparin used is marketed by the Roche-Organon Company under the trade name of "Liquaemin."

[1] Loewe, L., Rosenblatt, P., and Lederer, M., to be published.

[2] Deanesley, R., and Parker, A. S., *Proc. Roy. Soc., Ser. B.*, 1937, 124-279.

TABLE I.
Heparin—Pitkin Formulæ.

	L.P.	L.P.-1	L.P.-2	L.P.-3	L.P.-4
Cryst. sodium salt of heparin	100.0 mg	50.0 mg	50.0 mg	25.0 mg	25.0 mg
Epinephrine hydrochloride	1.0	0.25	0.1	0.25	0.1
Ephedrine sulfate	25.0	10.0	5.0	10.0	5.0
Chlorbutanol	0.5	0.5	0.5	0.5	0.5
Eucupin dihydrochloride	1.0	1.0	1.0	1.0	1.0
Pitkin menstruum q.s. ad.	1.0 cc	1.0 cc	1.0 cc	1.0 cc	1.0 cc

The initial formula (Table I—L.P.) contained 100 mg of heparin. The excessive content of epinephrine and ephedrine, however, induced in all of the 8 animals a severe vasoconstrictor effect. This was overcome by adjustment of the constrictor elements. The dose of heparin was also varied in an effort to reduce the total amount of the drug required to obtain the desired result (Table I—L.P.-1, 2, 3, 4).

The individual effects of the various formulae were evaluated in the course of 62 experiments performed on 52 rabbits. As compared with the average normal of 9 minutes for rabbits‡ a coagulation time of 30 minutes to 2 hours was considered a satisfactory heparin response. In practically every instance an acceptable prolongation of coagulation time was obtained. The effects of a single ampul lasted from 24 to as much as 72 hours.

In several animals heparinization was initiated with 50 mg of heparin (Table I—L.P.-1 or 2) and continued as required with 25 mg doses (Table I—L.P.-3 or 4). In this manner it was possible to maintain adequate heparinization over a two-week period with as little as 100 mg of heparin. This contrasts with a 2-week requirement of 630 mg commercial heparin given subcutaneously in fractional daily doses of about 45 mg.

Further revamping of the formula may yield more prolonged effects. Experience with humans may disclose the need for additional alteration in the proportions of the various ingredients. Such experiments in humans are being pursued with gratifying results.

The implications and applications of this approach are self-evident. A retarding influence to the more widespread use of heparin is the present cumbersome technic of intravenous administration. This has been circumvented in rabbits and we see no valid reason why it cannot be done in humans.

‡ The coagulation times in all instances were determined by the Lee-White modification of Howell's method, Gradwohl, R. B. H., *Clinical Laboratory Methods*, C. V. Mosby Co., St. Louis, 1935, p. 264.