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The Action of Specific Diuretics: The Inhibiting Effect of Intraperitoneal Distilled Water.

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Administration of theophylline ethylenediamine intramuscularly to rabbits calls forth an acute and profuse diuresis. In an extensive physico-chemical study of the initiating events, as well as of the subsequent diuresis, it was found that a slight but constant rise in the whole blood chloride occurs relatively soon after the administration, and as a rule precedes the maximal diuresis. The resulting diuresis may exceed 50 times the normal urinary output. The specific electric conductivity of the urine and particularly the concentration of the urinary chloride rise, even throughout the periods of increasing and maximum diuresis. Consequently so much as one third the amount of the total blood chloride may be excreted within an hour. However, at the end of the hour the whole blood chloride is even higher than during the control preadministration period. It follows that during the hour chlorides pass rapidly from the tissues into the blood stream, and thence through the kidney into the urine.

A consideration of these findings, the rise in blood chloride and the profuse excretion of urinary chloride, led to a consideration of the importance of the chloride in the mechanism of the induced diuresis. Cohnheim[1] had found that chloride soon passes into sugar solutions injected intraperitoneally. The intraperitoneal injection of sugar solutions results in a fall in the blood chloride, since chloride leaves the blood stream and enters the artificial transudate up to a concentration of 0.4%.[2] Other electrolytes are likewise deviated from the blood stream, after the laws governing permeability. When hypotonic sugar solution is injected intraperitoneally at the same time that the specific diuretic is administered intramuscularly, there follows a definite decrease of the diuretic response. This decrease is not so marked when isotonic sugar solutions are injected. The diuresis which remains is associated with an increased excretion of sugar. A similar diuresis follows the injection of the sugar solutions alone. The substitution of isotonic saline in a combined injection has no inhibiting effect, in fact the resulting diuresis is unusually large.

[1] Cohnheim, O., *Z. f. Biol.*, 1899, xxxvii, 443.

[2] Curtis, G. M., *Biochem. Z.*, 1925, clxiii, 109.

When distilled water is injected intraperitoneally at the same time the diuretic is administered intramuscularly no diuresis ensues.[3] The normal action of the specific diuretic is thus inhibited. There are no crystalloids to enter the blood. Also as high as 0.63% sodium chloride together with other electrolytes are rapidly deviated from the blood stream and tissues. There is a distinct fall in the blood chloride. At the end of an hour a secondary diuresis may ensue, and at that time a subsequent injection of the diuretic may become effective. However, then the peritoneal cavity contains an isosmotic fluid with about 0.6% sodium chloride. The same inhibitory effect occurs after the denervation of the kidneys.[4]

These experimental findings led to the conclusion that the deviation of chlorides and other electrolytes from the blood stream and tissues, and consequently from the kidney, was the important factor in the inhibition of the normal action of the specific diuretic employed. Objection has been made to this view on the basis that the intraperitoneal distilled water may produce some acute change in the freely exposed kidney, such as an acute edema, and that this is the factor inhibiting renal secretion. In the rabbit, to be sure, the kidney hangs nearly free within the peritoneal cavity, and is covered by but a thin serous layer, with some properitoneal fat. The present series of experiments was consequently designed to answer this and other similar questions.

In 15 experiments distilled water at body temperature was perfused through the peritoneal cavity at the rate of 500 cc. per hour. Within 15 minutes after the beginning of the perfusion there is, as a rule, a prompt decrease in the urinary output. Within an hour this often amounts to a complete anuria. In certain experiments there is a slight, irregular urinary secretion; however, this is consistently less than normal. In 5 of the experiments the diuretic was administered, 0.12 gm. intramuscularly, during this period of anuria or of lessened urinary secretion, from one-half to 2 hours after commencement of the perfusion. In no experiment was there an increased urinary output. During the perfusion chloride and other electrolytes are dialyzed away from the blood stream. Organic crystalloids, particularly glucose, also appear in the perfusion water. The blood chloride falls as low as 118 mgm. per 100 cc. From 300 to 836 mgm. of chloride is dialyzed from the blood stream and particularly the tissues.

In 15 experiments 0.12% glucose was added to the perfusion

[3] Curtis, G. M., *Biochem. Z.*, 1927, clxxxvi, 95.

[4] Curtis, G. M., and Shambaugh, N. F., *Biochem. Z.*, 1927, clxxxvi, 112.

water. The inhibiting effect upon the secretion of the urine is similar, though not so marked. The blood chloride falls as low as 143 mgm. per 100 cc. and the amount of chloride dialyzed away varies from 205 to 896 mgm. Administration of the specific diuretic during the perfusion is again without effect in increasing the urinary output. The similar perfusion of Ringer's solution, or of 0.9% sodium chloride, through the peritoneal cavity does not inhibit the urinary output; on the contrary it increases it.

The timed intravenous administration of salt solution of varying concentrations by means of the Woodyatt pump results in a diuresis. Consequently, an attempt was made to test renal function during the intraperitoneal perfusion of distilled water by simultaneously injecting timed adequate saline intravenously. In the 30 experiments during which either distilled water or distilled water with 0.12% glucose was perfused through the peritoneal cavity the amount of chloride dialyzed away from the bloodstream and tissues varied between 205 and 896 mgm. An effort was consequently made to supply pure sodium chloride in timed intravenous amounts to the blood stream at least as rapidly as it would be dialyzed away by the perfusion water. After calculation and a number of trials it was found best to give 2.5% sodium chloride intravenously at the rate of 1 cc. per minute during the time that distilled water was being perfused through the peritoneal cavity at the rate of 500 cc. per hour.

When this simultaneous perfusion of distilled water and intravenous injection of adequate saline is effected, kidney function is not inhibited and urinary secretion does not decrease. On the contrary it increases, even markedly. In 4 such experiments there was a definite increase in urine formation; in one as long as 13½ hours following the commencement of the simultaneous perfusion of distilled water intraperitoneally. In another experiment urinary secretion was resumed, after an anuria, upon starting the pump one hour after the transperitoneal perfusion began.

These experiments demonstrate that perfusion of distilled water through the peritoneal cavity does not inhibit kidney activity and the secretion of the urine by direct action upon the kidney cells through the thin peritoneal covering. The question of an associated acute edema of the kidney may be reasonably answered in the negative. If adequate salt is simultaneously injected intravenously, kidney function may be maintained for hours during the perfusion of distilled water through the peritoneal cavity. The conclusion that the inhibitory effect of intraperitoneal distilled water upon the action of the specific diuretic is due to deviation of chloride and other electrolytes from the blood stream and tissues is still reasonably warranted.