plication was, however, less effective than the intraperitoneal injection of either the acid or alkaline extract.

We have also investigated the effect of these substances on the sex organs of the guinea pig. This phase of our studies is not yet complete and we shall report on it more fully at a later date. But we may state that the effects on the thyroid gland and those on the sex organs do not parallel each other. For example, inoculation of anterior pituitary gland of the guinea pig is very effective in causing ovulation, hypertrophy of the uterus and the opening of the vagina, whereas, it has only a relatively slight effect in causing hypertrophy of the thyroid. Inoculation of anterior pituitary of rabbit is likewise effective on the sex organs of the guinea pig. On the other hand, inoculation of anterior pituitary of cattle apparently does not produce changes in the sex organs as observed above, yet it is effective in causing hypertrophy of the thyroid. Acid or alkaline extracts, as prepared in our laboratory, do not cause ovulation or opening of the vagina in the guinea pig, but do lead to the production of structures which correspond to the so-called interstitial gland in the ovary of the rabbit. Such marked hypertrophy of the theca constituents of atretic follicles may lead even to the production of structures which somewhat resemble small corpora lutea. However, these structures contain degenerating ova.

These findings suggest that there may possibly be several constituents in the anterior pituitary gland, each of which acts in a specific manner on the thyroid gland and on the sex organs.

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Interaction Between Substances in Tissue Extracts and Blood Sera. Effect of Mixtures of these Substances on Coagulation of Blood.

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Loeb[1, 2] and subsequently Hewlett,[2] Muraschew,[2] and Nolf,[2] have shown that tissue coagulins (thrombokinase of Morawitz, tissue fibrinogen of Wooldridge and Mills, thromboplastic substances of

[1] Loeb, Leo, *Montreal Med. J.*, 1903, xxxii, 507; *Virchow's Archiv.*, 1904, clxxvi, 10.

[2] Loeb, Leo. See review of older literature in *Biochem. Centralblatt*, 1907, vi, 829.

Schmidt and Howell, cytozym of Fuld, Spiro, and Bordet) are specific in different species of animals, the tissue coagulin of one species being relatively more efficient in causing coagulation of plasma from that species than from any other. Loeb,[3] and subsequently Loeb, Fleisher and Tuttle,[4] also found that when tissue extracts and blood sera are mixed together and incubated for varying periods of time, coagulation of plasma, added at the end of incubation, was delayed. In general, the longer the period of incubation the greater was the degree of inhibition of coagulation. Some evidence also pointed to a specific interaction between extracts and sera from homologous species and there was an indication that both accelerating and inhibiting effects were due to the interaction of substances specifically adapted to each other. The following experiments were carried out in an attempt to confirm and extend these observations.

Method. Constant amounts of kidney extracts and blood sera were incubated at 34° C. for periods varying from 0 to 80 minutes. At the end of these periods 1.0 cc. of heparized blood plasma was added and the time necessary for coagulation noted. Controls were made by substituting 0.9% NaCl solution for blood serum. Dog, goose, and chicken heparized plasma were used, and serum and kidney extracts were taken from the human, dog, rabbit, ox, sheep, goose, and chicken.

Results. Dog Serum with Various Kidney Extracts. Dog serum in combination with various kidney extracts produced inhibition of coagulation which became more pronounced with longer periods of incubation. In some cases an initial acceleration was noted. The degree of inhibition was always greater when dog kidney extract and dog serum were incubated together.

Human Serum with Various Kidney Extracts. Inhibitory effects were noticed when human serum was combined with human kidney extract or dog kidney extract. In many cases homologous combinations gave more inhibition than heterologous combinations, but in some experiments the reverse was noted, probably in consequence of the larger amount of inhibiting substance present in dog kidney extract. In such cases a relative specificity could be demonstrated.

Sheep Serum with Various Kidney Extracts. A specific acceleration of coagulation occurred when sheep serum and sheep kidney

[3] Loeb, Leo, *Hofmeister's Beitrage*, 1904, v, 534; 1907, ix, 185.

[4] Loeb, Leo, Fleisher, M. S., and Tuttle, L., *J. Biol. Chem.*, 1922, i, 1, 461 and 485.

extract were combined. With other extracts a mild inhibition was noted.

Ox Serum with Various Kidney Extracts. Acceleration of coagulation was also noted with combinations of ox serum and ox kidney extract, while with heterologous extracts, the absence of specific interaction between accelerating substances allowed mild inhibition to occur.

Rabbit Serum with Various Kidney Extracts. Varying degrees of inhibition without uniformity were noted when rabbit serum was combined with various kidney extracts.

Goose Serum with Various Extracts. Goose serum when incubated with goose kidney extract gave very marked inhibition, while combinations with other extracts produced only mild degrees of inhibition. These results obtained with both dog and goose plasma.

Chicken Serum with Various Kidney Extracts. Little change was noted when chicken serum was incubated with chicken kidney extract, but usually a mild inhibition occurred after longer incubation periods. Somewhat more marked inhibition was noted with heterologous combinations. In contrast to the experiments with goose serum and extract, where the action of these combinations was compared on goose as well as dog plasma, in the case of chicken serum extract, dog plasma alone was used. This, perhaps, may explain the indefinite results obtained with these latter combinations.

Discussion. These experiments are in agreement with the conclusions of Loeb that when blood serum and tissue extracts are incubated together, there are two substances which affect the coagulation of the plasma. One of these factors causes an acceleration beyond that which occurs when tissue extracts alone are added to the plasma and the other causes an inhibition of coagulation. The accelerating factors are evidenced first by the initial acceleration noted after short incubation periods, and by the pronounced acceleration observed in combinations of ox serum with ox extract, and sheep serum with sheep extract. The inhibitory substances manifest themselves in combinations of dog serum with various extracts especially, but also with human, rabbit, and goose serum.

Not only do these experiments indicate the presence of accelerating and inhibiting substances, but they also point to a specific adaptation between these factors in sera and extracts from homologous species. Thus the most marked inhibition is observed when dog serum is combined with dog kidney extract rather than with any other extracts. Human serum is always relatively or absolutely more effective in causing inhibition when combined with human

kidney extract than with dog kidney extract. Again, goose serum is much more effective in causing inhibition when combined with goose kidney extract. On the other hand, in those sera and extracts which tend to cause acceleration of coagulation, most marked accelerations are always noted when homologous combinations are used. Thus the greatest acceleration is noted when ox serum is combined with ox kidney extract or when sheep serum is combined with sheep kidney extract.

From these data it appears that not only are accelerating and inhibiting substances developed in combinations of sera and extracts, but that the latter are specifically adapted to each other so as to be most effective when homologous factors are combined.

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Oral Administration of Anterior Pituitary Tablets and Our Laboratory Preparations on Compensatory Hypertrophy of Thyroid Gland.

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In earlier investigations Loeb,[1] and Loeb and Kaplan[2] have shown that the compensatory hypertrophy of the thyroid gland of guinea pigs which takes place after extirpation of a great part of this organ, is very much diminished or entirely prevented if, following the extirpation, daily a tablet of Armour's anterior pituitary substance is fed to guinea pigs. In our first publication, we considered whether the effect observed by us was due to the anterior pituitary preparations as such or to an admixture. Analysis of the action of iodine preparations on the compensatory hypertrophy of the thyroid gland allowed us to exclude the addition of this substance as the cause of the prevention of compensatory hypertrophy. Furthermore, H. A. McCordock[3] showed in this laboratory that Armour's tablets prevent also the marked increase in mitoses in the thyroid otherwise produced by administration of KI to guinea pigs. We had planned several years ago to compare with the effect of Armour's preparation, the effect of oral administration of anterior pituitary of cattle prepared by

[1] Loeb, Leo, *J. Med. Res.*, 1920, xl, 481; *Am. J. Path.*, 1929, v, 71.

[2] Loeb, Leo, and Kaplan, E. E., *J. Med. Res.*, 1924, xliv, 557.

[3] McCordock, H. A., *Am. J. Path.*, 1929, v, 171.