A STUDY OF THE PATHOLOGICAL VARIATIONS IN THE ACIDITY OF THE GASTRIC CONTENTS, ESPECIALLY IN RELATIONSHIP TO MALIGNANT DISEASE

By BENJAMIN MOORE, M.A., D.Sc., *Johnston Professor of Bio-Chemistry
in the University of Liverpool*; W. ALEXANDER, M.D., M.Ch.,
F.R.C.S., *Hon. Surgeon Royal Southern Hospital, Liverpool*; R. E.
KELLY, M.D., B.Ch., B.Sc., *University of Liverpool*; and HERBERT E.
ROAF, M.D., *British Medical Association Research Scholar*.

From the Bio-Chemical Laboratory, University of Liverpool
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In a recent paper in the Proceedings of the Royal Society¹ we have drawn attention to the frequent absence or reduction in amount of the free hydrochloric acid of the gastric secretion in malignant disease whatever be the situation of the growth, and have referred this diminution of the free acid not to local conditions in the stomach but to altered conditions in the blood plasma.

Since the publication of this paper we have extended our observations from seventeen to thirty-four cases of carcinomata situated elsewhere than in the stomach, and have made determinations of the acidity in twenty other cases of patients not suffering from malignant disease.

We were induced to make the latter series of observations so as to obtain a more nearly analogous control than that of the four healthy laboratory workers given in our previous paper, and also on account of the contradictory results contained in the extensive literature of the subject. The differences obtained by different observers are, no doubt, due in great part to the use of different methods and indicators, to the small number of cases tested by most of the observers, and to the reliance placed on qualitative rather than quantitative results.

The same quantitative methods have been employed in each of our series of cases, under as nearly as possible like conditions of experimentation so as to make them strictly comparable with one another.

1. *Proc. Roy. Soc., B*, Vol. 96, 1905, p. 138.

The methods used have been described at length in the previous paper, and further statement may accordingly be now omitted.

The examination of the twenty non-malignant hospital cases has shown that the acidity of the gastric secretion is very sensitive to alterations in the general health and condition, as is obvious on comparing the average acidity in the case of the four laboratory workers (Table V) with that in the case of the hospital patients (Table IV). But there still remains a striking difference between the malignant and the non-malignant cases, as is seen on comparing Table I with Table IV. Thus, in the cases of carcinoma, the Günzburg Reagent shows an entire absence of free hydrochloric acid in twenty-three out of thirty-four cases, or in 67·6 per cent., and the amount of free hydrochloric acid is only appreciable (above 0·05 per cent.) in four cases (Nos. 23, 28, 29, and 31). On the other hand, although the non-malignant cases show much lower averages than obtained for the laboratory workers, there is complete absence, as shown by the Günzburg test, in only five out of the twenty cases, or in 25 per cent., and the amount lies above 0·05 per cent. in half the cases.¹

The average amounts of free hydrochloric acid in the non-malignant cases lie between two and three times as high as in the malignant cases for all the methods, excepting the Mörner-Sjoqvist method, which gives them much more closely together.

The ratios of the average amounts of acidity in the two series of cases may be expressed as follows :—

	Malignant	Non-malignant
Total acidity	= 816 :	1,453 = 0·56
Di-methyl indicator	= 352 :	925 = 0·38
Günzburg's reagent	= 163 :	502 = 0·32
Methyl acetate method	= 286 :	630 = 0·45
Mörner-Sjoqvist method	= 637 :	774 = 0·82

For purpose of comparison with the others, we have included in the tables of malignant cases the seventeen cases given in our previous paper, and we have placed in separate tables from the carcinoma cases the few cases of sarcoma and rodent ulcer which we have been able to examine.

1. It is clear from these figures that the presence or absence of free hydrochloric acid cannot be regarded as a diagnostic sign of any great value. All that can be said is that in the majority of malignant cases it is absent, and in the majority of non-malignant cases it is present. The same statement holds for cancer of the stomach wall itself.

TABLE I.—CARCINOMATA

No.	Sex	Age	Situation	Period of digestion in hours	Phenolphthaleïn	Di-methyl	Gunzburg	Mörner-Sjoqvist	After incineration	METHYL ACETATE METHOD			
										Initial	Final	Increase	Percentage HCl
1	F.	49	C. of uterus	1	0.0219	Negative	Negative	—	—	—	—	—	—
2	M.	...	C. of prostate	1	...	...	Negative	—	—	—	—	—	—
3	F.	71	C. of uterus	1½	0.0036	Negative	Negative	—	0.0066	—	—	—	—
4	F.	50	C. of uterus	1	0.1460	0.0821	0.0368	—	0.0146	—	—	—	—
5	F.	65	C. of liver	1½	0.0018	Negative	Negative	—	0.0000	—	—	—	—
6	F.	32	C. of rectum	1	0.0584	Negative	Negative	0.0013	0.0036	0.8	0.95	0.15	1.1649
7	F.	...	C. of tongue	1½	0.0292	0.0186	0.0109	0.0295	0.0000	0.4	2.2	1.8	14.429
8	M.	61	E. of floor of mouth	1	0.0018	Negative	Negative	Negative	0.0000	0.1	0.1	0.0	0.0000
9	F.	49	Coll. C. of mesentery	1½	0.1058	0.0401	0.0072	0.0738	—0.1350	1.55	3.65	2.1	16.934
10	F.	59	C. of breast	1½	0.0182	0.0091	0.0036	0.0023	0.0000	0.25	1.30	1.05	8.295
11	F.	59	C. of breast	1½	0.0511	0.0219	0.0036	—	0.0000	0.85	2.10	1.25	9.913
12	M.	65	E. of cheek	1	0.0018	Negative	Negative	0.0044	0.0000	0.025	0.05	0.025	0.00017
13	F.	66	C. of breast	1	0.0548	0.0019	Negative	0.0020	—0.0402	0.8	1.05	0.25	1.945
14	M.	63	E. of cheek	1	0.2847	Negative	Negative	0.1479	0.2044	2.7	2.7	0.0	0.00000
15	M.	57	C. of tongue	2	0.0365	Negative	Negative	0.1140	—0.0657	0.4	0.4	0.0	0.00000
16	F.	45	C. of uterus	2	0.0182	Negative	Negative	Negative	—0.0620	0.3	0.5	0.2	1.554
17	F.	77	E. of hand	1	0.1460	Negative	Negative	0.0207	+0.0839	1.8	1.5	—0.3	0.0000
18	F.	69	E. of cheek	1½	0.0018	Negative	Negative	0.0921	—0.0164	0.05	0.05	+0.0	0.00000
19	M.	54	E. of lip	1	0.0949	0.0328	Negative	0.0602	—0.0255	1.5	3.8	2.3	17.064
20	F.	43	C. of rectum	1	0.1606	0.0912	0.0146	0.0984	—0.0255	2.6	9.5	6.9	61.749
21	M.	60	E. of jaw	1½	0.0219	0.0073	Negative	0.0182	—0.0438	0.3	1.2	0.9	7.088

TABLE I—Continued.—CARCINOMATA

No.	Sex	Age	Situation	Period of digestion in hours	Phenolphthaleïn	Di-methyl	Günzburg	Mörner-Sjoqvist	After incineration	METHYL ACETATE METHOD			
										Initial	Final	Increase	K × 10 ⁵
22	M.	53	E. of Penis	1½	0.1131	0.0657	Negative	0.0827	— 0.0584	1.5	6.5	5.0	42.832
23	M.	59	E. of hand	1	0.2810	0.1898	0.1313	—	—	—	—	—	—
24	F.	63	E. of vulvae	1	0.1533	0.1022	Negative	—	—	—	—	—	—
25	F.	67	C. of breast	1½	0.0073	Negative	Negative	—	—	0.15	0.25	0.1	0.801
26	F.	55	C. of breast	1	0.0949	0.0657	0.0255	0.0338	+ 0.0073	1.2	6.7	5.5	47.653
27	F.	48	...	1	0.0109	Negative	Negative	—	—	—	—	—	—
28	F.	45	C. of uterus	1	0.2007	0.1351	0.0949	0.1648	0.0000	2.8	15.6	12.8	134.573
29	M.	68	E. of lip	1	0.2299	0.1277	0.0985	0.1504	+ 0.0292	3.2	21.9	18.7	247.490
30	M.	46	E. of face	1	0.0182	0.0073	Negative	Negative	— 0.0584	—	—	—	—
31	M.	35	E. of tongue	1	0.2080	0.1642	0.1277	0.1134	— 0.0182	2.8	18.5	15.7	182.450
32	F.	38	C. of uterus	1	0.0365	Negative	Negative	—	—	0.5	0.8	0.3	2.331
33	F.	52	C. of breast	...	0.0073	Negative	Negative	—	—	0.1	0.3	0.2	2.554
34	M.	45	C. of rectum	1½	0.0730	Negative	Negative	—	—	—	—	—	—
Averages	...	...	...	...	0.0816	0.0352	0.0163	0.0637	— 0.0679	...	...	...	...

NOTE TO TABLES.—The titration figure to phenolphthaleïn gives the total acidity, including acid combined with proteid and other organic substances capable of acting as weak bases, the figure to di-methyl gives approximately the total *free* acid, inorganic and organic, but not that in combination; the figure to Günzburg gives the free inorganic acid, chiefly hydrochloric; the Mörner-Sjoqvist method gives the total amount of chloride not combined with fixed bases; the figure after incineration the organic acids previously in combination minus ammonia previously in combination; and the last five columns the concentration of the secretion in hydrogen ions measured by the velocity of hydrolysis of methyl acetate—the first of these columns gives the titration before hydrolysis; the second the titration after hydrolysis for eight hours at 40° C; the increase in the third column shows the amount of acetic acid set free from the methyl acetate by the hydrogen ions of the sample of gastric juice; the fourth column gives the velocity constant in such case; and the fifth column the percentage of hydrochloric acid which would produce an equal effect.

TABLE II.—CASES OF SARCOMA

Sex	Age	Situation	Period of digestion in hours	Phenolphthaleïn	Di-methyl	Günzburg	Mörner-Sjöqvist	After incineration	METHYL ACETATE METHOD			
									Initial	Final	Increase	K $\times 10^5$ Percentage HCl
F.	43	General in liver, etc. (lympho-sarcoma)	1½	0.0146	Negative	Negative	—	—	—	—	—	—
M.	61	Neck	1	0.1861	0.0036	0.0072	—	0.1533	—	—	—	—
M.	35	Thoracic parieties (round celled angio-sarcoma)	1½	0.2263	0.1496	0.0949	0.1441	0.0000	3.2	15.7	12.5	130.187 0.1184
M.	56	Neck	1	0.1715	0.0474	Negative	—	—	—	—	—	—

TABLE III.—CASES OF RODENT ULCER

Sex	Age	Situation	Period of digestion in hours	Phenolphthaleïn	Di-methyl	Günzburg	Mörner-Sjöqvist	After incineration	METHYL ACETATE METHOD			
									Initial	Final	Increase	K $\times 10^5$ Percentage HCl
M.	69	Face	1	—	—	Negative	—	—	—	—	—	—
M.	63	Nose	1	0.2774	0.1752	0.0803	—	—0.0365	3.7	20.1	16.4	195.98 0.16837

TABLE IV.—HOSPITAL CASES—NON-MALIGNANT (ALL MALES).

METHYL ACETATE METHOD													
No.	Age	Disease	Period of Digestion in hours	Phenolphthaleïn	Di-methyl	Günzburg	Mörner-Sjoqvist	After incineration	Initial	Final	Increase	K x 10 ⁵	Percentage HCl
1	65	Chronic Bronchitis	I	0.0684	0.0438	0.0292	...	-0.0146	...	...	...	...	...
2	65	Chronic Bronchitis	I	0.1418	0.1058	0.0730	0.0965	-0.0403	2.0	11.7	9.7	93.170	0.08004
3	35	Apoplexy	I	0.1418	0.1058	0.0657	0.0971	-0.0365	2.0	11.4	9.4	89.568	0.07695
4	78	Healthy	I	0.0146	Negative	Negative	...	...	0.2	0.3	0.1	0.776	0.00067
5	44	Old fracture of thigh	I	0.1460	0.0693	Negative	0.0821	-0.0328	2.0	3.5	1.5	11.954	0.01027
6	49	Ulcer of leg	I	0.2080	0.1095	Positive	0.0633	+0.0073	2.7	11.3	8.6	80.255	0.06895
7	45	Injured shoulder	1½	0.2519	0.1898	0.1022	0.1353	-0.0109	3.5	18.2	14.7	164.372	0.14152
8	56	Injured scalp	1½	0.0109	Negative	Negative	Negative	-0.0474	0.2	0.2	0.0	0.000	0.00000
9	45	Old hip disease	1½	0.2628	0.1825	0.1095	0.1064	-0.0474	3.4	18.1	14.7	164.372	0.14152
10	57	Ulcer of leg	I	0.1825	0.0985	0.0401	0.0799	-0.0182	2.65	9.4	6.75	57.884	0.04972
11	41	Ulcer of leg	I	0.1533	0.0803	0.0182	0.0611	-0.0365	2.2	6.1	3.9	31.326	0.02691
12	43	Abscess of neck	I	0.0328	Negative	Negative	...	...	0.45	1.1	0.65	4.893	0.00420
13	31	Syphilitic eruption	I	0.1679	...	Positive	...	...	2.3	12.2	9.9	91.783	0.07885
14	49	Sprained arm	I	0.1679	...	Positive	...	...	2.3	14.9	12.6	126.373	0.10857
15	45	Ulcer of leg	I	0.2117	0.1715	0.1350	0.1096	-0.0036	2.9	18.4	15.5	171.703	0.14751
16	38	Tuberculous knee	I	0.2591	0.2080	0.1423	0.1109	0.0000	3.6	18.6	15.0	169.914	0.14590
17	34	Tuberculous thigh	I	0.1204	0.0766	0.0109	0.0144	-0.0474	2.0	6.0	4.0	33.539	0.02880
18	19	Tuberculous knee	I	0.1715	0.1314	0.0766	0.1203	-0.0109	2.5	11.0	8.5	79.199	0.06800
19	47	Tuberculous hip	I	0.0474	Negative	Negative	0.0069	-0.0073	0.6	0.8	0.2	1.555	0.00133
20	23	Tuberculous pelvis	I	0.1460	...	Positive	...	...	2.0	4.5	2.5	20.322	0.01750
Averages	...	...	...	0.1453	0.0925	0.0502	0.0774	-0.0231	...	...	...	...	0.06304

TABLE V.—CONTROL CASES IN NORMAL INDIVIDUALS

Sex	Age	Disease	Period of digestion in hours	Phenolphthaleïn	Di-methyl	Günzburg	Mörner-Sjoqvist	After incineration	METHYL ACETATE METHOD				
									Initial	Final	Increase	K × 10 ⁵	Percentage of HCl
M	25	Healthy	I	0.2117	0.1789	0.1579	0.1579	0.0078	3.05	17.9	14.85	167.300	0.14373
M	38	"	I	0.3285	0.2884	0.2571	0.2571	0.0000	4.8	25.5	20.7	305.740	0.26266
M	23	"	I	0.3139	0.2482	0.1862	0.3296	-0.3876	4.0	21.1	17.1	208.248	0.17892
M	28	"	I	0.2628	0.2336	0.2117	0.2212	-0.0511	3.9	24.7	20.8	309.134	0.26560
Averages ...	...	...	...	0.2792	0.2373	0.2007	0.2414	-0.0342	...	...	...	...	0.21279

In our previous paper, we drew attention to the fact that the Mörner-Sjoqvist method in some cases gave a higher result than the Günzburg or Methyl-acetate methods, and this difference is still more strikingly shown in the longer series of cases. Also, although the figure for the total acidity (to phenol-phthalëin) is very much higher than that given by the di-methyl, Günzburg, and Methyl acetate, indicating the probable presence of organic acids, yet a method specially designed for detecting and estimating such acids, failed to show any, giving instead a negative figure. This method consisted in neutralising to phenol-phthalëin, incinerating and again titrating. In this process, any organic acids would be changed first into salts, and then on incineration into alkaline carbonates; as a result the ash would have been alkaline, and the back titration would have shown the amount of organic acid plus organic salts in the sample of gastric contents. In the actual result of experiment it was found, however, that the ash was rarely alkaline; not only so, but on adding *excess* of alkali beyond the neutral point to phenol-phthalëin, there occurred an actual loss of alkali upon incineration.

Both the discrepancies in the Mörner-Sjoqvist method and the failure to show any organic acid might receive a common explanation on the supposition that there is present in such samples of stomach contents salts of inorganic acids with ammonia or organic bases.

For the ammonia or organic base being driven off in the process of incineration, the inorganic acid with which it was previously combined would combine with barium from the barium carbonate in the Mörner-Sjoqvist method, so increasing the amount of soluble barium salt, and hence ultimately the weight of the precipitate of barium sulphate. Also in the incineration with alkali for the purpose of obtaining the organic acid, the inorganic acid would similarly combine with and neutralize alkali and (provided the amount of inorganic acid combined with organic bases or ammonia exceeded the amount of organic acid combined with fixed inorganic bases) would give rise to such negative figures as we have obtained in the great majority of our cases.

This was the explanation which we put forward in our former

paper, but determination in such a sample in which the negative figure was large, of the amount of ammonia by Schlössing's method gave a very small amount, entirely inadequate to explain the negative figure.

The base in combination is therefore not ammonia or a volatile organic base, or it would have been detected in the Schlössing process.

Other substances which might be present in the fluid from the test meal in feeble combination with acid are the proteins and the products of their digestion, albumoses and peptones. Hydrochloric acid in combination with such bodies would not show itself to the Günzburg and di-methyl tests, and only in a very diminished degree in the case of the methyl-acetate hydrolysis method, on account of the much lowered ionization resulting from the combination of the hydrochloric acid with the protein; while such hydrochloric acid would be given completely by the phenol-phthalëin or Mörner-Sjoqvist methods. In the case of the Mörner-Sjoqvist method, on incineration in the presence of excess of barium carbonate the protein is destroyed, and the hydrochloric acid previously in combination with it acts upon the barium carbonate, forming barium chloride, exactly similarly to the free hydrochloric acid, and hence this amount appears as acid in the result. In the case of the phenol-phthalëin the hydrogen ion concentration necessary to maintain the protein-hydrochloric acid combination is sufficiently high to affect the indicator and associate it, and hence the pink colour due to the phenol-phthalëin ion does not appear until sufficient alkali has been added to entirely break up the protein-hydrochloric acid combination. In contrast with this, in the case of the di-methyl indicator we have a stronger salt to dissociate, and the protein-hydrochloric acid combination is able to exist at a hydrogen ion concentration which still leaves the indicator showing the alkaline colour (yellow), and hence the change from the acid colour (red) at first seen when either free hydrochloric acid or free organic acid is present in the test meal fluid, to the alkaline colour (yellow) occurs when all the free acid has been neutralized, and while the protein-acid combination still exists in solution.

Accordingly, the presence of protein in the test meal fluid would form an explanation of the differences in value given by the different methods. In our opinion, however, this is not the only factor, since the amount of protein as shown by the biuret test is often very small.

Another factor which might produce the divergences seen in the different methods is the presence of acid salts of less dissociated inorganic acids, instead of hydrochloric acid, such, for example, as the primary phosphates of the alkalies (MH_2PO_4).¹

Such salts possess a very low concentration in hydrogen ion ; as a result, their end point, or neutral point, to one indicator is very different to that with another. For example, in titrating phosphoric acid with an alkali, the neutral point with phenol-phthalëin lies at the point corresponding to the presence of M_2HPO_4 , while in titrating with di-methyl it lies at MH_2PO_4 . Hence if the test meal fluid contained any phosphate it would show quite a different acidity with these two indicators.

An experiment which we carried out to test the effect of the presence of phosphates upon the Gönzburg reagent gave interesting results, showing that this is also affected by the phosphates, and only begins to react sharply and typically when there is sufficient acid present to form free phosphoric acid.

Ten cubic centimetres of deci-molecular solution of mono-sodium phosphate were taken, and to this deci-normal hydrochloric acid was added, one c.c. at a time, the Gönzburg test being carried out after each addition. It was found that the acid phosphate alone gave a completely negative result, and continued to do so with 1, 2, 3, and 4 c.c. of successively added deci-normal hydrochloric acid ; at 5 c.c. there began to appear a faint pink colour which only gradually became more marked as more acid was added, and so with successive tests, until 10 c.c. of deci-normal acid in all had been added, which is the amount necessary to completely set free the phosphoric acid. Beyond this limit, addition of a single c.c. caused a marked increase in the intensity of the pink colour.

1. This explanation was first suggested to us by Mr. R. C. Cowley.

The gradual development of the test as hydrochloric acid was added, in presence of acid phosphate, furnishes a possible explanation of what we had observed in many of the cancer cases when titrating in the opposite direction with decinormal alkali to find out when the free hydrochloric was neutralized. Instead of the sharp reaction which one finds with dilute hydrochloric acid, or in the gastric juice of normal cases, one observes in malignant cases that as more and more alkali is added, there takes place instead of a sharp disappearance of the pink colour a slow fading of it in the successive tests so that it becomes somewhat difficult to identify the exact point at which the free acid has been neutralized.

Similarly in the reaction to phenol-phthalëin of the stomach contents of malignant cases after incineration in the presence of excess of alkali we had found the usual sharp reaction replaced by a very slow fading out of the pink colour of the phenol-phthalëin.

DISCUSSION OF RESULTS AND CONCLUSIONS

The chief result obtained in the series of analyses of gastric contents given above is that the percentage of hydrochloric acid is very sensitive to the general condition of the body, and is generally reduced in all cases of illness or enfeeblement.

In addition to this, in malignant disease there is a more pronounced drop in the degree of acidity, so that in the majority of cases free hydrochloric acid is entirely absent, and in practically all cases there is a very marked reduction.

Such absence, or reduction in percentage, of hydrochloric acid is in no wise related, as had been previously supposed, to the presence of a malignant growth in the gastric mucosa leading to a local action and perversion of the acid secreting function. This is shown by the fact that the percentage of absences in our series of carcinomata, in which the growth has been situated in widely different regions of the body, is as high as in most of the series of cases of carcinoma of the stomach recorded by earlier observers.

If we have as the result of these experimental observations to turn away from the view that the reduction or absence of acid is due to a

local effect upon the gastric cells, the only remaining cause is an alteration in the pabulum brought to the acid secreting cells by the circulating nutrient fluid, as a result of which the acid secreting power of these cells is enfeebled or destroyed. Such an action might be brought about either by an organic toxic agent which altered the metabolism of the cell ; or by an alteration in the balance of the inorganic ions of the plasma, and consequently of the lymph, as a result of which the concentration in acid or hydrogen ions diminished, so causing the work on the part of the cell of separating an acid secretion to be increased.

It must not be lost sight of that the latter of these two effects may be involved in the former, because the organic constituents of the plasma, particularly the proteins, are capable of acting either as feeble acids or feeble bases, and accordingly an alteration in the constitution of the protein molecules of the plasma (or of the protein constituents of the cells themselves) whereby these become more strongly acidic or basic in their properties than normal, would give rise to a different ionization in the plasma, whereby its concentration in hydrogen ions would be increased or decreased.

Investigations in the case of the leucocytes by means of acidic and basic stains have shown that the protein colloids which they contain vary in their degree of acidity or basicity, and that these properties change with pathological alterations. It is highly probable that the other cells of the body also can and do undergo similar variations in the degree to which their colloidal protein contents are capable of acting as weak acids or bases, and so altering the degree of acidity or alkalinity of the lymph bathing them. Also the action of the secreting cells of the kidney will depend upon the power of the protein constituents for combining with acid or base, for it is probably only the uncombined inorganic ions of acidic or basic character which are removed, while those combined with or adsorbed by the protein are unaffected, and left in circulation.

In considering the ionization of the plasma and the effects of variations in this upon the action of secreting cells (such as the acid secreting cells of the stomach), it is accordingly difficult or impossible

to entirely dissociate the two parts played by the proteins and the inorganic ions respectively, or to say how much, for any given alteration under pathological conditions, may be due to a change in the proteins in cells or plasma, or to a change in inorganic ions.

In order that the relationship of the observed decrease in acid secreting power of the gastric glands in carcinoma, to changes in the plasma may be understood, it may be pointed out that the plasma is a fluid in which normally the concentrations of hydrogen and hydroxyl ions are never so widely different as in dilute solutions of free acid or alkali, so that in this respect the plasma approximates in chemical reaction to distilled water. This has been shown by a number of observers¹ by direct measurements of the hydrogen ion concentration by means of hydrogen electrodes. So near does the reaction of the plasma lie to that of distilled water that the variations in the concentration of the hydrogen ions cannot be estimated by physical methods, which are only capable of showing that the plasma never becomes strongly acid or strongly alkaline.

Although the constituents of the plasma are so balanced that the concentrations of hydrogen or hydroxyl ions lie much closer together than in even a very dilute solution of a free acid or alkali, such as a $\frac{1}{1,000}$ normal solution for example; yet the behaviour of the plasma towards acids or alkalis is entirely different from a fluid neutral in the sense that distilled water is neutral. The difference lies in the fact that the plasma, on the addition of an acid or an alkali, is much more stable in the concentration of its hydrogen and hydroxyl ions than is the water, because of the fact that the plasma contains substances capable of acting either as acids or bases.

The understanding of this difference in behaviour of two fluids, which are both practically neutral in reaction, is of fundamental importance not only in regard to the immediate problem of the absence of hydrochloric acid in the gastric juice in cancer, but also in regard to the life of the cell and its reaction to changes in its environment.

1. Fraenkel, Arch. f.d. ges. Physiol. vol. 96, 1903, p. 601.

1. Höber, Ibid., vol. 99, 1903, p. 572.

1. Farkas, Ibid., vol. 98, 1903, p. 352.

Without a fluid, in which the reaction was not only nearly neutral but stable in its neutrality, the life of the cell, as at present constituted, would be impossible. The cell and also the organism of which such cell is a part always reacts in such a way as to preserve this approximate neutrality against any change from without. The plasma with its almost neutral reaction (just on the alkaline side and nothing more than this) is a special mechanism provided to protect the cells against any sudden or excessive change in the relative concentration of hydrogen and hydroxyl ions, or in other words, against variations in chemical reaction.

Without such a protective action, the cell would at once be killed by the acid products of its own metabolism, for the limits of relative concentration of hydrogen and hydroxyl ions, within which life is possible, are very narrow. An excess of either hydrogen or hydroxyl ion at once combines with and fixes the protein of the cell, and by so doing, stops the power of the protein for combining with other substances, metabolism is accordingly abruptly stopped and life becomes impossible.

Thus, as has been shown by Moore, Roaf, and Whitley,¹ addition of as little of either acid or alkali as suffices to produce a solution of $\frac{1}{1000}$ to $\frac{1}{500}$ gram molecular acid or alkali,² at once kills organisms which have no protective mechanism, and short of these concentrations most profound changes in growth and nuclear division are obtained, which will be referred to later. These results show how exceedingly narrow are the limits of hydrogen and hydroxyl ion concentration, within which, normal metabolism, and even life itself are possible.

On the other hand, in an organism which possesses a protective mechanism, such as the plasma, sufficient amounts of either acid or alkali to produce twentyfold the above concentrations may be added by direct venous injection, with perfect impunity. It is not that the higher organism is able to withstand change in reaction any better, but that it is able to protect itself against such change.³

1. *Proc. Roy. Soc., B*, Vol. 77, 1905, p. 102.

2. The minute dosage is perhaps better shown when one states that these strengths correspond approximately to 1 part in 10,000 of hydrochloric acid or sodium hydrate.

3. It is this very protective action which stands in the way of any interference in the reaction of the plasma, by drugging with acid or alkali.

The action of the tissue fluids, and of the fluids of the cell, as a regulating and controlling mechanism upon variations in concentration of hydrogen and hydroxyl ions (*i.e.*, upon acidity or alkalinity) can perhaps best be understood by comparing the effects of addition of small quantities of acid or alkali upon the ionization in the case of distilled water, and of a solution such as the plasma or lymph containing bi-carbonate of sodium with an excess of carbonic acid, a mixture of mono and di-sodic phosphates, and a quantity of protein, capable of playing the rôle of either acid or base.

In distilled water almost all the water molecules are in the non-ionized condition, as shown by the very feeble conducting power of the water, and but a relatively small number of molecules are in the ionized condition as hydrogen and hydroxyl ions. Since only water is present, all the ionized molecules must come from water molecules, and, as each of these yields one H^+ and one HO^- ion, it follows that the numbers of hydrogen and hydroxyl ions must be equal. This is the condition of exact neutrality, and the distilled water is accordingly an exactly neutral solution containing a very low and equal concentration of hydrogen and hydroxyl ions.

If now there be added to the distilled water but a slight trace of a strongly dissociating acid, such, for example, as sufficient hydrochloric acid to make a $\frac{1}{1000}$ gram molecular solution, then the distribution of the hydrogen and hydroxyl ions becomes an entirely different one. The slight trace of added acid is sufficient to alter the relative concentration of hydrogen and hydroxyl ions, so that instead of the original equality there are now, at least, 10,000 hydrogen ions for one hydroxyl ion. Exactly a similar change, but in an opposite sense, occurs if a trace of a caustic alkali be added instead of the acid, the concentration of the hydroxyl ions becoming more than 10,000 times that of the hydrogen ions.

Two factors are responsible for bringing about this immense swing in the relative concentration of the two ions.

In the first place, the dissociation of the water is very low, while the trace of added acid becomes at once almost completely dissociated or ionized into hydrogen (H^+) and chlorine (Cl^-) ions. As a result,

although the mass of the acid added is small relatively to that of the water, the complete ionization of the acid leads to the concentration of the hydrogen ion being enormously increased relatively to its former value.

Secondly, the concentration of the hydroxyl ion is depressed in equal degree as the concentration of the hydrogen ion is increased. For the product of the two concentrations of ions remains throughout practically constant, being dependant almost solely on the dissociation factor of the water. If we write c_H for the concentration of the hydrogen ions, and c_{OH} for the concentration of the hydroxyl ions, then the law holds that $c_H \times c_{OH} = k$, where k is practically a constant dependant upon the physical characteristics of water. Accordingly, in order that this product may remain constant, if c_H be increased 100 fold, as it easily is with the small amount of acid we have been considering, then c_{OH} must be diminished 100 fold. The ratio of $c_H : c_{OH}$ accordingly becomes 10,000 to 1. But it is the ratio of these two ions upon which the reaction depends, and hence the solution acquires marked acid properties. The change is shown and can be followed quantitatively by the physical methods used for determining ionic concentrations (such as hydrogen electrodes or hydrolysis methods) and it is found experimentally that there is such a rise as described above in hydrogen ions. The same is shown by the behaviour of the very dilute acid solution to coloured indicators ; it is acid to the very strongest of these, such as methyl orange or di-methyl, and reacts positively to Günzburg's reagent. Exactly similar reasoning follows for the addition of a trace of caustic alkali, the hydroxyl ions being here increased and the hydrogen ions depressed.

The case is however quite different even if a considerably greater amount of a bi-carbonate or of a mixture of primary or secondary phosphates, such as are present in blood plasma, be added instead of the acid or caustic alkali. For here, instead of adding to the distilled water a substance which on dissociating yields only one of the two ions concerned in determining the reaction, we are adding substances which, on dissociating, add both ions. Accordingly, the swing in the ratio of concentration of the two ions is very slow, and by adding either

(a) a mixture of sodium bi-carbonate and carbonic acid in proper proportions, or (b) a definite mixture of mono-sodium-phosphate (NaH_2PO_4) and di-sodium phosphate (Na_2HPO_4), we may obtain a solution in which the relative concentrations of hydrogen and hydroxyl ions do not vary from their values in distilled water. Not only so, but by the presence of such salts in the solution, the concentrations of the two ions are steadied, so that free acid or alkali can now be added or taken away from the solution without causing any such enormous change in relative concentrations as have been shown above to occur in the case of distilled water. This is most important in that it enables the secretion of an alkaline or acid fluid to occur by the secreting cells of the glands of the body, and also renders possible the metabolic processes of the cells.

Taking as the simplest case, the addition of sodium bi-carbonate to water, the processes occurring can be most simply understood if represented as happening in two stages.

First, the molecule of NaHCO_3 takes up a molecule of water, and partially dissociates into NaOH and H_2CO_3 , as represented by the equation :—

Next, the molecules of NaOH and H_2CO_3 ionize, the former yielding ions of Na^+ and OH^- , and the latter ions of H^+ and HCO_3^- .

The final result is that both H^+ ions and OH^- ions are added, and there is not, as in the case of addition of NaOH , or of H_2CO_3 alone, an addition of OH^- ions only, or of H^+ ions only. Accordingly, the displacement of the ratio of the two ions is much smaller, and in fact, whether the reaction becomes alkaline or acid will depend upon the relative amounts of alkali and carbonic acid.

In dilute solutions of NaHCO_3 the reaction is almost neutral ; a trace of CO_2 bubbled through renders the solution acid, and a trace of NaOH in excess gives an alkaline reaction. Exactly similar reasoning holds for a mixture of primary and secondary phosphates, and whether the mixed solution will be acid or alkaline depends on the relative amounts of the two salts.

These conclusions are confirmed both by modern physical methods for determining ionic concentrations and by the effects of the solutions upon coloured indicators.

For example, determinations in the case of the plasma of the hydrogen ion concentration by many observers have, as mentioned above, shown that this lies around the same limits as in the case of distilled water.

Again, although all the coloured indicators used in acidimetry and alkalimetry change colour at extremely low concentrations of acid or alkali (usually much less than $\frac{1}{10,000}$ gram molecular concentration of free acid or free alkali), yet the blood plasma is alkaline to some of these and acid to others; thus showing that its own concentrations in hydrogen and hydroxyl ions lie intermediate between the low values at which changes occur to these indicators. Thus blood is acid to phenol-phthalëin and alkaline to di-methyl, but less than $\frac{1}{5,000}$ gram. molecular caustic alkali in distilled water will turn phenol-phthalëin acid, and less than that concentration of hydrochloric acid in distilled water will turn di-methyl acid. It follows that the reaction of the plasma must lie well within these two very narrow limits of alkalinity or acidity. The difference between the blood plasma and distilled water with regard to what might perhaps be termed its '*reactivity*,' since it cannot, properly speaking, be termed its *reaction*, is seen on the addition to the plasma of alkali or acid.

Although the plasma, as shown above, is so near the neutral point, it behaves in a striking manner to alkalies and acids in that it is able practically to neutralize either of these without large changes in the ratio of its own hydrogen and hydroxyl ion concentration, that is to say in its reaction.

The recent results of Moore and Wilson¹ show that before the plasma becomes neutral in its reaction to phenol-phthalëin enough *alkali* must be added to it to correspond to $\frac{1}{20}$ th to $\frac{1}{40}$ th gram molecular solution; while in order to neutralize it to di-methyl enough *acid* must be added to correspond to so high a figure as $\frac{1}{5}$ to $\frac{1}{6}$ gram molecular. That is

1. This Journal, Vol. 1, 1906, p. 297.

to say, between these wide limits the relative ionic concentration in hydroxyl ions changes very slowly compared with the changes in presence of alkali or acid.

Let us now turn to the practical application of these considerations to the secretion of the hydrochloric acid by the gastric cells and to the cause of its suppression in carcinoma, and to the effects upon the cells of the body of slight variations (such as can occur within the limits of life) in concentration of hydrogen and hydroxyl ions under pathological conditions.

To make the matter clearer, let us suppose that the plasma instead of having its balancing supply of carbonates, phosphates, and protein substances capable of acting either as weak acids or weak bases, is devoid of this, and consists of a solution of neutral saline, such as sodium chloride. Suppose the gastric gland cells commence to remove hydrochloric acid from such a saline solution, then the merest trace of removed acid with the accompanying removal of hydrogen ions, would cause at once an immense swing up in alkalinity of the plasma, because the ionization of the water of the saline solution is so low. The result would be either that acid secretion must at once stop or the body cells be killed by the alkali which would be absorbed by the proteins of the cells and stop all activity. Further, the merest trace of carbonic acid formed in any act of metabolism by any cell in the absence of alkaline carbonates or phosphates would lead to rise of hydrogen ion concentration and cause the death of the cell.

In the normal process of acid secretion by the gastric cells, such a rise in alkalinity of the plasma is enormously diminished by a slight change in dissociation of the carbonates and phosphates of the alkalies present in the plasma. As a result of such readjustments in dissociation, considerable amounts of acid can be secreted from the plasma without any marked change in the ratio of concentrations of hydrogen and hydroxyl ions, such as would injure the cells.

The work of the acid secreting cells of the stomach then consists in removing the hydrogen ions from the plasma at the exceedingly low concentration at which these ions exist in that fluid and concentrating the solution in hydrogen ions to the value which they possess in the

gastric secretion. Much as in the case of the kidney, the secreting cells of that gland take out urea at the low concentration of urea molecules found in the plasma, and concentrate the solution until the urea molecules possess the concentration found in the urine.

It is clear, therefore, that the rate at which the acid secreting cells will be able to secrete acid, other things being equal, will depend upon the concentration of the hydrogen ions in the plasma. For the lower the concentration of hydrogen ions in the plasma, the greater will be the amount of concentration necessary to produce an acid secretion of a given concentration in hydrogen ions, and the greater will have to be the amount of work done by the plasma in order to produce the secretion.

Now, although as shown above, the variations in ratio of hydrogen and hydroxyl ion concentration in the plasma are small compared to those in a solution containing only free acid or free alkali, where the concentration of the one ion may exceed that of the other by many thousands of times, yet the variations within the narrower limits possible may be very considerable. Thus the determinations of the hydrogen ion concentrations by means of hydrogen electrodes, show variations of about one hundredfold in the hydrogen concentrations.

The position of affairs may be summarized as follows :—

1. Even a very dilute solution of free alkali or acid (such as $\frac{1}{1000}$ gram molecular solution) leads to an enormous change in ratio of hydrogen and hydroxyl ions (10,000 : 1), which, if it were allowed to occur would instantly lead to the death of the cells.
2. The cells are protected against any such great change by the alkaline carbonates and phosphates.
3. Within much narrower limits (say 100 : 1) changes in ratio of hydrogen and hydroxyl ions can occur, due to alterations in the distribution of carbonates and phosphates, and also probably of the basic and acidic affinities of the circulating and tissue proteins.
4. The rate of secretion of hydrochloric acid, other things being equal, will be directly proportional to the concentration of hydrogen ions in the plasma. Accordingly, the rate of secretion may vary enormously although to ordinary titration methods there appear to be only slight variations in alkalinity of the plasma.¹

1. The variations in the hydrogen ion concentration of the plasma, which are capable of producing the observed differences in rate of secretion of acid, lie also outside the limits of accuracy of any of the physical methods of determining hydrogen ion concentration, since two readings in the same solution may easily vary by $0.5 \times 10^2 = 50$ fold.

According to the relative distribution of sodium carbonate and carbonic acid, and of the different alkaline phosphates in the plasma, and also of variations in the acidic power of the proteins of the plasma, the concentration of the hydrogen ion may therefore vary within limits capable of effecting very considerably the rate of secretion of the hydrochloric acid, although such variations are small, compared to the variations occurring in a solution containing only free acid or alkali.

The reduced secretion of acid which occurs in cancer points accordingly to an alteration in the plasma from the normal, as a result of which the hydrogen ion concentration is diminished.

Observations by Moore and Wilson¹ of the alkalinity of the inorganic constituents of the plasma have given the result that in carcinoma there does occur a small but definite increase in the alkalinity.

Whether the organic constituents of the plasma and also the constituents of the tissue cells are similarly affected in cancer, is a question urgently requiring attention, but the experimental difficulties of such an enquiry are very considerable.

An increase in the alkalinity of the circulating fluid cannot leave the tissue cells unaffected, for experiment shows how extremely sensitive living cells are to even slight changes in concentration of hydrogen and hydroxyl ions.

An experimental enquiry into the effects of a small chronic change in degree of alkalinity upon living organisms is most difficult to carry out, and one rendered almost impossible in all higher organisms by the adjusting changes in the opposite direction made by the cells of the organism.

Thus, if acids be administered, the cells form ammonia or organic bases to neutralize the acid, and if alkalies be administered they are neutralized by excess of carbonic acid or by organic acid formed by the cells of the organism. In addition, the acid or alkali is removed as rapidly as possible by the excretory cells of the organism, and the amount capable of administration is also limited by the irritability

1. *Loc. cit.*, p. 317

of stomach and intestine, leading to the rejection of the drugs by vomiting, or the appearance of a profuse diarrhoea by which they are carried off without absorption.

A more acute acid or alkaline intoxication can be obtained by intravenous injection, but this does not properly imitate the desired condition.

It is accordingly only in simpler organisms, where a complete protective mechanism does not exist, that experimental results can be obtained.

The fertilized egg of *Echinus esculentus* has been used by Moore, Roaf, and Whitley¹ for studying the effects of acids and alkalies upon cell growth, and division of the nucleus, and their experiments have shown that minute traces of added alkali or acid produce marked and characteristic results.

As stated above, the limits of acidity and alkalinity within which life is possible were found to be very narrow, cell division being entirely stopped, and the cells killed by so low concentrations as $\frac{1}{1000}$ to $\frac{1}{500}$ gram molecular acid or alkali added to sea-water. In the still more dilute solutions, in which growth and cell division still continued, it was found that characteristic differences existed between the action of acid and alkali respectively.

The acid solutions caused at no dilution an increase in rate of growth or a stimulus to nuclear division. From the beginning the growth was slowed, mitotic figures were less frequent, and the chromatin showed signs of disintegration and stained more feebly with chromatin stains.

On the other hand, the more dilute alkaline solutions produced a marked favouring action upon cell growth, the organisms developing in these solutions being more advanced in cell division than the controls. Also at a certain level of concentration the growth became most irregular, so that the organisms became misshapen, and the cells irregular in shape and size. The division of the nucleus also was more strongly stimulated than that of the cytoplasm, so that many of

1. Proc. Roy. Soc. B. vol. 77, 1905, p. 102.

the cells became multinucleated. The character of the nuclear division was also changed, so that many tri- and multipolar spindles were formed, and the distribution of chromosomes to the poles became unequal, leading to the formation of unequal sized nuclei. The length of the chromatin rods was altered, so that these appeared shortened and thickened upon the spindle as rounded vesicles which were less in number than the normal.

It is hence clear that a slight increase in hydroxyl ion concentration leads to a marked stimulation of nuclear division, and to abnormalities in the process, some of which strongly suggest the irregularities often described in the dividing cells of malignant growths.

One of the most important facts which has been noted with regard to the local situation of primary malignant growths is that such growths often occur in situations which are liable to or have been the seat of chronic inflammation and irritation. It may be pointed out in relationship to the views expressed above, that such situations would be chronically exposed to a higher alkalinity than other parts of the body.

It has been shown that passing carbon dioxide into blood causes alkali to leave the corpuscles, and so increases the alkalinity of the plasma; as a result, the alkalinity of the plasma of venous blood is always higher than that of arterial blood, and the lymph of parts subjected to venous congestion is therefore of higher alkalinity than the lymph of parts with a normal circulation.

The experiments mentioned above show that such increased alkalinity will cause a tendency to increased cell growth, and such cell growth within normal bounds is often seen in inflamed or injured situations as a reparatory or protective process. When the irritation and inflammation are long continued, this stimulus by the increased alkalinity to growth and cell division may ultimately lead to malignant growth in such a situation, and the highly venous lymph coming from such a congested area would also act as an irritant to cells along its course.

SUMMARY

1. The secretion of hydrochloric acid in the gastric juice is very sensitive to any variation in the general health of the body, any enfeeblement in general condition leading to decreased percentage of acid. (Contrast Tables IV and V).

2. The reduction in acid secreting power is much more marked in cancer than in other conditions, free acid being entirely absent in about two-thirds of the cases, and much reduced in most of the remainder. (See averages given on p. 275).

3. The absence of acid or reduction of acid secreting power is independent of the situation of the growth, being seen in cases of cancer of all regions.

4. This points to the change being due to a change in the concentration in hydrogen ions in the plasma and lymph, which may be due to alterations in the inorganic salts or to changes in the organic constituents capable of acting as acids or bases.

5. The alkalinity of the inorganic constituents of the plasma is increased in cancer (Moore and Wilson).

6. Increase in alkalinity up to a given degree leads to increased cell growth and pathological nuclear divisions in organisms which are unable to protect themselves against artificially increased alkalinity (Moore, Roaf, and Whitley).

7. Irritation and inflammation are accompanied by increased alkalinity of the lymph, which is a factor in stimulating cell growth and when long continued may lead to the excessive nuclear division and cell growth of malignancy.