repeated at weekly intervals to check the thresholds.

We have employed the natural *l* (+) glutamic acid by intravenous injection in an attempt to prevent ammonium convulsions. In a series of preliminary experiments, we have found *l* (+) glutamic acid to give complete protection from the convulsant effects of the ammonium chloride solution. In 8 experiments 50 cc of *l* (+) glutamic acid (5% glutamic acid and 3% sodium bicarbonate) was given intravenously shortly before the injection of ammonium chloride (also dissolved in sodium glutamate solution) and no convulsion resulted in any instance even after 50 cc of the 2½% solution of ammonium chloride was injected. As a control, similar experiments with equimolar amounts of *l* aspartic were performed in the same rabbits. Aspartic acid fails to protect from the convulsant activity of ammonium chloride, indicating the specificity of the glutamic acid reaction.

If *l* (+) glutamic acid is capable of preventing ammonium convulsions, it should be effective in other types of convulsive activity, which are associated with disturbances in ammonium metabolism, perhaps including human epilepsy. We have injected intravenously as much as 500 cc of 5% *l* (+) sodium glutamate into humans within a few hours without any apparent toxic effects. We are now investigating its action in human epileptic seizures.

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Blood Histamine in Gastric Cancer and Peptic Ulcer.

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The production of peptic ulcers in experimental animals injected with histamine,[1] and the presence of a gastric secretory depressant in the extracts of achlorhydric cancerous stomachs and juices from such stomachs[2] suggested the investigation of the histamine content of the blood of patients with gastric carcinoma and with peptic ulcer. Histamine determinations in some cases of Hodgkin's disease, leukemia, and polycythemia vera are also reported.

Experimental Procedure. The blood samples were obtained from adult male patients. The diagnosis of gastric carcinoma or of gastric ulcer was established at subsequent operation and by microscopic examination of the tissue. The diagnosis of duodenal ulcer was made clinically on the basis of roentgenographic findings, and the cases of hemorrhagic and atrophic gastritis were studied roentgenographically and gastroscopically. Biopsy of the lymph nodes was made in all cases of Hodgkin's disease.

The histamine content of the whole blood was determined by the method of Barsoum and Gaddum,[3] as modified by Code.[4] The values are expressed as μg of free base per 100 cc of blood.

Results. As given in Table I, the blood histamine in patients with gastric carcinoma and with peptic ulcer was between 1.2 and 8.5 γ per 100 cc. There was no difference between the two groups, and the values did not deviate significantly from the normal range, reported to be between 1.8 and 7.8 γ (average 4.0 γ) in 173 normal individuals

1 Hay, L. J., Varco, R. L., Code, C. F., and Wangensteen, O. H., *Surg. Gyn. Obst.*, 1942, **75**, 170.

2 Brunschwig, A., Schmitz, R. L., and Rasmussen, R., *J. Nat. Cancer Inst.*, 1941, **1**, 481.

3 Barsoum, G. S., and Gaddum, J. H., *J. Physiol.*, 1935, **85**, 1.

4 Code, C. F., *J. Physiol.*, 1937, **89**, 257.

TABLE I.
Blood Histamine in Patients with Gastric Carcinoma and with Peptic Ulcer, and Other Conditions.

Case No.	Name	Age	Diagnosis	Leukocytes No./cmm × 100	Neutrophiles* No./cmm	Eosinophiles* No./cmm	Free hydrochloric acid in stomach† degrees	Blood histamine as free base γ/100 cc
1	O.W.	51	Gastric carcinoma	90	6,390	0	0	1.9
2	H.J.	49	" "	75	5,840	150	0	1.5
3	E.C.K.	42	" "	74	5,920	75	—	2.8
4	J.A.R.	46	" "	—	—	—	0	3.9
5	A.G.T.	50	" "	93	8,000	90	0	4.9
6	S.I.A.	55	" "	76	4,030	0	42	4.4
7	W.F.B.	46	" "	74	5,330	130	0	6.7
8	W.P.G.	42	" "	56	3,280	55	0	6.0
9	W.W.	63	" "	51	2,040	0	0	1.2
10	R.B.L.	57	" "	69	3,190	0	0	2.1
11	J.H.S.	66	Gastric ulcer	107	8,990	0	80	2.6
12	J.D.	43	" "	75	4,420	225	25	5.0
13	W.McK.	51	" "	122	9,800	120	35	5.3
14	W.K.	49	" "	93	6,550	185	15	4.4
15	H.S.	48	" "	48	2,670	100	30	2.9
16	E.S.P.	46	" "	120	8,430	0	25	2.6
17	H.W.	54	Duodenal ulcer	96	6,180	290	76	6.0
18	J.P.W.	62	" "	—	—	—	40	8.5
19	R.C.D.	46	" "	114	9,570	0	0	5.4
20	C.J.L.	36	" "	62	2,910	125	40	5.5
21	C.J.O'L.	44	" "	63	5,230	0	25	1.4
22	C.J.	49	Hemorrhagic gastritis	54	3,350	110	0	5.0
23	G.C.	52	Atrophic gastritis	113	7,910	115	0	5.0
24	J.H.D.	53	Hodgkin's disease	26	2,110	35	—	1.9
25	J.S.G.	27	" "	117	8,460	175	—	3.9
26	P.W.	66	" "	37	2,000	220	—	6.0
27	H.S.McW.	46	" "	116	9,860	0	30	1.4
28	C.H.	20	" "	68	5,460	410	—	8.3
29	E.O.L.	19	" "	188	16,590	0	—	1.2
30	L.G.T.	78	Mycosis fungoides	84	6,720	505	—	2.3
31	W.D.B.	46	Polycythemia vera	196	16,860	1,175	—	12.6
32	E.E.	44	Chronic myeloid leukemia	2,961	254,500‡	11,800§	30	575.0
33	J.E.T.	35	Acute myeloid leukemia	850	79,050‡	0	—	3.2
34	H.E.A.	62	Chronic lymphatic leukemia	965	3,860	0	35	4.6

* Calculated from differential counts of 100-200 cells.
† 20-30 minutes after 1.0 mg of histamine subcutaneously; cases 17 and 21, fasting.
‡ Including premyelocytes and myeloblasts.
§ Including eosinophilic premyelocytes.

studied by Haworth and Macdonald,[5] Rose,[6] and Randolph and Rackemann.[7] There was no correlation between the histamine of the blood and the presence or absence of free hydrochloric acid in the stomach.

No constant alteration in blood histamine was encountered in patients with Hodgkin's disease, chronic lymphatic leukemia, and mycosis fungoides. The blood histamine was definitely elevated in the patient with polycythemia vera.

In the patient with chronic myeloid leukemia the blood histamine was one hundred times above normal. The white blood cell count was 296,150, with 46% neutrophiles, 23% premyelocytes, 22% myeloblasts, 2% eosinophiles and 3% eosinophilic premyelocytes. Extremely high blood histamine levels in chronic myeloid leukemia have been reported by Code and Macdonald[8] and others.

[5] Haworth, E., and Macdonald, A. D., *J. Hyg.*, 1937, **37**, 234.

[6] Rose, B., *J. Allergy*, 1941, **12**, 327; **12**, 522 (correction).

[7] Randolph, T. G., and Rackemann, F. M., *J. Allergy*, 1941, **12**, 450.

[8] Code, C. F., and Macdonald, A. D., *Lancet*, 1937, **2**, 730.

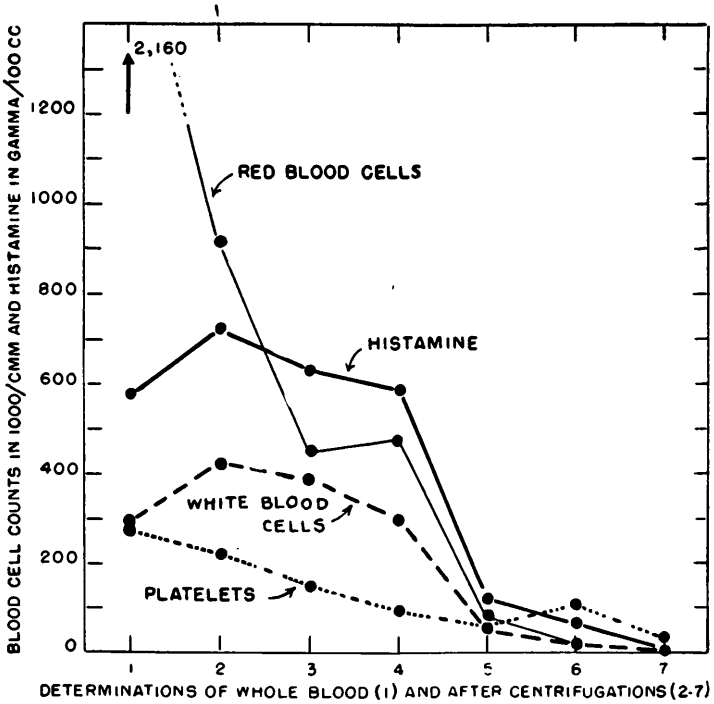

FIG. 1.

Relation of histamine to the number of blood cells in whole blood (1) and in washed blood cells after serial centrifugations (2-7), in a patient with chronic myelogenous leukemia.

The patient with acute myeloid leukemia died 2 months after the onset of illness. He had been treated with Fowler's solution. The white blood cell count was 85,000, of which 44% were neutrophiles, 27% premyelocytes, and 22% myeloblasts; no eosinophiles were seen among 400 cells. The blood histamine in this patient was normal. It is possible that the finding is attributable to the treatment with arsenic or the absence of eosinophiles. It would be of interest, however, to determine the blood histamine in additional cases of acute myeloid leukemia as compared with chronic myeloid leukemia.

Code and Macdonald[8] and others have established that the blood histamine in man is carried chiefly by the granulocytes. This is well shown by separation experiments carried out on the blood of the patient with chronic myeloid leukemia, in whom the high histamine facilitated the determinations in various fractions of the blood separated by centrifugation. Fig. 1 shows that the blood histamine closely paralleled the number of white blood cells. The reduction of the red cells from 2,160,000 to 425,000 and the removal of most of the plasma did not alter the histamine level. The blood histamine fell sharply between the fourth and sixth centrifugations, despite the maintenance of the platelets at 100,000 per cmm.

The normal blood histamine in chronic lymphatic leukemia and the low histamine in lymph nodes[8] indicate that the lymphocytes do not contain appreciable amounts of histamine. Randolph and Rackemann[7] concluded that there was no constant relationship between the number of eosinophiles and blood histamine, although Code and Macdonald[8] reported raised values in patients with eosinophilia. In one patient with eosinophilia (34% of 10,500 white blood cells) studied here, the blood histamine was 7.9 γ.* It is interesting,

* In this and in the subsequent case mentioned but not included in the table, the blood was not extracted with absolute alcohol saturated with sodium chloride. The values are higher than after alcohol extraction, but wide fluctuations in blood histamine are adequately shown by either method.[9]

[9] Zon, L., Ceder, E. T., and Crigler, C. W., *Pub. Health Rep.*, 1939, **64**, 1978.

however, that the eosinophiles were increased in the 2 patients with elevated blood histamine (31 and 32), although the analysis of the remainder of the data shows little, if any, correlation between blood histamine and the number of eosinophiles. The data also show no constant relationship between the number of neutrophiles and blood histamine. As further evidence may be cited a patient whose blood histamine was 8.8 γ with a white blood cell count of 5,480; after an injection of typhoid vaccine, resulting in an increase of the white cells to 12,650, the blood histamine dropped to 3.7 γ.

Summary. Blood histamine is within normal limits in patients with gastric carcinoma and with peptic ulcer. There is no relationship between blood histamine and the presence or absence of free hydrochloric acid in the stomach.

Blood histamine in man is carried chiefly by granulocytes, but is not directly related to the number of granulocytes in the blood.

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Bacterial Synthesis of *p*-Aminobenzoic Acid.

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Fildes[1] and Woods[2] have postulated that the sulfonamide drugs prevent bacterial growth by interfering with the utilization of an "essential metabolite,"* *p*-aminobenzoic acid (PAB), by virtue of their similarity in structure to this compound. At the time this theory was proposed it was assumed that PAB was an essential metabolite for bacteria, although for technical reasons, it had not yet been isolated from them, nor had it been proved to be a growth factor in the absence of a bacterium which could not synthesize it. Recent investigations have done much to substantiate Fildes' conception of the role of PAB in sulfonamide bacteriostasis.[3,4] PAB has been found to be a growth essential for *Clostridium acetobutylicum*,[5] *Acetobacter suboxydans*[6] and evidence now indicates that it may be a growth factor for certain Lactobacilli[7,8] and Corynebacteria[9] as well.

If PAB is truly an essential metabolite, the fact that it is a growth factor for a few organisms should be supplemented by evidence that it is important in the nutrition of bacteria generally, namely proof of its synthesis by organisms able to grow in PAB-free culture media. Analogy to other growth factors indicates that this is a situation which might well exist. It has been repeatedly observed that while a few organisms may require the presence of growth factors, others (the majority) usually synthesize these vitamins in apprecia-

1 Fildes, P., *Lancet*, 1940, **1**, 955.

2 Woods, D. D., *Brit. J. Exp. Path.*, 1940, **21**, 74.

* According to Fildes[1] an essential metabolite is a substance which takes an essential part in a chain of syntheses necessary for bacterial growth. A "growth factor" which must be supplied in the nutrients is an essential metabolite which the cell cannot synthesize, *e.g.*, nicotinic acid is an essential metabolite for all bacteria but a growth factor for only a few.

3 Green, H. N., and Bielschowsky, F., *Brit. J. Exp. Path.*, 1942, **23**, 1.

4 McIlwain, H., *Brit. J. Exp. Path.*, 1942, **23**, 265.

5 Rubbo, S. D., Maxwell, M., Fairbridge, R. A., and Gillespie, J. M., *Austral. J. Exp. Biol. and Med.*, 1941, **19**, 185.

6 Lampen, J. O., Underkofler, L. A., and Peterson, W. H., *J. Biol. Chem.*, 1942, **146**, 277.

7 Isbell, H., *J. Biol. Chem.*, 1942, **144**, 567.

8 Lewis, J. C., *J. Biol. Chem.*, 1942, **146**, 441.

9 Chattaway, F. W., Happold, F. C., Lythgoe, B., Sandford, M., and Todd, A. R., *Biochem. J.*, 1942, **36**, vi.