

THE RELATION OF THE GASTRO-ENTERIC
TRACT TO BLOOD PRODUCTION

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The Relation of the Gastro-Enteric tract to the
Blood Production.

It is a well recognized fact that pernicious anemia is always associated with atrophic disturbances in the gastro-enteric tract. Gastric achylia is a condition always present in pernicious anemia according to Willson and Evans "the presence of free hydrochloric acid in the gastric contents of pernicious anemia patients should put the diagnosis under suspicion." Detre¹ makes much the same statement and Strieck⁶ says the more severe the anemia the more gastro-intestinal disturbances.

Seyderhelm⁵ believes that pernicious anemia develops, due to absorption of blood toxia substance resulting from bacterial action in the small intestine. He ran a series of ten dogs in which artificial stenosis of the ileum was produced. The dogs showed the following:

1. Two dogs developed P. A. within one week. Autopsy showed abundant growth of B. coli in the small intestine. The B. coli is thought to have spread from the colon to the small intestine due to stasis.

2. The other eight dogs did not develop P. A., and an autopsy the small intestine was found to be sterile in every case in contrast to the above two dogs.

Seyderhelm reports another case of P. A. in which an anus praeternaturalis was preformed on the lower ileum. The P. A. disappeared and in three months the R. B. C. count went from 1,690,000 to 4,900,000. The artificial opening was then closed. The P. A. came back and the patient died.

So, in the latest articles in the literature on pernicious anemia we find repeated statements that it is associated with a change in the gastro-enteric tract. Hartman³ records two cases where patients died of severe pernicious anemia within two years after gastroectomy performed for cancer.

And not only has gastricachylia been demonstrated to be associated with P. A. but in some cases under long observation it has been shown that gastric achylia has preceded the disease as long as twelve years; Faber and Gram,² and Hunter⁴.

These observations would seem to point out that at least some cases of P. A. develop as a result of gastro-enteric disturbances. And following this train of thought it does not seem impossible to produce experimental pernicious anemia in animals by destroying the stomach mucosa. In this work sodium fluoride was chosen as the drug to destroy the stomach mucosa. The dogs received a hypodermic injection of 0.005 gm. of morphine per kilo body weight before administration of the sodium fluoride in order to evacuate their stomachs. The dogs were watched and when emesis took place the vomitus was collected in a large evaporating dish. Hereupon the dogs were muzzled and tied to an operating board. A gag with a hole in the center was used to keep the mouth open. An Ewald stomach tube was passed thru the hole in the gag to the stomach. The lips of the dog were wiped with sodium bicarbonate solution in order to prevent irritation in case some of the sodium fluoride should accidentally drop on them. Having made

certain that the tube was not in the trachea, 30 cc. of 5 to 10% solutions of sodium fluoride by means of a large syringe, was forced into the stomach. The sodium fluoride was allowed to act in the stomach for about two minutes, the dogs being rolled from side to side several times in this interval in order to insure contact with the whole gastric mucosa. About 100 cc. of sodium bicarbonate was now forced into the stomach to stop the irritating action of sodium fluoride. This was followed by one syringe full of air, the tube was removed and the dogs set free.

The oxygen capacity of the blood of the dogs treated in the above manner was determined with the VanSlyke ^{7&8} apparatus by the following method:

- (1) Mercury was allowed to fill the VanSlyke apparatus.
- (2) 6 cc. of distilled water, 0.3 cc. of 1% saponin, and 2-3 drops of caprylic alcohol was introduced into the apparatus.
- (3) Mercury bulb was lowered and a vacuum formed. The air physically dissolved in the above fluids was thus extracted.
- (4) 5 cc. was drawn up into the cup.
- (5) The fluid in the cup and 2 cc. of airated blood was allowed to flow into the apparatus at the same time.
- (6) 1 cc. of potassium ferricyanide.
- (7) A vacuum was again formed and the apparatus inverted 15 times.

- (8) The vacuum was released.
- (9) 0.5 cc. of 0.5 N NaOH with a few drops of mercury allowed to trickle into apparatus. This absorbed the carbon dioxide leaving the oxygen.
- (10) The mercury bulb was leveled with the mercury in the apparatus and the reading made.

Methods of Calculation.

See table for calculation of oxygen capacity.

Example:-

Volume reading on VanSlyke apparatus - .56cc.

Temperature - 25° C

Barometer - 742. mm

$0.56 - .031 = 0.529$ (correction for temperature)

$44.2 \times \frac{742}{760} = 43.1$ (correction for barometric reading)

$0.529 \times 43.1 = 22.79$ volume per cent.

Table for Calculation of Oxygen Capacity.

Temperature	Subtract	Multiply.
15	.037	46.5 x $\frac{B}{760}$
16	.036	46.3
17	.036	46.0
18	.035	45.8
19	.035	45.6
20	.034	45.4
21	.033	45.1
22	.033	44.9
23	.032	44.7
24	.032	44.4
25	.031	44.2
26	.030	44.0
27	.030	43.7
28	.029	43.5
29	.029	43.3
30	.0	43.1

Differential white blood cell counts were made and smears taken after each injection of sodium fluoride. In making these counts polymorphonuclear neutrophils, basophils, and eosinophils were all classified under the heading "polymorphonuclears." It was noted that there was many more eosinophils present than normally. The other cells tabulated were: "lymphocytes" "large mononuclears," "Nucleated red cells," and "other odd cells." Under odd cells were classified myeloblasts and myelocytes and cells not present in normal blood.

Protocol.

Three dogs were successfully followed P.A 2 , P. A. 4, and P. A. 5.

I. P. A. 2 - Feb. 26 - 1925. Male dogs very fat and in good nutrition Wt. 13 Kg. Drew blood for counts and O₂ capacity, morphine for vomitus. Etherized at 2.40 - Washed stomach with 30 cc. H₂O. Then introduced 30 cc. of 10% NaFl and at once followed with 100 cc of 25% CaCO₃. Off board 2:50.

3 P. M. vomited large quantity of brown fluid and food particles. Froth streaked with CaCO₃.

Feb. 28. 1925. Blood picture Normal.

RBC's 6,920,000 - Resistance picture 0.7% 6,640,000

0.6% = 6,410,000 - 0.5% = 1,210,000 - 0.4% = 80,000

O₂ content in artery. 21.20 vol %

Gastric acidity of filtrate of 1st. vomitus 1.8%

21/10 NaOH to neutralize 10 cc. .00365 plus 18 = .065% total HCl.

March 4 - 1925.

Dog in good condition Wt. 13.2 Kg. - Peppy and has good appetite. RBC's - 6,900,000.

March 13 - 1925.

Gets meat once daily Wt. 12.7 Kg. In good condition - appetite good and dog peppy. 10.00 a m 30 mgms. morphine SO₄ subcut. Collected vomitus 1.0 cc 21/10 NaOH to neutralize. 10 cc. filtrate. .00365 x 10 = 0.036% total HCl. Animal rather restless after morphine. Drew 10 cc. blood at 11 a. m. RBC's = 6,750,000

O₂ cap. 20.5 vol %. Introduced 30 cc. of 10%
NaFl and at once followed with 60 cc. of 25%
CaCO₃ - no vomiting. Continued on meat diet.

March 20 - 1925. Wt. 12.2 Kgs.

2:30 P. M. 60 mgms morphine - collected vomitus.

RBC = 6,310,000

O₂ cap. 20.0 vol %

Resistance picture. Unit 6,220,000

0.7% = 6,170,000

0.6% = 5,390,000

0.5% = 810,000

0.4% =

Gastric acidity 4.07 cc. n/10 NaOH to neutralize
10 cc filtrate. .00365 x 40.7 = 0.148% total HCl.
Checked with n/20.

March 24, 1925 - Wt. 11.4 KG.

2:30 P. M. 60 mgms. morphine SO₄ - collected
vomitus. Gastric acidity = 1.00 cc. n/10 NaOH
to centralize 10 cc. filtrate .00365 x 10 = 0.036%
total HCl. RBC = 6,280,000. O₂cap = 17.5 vol %
(corrected.)

March 27, 1925.

Dog found in kennels. Ate meat which had been fed
yesterday.

Autopsy Notes:

Eyes closed, with greenish purulent exudate from
left eye - Sphincters had relaxed. Tissues in good
condition. (Esophagus in good condition. Stomach
was deep below liver mass, contained practically
no food; was congested on external surface; washed

out and opened; greensih gray in color with marked congestion through fundis portion, deeoly ridged and furrowed. Took section. Spleen seemed all right - Section. Took section of bone marrow from middle 1/3 of left femur. Was deep rasp-berry red when opened.

P. A. 4

March 31-1925 P A₄ Wt. 11.34 Kg. Male cross airdale and collie. Gave 50 mgms morphine SO_4 subcutaneously. Vomited dog biscuit meal. Filtered. 10 cc. of filtrate took 3.2 cc n/20 NaOH to neutralize $0.00365 \times 16 = 0.584$ % total HCl. Bled 8 cc. from femoral.

$\text{O}_2 = 20.4$ vol %

RBC's = 7,540,000

Ristance picture:

0.7% = 7,600,000

0.6% = 6,110,000

0.5% = 3,520,000

0.4% = 10,000

Washed stomch with 30 cc. 10% NaFl, by means of syringe and stomach tube. Followed by 90 cc. of 25% CaCO_3 . Put animal on meatt diet , with dog biscuit and occasional milk (every other day) Put in up stairs kennel, exposed to direct sun light in morning.

Apr. 3 - 1925.

Appetite good - eats well.

Apr. 6, 1925. Wt. 10.9 Kgs.. In good spirits.

Gave 50 mgms. Morphine SO_4 . Vomitus of biscuit and meat. Filtered. Gave 1 mgms atropine SO_4

10 cc gastric filtrate took 1 cc n/20 NaOH.

0.00365 x 5 = 0.0160% total HCl. Bled 8 cc.

from femoral. Washed stomach with 20 cc. and

$\frac{1}{2}\%$ NaFl followed with 90 cc - 20% CaCO_3

Apr. 6, 1925.

RBC = 6,340,000

O_2 cap. = 18.17 vol %

Resistance

0.7% = 5,530,000

0.6% = 2,460,000

0.5% = 1,560,000

0.4% = 20,000

Kept on meat and sun light.

April 10, 1925.

Appetite hearty - kept on meat diet.

April 16 - 1925. Wt. 10.0Kg. Lively and peppy.

50 mgms morphine SO_4 . Collected biscuit vomitus filtered. 1 mgm atropine SO_4 . Bled 8 cc. from

femoral artery. Washed stomach with 60 cc. of

$2\frac{1}{2}\%$ NaFl and followed with 90 cc. 10% CaCO_3 . NaFl

in one minute before CaCO_3 . 10 cc. of gastric

juice took 0.5 cc. n/10 NaOH to neutralize.

0.016% total acidity.

RBC = 6,190,000

O_2 cap = 20.4 vol %

Resistance.

0.7% = 5,410,000

0.6% = 4,540,000

0.5% = 650,000

0.4% = 4,000

Apri. 24 - 1925. Wt. 10.7 Kgs.

Very lively and in excellent condition.

Morphine - vomited 3 times, seemed very susceptible, biscuit vomitus filtered. 10 cc of filtrate took 5 cc. n/20 NaOH to neutralize.

.00365 x 30 = 0.09% total HCl. Atropine.

Bled 8 cc. from femoral. Washed stomach with 25 cc. of 8% NaFl and left it in 3 minutes.

Followed with 90 cc. CaCO₃ 10%.

RBC = 5,110,000

Ø₂cap = 18.7 vol%

Resistance.

0.7% = 4,370,000

0.6% = 3,620,000

0.5% = 320,000

0.4% = 8,000

April 25, 1925

Dog found dead at 7:00 P. M. Bloody fluid running from anus. Pupils moderately dilated.

Probably dead 3 hrs. flesh warm.

Autopsy.

Diffuse small hemorrhages of right lung. Dilated right heart, both auricles and ventricles.

Blood clotted normally. valves and cavities O. K.

Gall bladder brilliant green, externally. Mark-

ed congestion of liver. Kidney small yellowish punctate spots scattered evenly throughout, both sides. Hemorrhages into medullary portion of adrenals, both sides. Thyroid O. K. Stomach shows markedly congested hemorrhagic mucosa and partly filled with blood, shows congestion but no evidence of necrosis. Bone marrow looks hyperplastic in gross, raspberry red in color.

Female Airdale.

P. A. 5 Wt. 18.5 Kg.

April 2, 1925.

Gave 50 mgms. morphine SO_4 subcut. Vomited dog biscuit meal. Filtered vomitus. 10 cc. of filtrate took 3.6 cc. n/20 NaOH to neutralize. $0.0036 \times 18 = .066\%$ total HCl. Gave 2 mgms. atrophine sulphate (to relax stomach and smooth out folds) 8 cc. of blood from femoral. O_2 capacity = 22.8% vol RBC = 7,330,000.

Resistance picture =

0.7% = 6,840,000

0.6% = 6,830,000

0.5% = 170,000

0.4% = 20,000 - 10,000

Blood cholesterol = 138 mgms. per 100 cc. Washed stomach with 90 cc. of $2\frac{1}{2}\%$ NaFl for 5 min.

Followed with 90 cc. CaCO_3 (10%) Animal on meat diet, biscuit and milk - upstairs kennel for sunlight when possible.

April 3, 1925.

No appetite - won't eat meat. Drinks all right.

April 5, 1925.

Eating heartily.

April 6, 1925.

Eats meat with great appetite. Very hungry.

April 9, 1925. Wt. = 15.7 Kgs. Looks good, and cheer-

ful. 50 mgms morphine sulphate. Vomitus 0 thin
foul smelling fluid. Not bile stained. Evidently
had eaten no food this A. M. 10cc. of filtrate
took 4 cc. n/20 NaOH to neutralize $0.0036 \times 20 =$
.072 % HCl. Gave 2 mgms atropine sulphate. 8cc.
blood from femoral.

O_2 cap. = 21.2 vol %

RBC = 6,970,000

0.7 % = 2,600,000

0.6% = 170,000

0.5% = 130,000

0.4% = 120,000

Washed stomach with 30 cc. 2% NaFl and followed
with 60 cc. 10% $CaCO_3$. Kept on meat and biscuit
diet and given sunlight daily.

April 17, 1925 Wt. = 16 Kg.

In good shape and peppy. No vomitus from 40 mgms
morphine sulphate. 1 mgm atropine. 8 cc. of blood
taken from femoral. Washed stomach with 60 cc.
3 % NaFl and followed with 60 cc. 10% $CaCO_3$

O_2 cap. = 27.1 vol %
 RBC = 6,940,000
 0.7% = 4,510,000
 0.6% = 3,860,000
 0.5% = 60,000
 0.4% = 40,000

April 24, 1925 Wt. = 16.4 Kgs.

In fine shape. Eyeballs clear and no discharge.
 No vomitus from morphine. atropine. Drew 8 cc.
 blood. Washed stomach with 75 cc. 8% NaFl for
 3 min. Gagged her with wretching movements. Followed
 with 90 cc. 10% $CaCO_3$.

RBC = 5,810,000

O_2 cap = 25 vol. %

Cholesterole = 92 mgms per 100 cc.

0.7% = 5,520,000

0.6% = 3,590,000

0.5% = 190,000

0.4% = 20,000

May 1, 1925 Wt. = 16.6 Kgs. O. K.

Morphine vomitus. 10 cc. filtrate took 2.1 cc.

n/20 NaOH to neutralize. $0.0036 \times 11 = .039$ % HCl.

May 15, 1925. Wt. 17.1 Kgs.

Eyes running otherwise peppy and in good condition.

Drew 8 cc. of blood from femoral.

RBC = 5,970,000

0.7% = 4,090,000

0.6% = 3,490,000

0.5% = 2,100,000

0.4% = 60,000. $O_2 = 20.6$ vol. %

Summary of Oxygen Capacity.

Dog	Date	Vol. % of O ₂
P. A. 2	2-26-25	21.2
	3-13-25	20.5
	3-20-25	20.0
	3-24-25	17.58
P. A. 3	3-16-25	19.4
	3-17-25	22.6
	3-19-25	20.6
	3-20-25	20.4
	3-23-25	20.4
	3-24-25	18.4
	3-25-25	17.5
P. A. 4	3-31-25	20.49
	4- 6-25	18.17
	4-16-25	20.49
	4-24-25	18.72
P. A. 5	4- 2-25	22.79
	4-17-25	27.11
	4-25-25	25.8
	5-15-25	20.67

Data on Blood Counts

Dog	Polymorpho: nuclears	Lymphocytes	Nucleated Reds	Large Mononuclears	Other Odd cells
P.A. 1 Normal Feb. 3/25	68%	29%	0%	1%	2%
P.A. 2 Normal Mar. 13/25 From Artery	70%	25%	1%	1%	3%
P.A. 2 Mar. 20/25	61%	34%	3%	1%	1%
Mar. 20/25 2nd. count	69%	26%	0%	0%	4%
P.A. 3 Normal Mar. 16/25	75%	25%	0%	0%	0%
P.A. 3 Mar. 17/25	72%	24%	0%	2%	4%
P.A. 3 Mar. 19/25	74%	22%	0%	0%	4%
P.A. 4 Normal Mar. 31/25	81%	19%	0%	0%	0%
P.A. 4 Apr. 6/25	66%	30%	0%	3%	1%
P.A. 4 Apr. 16/25	58%	39%	0%	2%	1%
P.A. 4 Apr. 24/25	63%	34%	1%	1%	1%
P.A. 5 Apr. 2/25	80%	14%	0%	4%	2%
P.A. 5 Normal Apr. 17/25	62%	35%	0%	3%	0%
P.A. 5 Apr. 24/25	60%	35%	2%	1%	2%

In view of the fact that such a short series of dogs were successfully carried through the experiment, no exact statements can be made relating to the fact that destruction of the stomach mucosa will bring about pernicious anemia. But in the dogs carried through an anemia did develop. As seen in the protocol of the various dogs the RBC count fell, and the oxygen capacity fell, showing that there was a destruction of red blood cells proceeding at such a rate that the hemopoietic system cannot compensate for the loss. The differential counts on these dogs give evidence of a developing picture similar to that encountered in pernicious anemia, for myeloblasts and myelocytes and a few nucleated red cells were found. So, although, as has already been said, this work does not settle the point that pernicious anemia is casually related to a destruction or degeneration of the stomach mucosa or the mucosa of the gastro-enteric tract, it serves to point out a possible method of further investigating the problem. With further work on this phase of the subject some light should be shed on the etiology of this here-to-fore unknown disease.

Whatever the cause of pernicious anemia may be, it can be said that it is due to some toxin which is absorbed slowly or acts slowly. The course of the disease clearly indicates this fact. The questions which may be asked are, might not this toxin be in a healthy individual in the gastro-enteric tract, but not absorbed due to perfect condition of the mucosa? Or, is it a new substance produced by bacterial action?

Now, in producing atrophic gastritis with sodium fluoride, one may theorize and say that this condition of the stomach makes it possible for some toxin, possibly in the food, which is normally, not absorbed by the stomach, to be absorbed. It is quite inconceivable how the gastritis alone should produce pernicious anemia, especially when there were no known hemorrhages. It is doubtful that the toxicity of sodium fluoride should produce pernicious anemia. If the experimental results obtained are correct and pernicious anemia was produced, then conditions point to an absorption of a toxin from the stomach. Possibly the split proteins normally not absorbed by the stomach were in this condition absorbed.

However, one may also attempt to explain the production of pernicious anemia by the toxins produced by bacterial action. Bacterial action in the stomach being made possible through the lowering of the HCl in the gastric juice. Normally the HCl keeps the stomach sterile. The gastritis assists in the absorption of toxins.

Conclusions.

1. Sodium fluoride injected into the stomach of a dog causes atrophic degeneration of the stomach mucosa.
2. Atrophic gastritis in the dog caused by sodium fluoride is accompanied with a reduction in the red blood cell count of the dog.
3. Atrophic gastritis in the dog caused by sodium fluoride is accompanied by a reduction in the oxygen capacity

Bibliography.

1. Detre, Sodislaus: Kryptogenetische perniziose Anaemie and Magenazidetat! Med. Klin! 20: 16.49, 1924.
2. Faber, Knud, M. D., and Gram, H. C. M. D.: Relations between gastric achylia and Simple and Pernicious Anemia. Archives of Int. Med. : 34:658; 1924.
3. Hartman, H. R.: Blood changes in gastro-ectomized patient simulating those in pernicious anemia:
:162: 1921L
4. Hunter, Wm.: Causes of Pernicious Anemia, its relations to Achlorhydria and its Familial occurrence. Brit. Med. Jour. June 9: 469, 1924.
5. Seyderhelm, R; Lehmann, W,; and Wickels, P.; Experimental Intestinal Perniziose Anaemie beim Hund: Kein, Wchnschr., 3:1439 (Aug.5) 1924 Seyderhelm,R.: Die Bedinting des Dunndarms fur die Genese der Perniziosen Anaemie.: Klin, Wchuschr., 3:568 (April) 1924.
6. Striech, Fritz : Zur Symptomatologie der Biermerschen Krankheit: Med. Klin. 20; 1538: 1924
7. Van Slyke, Donald: Gasometric Determination of the oxygen and Hemoglobin of blood.: Jour. of Biol. Chem. : 33:127:1918.
8. Van Slyke, Donald, and Stadie, Wm. C.: The determination of the gases of the blood Jour. of Biol. Chem. : 49: 1 : 1921

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