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Research Article

STUDIES ON THE ACTION OF DIURETICS. II. THE EFFECT OF SALYRGAN UPON THE WATER CONTENT OF THE PLASMA AS MEASURED BY THE REFRACTIVE INDEX

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There are conflicting reports in the literature concerning the effect of the mercurial diuretics upon the water content of the plasma. Saxl and Heilig (1), Bohn (2, 3) and Crawford and McIntosh (4) have reported that the concentration of protein in the plasma falls before the onset of novasurol diuresis. Mühling (5), Nonnenbruch (6) and Bleyer (7), on the other hand, found no such evidence of plasma dilution.

In a previous publication (8) evidence was presented that salyrgan diuresis is the result of decreased reabsorption of water in the renal tubules. It was suggested that this decrease in reabsorption is produced by a depressant action of the drug on the tubular epithelium. The occurrence of hydremia preceding the onset of diuresis would be inconsistent with this hypothesis and would point to a primary extrarenal action, occurring alone or in conjunction with a direct action on the kidney. Carefully controlled studies of the effect of salyrgan upon the refractive index of the plasma have, therefore, been carried out. For purposes of comparison similar studies have been made with intravenously administered physiological saline solution.

PROCEDURE

The experiments were performed upon unanesthetized female dogs who had gone without food for twelve hours or more. In Control Experiments 1 to 7 inclusive, and in the first seven salyrgan experiments, the animals were permitted to drink water as desired until two hours before the beginning of the experiment. In all other experiments the dogs were allowed no water for five hours preceding the period of observation. During the experiment the dog was tied down on a table. After a period of training the animals would remain in this position for two to three hours without struggling. Urine was collected from the bladder directly into graduated cylinders by an inlying catheter. Blood samples were drawn from the external jugular vein without stasis. Heparin (0.01 cc. of a 4 per cent solution to each cc. of blood) was used to prevent clotting. In Control Experiments 1, 2, 3, and 4 and in salyrgan Experiments 1 and 2 the blood samples were from 5.5 to 6.0 cc. each. In all other experiments about 1.5 cc. of blood were drawn at each venepuncture. Immediately after withdrawal the blood specimens were centrifuged for two minutes at 1800 r.p.m., and the refractive index determined on a drop of the plasma in an Abbe refractometer at room temperature. The temperature seldom varied as much as one degree centigrade during the course of an experiment. A rise of one degree in the temperature was found to produce a fall of approximately 0.0001 in the refractive index of the plasma. Changes in temperature of less than one degree were therefore ignored. On the few occasions when greater variations than this occurred the refractive index was corrected correspondingly.

RESULTS

(*a*) *Control experiments*

The refractive index of the plasma was found to fluctuate considerably under controlled conditions (Figs. 1*A* and 1*B*). Of particular interest in connection with this investigation are the decreases which occurred in Control Experiments 3, 4, 5, 6 and 7. In these five experiments the index

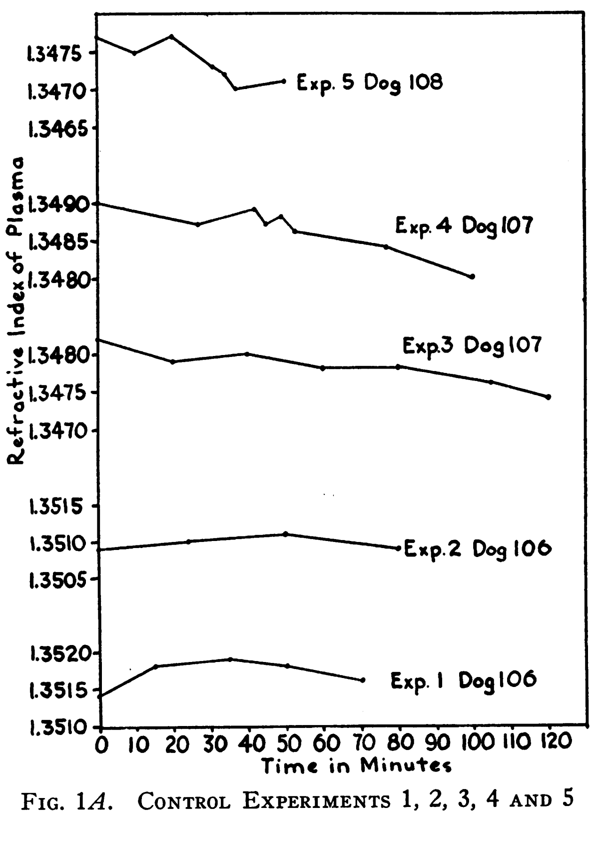

FIG. 1*A*. CONTROL EXPERIMENTS 1, 2, 3, 4 AND 5

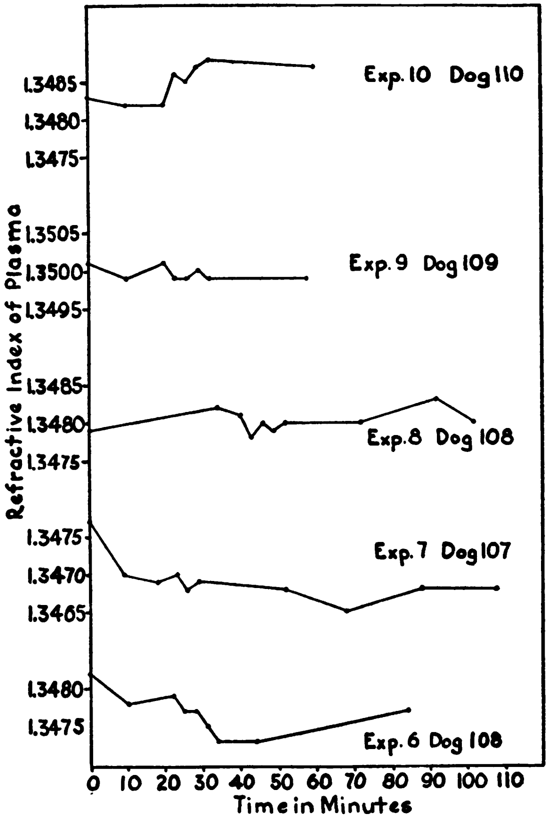

FIG. 1B. CONTROL EXPERIMENTS 6, 7, 8, 9 AND 10

of refraction dropped 0.0008, 0.0010, 0.0007, 0.0009 and 0.0012 respectively. Expressed in terms of protein concentration on the basis of Robertson's (9) figure (0.00195 = 1 per cent protein) these decreases in the index of refraction amount to 0.41, 0.51, 0.36, 0.46 and 0.61 gram per cent, respectively.

The withdrawal of fairly large amounts of blood (5.5 to 6.0 cc.) at frequent intervals was considered a possible explanation when decreases of this degree were first observed in Experiments 3 and 4. However, decreases of the same magnitude occurred in Experiments 5, 6 and 7 in which only 1.5 cc. of blood was drawn at each venepuncture.

Possibly such decreases are related in part to the fluid intake preceding the period of observation. All decreases of considerable degree occurred in the first seven experiments, in which the dogs were permitted to drink water ad libitum until two hours before the beginning of the experiment. In Experiments 8, 9 and 10 the animals were denied water for five hours preceding the period of observation. In these three experiments the index of refraction showed less tendency to fall. In Experiment 10, in fact, a considerable rise occurred. These results may, however, be merely a matter of chance. A rise in the index occurred in Experiment 1, and the index remained fairly constant in Experiment 2, although water was withheld for only two hours in both of these experiments. In the control period of salyrgan Experiment 10, on the other hand, a precipitous drop in the index occurred even though the dog had received no water for five hours.

The urine output in all of the control experiments either remained at about the same level or slowly declined during the period of observation. The spontaneous decreases in the index of refraction of the plasma were never followed by diuresis.

(*b*) *Salyrgan experiments*

No consistent change in the refractive index of the plasma was observed before the onset of salyrgan diuresis (see Figures 2*A*, 2*B*, and 2*C*).

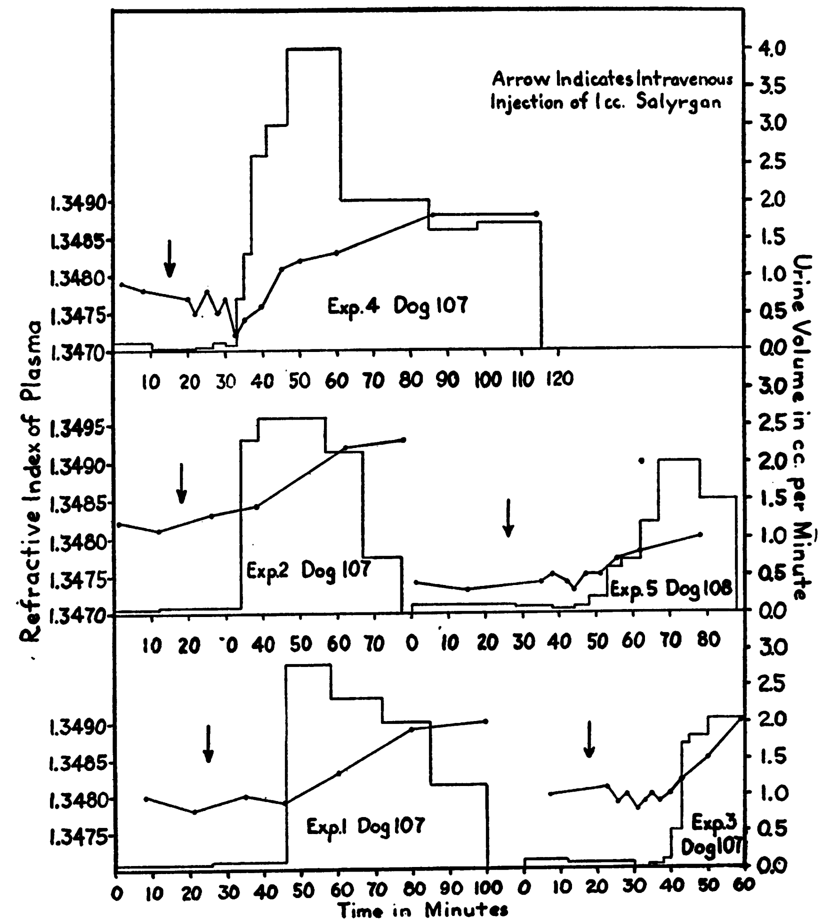

FIG. 2*A*. SALYRGAN EXPERIMENTS 1, 2, 3, 4 AND 5

In Experiments 1, 2, 3, 5 and 10 the index did not vary more than plus or minus 0.0002 from the control period level. In Experiment 9 a temporary increase of 0.0005 occurred after the administration of salyrgan. The index then returned to and remained at approximately the control period level until diuresis began. In another instance (Experiment 8) a more persistent rise in the index occurred. In the remaining three experiments

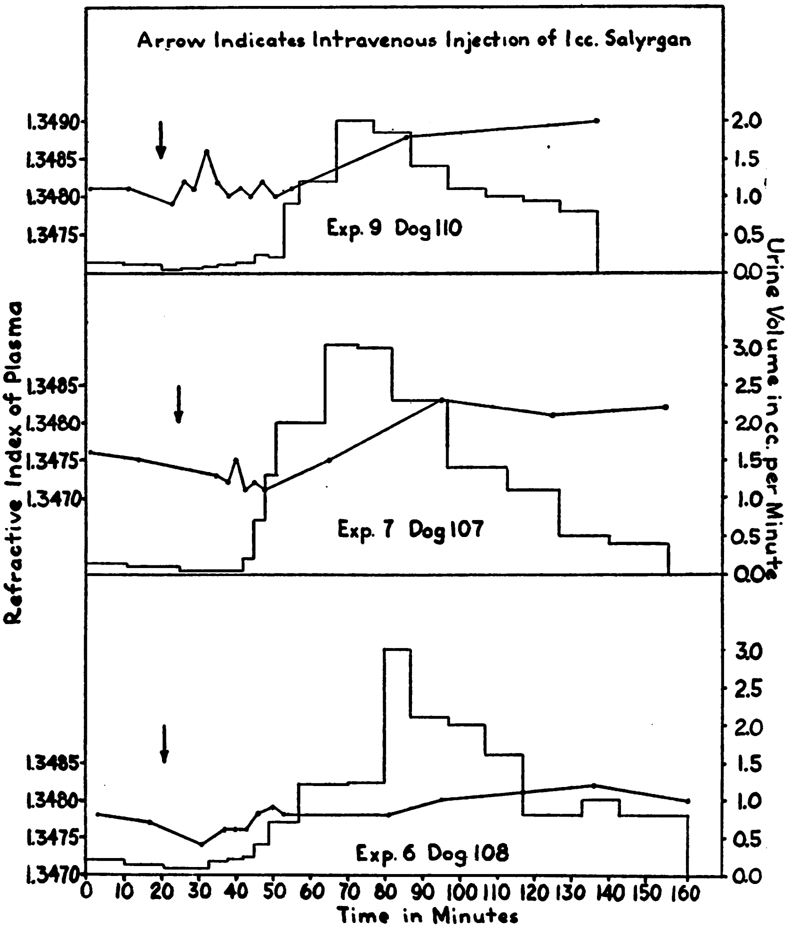

FIG. 2B. SALYRGAN EXPERIMENTS 6, 7 AND 9

(4, 6 and 7) the index fell 0.0006, 0.0003 and 0.0004 (0.3, 0.15 and 0.2 gram per cent of protein) respectively. Decreases of equal magnitude and occurring within a similar period of time were observed in the control experiments without any subsequent increase in urine volume.

In all ten salyrgan experiments the refractive index of the plasma increased gradually during the early part of diuresis. When the index had risen approximately 0.0010 (representing an increase of 0.5 gram per cent in the protein concentration) no further increase occurred.

(*c*) *Saline experiments*

Varying amounts of 0.9 per cent saline solution were injected intravenously at the rate of 10 cc. per minute (see Figures 3*A* and 3*B*). In

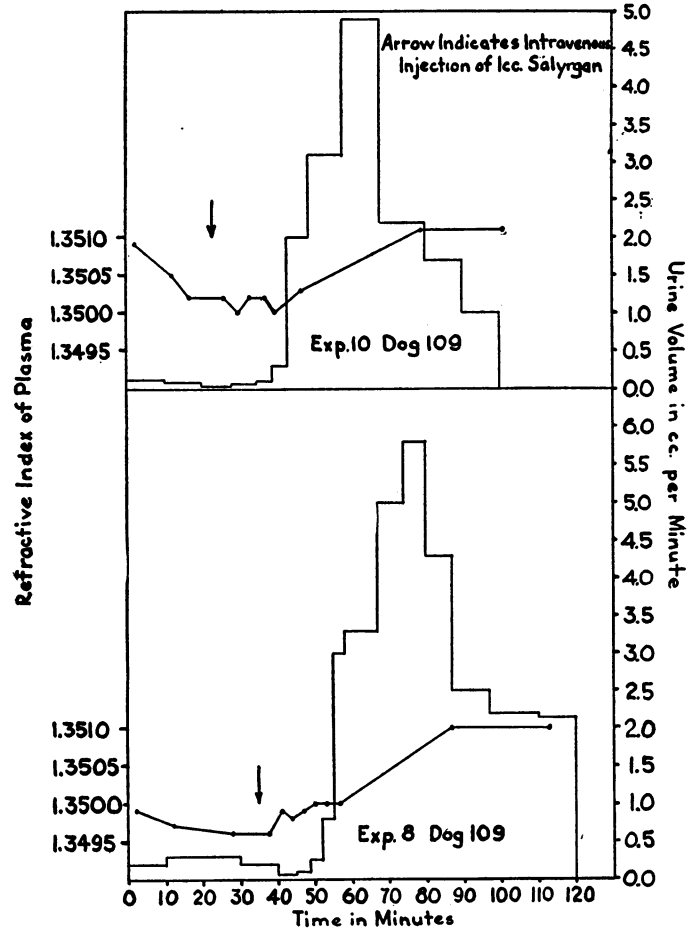

FIG. 2*C*. SALYRGAN EXPERIMENTS 8 AND 10

Experiments 1 and 2 the index of refraction of the plasma fell 0.0006 and 0.0009, respectively, without any increase in the urine volume. In the other four experiments, in which the index was lowered more than 0.0010, diuresis occurred. There was no correlation, however, between the magnitude of the urine volume and the degree to which the index of refraction was decreased. Only slight diuresis occurred in Experiments 3 and 5, in which the index fell 0.0015 and 0.0023 respectively, whereas the urine output was augmented considerably in Experiments 4 and 6, in which the index dropped 0.0017 and 0.0013, respectively, below the control period level.

COMMENT

Bohn has suggested that the contradictory reports in the literature concerning the effect of novasurol upon the water content of the plasma are

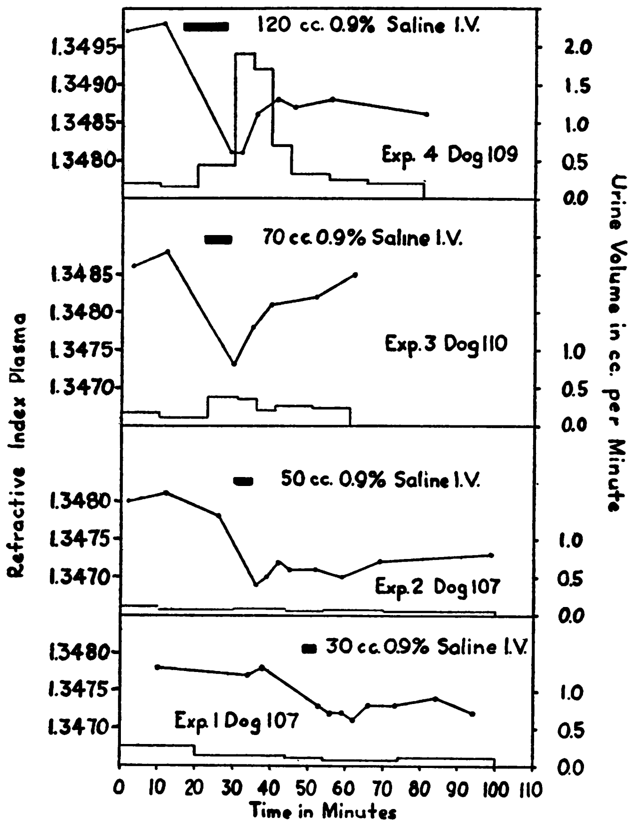

FIG. 3*A*. SALINE EXPERIMENTS 1, 2, 3 AND 4

due to the fact that blood samples were taken at different times and that the temporary hydremia was missed by some investigators. In the present experiments samples of blood were taken at approximately three minute intervals during the period between the administration of salyrgan and the onset of diuresis. There is no evidence in these experiments that diuresis is preceded by a mobilization of fluid from the tissue spaces. The refractive index of the plasma showed no consistent change before the onset of diuresis and such decreases as were observed fell within the limits of variation noted in the control experiments.

The argument has been advanced that the kidneys respond so promptly with diuresis when a shift of fluid from the tissues to the blood occurs that it is impossible to demonstrate appreciable dilution of the plasma. The results of the saline experiments do not support such a hypothesis. They demonstrate that the refractive index of the plasma may be lowered markedly by the injection of physiological saline solution without producing sig-

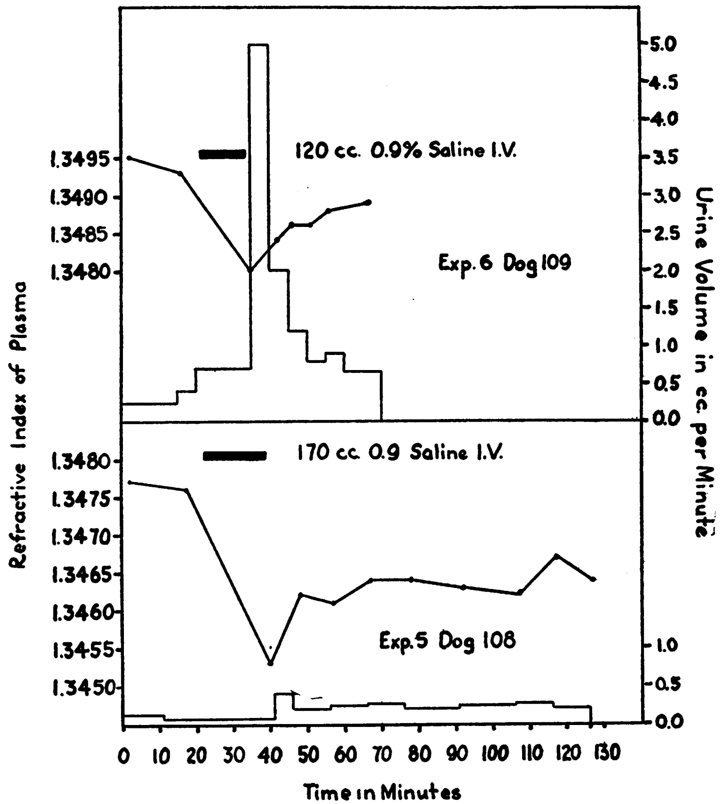

FIG. 3*B*. SALINE EXPERIMENTS 5 AND 6

nificant diuresis. This is additional evidence that the moderate decrease in the refractive index of the plasma observed in some of the salyrgan experiments played no significant rôle in the production of diuresis.

The refractive index of the plasma rises gradually during the early part of salyrgan diuresis. When the index has increased approximately 0.0010 no further concentration of the plasma occurs. Apparently sufficient fluid flows into the plasma from the tissue spaces to balance the loss by way of the kidneys.

The amount of water lost from the plasma may be calculated roughly from the change in the refractive index. Salyrgan Experiment 3, in which a comparatively moderate diuresis occurred, may be used as an example. Dog 110 weighed 14 kilograms. If we estimate the plasma volume as 600 cc. and assume a protein concentration of 6 grams per 100 cc., then an increase of 0.5 gram per cent in the protein concentration (a rise of 0.0010 in the refractive index) would mean a loss of approximately 50 cc. of water from the plasma. The total amount of urine passed from the onset of diuresis to the end of the experiment was 105 cc. In Experiment 8 the urine exceeded the calculated loss of water from the plasma by approximately 150 cc.

The excess of urine volume over the calculated loss of fluid from the plasma points to an inflow of tissue fluids into the blood. The absence of hydremia preceding the onset of diuresis, the gradual rise of the refractive index of the plasma during the early part of diuresis and the maintenance of a level after the index has risen approximately 0.0010 indicate that this inflow is secondary to the loss of fluid from the blood by way of the kidneys. This secondary withdrawal of fluid from the tissue spaces is probably the mechanism by which the mercurial diuretics remove accumulations of fluid in the subcutaneous tissues and in the peritoneal cavity.

SUMMARY

The effect of salyrgan upon the water content of the plasma has been studied by means of the refractometer.

There is no evidence in these experiments that salyrgan diuresis is preceded by a mobilization of fluid from the tissue spaces.

The results point strongly to a primary direct action of salyrgan on the kidney with a secondary inflow of fluid from the tissue spaces to prevent excessive dehydration of the plasma.

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