

constant effects on the oxygen consumption, carbon dioxide production or respiratory quotient in rabbits. They used anesthetized animals, however, gave enormous doses, 200 to 4000 units of the material subcutaneously and followed the metabolism for only a few hours after each injection. We have used what are presumably more physiological doses, without anesthesia, and have followed the metabolic level during and after periods of continued daily administration.

Two sources of the sex maturity or gonad stimulating principle were used. One was an extract of sheep anterior lobe* and the other we prepared from the urine of women in the first half of pregnancy after the method of Biedl.² The potency of the extracts used was assayed by testing on infantile rats. Twelve rats were used, 9 females and 3 males. Twenty determinations made in the first 1 to 4 hours following the subcutaneous administration of the extracts in doses of 2 to 8 units showed no significant changes in the metabolic rates, although the tendency was towards an increase. No effects on the respiratory quotient were found.

These same rats were given doses of 1 to 6 rat units per day for periods of 8 to 24 days. Frequent metabolism determinations made during and after the periods of treatment showed no significant changes from the preliminary average level. The total average of the metabolic rates during the period of administration of the extracts was only 2% higher than the normal average rate. These results would indicate that in rats this material is without any general metabolic effect.

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Effect of Growth Promoting Extracts of the Anterior Pituitary on Basal Gaseous Metabolism in Rats.

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Lee, Teel and Gagnon¹ have previously reported that in giant rats produced by the daily administration of alkaline extracts of beef

* Prepared by Parke, Davis & Co.

² Biedl, A., *Endokrinologie*, 1928, 2, 241.

¹ Lee, M. O., Teel, H. M., and Gagnon, J., *PROC. SOC. EXP. BIOL. AND MED.*, 1929, 27, 23.

anterior lobe pituitary, the basal gaseous metabolism was found to be somewhat reduced. We have made a further study of the effects of similar extracts in rats before there has been a great increase in weight and before the marked splanchnomegaly has had time to develop.

The immediate effects of growth stimulating extracts* were determined in 11 experiments on 3 male and 4 female rats. Doses of 1 or 2 cc. were given intraperitoneally either after preliminary metabolic rate determinations on the same day or to rats in which the basal level had been well established. The metabolic rates were then followed for 3 to 6 hours. In 9 instances there occurred definite increases in the heat production over the basal levels, ranging from 6 to 17% and with an average of 10.5%. This increase reached its maximum in 2 to 4 hours after the injection. In 2 experiments there was no apparent effect. Boiled extracts, in which the growth principle was destroyed, also caused an increased heat production of about the same magnitude (5 to 13%) in 4 rats. The extracts contained some protein and we believe that this increased metabolism may be due to the specific dynamic action of such protein products.

In 18 rats, 7 males and 11 females, frequent metabolic rate determinations were made before, during and after periods of daily administration of the extracts ranging from 15 to 72 days. In these experiments at least 24 hours elapsed after a dose of the extract before a metabolic rate determination was made. In 10 of the rats, 6 females and 4 males, there were significant decreases in the basal metabolic levels ranging from 12 to 39%. In 8 rats no significant effects were noted, but only one of these rats showed an increased growth rate and 4 received extracts which were found to be of slight potency. In no animal of the series was a significant increase in the basal metabolic level found.

There was a characteristic inertia in the metabolic response to the growth extracts in all of the rats showing a decrease. The fall did not begin until several days after the injections were started, and continued for 8 to 14 days after they were stopped. This lag is well illustrated by the female rat which showed the greatest response to the extracts. The average normal metabolic level in 8 determinations was 766 calories per day per square meter of body surface, with extreme ranges of 735 and 807 calories. Growth promoting extract was given for 19 days. During this period 6 determinations at 3 day intervals gave rates of 764, 728, 771, 640, 577 and 538

* These extracts were prepared and furnished by Parke, Davis & Co.

calories. After stopping the extract, the metabolic rate in 4 days fell to 470 calories and 5 days later it was found to have the same value. This represents a decrease of 39% from the original level. There was then a slow, gradual rise of the rate to a new level of about 740 calories, which was attained within 6 weeks. Although the response of this rat was greatest in magnitude, it was otherwise typical of the responses in the other rats.

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Differentiation of the *in Vivo* and *in Vitro* Actions of Tissue Extracts.

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In our earlier work^{1, 2} on tissue extracts, we found them active in promoting clotting of the blood *in vitro* or when intravenously injected, and also when administered to animals or man subcutaneously, intraperitoneally or orally during fasting conditions. During those studies we were dealing with fresh extracts or freshly purified fractions. More recently we have noticed that certain batches of tissue fibrinogen, after weeks of storage, lose entirely their effectiveness on intraperitoneal injections into animals, although they retain their full activity *in vitro*. Other batches made apparently in the same manner, are active with all forms of administration.

This raises the question as to whether we are dealing with 2 different actions of tissue fibrinogen, one of which is destroyed on standing, or whether 2 separate coagulants are present, one acting only when added directly to blood, and the other capable of accelerating clotting after absorption into the blood through the intestine or peritoneum. We offer evidence here that there are 2 distinct substances of this nature existing in crude tissue extracts or fresh preparations of tissue fibrinogen.

Healthy rabbits of about 4 pounds body weight, and fasted for 24 hours, were used for the injection tests. Two rabbits were used for the testing of each sample and for control in each series. In

¹ Mills, C. A., *J. Biol. Chem.*, 1921, **46**, 135, 167.

² Mills, C. A., Dorst, S. E., Mynchenberg, G., and Nakayama, J., *Am. J. Physiol.*, 1923, **63**, 484.