

the lowered efficiency of respiration resulting from impaired distensibility and elasticity. That this compensation was adequate at rest is witnessed by the fact that the arterial blood oxygen saturation was normal, *i. e.*, 94%.

It should be noted that clinical manifestations and physiological measurements indicative of seriously impaired pulmonary function were present months before unequivocal X-ray evidence of fibrosis was detected. Roentgenograms at no time reflected the severity of the pulmonary lesion in this case. This is probably due to the fact that the fibrosis is diffuse, with no large masses or nodules of collagen being formed.

The fact that the lung volume and its subdivisions were not changed when the patients were exposed to cold indicates that the blood vessels of the lungs do not react in a manner similar to those of the hands and feet. This conclusion was strengthened by the observation that exposure to cold did not result in a change in the circulation time through the lungs.

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Renin-Like Substance in Blood after Hemorrhage.*

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The stimulus adequate to cause the isolated perfused kidney to release renin has been shown by Kohlstaedt and Page¹ to be a fall in the pulse pressure. It seems probable that a similar fall in pulse pressure in the intact animal would affect the kidney similarly. Wakerlin and Chobot² were unable, however, to find any change in the renin content of kidneys after their dogs had been subjected to either hemorrhage or splanchnic stimulation. In view of the considerable variation in the renin content of normal kidneys, and of the possibility that the amount of renin liberated is very small in relation to the amount originally present in the kidney, these results

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¹ Kohlstaedt and Page, *J. Exp. Med.*, 1940, **72**, 201.

² Wakerlin and Chobot, *Proc. Soc. Exp. Biol. and Med.*, 1939, **40**, 331.

cannot be accepted as excluding the possibility that renin is liberated after hemorrhage.

The experiments here reported demonstrate that after hemorrhage the blood has renin-like properties. The rôle of the kidneys, however, remains to be studied.

Methods. The blood was assayed by a modification of a technic originally described by Page³ for the assay of renin activator. This is based on the observation that whereas either renin or renin activator alone has only slight action on the (rabbit) gut, the two in combination cause a powerful contraction due to the liberation of angiotonin (the gut stimulating agent). Furthermore, gut treated with renin adsorbs enough of it so that even after it is washed an amount remains sufficient to react with added activator and cause contraction.

In the present experiments the guinea pig ileum was used instead of rabbit gut and its behavior appears to be similar. The sensitivity to renin alone, however, seems to be considerably greater than that of rabbit gut.

A section of guinea pig ileum about one inch long is suspended in a bath of warm, flowing, oxygenated Tyrode's solution, its movements being recorded on a kymograph. Introduction of small amounts (0.2 cc) of purified renin[†] is followed by a prolonged slow contraction (Fig. 1A). Angiotonin solutions[†] cause a sharp rapid contraction which soon subsides. Normal blood (renin activator) applied to a previously untreated gut has no effect. If, on the other hand, the gut has previously been treated with renin, normal blood causes a sharp contraction similar in character to that caused by angiotonin (Fig. 1B).

These responses were used as qualitative indicators of the presence of renin and renin activator. No attempt was made to quantitate the assay.

Five dogs were used in the following series of experiments: A preliminary blood sample was taken and heparinized. The dog was then bled from the femoral artery till two-fifths of the blood volume (assumed as 7% of the body weight) had been removed. No medication was used except a local infiltration of the region of the femoral triangle with 1.0% procaine hydrochloride without epinephrine. Signs of cardiovascular distress (rapid, shallow respiration, restlessness, rapid pulse, pallor of gums and tongue) usually appeared

³ Page, *Am. J. Physiol.*, 1940, **130**, 29.

[†] The purified renin and angiotonin preparations used in these experiments were generously supplied by Dr. I. H. Page.

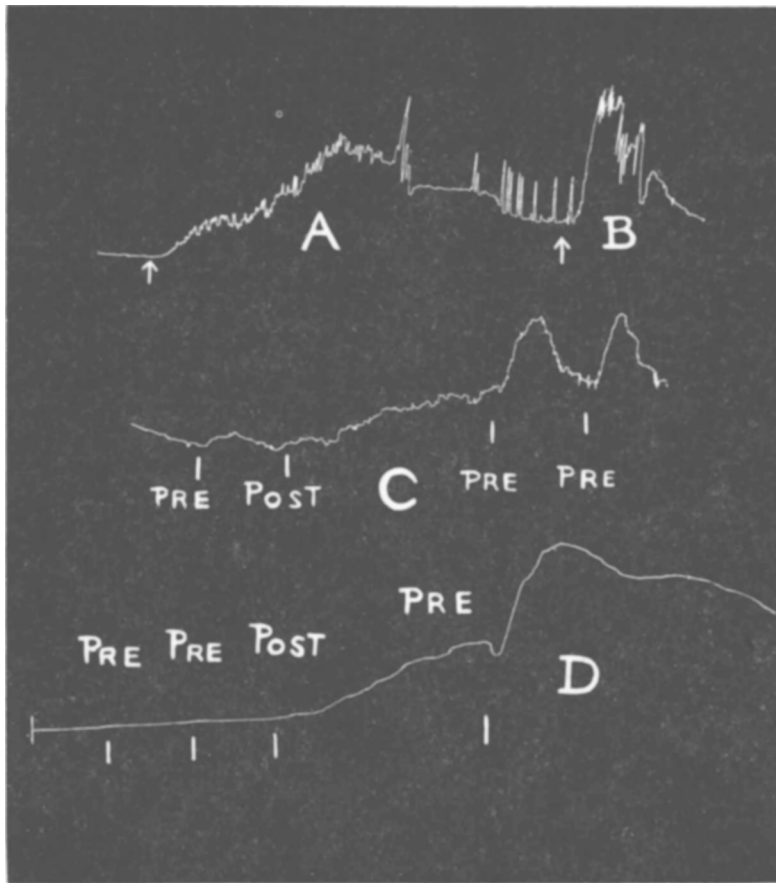


FIG. 1.

A. Response of guinea pig ileum to treatment with .2 cc of a purified renin preparation.†

B. Response to injection of normal blood after preliminary treatment with renin. Note the difference in character of the responses in A and B.

C and D. Responses to normal (pre) and posthaemorrhagic (post) bloods of otherwise untreated guinea pig gut.

before the bleeding was complete. A second blood sample was taken 24 hours after the hemorrhage and heparinized. Both the first and second blood samples were placed on ice immediately after withdrawal. To minimize effects due to difference in storage time the assay of both samples was delayed until 24 hours after the withdrawal of the second sample. The samples were then assayed on the guinea pig ileum prepared as previously described.

Findings. In each of the 5 experiments reported[†] the 2 samples of blood were tested in varying orders. Table I expresses the findings in 4 of these experiments. Figure 1C shows some of these responses selected for purposes of illustration (see legend).

In the fifth experiment, typical responses were given by the post-hemorrhagic blood, but the prehemorrhagic blood was totally inactive on gut "sensitized" by posthemorrhagic blood.

TABLE I.
Tabular Summary of the Typical Result of Exposing the Gut Segment to Pairs of Blood Samples in Varying Order.

1st sample	Effect	Second sample	Effect
normal blood	0	normal blood	0
" "	0	blood after haem.	prolonged slow contr.
Blood after haemorrhage	prolonged slow contraction	normal blood	sharp transitory contraction

Discussion and Conclusions. The observed phenomena are consistent with the concept that the blood of the normal animal, with normal pulse pressure, contains activator but no renin whereas blood taken after hemorrhage when the pulse pressure may be low contains demonstrable amounts of a renin-like substance. Moreover, since the gut always responds slowly to posthemorrhagic blood, it seems likely that this blood contains a diminished amount of activator, since the usual response to a mixture of renin and activator is prompt. Prehemorrhagic blood, which according to this concept contains no renin is incapable of sensitizing the gut to either pre- or posthemorrhagic blood. The results in the single exceptional experiment already cited might be explained by assuming a low renin activator or high renin inhibitor content in the normal blood of the animal in question.

If, as it appears, the renin content of blood increases after hemorrhage, when the effect of such an increase would help restore the blood pressure to normal levels, these findings support the view that the kidney acts as an organ of internal secretion, preserving the homeostasis of the whole circulatory system by a humoral mechanism.

The assay method here described is not specific for renin or renin activator and further experiments to make the identity of the active substances involved more certain are in progress.

[†] A preliminary group of 6 dogs studied before the technic was adequately standardized gave results which were in all cases compatible with the findings here reported.