On the Absence or Marked Diminution of Free Hydrochloric Acid in the Gastric Contents, in Malignant Disease of Organs other than the Stomach.

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It is well known that free hydrochloric acid is absent in a large proportion of cases of cancer of the stomach.

This was first noticed by Reinhard von den Velden* in 1879, and evoked a great deal of attention and experimental work, as a result of which some observers confirmed, while others disputed von den Velden's statement. But in the end the result that free hydrochloric is absent in the majority of cases of cancer of the stomach has become firmly established as one of the few experimental facts amid a mass of theory that we know regarding cancer.

It would be out of place in a preliminary paper such as the present to attempt a complete history of the enormous literature on the presence or absence of free hydrochloric acid in the stomach contents in cancer of that organ, so only a few of the prominent results recorded will be noticed as an introduction to the observations which form the subject of this communication.

In his original paper, von den Velden used methyl-violet as an indicator for free hydrochloric acid, and examined cases of dilatation of the stomach, due on the one hand to stenosis of the pyloric opening caused by carcinomatous growth, and on the other to various other causes. He found in ten cases of dilatation which were not due to carcinoma that free hydrochloric acid was always present, while in eight cases of cancer of the pylorus, free hydrochloric acid was uniformly absent, and he suggested such testing as a diagnostic sign for cancer of the stomach.

C. A. Ewald† raised objections to methyl-violet as not being a sufficiently sensitive indicator for free hydrochloric acid, and stated that in 23 cases of

* 'Deutsches Archiv f. klin. Medicin,' vol. 23, 1879, p. 31.

† 'Zeitsch. f. klin. Medicin,' vol. 1, 1880, p. 619.

cancer of the stomach he obtained a clear reaction even with this indicator in 13 cases, a doubtful reaction in 5 cases, and no reaction in 5 cases.

In a reply to this, von den Velden* stated that he had only claimed, in the original paper, the absence of free hydrochloric acid in cancer of the stomach, leading to pyloric stenosis and accompanied by typical dilatation; and that he had stated that it still remained to investigate, as to the stage of the development of the disease at which the free hydrochloric acid disappears, if all forms of carcinoma of the stomach are alike in this respect, and if it makes any difference on which part of the stomach the growth is localized

Kredel,† in 17 cases of dilatation not due to carcinoma found free hydrochloric in every case, and in 19 cases of dilatation due to carcinoma that the free acid was invariably absent.

The next important contribution was made by F. Riegel,‡ who found in observations of the free hydrochloric acid repeated in the same cases over a period of several months, that von den Velden's rule was nearly always true. In a later paper Riegel stated that he found that more forms of gastric disease give an increase than a decrease in the amount of free hydrochloric acid, for example, in 128 cases, 19 showed an absence of free hydrochloric acid, 69 a hyperacidity, while the remainder gave an approximately normal amount of free hydrochloric acid. Of the 19 cases which showed absence of free hydrochloric acid, 16 were undoubtedly carcinoma, one amyloid degeneration of mucosa, and in one a backflow of bile was the cause.

A. Cahn and J. v. Mering§ as a result of finding free hydrochloric acid in about normal quantity in eight cases of *carcinoma ventriculi*, denied that absence is the rule. On the other hand, E. Korczynski and W. Jaworski‖ affirmed that for the great majority of cases the rule is absence of free hydrochloric acid.

The experimental methods of Cahn and v. Mering were subjected to adverse criticism by G. Honigmann and C. v. Noorden,¶ and their results shown to be due to organic acids being mistaken for free hydrochloric acid. In 14 cases of gastric cancer, Honigmann and v. Noorden showed that the acids present were chiefly organic, only traces of hydrochloric acid being present, and that free hydrochloric acid, added to the gastric contents in such

* 'Deutsches Archiv f. klin. Medicin,' vol. 27, 1880, p. 186.

† 'Zeitsch. f. klin. Medicin,' vol. 7, 1884, p. 592.

‡ 'Deutsches Archiv f. klin. Medicin,' vol. 36, 1884, p. 100; 'Berl. klin. Wochensch.,' 1885, No. 9; 'Zeitsch. f. klin. Medicin,' vol. 12, 1887, p. 426.

§ 'Deutsches Archiv f. klin. Medicin,' vol. 39, 1886, p. 233.

‖ 'Deutsches med. Wochensh.,' 1886, Nos. 47 to 49.

¶ 'Zeitsch. f. klin. Medicin,' vol. 13, 1887, p. 87.

cases of carcinomatous stomach dilatation, disappeared as such, being neutralized by salts of organic acids present, and setting free an equivalent amount of these organic acids.

Further, these authors stated that they had observed cases of great dilatation, without carcinoma, accompanied by absence of absorption and retention of food in the stomach, as great as in the cases of carcinoma cited by them; yet in these cases of dilatation unaccompanied by carcinoma soon after ngestion of food there was plenty of free hydrochloric acid present.

In the literature subsequent to this period one finds chiefly records of a smaller number of cases, often of one case only, where regarded from the point of view of diagnosis, the absence of hydrochloric acid demonstrated the presence of malignant disease where the other signs were obscure; or, contrariwise, the presence of free hydrochloric acid was shown where there was undoubted malignant disease.

It is now well established that free hydrochloric acid is not absent in every case of cancer of the stomach, and also that it may be absent in other conditions than cancer, but the percentage of cases of cancer of the stomach in which it is absent is so large, that, taken in conjunction with other signs, it is a valuable aid in cases of doubtful nature. Thus Osler* records that in 94 cases in which the stomach contents were examined, in 84 free hydrochloric acid was absent; and v. Jaksch† in 17 cases found free hydrochloric acid, either absent, or only present in traces, in 14 cases.

The variations in results obtained by the earlier observers are due in part to the employment of different indicators of varying degrees of delicacy, and partly to the fact that the attention of these observers was turned almost wholly upon entire *absence* of the free acid as a diagnostic sign, so that little care was given to quantitative determinations of the variations in amount of the acid, or the relationship of this to the disease, which are far more important points.

If with the improved means for testing the matter both qualitatively and quantitatively now at our disposal, the extensive series of observations made by earlier workers were now repeated, it would probably be found, on the one hand, that in the long series of cases where the free acid was always found to be absent, there were in a certain number of cases traces present which were missed by the methods employed, and on the other hand, that in those series where in the majority of cases free hydrochloric acid was found to be present, the tests were given by larger amounts of organic acid, or the positive

* 'Principles and Practice of Medicine,' 3rd edition, p. 491.

† 'Klinische Diagnostik innerer Krankheiten,' 3te Auflage, p. 173.

results were due to minimal amounts of free hydrochloric acid which were not determined quantitatively, and the small amount of free hydrochloric acid present was almost as good an indication of cancer as its entire absence. The entire absence of free hydrochloric acid is not in the nature of things to [be expected in every case, and the amount of such acid, as shown by quantitative tests, is the proper subject of enquiry both from the point of view of diagnosis and in regard to its relationship to the diseased condition itself.

Before coming to the proper subject of this paper, a little may be said with regard to the absence or diminution of the free hydrochloric acid in other forms of disease than cancer of the stomach. With the exception of atrophy of the gastric mucosa, where the gastric secretion and naturally the free acid is absent, there is no other diseased condition of the stomach in which the acid is absent in such a high percentage of cases as in cancer. Mörner* found in 12 cases of chronic gastritis that free hydrochloric acid was absent in two, and varied in amount in the other 10 from 0·02 to 0·12 per cent.

The free hydrochloric acid appears to be present in normal amount in phthisis, except in the last stages of the disease.†

It is often absent in acute infectious diseases, but much less commonly in other febrile conditions.‡ Other conditions in which absence has been noted are chronic kidney disease, anæmia, neurasthenia, hysteria, tabes, Addison's disease. It is also absent in prolonged inanition, so that in all cases the condition of the patient's appetite should be noted in applying tests for free hydrochloric acid.

Returning to diseases of the stomach in which the free hydrochloric acid is absent or greatly reduced in quantity, it may be stated that the conditions in addition to carcinoma in which the acid fails are those of atrophy of the gastric mucous membrane and chronic gastritis.

Now, in such cases, there is a very obvious and long continued perversion of the activity of the secreting cells, and, hence, it is not difficult to understand that continued local irritation on the one hand, or atrophy of the cells on the other, can lead to a suppression of the acid secreting function. But in cancer of the stomach the absence of free hydrochloric acid may be noted before the gastritis becomes chronic, and in cases where gastritis is

* 'Upsala Läkareförenings Förhandlingar,' vol. 24, 1889, p. 483; Maly's 'Jahresberichte ü. d. Fort. der Thierchemie,' vol. 19, 1890, p. 253.

† Immermann, 'Beiläge zu Centralblatt f. klin. Medicin,' vol. 10, 1889, p. 21.

‡ Gluzinski, 'Deutsches Archiv f. klin. Medicin,' vol. 42, 1888, p. 481.

not particularly marked. Also, complete suppression of the secretion of the acid may occur when only a small patch of the mucous membrane is involved by the disease, and where that portion is in the pyloric part in which normally no acid is secreted. The usual explanations of the absence of the acid in cancer of the stomach, viz., that the absence is due, as in chronic gastritis, to local irritation, or to neutralisation of the acid by alkali poured in from the ulcerating cancerous surface, seemed to me, therefore, scarcely to fit the facts of the case.

That a small cancerous patch in one region of the stomach, occasionally so situated that it leads to no marked dilatation of the organ nor to any continued retention of food, should, *by some local irritation,* cause the suppression of the acid secretion in the remaining apparently healthy portions of the mucosa, did not seem to present a very feasible explanation. But if the suppression were not due to local action, to gastritis, or to the pathological condition of one portion of the mucosa affecting all the remaining portions, what could the explanation be?

The idea presented itself that the suppression of the acid might be due to a general condition in the body, to alterations of the circulating fluid in some way, either by products thrown out by the cancer cells, or as a result of changes in the blood which might lead both to the abnormal growth and atypical mitosis of the cancer cells, and to such changes in the nutrient medium of the oxyntic cells, that these could no longer separate hydrochloric acid from the inorganic constituents of the plasma.

Such a view, if it could be substantiated experimentally, would naturally give a new importance and a different aspect to what is already one of the most important experimental facts known about carcinoma.

The testing of this view was the object set forth in the observations recorded below, which have shown that *the absence of free hydrochloric acid in cancer of the stomach is not due to local action in that organ, for hydrochloric acid is absent or reduced greatly in amount whatever may be the situation in the body of the malignant growth.*

It follows that the absence of the acid is due to some change in the blood, which change may either be a common cause of the growth and the absence of the acid, or may be the result of the growth and the cause of the absence of the acid. The significance of this fact will be reverted to after the results of the observations have been described.

It is somewhat remarkable that no systematic observations have hitherto been made upon the condition of the gastric juice with regard to hydrochloric acid in malignant disease in other situations than the stomach, or

if such observations have been made that they have excited so little attention. The literature on carcinoma is so enormous that it is possible such observations, although unknown to me, may have been made already, but such search as I have been able to make has revealed none, and if they do exist they have been awarded so little attention that they have been quite forgotten, and so it needs no excuse to publish the results of the observations given below.*

On placing the view outlined above before my colleague Dr. Alexander, he agreed to superintend the clinical side of the work.

The cases have been collected, under Dr. Alexander's directions, the administration of the test meals superintended, and the gastric contents obtained by Mr. Kelly.

The chemical analyses have been carried out in the bio-chemical laboratory of the university by Mr. Kelly, Mr. Roaf, and myself.

I desire here to express my thanks to my co-workers in the research, whose energetic co-operation has rendered the task of combining clinical and laboratory work an easy one, and also to those physicians and surgeons in Liverpool who have assisted us with further clinical material.

Methods of Examination.

The test meal given in each case was that recommended by Ewald of a pint of tea without sugar or milk, and a round of dry toast. Except in Case IX, where the toast could not be taken on account of the situation of the growth, and the test meal was a pint of gruel and two pints

* When the series of observations had been nearly completed, in a search through the literature in Maly's 'Jahresberichte über die Fortschritte der Thierchemie' (from which most of the quotations given in this paper have been cited on account of the inaccessibility to me at present of the original papers), I came upon a remarkable footnote by Maly to an abstract of the paper by Kredel, quoted above. The note occurs in vol. 14, p. 288, and is as follows:—"The fact that the portion of the mucosa of the stomach still intact secretes no hydrochloric acid is impossible to understand. If the carcinoma itself does not secrete an alkaline or neutralizing secretion, which ought to be observable in such new growths in other situations, a plasma richer in alkali must be considered as probable in cases of carcinoma. So that a failing acid formation may represent not so much a consequence as a cause or accompanying condition of cancer. Systematic investigation of urine, blood-serum, etc., in carcinomatous cases in regard to the alkali and acid relationships compared with those of normal individuals are accordingly much to be desired." It is curious that in spite of this view, which is practically the same as that which independently suggested the observations recorded in the present paper, no experiments were made in the direction suggested by such a distinguished physiological chemist as Maly, and that the matter should have been allowed to remain dormant for so many years.

of water, administered by the stomach tube, and withdrawn after one and a-half hours. The length of time before withdrawal of the test meal is noted in each case, in the table.

The contents before testing were filtered from undigested residues of the food, and the tests in all cases were commenced as soon as possible afterwards.

The quantitative volumetric testing was performed by neutralising with decinormal caustic soda solution, with the indicator mentioned in each case. For convenience of comparison the results are expressed in terms of the equivalent amounts of hydrochloric acid. But it must, of course, be understood that in the case of the phenol-phthalëin, and di-methyl-amido-azo-benzol indicators, the figures do not represent actual free hydrochloric acid, but acidity expressed as the equivalent amount supposing it were all hydrochloric acid.

(a) *Total Acidity.*—This was determined in the usual way by titration of 10 c.c. of the gastric contents with phenol-phthalëin as indicator. The amount so obtained gives the total acidity due to hydrochloric acid (when present), organic acids, and acid salts (such as acid phosphates).

(b) *Acidity to "Di-methyl" Indicator.*—This indicator does not give as originally supposed by its introducer (Töpfer),* the free hydrochloric acid alone, but in addition, any acidity due to free, strong organic acids, such as acetic, lactic, and butyric. Accordingly, this figure is usually higher than that for the free hydrochloric acid given by the other methods described below, and the free hydrochloric acid may safely be taken as below the value of this reading. When the organic acids are low in value it gives an approximation to the free hydrochloric acid, and as it is often used as a clinical method, it is here given for purposes of comparison.

(c) *Acidity to Günzburg's Reagent*† (Phloroglucin and Vanillin).—We have found this reagent most reliable, both as a qualitative and a quantitative test. We have convinced ourselves by experiment that the test unmistakably shows 1 part of free hydrochloric acid in 30,000 parts by volume, and can be relied upon for accurate results in rapid clinical work where quantitative results are desired, as they always should be.

The use of the Günzburg reagent, in conjunction with titration with deci-normal alkali, which was first recommended by Mintz,‡ was carried out by us as follows:—

Ten c.c. of the filtered gastric contents are taken, two drops are removed with a

* 'Zeitsch. f. physiol. Chem.,' vol. 19, 1894, p. 104.

† Günzburg, 'Chem. Centralblatt,' 1887, p. 1560; 'Centralblatt f. klin. Medicin,' 1887, No. 40.

‡ 'Wiener klin. Wochensch.,' 1889, No. 20; *ibid.*, 1891, No. 9. Maly's 'Jahresberichte ü. d. Fort. d. Thierchemie,' vol. 19, 1890, p. 255; *ibid.*, vol. 21, 1892, p. 222.

glass rod to a porcelain capsule, a drop of the reagent added from a dropping bottle, and the mixture evaporated to dryness, preferably on a steam or water bath. If even a trace of free hydrochloric acid is present, the characteristic red colour appears. In that case, a quantity of deci-normal alkali is added to the 10 c.c. of filtered contents, from one- or two-tenths of a cubic centimetre to 1 c.c., according to the depth of colour obtained on the initial testing. The process of testing is then repeated, if a positive result is obtained more alkali is added, the testing repeated, and so on, until a negative result is obtained. Near the end, when the reaction is less marked, the alkali is added in quantities of 0·1 c.c. at a time. A little practice enables one to carry out the testing in about five minutes in all, and reduces the number of operations to four or five. As only about 0·1 c.c. is removed for each test, and the acid is almost neutralised when the final drops are removed, the loss in this way is very small.

In many of the cases of malignant disease it will be observed that the test was negative from the outset, showing entire absence of free hydrochloric acid.

(d) *Modified Mörner-Sjöqvist Determinations* of Free and Combined Hydrochloric Acid.*—We have used this method as a gravimetric one in the modification described by v. Jaksch.† The method consists in converting all the acids present into barium salts by the addition of barium carbonate (previously tested, and found free from soluble barium salts). Ten c.c. of the gastric contents are taken,‡ and about half-a-gramme of the fine dry barium carbonate powder added. The mixture is well shaken up and allowed to stand for about an hour, it is then evaporated down to dryness in a platinum or nickel crucible, and incinerated. In the process of incineration, the barium salts of the organic acids, if any are present, are destroyed, and barium carbonate is re-formed, while the barium chloride formed from the hydrochloric acid (free or combined with proteid) present in the gastric contents is unchanged in the process of incineration. After incineration, the incinerated mass is extracted several times with hot water, and the washings filtered free from barium carbonate.

The clear solution from the united washings measures approximately 50 c.c., when the washing is complete, and contains an amount of barium chloride which represents the total amount of free and combined hydrochloric acid in the original 10 c.c. of gastric contents.

The end of the process consists in determining the amount of barium chloride in the solution. Different volumetric methods have been proposed for this determination, but we have considered it more accurate to follow v. Jaksch's recommendation of weighing the precipitate.

The barium is precipitated in the usual way, at the boiling point, as sulphate by addition of a few drops of dilute sulphuric acid, kept at near 100° C. for about an

* 'Zeitsch. f. physiol. Chem.,' vol. 13, 1889, p. 1.

† 'Monatsheft. f. Chemie,' vol. 10, 1889, p. 211; 'Klinische Diagnostik innerer Krankheiten,' 3te Auflage, 1892, p. 155.

‡ Where previous titration in the malignant cases had shown that the total amount of acid was low, 20 to 50 c.c. were taken where available, so as to give a better chance of obtaining a figure for any minimal trace of hydrochloric acid which might be present.

hour in order that the precipitate may become granular, filtered through a Gooch crucible, dried and weighed.

From the weight of barium sulphate the amount of total hydrochloric acid (free and combined with organic matter) is then calculated.

In regard to this method, it must be stated that it gives not only the total amount of hydrochloric acid free or combined with proteid; but also the entire amount of inorganic acid (hydrochloric or other acid possessing a soluble barium salt) free or *combined with organic matter or a volatile base.*

The amount of such organic salts in normal stomach contents is small, but in the carcinoma cases the amount is probably larger. Thus in Cases XI, XVI, and XVII, the amount of hydrochloric acid given by this method is out of proportion both to the other cases and to the amounts of acid given by the other methods, this result can only be explained by the presence of compounds of inorganic acids probably hydrochloric, with volatile or organic bases, or with amido acids.*

This is further shown by the fact that in carrying out the incineration method for the determination of total organic acids,† although the titration figure with phenol-phthalëin is high, a negative result was obtained. In fact, of 10 c.c. of deci-normal alkali added in excess in Case XI, 6·6 c.c. disappeared, which could only arise from the presence in combination with inorganic acid of some organic base.

(e) *Total Free and Combined Organic Acids.*—An attempt was made to investigate this quantity by the following method. Ten c.c. of the filtered gastric contents are taken and titrated with phenol-phthalëin as in (a) for determination of total acidity. In this process as mentioned above, there are neutralised, the hydrochloric acid, the organic acids, and the acid salts (such as acid phosphates). The neutral solution is next evaporated to dryness, incinerated, taken up with hot water and boiled. In this process the sodium chloride formed from the hydrochloric acid remains unaltered, the neutral salts formed from the acid salts remain neutral; but the neutral organic salts formed from the organic acids, as well as any neutralised organic salts originally present in the gastric contents, are converted into carbonates and give an alkaline reaction. Accordingly the total organic acids present in the gastric contents, whether free or combined, are given, by now titrating the solution with excess of acid, boiling to remove carbonic acid, and back titration with deci-normal alkali.

The results, as given in the table, show that the amount of organic acids present, both in the normal controls and in the malignant cases, is very small, in fact, in some of the malignant cases, the results yield a negative value.‡ As indicated under the Mörner-Sjöqvist method this, however, indicates the presence of salts of organic bases with inorganic acids in the stomach contents, and hence, for both this

* Determinations in Case XI of the amount of ammonia by Schlössing's method showed that the amount of ammonia is small, so that the acid must be present in combination with organic bases.

† *Vide infra.*

‡ As shown by the fact that on incineration in the presence of excess of alkali, the amount of alkali recovered afterwards was less than that added in excess of amount necessary for neutralisation.

method and the Mörner-Sjöqvist method it would be necessary to know the amount of organic bases present in order to obtain accurate results. The figures are given as of interest in showing that organic bases in combination with inorganic acid must be present in the stomach contents in these cases, and on account of the light they shed on the high result in Cases XI, XVI, and XVII with the Mörner-Sjöqvist method.

The presence under the pathological conditions of such compounds of organic bases with inorganic acid is in itself of high interest, and requires further investigation.

Determination of the Concentration of Hydrogen Ions by the Velocity of Inversion of Methyl-Acetate.

A determination of the concentration of the hydrogen ions in the gastric contents gives not only one of the best means of determining the character of the acid present, but furnishes the best guide to the real degree of acidity in the fluid.

The figures obtained by titration to the neutral point (or by a gravimetric method such as that of Mörner-Sjöqvist) give only what might be termed the total or potential acidity or alkalinity of a solution, and not the active acidity or alkalinity *at any given moment*. Thus, a deci-normal solution of any organic acid, such as acetic, lactic, or butyric, requires for titration to neutrality with a sensitive indicator such as phenol-phthalëin, just as much of a deci-normal alkali solution as does a deci-normal solution of an inorganic acid such as hydrochloric, sulphuric, or nitric, and, again, a solution of caustic alkali requires no more acid of any nature for neutralisation than does a solution of equi-normal strength of alkaline carbonate, or of an alkaloid. Yet we clearly recognise by the effects of such acids and alkalies that the state of affairs in such solutions are quite different, and that in popular language we have weak and strong acids and alkalies.

The explanation lies in the fact that only a certain fraction of the acid or alkali in the solution is effective at any given concentration, and the value of the effective fraction varies within wide limits with the nature of the particular acid or alkali in question.

When an acid is dissolved in water it becomes partially ionised into a hydrogen ion, and an ion represented by the remainder of the formula of the particular acid, while the remaining un-ionised portion maintains a balance or equilibrium in the solution, and is inert as regards acid properties, the degree of acid activity of the solution depending entirely upon the concentration of the hydrogen ions.

Similarly, when an alkali is dissolved, it becomes partially ionised into a hydroxyl ion, and another ion, dependent in constitution upon the alkali in question; and in part remains un-ionised. Here the hydroxyl ion, by its concentration determines the degree of activity as an alkali, just as in the case of the acid, the concentration of the hydrogen ion determines the acidity.

Taking, as examples, hydrochloric acid and potassium hydroxide, the condition of things when solution takes place may be represented by the equations:—

$$(m+n)\mathrm{HCl} = m\mathrm{HCl} + n\overset{+}{\mathrm{H}} + n\overset{-}{\mathrm{Cl}}$$

$$(m+n)\mathrm{KOH} = m\mathrm{KOH} + n\overset{+}{\mathrm{K}} + n\overset{-}{\mathrm{OH}}$$

The + and − signs indicate the ionic condition, and the fact that in electrolytic conduction the property of carrying the current lies in the ionised portions. Similarly, many other properties are due to the ionised condition, and amongst other, the acid and alkaline properties.

Now, for equilibrium in solution, a definite ratio must exist between m and n, which is dependent upon the nature of the acid or alkali and the concentration of the solution, and it is the variation of this ratio which is of interest to us here, and gives an experimental basis for determining the effective amount of acid or alkali in a given solution, which is not given by titration.

For example, hydrochloric acid in the neighbourhood of such concentrations as are found in the gastric contents is over 95 per cent. dissociated into its ions and is correspondingly effective as an acid, while acetic acid in similar concentration is only dissociated to the extent of about 3 per cent.* and is correspondingly weakened in its activity as an acid, and the same is true of all the other organic acids occasionally present in the gastric contents.

The same differences occur in the solutions of strong and weak alkalies, thus it was shown by Shields† that for dilute solutions of caustic soda and sodium carbonate of equi-molecular strength that the effective strength, or hydroxyl concentration, in the latter was only about 3 per cent. of the former. Such figures, as we shall see later, are of the utmost importance when we come to consider the relationship of the results we have obtained regarding the effective acidity of the gastric secretion to the effective alkalinity or acidity of the blood.

The blood owes its reaction to indicators (such as phenol-phthalëin, litmus, etc.) to such substances as sodium carbonate in presence of excess of carbonic acid, and to phosphates of the alkalies containing varying amounts of base and acid.

In such solutions the amount of effective acid ($\overset{+}{H}$ ion) or alkali ($H\overset{-}{O}$ ion) concentration is very low, and accordingly dependent upon the indicator used, the blood (and other fluids of the body, the various secretions, urine, milk, etc.) possesses an alkaline reaction (for example, to litmus or di-methyl) or an acid reaction (for example, to phenol-phthalëin). That is to say, in the case of the blood and many other fluids of the body there is both acidity and alkalinity according to the indicator used, for both acid ions and alkali ions are present, and the result obtained on testing will be dependent upon how the particular indicator is affected by these ions in the concentration in which they happen to be present.

In an analogous fashion to the different indicators, the different cells of the secreting and excreting glands of the body will separate from the same solution, the blood plasma, which bathes them, the ions for which they possess a greater permeability or greater affinity, and furnish secretions or excretions of varying reaction and degree of reaction, that is to say, of varying concentration in hydrogen and hydroxyl ions.

The varying reactions given with different indicators in the same fluid, looked at from the proper point of view, instead of being a source of confusion, hence serves

* See Ostwald, 'Lehrbuch d. allgem. Chemie,' 2te Auflage, vol. 2, p. 729.

† 'Zeitsch. f. Physik. Chemie,' vol. 12, 1893, p. 167.

to orientate us as to the cause of the reaction, and to furnish some conception of how acid or alkali can be secreted from the same common fluid.

Now other things being equal in the way of permeability and affinity of the cell concerned in secretion, for the acid or alkali causing ions, it is evident that the power to secrete an acid or alkaline secretion will depend upon the concentration of these ions in the fluid which supplies the cell, that is the blood plasma.

But it must be carefully borne in mind that this factor cannot be obtained by titration of the plasma to neutrality in presence of an indicator. This does not give the effective concentration of the ions in solution, as is shown experimentally by the fact that the figure so obtained varies not only in amount but in algebraic sign with the indicator used, blood plasma being alkaline to "di-methyl," methyl orange, and litmus, and acid to phenol-phthaleïn, and urine *alkaline* to the two former and acid to the two latter indicators.

The reason why such titration does not give the effective acidity or alkalinity is that an equilibrium is disturbed as the alkali or acid respectively are added.* Suppose, for example, that we are titrating the alkalinity of blood serum to litmus by means of a standard acid solution, then as the acid is added the hydroxyl ions are reduced by combining with the hydrogen ions of the added acid to form water. As a result equilibrium is disturbed, more hydroxyl ions are formed by breaking up of the undissociated carbonate or phosphate molecules to replace those used up, and the alkaline reaction persists until all the carbonate or alkaline phosphate has been used up.

Hence no knowledge is obtained by titration, of the real effective alkalinity at any instant, as determined by the hydroxyl ion concentration at that instant, but instead the titration figure gives the amount of acid necessary to reduce the bicarbonatè and disodic phosphate to a certain condition with regard to the particular indicator used; that is, we do not get the value of the concentration of the hydroxyl ions when we began the titration, but instead, the amount of acid necessary to reduce the concentration of the hydroxyl ions to a dilution, at which the particular indicator in use is no longer affected, and this figure may bear no relationship to the concentration of hydroxyl ions, or effective alkali in the blood serum.

The consideration of this subject has been given at some length, because it affects not only the method we have here in view for determining the degree of effective acidity of the gastric contents, and incidentally the nature of the acid present, but casts a light upon the bearing of the absence or diminution of the

* The formula for equilibrium is deduced as follows:—Suppose we have a solution represented by the equation $KOH = \overset{+}{K} + \overset{-}{OH}$, and let the concentrations of the molecules in solution be represented by C^{KOH}, C_K, and C_{OH}, then the tendency for K and OH to combine will evidently be proportional to the product $C_K \cdot C_{OH}$, and the tendency of KOH to split up into ions will be proportional to C_{KOH}. For equilibrium these two tendencies must balance, and hence $C_K . C_{OH} = K \cdot C_{KOH}$, accordingly if one concentration varies such as that of C_{OH} on the addition of an acid, then the other concentrations must change correspondingly, that is, more KOH must dissociate.

hydrochloric acid on the probable changes in the blood giving rise to this condition.

It is clear that to obtain an estimate of the effective acidity or alkalinity of such solutions as occur in the body, we must make use of methods which do not disturb the equilibrium in the solution, and give us a measure from some activity of the hydrogen or hydroxyl ions. Such methods have already been elaborated in physical chemistry, and, at the suggestion of Ostwald, were first applied to estimation of the degree of acidity of the stomach contents by F. A. Hoffmann.*

The methods depend upon the fact that the velocity with which an acid solution hydrolyses a substance capable of hydrolysis, such as cane-sugar or methyl-acetate, is proportional to the concentration of the hydrogen ions in the solution.

For example, if cane-sugar solutions of equal strength be subjected to attack by equi-molecular solutions, on the one hand, say, of hydrochloric acid, and, on the other, of an organic acid, such as acetic. On account of the high state of ionisation of the hydrochloric acid, the cane-sugar is rapidly hydrolysed into invert sugar, and the rate of change can be accurately followed by the polarimeter, while, in the case of the acetic acid, which is but feebly ionised, the change is exceedingly slow. In fact, the change in the latter case is negligible compared with the former.

The application of the method with cane-sugar solutions and the polarimeter is, however, cumbrous, laborious, and slow, requiring a polarimeter, accurate readings, and the use of controls, since the gastric contents themselves rotate the plane of polarisation. Hence, the more recent method used by Hoffmann, which is an application of Ostwald's method of the catalysis of methyl-acetate, is much to be preferred, since it is much easier of application, can be applied in any laboratory where there is a thermostat or incubator, and facilities for volumetric analysis, and yields quite as accurate results as the other. The principle of the method is that methyl-acetate in aqueous solution changes with extreme slowness into methyl alcohol and acetic acid, according to the equation

$$CH_3.COO.CH_3 + H_2O = CH_3.COOH + CH_3.OH,$$

that this change can be increased enormously in velocity by the presence of an acid, and that the velocity is proportional to the concentration of the hydrogen ion of the acid, and the concentration of the methyl-acetate at any given moment.

The amount of acetic acid formed in a given time when acids of different concentration act upon the same concentration of methyl-acetate, gives, at once, an indication of the relative degrees of concentration of the hydrogen ions of the acids, or a simple calculation gives from this figure the effective concentration of the acid in hydrogen ions.

The determinations have been carried out by us as follows:—Ten c.c. of the gastric contents are taken in a small corked Erlenmeyer flask, 0·5 c.c. of the methyl acetate is added, and 5 c.c. of the mixture is titrated at once with decinormal alkali, free from carbonate, using phenol-phthalëin as indicator.

* 'Centralblatt f. klin. Medicin,' vol. 10, 1889, p. 793; 'Verhand. d. Internat. med. Congresses,' 1890, Abth. V, Abstract in Maly's 'Jahresber.,' vol. 21, 1892, p. 219.

The flask is then placed for a definite time in a thermostat at a temperature of 45° C. (we have used a period of eight hours, but a shorter period would suffice), and at the end of the period the contents of the flask are titrated again, the increase in the amount of alkali required for neutralisation gives the amount of acetic acid set free by the action of the hydrogen ions of the gastric contents during the interval, and hence an indication of the concentration of these ions. A simple calculation then gives the concentration of the hydrogen ions. For the purposes of this calculation, the total amount of acetic acid capable of being set free from the 0·5 c.c. of methyl-acetate added is required, and to obtain this a control is made in which deci-normal hydrochloric acid is allowed to act on methyl-acetate in the same concentration until the titration gives a constant figure for 5 c.c. of the mixture. This figure can be obtained once for all for any series carried out about the same time with the same sample of methyl-acetate.*

A comparison of the results given in the table of the titrations for acetic acid, formed from the methyl-acetate in the cases of malignant disease, as compared with those in the case of the normal control specimens, demonstrates clearly the value of the method, and shows the great contrast between the cases of malignant disease and the others.

The equation giving the velocity constant of the reaction (K), which is proportional in each case to the concentration of the hydrogen ions, takes the form—

$$K = \frac{1}{t} . \log \frac{A}{A - x},$$

where t is the time, expressed in minutes, A is the amount of methyl-acetate available for hydrolysis in the beginning, and x the amount of methyl-acetate hydrolysed at the end of the time t. The column in the table gives the values of $K \times 10^5$, to which the concentrations of hydrogen ions, or the effective acidities are proportional, and the last column gives the percentage concentration reckoned as effective hydrochloric acid, by comparison with the constant for a deci-normal solution (0·365 per cent.) of hydrochloric acid.

Deductions from the Results given in the Table.

1. The *total acidity* in malignant disease, wherever situated, is, as a rule, very low. In the 17 cases recorded, the total acidity only rises above 0·1 per cent. in four cases (Nos. V, VI, XI, XVI), and reaches the normal amount of approximately 0·28 per cent. in one case only (No. XVI). In the great majority of the cases one or two drops of deci-normal alkali, added to 10 c.c., is sufficient to render the reaction alkaline to phenol-phthelëin. In the few cases where the total acidity rises above a trace only, the other tests

* The methyl-acetate should be as pure as possible, give practically no acetic acid on titration alone, and a control as indicated above should be carried out at intervals, if the series of experiments is a prolonged one.

Table of Amount of Acidity of Gastric Contents in Cases of Malignant

No. of case.	Sex.	Age.	Disease and region.	Period of digestion.	Total acidity to phenol-phthalëin.	Acidity to di-methyl.	Free hydro-chloric, Günzburg.
I.........	F.	49	Carcinoma of uterus.........	1 hour	0·0219	Negative	Negative
II.........	M.	—	Carcinoma of prostate	,,	—	—	,,
III.........	F.	—	Sarcoma, general, liver, etc.	1¼ hours	0·0146	Negative	,,
IV.........	F.	71	Carcinoma of uterus.........	,,	0·0036	,,	,,
V.........	F.	50	,, ,, ...	1 hour	0·1460	0·0821	0·0365
VI.........	M.	61	Sarcoma of neck	,,	0·1861	0·0036	0·0072
VII.........	F.	65	Carcinoma of liver	1¼ hours	0·0018	Negative	Negative
VIII.........	F.	32	Carcinoma of rectum	1 hour	0·0584	,,	,,
IX.........	F.	—	Carcinoma of tongue	1½ hours	0·0292	0·0186	0·0109
X.........	M.	61	Epithelioma of floor of mouth	1 hour	0·0018	Negative	Negative
XI.........	F.	49	Colloid cancer of mesentery	1¼ hours	0·1058	0·0401	0·0072
XII.........	F.	59	Carcinoma of breast, removed 10 weeks previously	1½ hours	0·0182	0·0091	0·0036
XIII.........	F.	59	Recurrence of carcinoma in breast, removed 4 years before	,,	0·0511	0·0219	0·0036
XIV.........	M.	65	Epithelioma of cheek	1 hour	0·0018	Negative	Negative
XV.........	F.	66	Carcinoma of breast.........	,,	0·0548	0·0019	,,
XVI(*a*)	M.	63	Epithelioma of cheek ...	3 hours	0·2665	Negative	,,
XVI(*b*)				1 hour	0·2847	,,	,,
XVII.........	M.	57	Recurrence of carcinoma of tongue, removed 6 years ago	2 hours	0·0365	,,	,,

Control Cases in

No. of case.	Sex.	Age.	Disease and region.	Period of digestion.	Total acidity to phenol-phthalëin.	Acidity to di-methyl.	Free hydro-chloric, Günzburg.
R. E. K. ...	M.	25	—	1 hour	0·2117	0·1789	0·1533
B. M.........	M.	38	—	,,	0·3285	0·2884	0·2519
H. E. R. ...	M.	23	—	,,	0·3139	0·2482	0·1862
Average......	—	—	—	,,	0·2847	0·2385	0·1971
N/10 HCl ...	—	—	—	—	—	—	—

* See text, pp. 146–7. † Total amount hydrolysed in 24 hours, 31·6 c.c.;

Disease in Different Situations as determined by Methods indicated.

Total hydrochloric, *i.e.*, free and organic combined, Mörner and Sjöqvist.	Alkali after incineration, reckoned as HCl.	Increase in titration in cubic centimetres after hydrolysis of methyl-acetate.			Constant of velocity of reaction, proportional to real acidity, as shown by concentration of hydrogen ions, $K \times 10^5$.	Effective acidity reckoned as percentage of HCl from velocity constant.
		Initial.	Final.	Increase.		
—	—	—	—	—	—	—
—	—	—	—	—	—	—
—	0 ·0329	—	—	—	—	—
—	0 ·0066	—	—	—	—	—
—	0 ·0146	—	—	—	—	—
—	0 ·1533	—	—	—	—	—
—	0 ·0000	—	—	—	—	—
0 ·0013	0 ·0036	0 ·8	0 ·95	0 ·15	1 ·1649	0 ·00100
0 ·0295	0 ·0000	0 ·4	2 ·2	1 ·8	14 ·429	0 ·01239
Unweighable	0 ·0000	0 ·1	0 ·1	0 ·0	0 ·000	0 ·00000
0 ·0738(?)*	−0 ·1350*	1 ·55	3 ·65	2 ·1	16 ·934	0 ·01455
0 ·0023	0 ·0000	0 ·25	1 ·30	1 ·05	8 ·295	0 ·00713
—	0 ·0000	0 ·85	2 ·10	1 ·25	9 ·913	0 ·00852
0 ·0044	0 ·0000	0 ·025	0 ·05	0 ·025	0 ·1937	0 ·00017
0 ·0020	−0 ·0402*	0 ·8	1 ·05	0 ·25	1 ·945	0 ·00179
	0 ·1533	2 ·7	2 ·8	0 ·1	0 ·7759	0 ·00067
0 ·[illegible](?)*	0 ·2044	2 ·7	2 ·7	0 ·0	0 ·0000	0 ·00000
0 ·1140(?)*	−0 ·0657*	0 ·4	0 ·4	0 ·0	0 ·0000	0 ·00000
Normal Individuals.						
0 ·1579	0 ·0018	3 ·05	17 ·9	14 ·85	167 ·300	0 ·14373
0 ·2571	0 ·0000	4 ·8	25 ·5	20 ·7	305 ·740	0 ·26266
0 ·3296(?)*	−0 ·0876*	4 ·0	21 ·1	17 ·1	208 ·248	0 ·17892
0 ·2482	—	—	—	—	227 ·096	0 ·1951
—	—	4 ·8†	28 ·2†	23 ·4†	424 ·870	—

in 48 hours 31·7 c.c., leaving 26·9 as total available amount of acetate hydrolysable.

demonstrate that the reaction is not due to free hydrochloric except in minute traces.

2. The "di-methyl" indicator shows entire absence of acidity in nine out of 16 cases in which it was applied, and in the remaining cases gives very low values, approaching half-way towards normal in only one case (No. V).

3. The Günzburg test shows entire absence of free hydrochloric acid in 11 out of 17 cases, and in the remaining cases the quantitative use of the test shows that, with one exception (Case V), the amount of hydrochloric acid present was only a minute trace (0·0036 to 0·0109 per cent.). Case V was the only one which had an appreciable amount of free hydrochloric acid, and even here the amount present was less than one-fifth the normal quantity.

4. The Mörner-Sjöqvist method gave, as a rule, low results, but in Cases XI, XVI, XVII much higher results were given than by the other methods. There is little doubt that this result arose in those cases from the presence of salts of inorganic acids with organic bases, and not to hydrochloric acid either free or loosely combined with proteïd.

5. The presence of inorganic acid combined with organic base is shown by the zero or negative value obtained on incineration with excess of alkali in the attempt to determine the amount of organic acid.

6. The methyl-acetate inversion method shows clearly what small traces of effective acid are present as compared with the normal cases. In all the cases tested the concentration of hydrogen ions never exceeds one-fifteenth part of the normal amount, and in the majority of cases sinks incomparably lower even than this low fraction.

7. Attention may be drawn to Case XII, in which a carcinomatous breast had been removed ten weeks previously, recovery was completed and appetite good. Here it is to be noted that the gastric contents possess scarcely any "total acidity," requiring only 0·5 c.c. in 10 c.c. of deci-normal alkali for neutralisation, and that of this trifling amount only one-fifth or less (0·1 c.c. N/10 in 10 c.c. of the contents) is shown to be free hydrochloric acid by the Günzburg test.

This shows, so far as any conclusion can be drawn from a single case, that the suppression of acid is not due to secondary products thrown out by the growth, neutralising the acid ions of the plasma. For in that case the acid secretion should be re-established after removal of the growth. The persistence of absence of acid secretion after the growth has been removed points to the view that the condition of the blood, and most probably the absence or marked diminution of acid ions in it, is to be regarded as a cause pre-

disposing to growth formation, and not as an effect of the growth. In this case there persist, even after the growth has gone, the same factors, as indicated by the absence of the acid, which initially lead to the growth occurring, and the patient, on account of this condition, lies open to the risks of a recurrence.

It is clear that the study of the condition of the gastric contents with regard to acid subsequent to operation carried out in a large number of cases, must cast interesting light upon the problem before us, and we are now attempting to obtain as many as possible such cases.

The results of Case XIII, in which recurrence had just begun to be obvious, are also interesting from this point of view.

8. In the table are included two cases of sarcoma, in which similar results were found as in carcinoma. It was at Mr. Kelly's suggestion that such cases were included, and we are at present in the position of waiting for further material, but if the results in these two cases are confirmed in others, an interesting parallelism between the two types of malignancy will have been established, pointing to something very common in mode of origin of malignant tumours.

Discussion of Results.

1. The importance of the marked depression or entire suppression of the acid-secreting function, no matter what the situation of the growth, as an aid to diagnosis in doubtful cases of cancer, need not be insisted upon.

It must, however, be pointed out that we have not up till the present been regarding the subject primarily from that point of view, and hence most of our cases were well advanced. Accordingly, observations are still required at early stages in the disease, before conclusions can be drawn as to the diagnostic value of the sign, and such observations should be quantitatively directed towards determining amount of free hydrochloric acid, and not merely its qualitative presence or absence, as is too often done.

2. The bearing of the results upon the cause and possible prevention of the malignant growths is the most important aspect to be considered. Instead of regarding absence or diminution of hydrochloric acid in cases of cancer of the stomach as being due to some local effect in that organ, we obtain from the observations recorded above the information that both in stomach cases and all other cases the change in acid secretion is not due to local influence on the secreting cells, but to an altered condition of the blood. That the reduction of acid-secreting power is a general effect accompanying malignancy wherever the growth may occur in the body.

So far, we are dealing with experimental fact, and not with theory or

hypothesis, and continued observations of the acid-secreting function under varying conditions (such as early in the disease, soon after removal of growth, repeated observations at varying intervals after operation, and observations early in recurrence), must teach us the relationships of the variations in acid production to the appearance of new growth.

It may be allowable, however, in concluding this paper, to throw out a few suggestions, as to the probable cause of the change in the secretion of the acid, which are capable of forming the basis for additional investigation.

(*a*) The diminution in acid secretion may be due to atrophy or loss of function of the oxyntic or acid-secreting cells.

A diminution in the percentage of hydrochloric acid has been observed in old and senile individuals, the average amount of free hydrochloric acid being, it is said, only slightly over 0·1 per cent. instead of 0·2 per cent. This diminution is, of course, very much less than in the malignant cases, but it shows that there is a tendency to diminution of acid-secreting power in the cells with advancing age, and hence suggests that in carcinomatous cases there may be an abnormal diminution in this power of the cells to secrete acid.

Accordingly an investigation of the histology of the gastric mucous membrane is suggested in cases of malignant disease, especially where the growth has not invaded the stomach. Such investigation would have to be done most carefully, because long continued perversion of function might lead to atrophy as a secondary and not a primary effect. Also *post-mortem* work alone might easily lead to wrong results, because the gastric cells must share in the general wasting due to the growth. The experiments indicated might hence best be taken up in the case of animals suffering from malignant disease.

(*b*) The diminished acid secretion may arise from changes in the circulating medium, which do not cause atrophy of the cells, but which alter the activities of the cell so that it can no longer form acid; or the materials for the formation of the acid may be lacking in the material supplied to the cell.

First, toxic substances may be formed at the seat of growth which circulate to the oxyntic cell and pervert its functions, alter its permeabilities for different ions, or in some manner destroy its normal power of secreting the acid. In this case if the growth were early removed, before the oxyntic cells had been long thrown out of normal action, then one would expect a return to the normal condition of affairs. Accordingly, we here require systematic and careful investigation of the effects of early removal of the growth upon the acid secretion

Secondly, the action may not be a toxic one in the above sense, but may be

due to the absence or marked diminution of the sources from which the cell prepares the acid in the plasma supplied to it.

In such a case there would not be a rebound towards normal acidity on removal of the growth, the sub-acidity would remain, and also the condition of which it is the reflex would remain in the blood, and favour a reappearance of new growth wherever in the body there was a tendency for the cells to take on the abnormal type of reproduction. Let us consider briefly the conditions under which the cell forms free hydrochloric acid from the blood plasma, apart from theories of an older date as to particular salts between which hypothetical reactions were regarded as taking place.

The end result of the normal secretory activity of the oxyntic cell is the production from the blood plasma of an acid solution containing 0·2 to 0·3 per cent. of free hydrochloric acid. That is to say, a solution has been produced containing hydrogen and chlorine ions in a certain concentration. Now the plasma already contains chlorine ions in higher concentration than is necessary to yield the concentration present in the gastric juice, but the concentration of the hydrogen ions has to be largely increased in the process of secretion, and hence it is evidently upon the concentration of the hydrogen ions in the plasma that the work and speed of separation of hydrochloric acid in the gastric secretion must depend.

Whatever view or theory may be taken of the process; whether the secretion of acid be ascribed to a greater permeability of the oxyntic cell for the hydrogen ion, or a selective absorption for that ion, or an intermediate organic compound be supposed to be formed, or a double decomposition between acid phosphates of alkalies and calcium, or whatever be the supposed process; it is clear that the rate of production of acids, other things being equal, must depend on the concentration of the hydrogen ions in the plasma. A drop from any cause of hydrogen ions in the plasma must mean a corresponding fall in rate of production of acid.

Now blood plasma is a fluid which is, at the same time, alkaline and acid; it contains hydrogen ions and hydroxyl ions, and accordingly affects indicators in different directions (see p. 149). The reaction to phenol-phthalëin shows clearly the presence of hydrogen ions, and the work of the oxyntic cell is to increase the concentration of these ions in the process of secretion.

The concentration of hydrogen ions in the blood plasma is excessively low, so low that it cannot be estimated by such a method as the methyl-acetate inversion method. An attempt has been made by Höber* by the concentration

* Pflüger's 'Arch. f. d. ges. Physiol.,' vol. 81, 1900, p. 535, and 'Physikalische Chemie der Zelle und der Gewebe,' Leipzig, Engelmann, 1902, p. 240.

cell method, but the results are so low as to cause one to doubt the accuracy of the method as a quantitative one, although it shows that the amount of effective alkalinity or acidity of the plasma is very low indeed.

It is accordingly difficult, without some new method of attack, to investigate the effective acidity of the blood, and it is probable that in the end some physiological method alone, some application, for example, of the effect of minute quantities of acid or alkali upon the rate of growth or activities of living cells, will furnish a delicate enough test for such measurements of reaction as are here required.

It is scarcely necessary to repeat after what has been said under the heading of the methyl-acetate method, that we cannot arrive at the degree of acidity or alkalinity of the blood by simple titration in presence of an indicator. But such determinations ought to be made for the purpose of giving some orientation as to the amounts and relative quantities of the acid and alkali producing salts, the carbonates and phosphates, present in the plasma. A series of such determinations is at present being carried out.

We are hence at present without a method delicate enough to show us how the concentration of the hydrogen ions is varying in the blood plasma in health, or in conditions such as malignant disease, but if we suppose that the failure or reduction in quantity of the acid, is an indication *through the mechanism of the oxyntic cell,* that the concentration of the hydrogen ions in the blood of carcinomatous patients is decreased, and the concentration of the hydroxyl ions increased, then we have indications, from analogy with the changes which occur in other growing cells under like conditions, that such a change would probably give rise to increased cell growth and division.

Thus, Loeb* has shown that addition of 1 c.c. of deci-normal caustic soda solution to 100 c.c. of sea water, that is an addition of only 0·04 gramme per litre, increased the development and growth of the eggs of the sea urchin at such a rate that one could scarcely believe that the two sets of eggs belonged to the same culture. It is only a trace of additional alkali which causes the ncreased growth, more than a trace stops it entirely.

Now, given a potential tendency to atypical cell growth and mitosis, to reversion to the sexual type of cell-reproduction, it is possible that an increased concentration of hydroxyl ions and diminished concentration of hydrogen ions, would form just the necessary chemical stimulus to start a new growth and determine its continuance and exuberance when started.

It might be urged that the testing of such a view was exceedingly simple,

* 'Archiv f. Entwickelungsmechanik,' vol. 7, 1898, p. 631. Quoted from Höber 'Physikalische Chemie d. Zelle u. Gewebe,' p. 235.

merely by the administration of acid, so as to give hydrogen ions to the blood plasma; but the matter is not so simple as it at first sight appears. It certainly is indicated that some attempt should be made to modify the reaction of the blood plasma, and if possible, restore the acid-secreting function of the oxyntic cells, and we are at present making attempts in this direction.

But to keep permanently altered, even by continued therapeutic action, the reaction of the blood plasma is by no means easy of attainment. The reaction of the blood is determined by the agency of the liver and kidney cells, and if these have become set at a definite wrong level of action, all the regulating mechanism of the body is then at work against change of the reaction by therapeutic means. When acid is administered, urea is taken and broken up in the body, and ammonia obtained, which is used to neutralise the administered acid.

Hence, it is only with large and continued doses of acid, and on approaching the limits of acid intoxication, that any diminution in alkalinity can be hoped for, and as soon as acid administration is slackened, the acid is neutralised by more ammonia obtained from oxidised proteid.

Thus, even admitting that the diminished acid secretion is due to diminished concentration of hydrogen ions in the blood plasma, we are still face to face with the problem of how to maintain that hydrogen ion concentration in the blood plasma permanently at a higher level, against the competition of the kidney and other cells in the body which are all the time tending to reduce it to its old vicious level.