

TABLE II.

Shows the van den Bergh reaction, free hydrochloric acid in the gastric juice, and the lack of response to liver extract.

Case	Before liver			van den Bergh	Daily liver dosage	Days receiving liver	Free HCl	After liver		
	Hgb.	RBC	Ret. %					Hgb.	RBC	Ret. %
1	83	4.2	1.6	2.0 Ind.	6 vials	10	normal			2.8
2	54	2.7	0.8	neg.	"	41	low after H	55	3.2	5.2
3	68	3.7	0.0	"	"	10	0	54	3.0	0.2
4	75	4.0	0.2	"	"	10	0	83		0.8
5	65	3.6	0.2		"	10	normal	64	3.5	0.6
6	72	3.8	0.4	1.2 Ind.	4 oz.	20		66	3.5	0.0
7	75	3.1	0.2	0.1 "	3 cc. S.C.	14	0	74	3.4	2.8
					every other day					
	83	3.4	0.6		4 oz.	34		82	3.7	0.8
8	80	4.4	0.0		total 7 doses	10	normal			0.6
					3 cc. S.C.					
9	82	3.7	1.4		I.M 100 gm.	equiva- lent of 100 gm. intramus- cular for 11 days	low	80	3.4	3.0
10	55	3.5		neg.	6 vials	13		55	2.9	
11*	20	2.5	1.6	"	12 cap Extra.	10	0	30	3.4	1.2

* Case 11. Anemia partly due to recent hemorrhage.

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Effect of Fluorine on Blood and Respiration.

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The interest of the authors in fluorine dates from the discovery by Ostrem, Nelson, Greenwood, and Wilhelm¹ of fluorine in the drinking waters of communities in the State of Iowa, with the resulting production of mottled enamel of the teeth. Smith, Lantz and Smith² have produced considerable evidence that excessive fluorine in water will cause mottled enamel in man. The question arises as to whether fluorine produces other harmful effects in the body.

The following work relates to the effect of fluorine on respiration, blood pressure, hemoglobin, blood calcium, blood phosphorus, and coagulation of blood. Sollmann³ refers to the work of Tappeiner

¹ Ostrem, C. T., Nelson, V. E., Greenwood, D. A., and Wilhelm, H. A., *Science*, 1932, **76**, 575.

² Smith, M. C., Lantz, E. M., and Smith, H. V., *Ariz. Agr. Exp. Sta. Bull.*, 1931, **32**, 253.

³ Sollmann, T., *A manual of pharmacology*, 1932, 898.

and states that in mammals NaF causes salivation, gastro-enteritis, dyspnea, muscular weakness and tremors, epileptic convulsions, fall of blood pressure, and stoppage of respiration and heart. Schulz⁴ observed similar results. Gerschmann⁵ reports that injection of NaF reduces blood calcium. Stuber and Lang⁶ observed hemophilic patients with high amounts of F in the blood, and they accept the idea that high F content of blood accompanies a long clotting period. Schwyzer⁷ observed a high degree of coagulability of the blood of rabbits, dogs, and pigeons which received F. Hauck, Steenbock, Lowe, and Halpin⁸ reported analyses of the calcium and phosphorus of the blood of chickens receiving fluorides, but they admit that their data are insufficient to draw any definite conclusions. Phillips⁹ states, "Very little work is reported dealing with the influence of fluorine on blood composition."

Seven dogs, 5 females and 2 males, were employed in studies on respiration and blood pressure. They weighed from 6 to 26.8 kg. The remainder of the experiments were performed on puppies—13 in number, 5 males and 8 females. Nembutal in distilled water was used as the anesthetic. It was administered intraperitoneally at the rate of 30 mg. per kilo body weight. NaF was injected into the femoral vein. Blood pressure records were taken from the central (heart) end of a ligated carotid artery with a mercury manometer writing on a long paper kymograph. Eight per cent citrate solution was used to prevent clots in the cannulae and tubes. Respiratory tracings were made with a Becker air tambour connected to a pneumograph tied around the chest. Newcomer's method was used for hemoglobin determinations. The Brodie-Russell-Boggs coagulometer was used in studying the time of coagulation of blood. Calcium was determined in blood plasma by the Clark and Collip modification of the Kramer Tisdall method and acid soluble inorganic phosphorus of Youngberg's method.

Table I summarizes the results obtained on respiration and blood pressure; the data show that injection of 1.5 to 5.3 mg. of F as NaF per kilo of body weight produces a detectable effect on respiration. The average respirations increased from 15 per minute to 22 per minute, by injecting from 1.5 to 5.3 mg. of F as NaF per

⁴ Schulz, H., *Arch. Exp. Path. v. Pharm.*, 1889, **25**, 326.

⁵ Gerschmann, R., *Ann. farm biochim.*, 1930, **1**, 77.

⁶ Stuber, B., and Lang, K., *Biochem. Z.*, 1929, **212**, 96.

⁷ Schwyzer, F., *Biochem. Z.*, 1914, **60**, 32.

⁸ Hauck, H. M., Steenbock, H., Lowe, J. T., and Halpin, J. G., *Poultry Sci.*, 1933, **12**, 242.

⁹ Phillips, P., Thesis, Univ. of Wis., 1933.

TABLE I.
Effect of Intravenous Injection of Fluorine as Sodium Fluoride on Respiration and Blood Pressure.

Dog No.	Respirations per min. before injection of F	Mg. F per kilo body wt. required to produce detectable change in respiration	Respirations per min. after injection of F	Blood pressure in mm. Hg before injection of F	Mg. F per kilo body wt. required to produce detectable change in blood pressure	Blood pressure in mm. Hg after injection of F	Mg. F per kilo body wt. which caused death of animal
1	*			145	31.7	120	92.6
2	12	5.3	16	150	20.4	114	47.5
3	†			200	23.8	164	32.5
4	12	1.5	20	180	22.7	120	30.4
7	22	2.0	32	175	16.0	160	31.9
Averages	15.3	2.9	22.6	170	22.9	135.6	47.0

* Artificial respiration was used during the first part of the experiment.

† Artificial respiration was used throughout experiment.

kilo of body weight. Furthermore, the data reveal that injection of 16 to 31.7 mg. of F as NaF per kilo of body weight causes a perceptible lowering of blood pressure. The average blood pressure was lowered from 170 mm. Hg. pressure to 135.6 mm. Hg. pressure, by increasing the concentration of F as NaF from 0 mg. per kilo body weight to a level of 16 to 31.7 mg. of F as NaF per kilo body weight. The above amounts of NaF were initial doses. At intervals following the initial dose larger amounts of NaF were injected into the femoral vein. Following increased doses, respiration increased to as high as 150 per minute, and blood pressure fell to as low as 40 mm. Hg. In all cases there was respiratory paralysis before stoppage of the heart. Two dogs received orally per kilo of body weight 20 times the amount of F as NaF ordinarily consumed daily by human beings in an area where mottled enamel is endemic, without noticeable effect on respiration and blood pressure. The dogs received orally 4.5 mg. F as NaF per kilo of body weight, which was followed in a few minutes by 9 mg. of F as NaF and then up to higher doses at intervals of a few minutes. When the oral dosage of F reached 22.6 mg. per kilo of body weight, a detectable effect on respiration and blood pressure resulted. At the higher levels vomiting and salivation occurred which prevented accurate determinations. Autopsy of these dogs showed gastroenteritis and congestion of the kidneys. Dr. A. E. Merkel of Ankeny has made blood pressure studies on 65 school children who received fluorine

water and exhibited mottled enamel, and he has observed that there is no significant variation in blood pressure from the normal.

Determinations of hemoglobin, coagulation time of blood, blood calcium, and blood phosphorus were made every 2 weeks for 18 weeks on puppies (5 to 9 months old) receiving the following amounts of F in mg. per kilo body weight: 0.0, 0.45, 0.90, 2.26, and 4.52. The average values of hemoglobin, expressed in gm. per 100 cc. of blood, were: 11.86, 12.37, 12.26, 11.96, and 12.18 respectively; and the coagulation times of blood in seconds were: 84.0, 72.5, 85.3, 95.4, and 91.4 respectively. The average values for calcium, expressed as mg. calcium per 100 cc. of blood plasma, were: 12.17, 12.05, 12.0, 12.15, and 12.07; and the results, obtained on acid soluble inorganic phosphorus, expressed as mg. P per 100 cc. blood plasma, were: 5.58, 5.48, 5.29, 5.24, and 5.13 respectively. The fluorine was given orally as NaF.