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The determination of small quantities of sugar in urine, including observations on the polysaccharide content of human urine.

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Conditions have been found for carrying out the reaction between sugar and picric acid which render it possible to determine sugar in the presence of three or four times its weight of creatin or creatinine without affecting the results. When this reaction is applied directly to urine, figures for sugar are obtained which are only a few hundredths of a per cent. higher than those obtained after precipitation with mercuric nitrate as described by Benedict and Osterberg. After treatment of the urine with a suitable purified bone-black the figures obtained duplicate very closely those found with the mercuric nitrate method. The procedure recommended will be described in detail in the near future.

Using the new technique, observations have been made on the increase in reducing substance of normal urine which results from mild hydrolysis with hydrochloric acid. The increase in reducing substance thus obtained amounts to about 0.5 gm. per day calculated as glucose, for the 24 hour elimination of a normal human adult. Very much higher figures (several grams per day) have been observed in cases of diabetes mellitus which were under treatment, and where the glucose eliminated amounted to from 3 to 20 grams per day.

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Disturbances in the development of mammalian embryos caused by radium emanation.

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As has been shown by various observers, the exposure of living tissues to the influence of radium rays leads to a severe injury and

ultimate destruction of these tissues. In our work an attempt was made to study this destructive influence on mammalian embryos in utero, in the hope that a partial or complete destruction of one or more tissues might lead to definite abnormalities or malformations in these fetuses.

Bagg had lately used a method of applying radium, which was described in the *Journal of Cancer Research*, Vol. V, 1920. Radium emanation, carried in a very small amount of saline solution, was injected in measured quantities into adult rats, either subcutaneously or intravenously. This solution contained all the properties of the radium metal itself, and, no doubt, the resulting physiological changes were due mainly to the activity of α -rays. Such an injection produced peculiar destructive changes in the inner organs of the animals.

The same method was used in our experiments. After long experimentation we found that a dose of 5 mc. (= milli-curies, a standard unit in radium experimentation) was about the optimal dose. Such an amount was injected into female rats, pregnant and non-pregnant, with the purpose of either injuring the ovarian or uterine tissues, or, in case of pregnancy, the embryonic tissues. While the results were not those which we expected, viz., the production of various types of monstrosities, yet a definite influence of radium on the fetal and placental tissues was noticeable. Radium-treated rats were killed at different periods of pregnancy, so as to procure a series of fetuses of various ages.

The most destructive results of radium emanation, injected subcutaneously, were seen in a number of pregnant females, in which the embryos were killed in the uterus and, instead of being aborted, remained attached to the uterine wall and were gradually absorbed (group I). Whether the embryos were killed primarily, or their death was due to the destructive influence of the radium on the maternal, placental tissues, cannot, of course, be determined. Probably the first assumption is correct, since other findings (group II) showed, that the toxic agent *does* pass the placenta and affects the embryos directly.

A number of such partially absorbed embryos were found, the age of which, naturally, could not be determined. Judging from the sizes of their respective placentæ, however, development must

have proceeded to some extent before the radium was applied. The remnants of the embryos were small, nodular bodies attached to the placenta (figures were shown) and had lost all resemblance to properly developed fetuses.

In one case a small, ovoid shaped sac was found, attached by a thin stalk to the uterine wall (figure shown). This apparently represented the remnants of a former embryo and placenta, although neither one could be recognized any longer. In the sac extravasated blood and cell detritus were found. A great many large cells of an epithelioid nature probably belonged to the former embryonic syncytium. The wall of this cyst was formed by fibrous connective tissue.

In a number of other cases (group II), the fetuses were not killed by the radium emanation, but peculiar macroscopic lesions appeared in their skin vessels.

When the fetuses were removed from the uteri, peculiar hemorrhagic areas were noticeable, in some cases just along the dorsal midline, in other cases, spreading over the entire body with the exception of the ventral surface. These extravasations took place in the vessels of the subcutaneous connective tissue and along the meningeal sinuses. In all cases, one or more hemorrhages appeared in the midline, mainly in the head and thoracic region. It seems that the vessels in this dorsal median zone are especially liable to injury. In one instance, there was a large area of hemorrhage extending over the thoracic and lumbar region. Its outline was just symmetrical to the dorsal midline (figure shown). In other cases, a great number of such hemorrhagic areas, some extremely small, were found over the lateral aspects of the head and body. Probably these affected fetuses would have died, if left longer in the uterus, and would have undergone absorption. In many animals which we killed in the early parts of the experiments we failed to find any fetuses, although we definitely believed that these animals had been pregnant before. We probably waited too long after treatment, so that the embryos were completely absorbed, when the animals were opened.

Not all of the fetuses of one litter are affected in the same degree. In one case, for instance, we found among 7 fetuses 3 showing hemorrhagic lesions, 2 beginning to macerate and 2 in the process

of absorption. This difference in resistance may be due either to the higher or lower vitality of the embryos themselves or to the amount of radium which passes the placenta. In another case the fetuses, although injured, were carried to full term and among 6 young of one litter we found two normal and four showing hemorrhagic spots on head, face and along the dorsal midline.

In one very remarkable instance the female had been treated 22 days previous to conception and yet the fetuses, approximately 16 days old, showed areas of extravasation (one of considerable size shown in figure). These lesions were much more widely distributed than in previous cases, extending over both lateral and dorsal surfaces (figure shown). These results cannot be explained at present. It would seem as if the treatment of the mother previous to conception had lessened the faculty of the later embryos to form proper endothelial walls. The wide distribution of the lesions would seem to substantiate such a view. This is in accordance with findings in adult animals treated with radium in which the extravasations in the organs are due not only to increased blood pressure, as would seem at first, but to the actual breaking down of the endothelial tubes. In other words, the effect of radium on endothelium might be selective.

When the radium was injected intravenously (group III) instead of subcutaneously, the same lesions resulted along the vascular channels. Females of about 19 days pregnancy were injected intravenously and the young, born dead 24 hours later, showed the hemorrhagic lesions along the dorsal midline (figures shown). In one case we found a striking difference in the size of the placentæ of different fetuses. One fetus, for instance, had a markedly enlarged placenta completely filled with blood, so that it had the appearance of a large hemorrhagic sac. This fetus did *not* show any hemorrhagic lesions, while their placentæ were of normal size and moderately filled with blood. It would seem as if in the first case the placenta functioned as an effective "shock-absorber," while in the other cases the radium emanation passed through the placentæ to the fetuses.

Lately Bagg exposed pregnant females, near full term, directly to the action of γ -rays (group IV). This radiation of the fetuses in utero, through the abdominal walls produced hemorrhagic

lesions of the same nature as described above. However, the lesions did not appear until about 10 days after exposure. The young were born 2 days after treatment and appeared normal. After about a week they began to fail considerably, hemorrhagic areas appeared along the mid-dorsal line, especially in the head region and death followed. The hemorrhages in these animals were mainly along the meningeal sinuses (figures shown), in some cases frontal and occipital hemorrhages were just beginning, in others they extended considerably over the cerebral hemispheres. Additional lesions on the dorsal side of the thorax were found.

The interval of 10 days after treatment strictly corresponds to the time at which a primary skin erythema develops in radium treated patients. Again it seems as if the endothelial walls had been injured at the time of exposure and gradually gave way to the blood pressure.

In the course of the experiments, we also found numerous hemorrhagic areas in the uteri and especially in the ovaries (figures shown). Congestion of the uterine vessels always was pronounced.

While in experiments on adult animals reported by Bagg before, the injection of radium emanation led to considerable injuries in the internal organs, in our experiments the weaker doses did not produce any macroscopically visible effects on the *maternal* tissues. However, the *embryonic* differentiating tissues were easily affected. This fact might be of some biological significance, when one remembers that radium rays have a decided effect on fast growing tumor and cancer tissues.

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The influence of phenylcinchoninic acid and its methyl derivative on the uric acid and urea content of the blood.

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It has been recognized now for some time that the administration of salicylates and phenylcinchoninic acid (cinchophen)