standing while much of that of the right column of Goll was of recent date. Serial sections were made of the medulla and the recently degenerated fibres in the right column of Goll could be traced upwards to the right nucleus gracilis where they could be seen to end. Sections of the upper part of the medulla, of the pons, and through the region of the corpora quadrigemina were made and stained by Weigert's method and by Marchi's method. Nothing abnormal was detected. Sections of the posterior roots were made below and above the twelfth thoracic segment. No difference could be observed between the two sides. As to the posterior root ganglia, these were stained by Nissl's methylene blue method. No evidence of gross changes in the nerve cells were observed.

Harley-street, W.

HYDROCHLORIC ACID IN THE GASTRIC CONTENTS IN CANCER:

A REPLY TO PROFESSOR B. MOORE.

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In a paper entitled, "Variations in the Free Hydrochloric Acid of the Gastric Contents in Cancer and the so-called 'Physiologically Active' Hydrochloric Acid,"¹ Professor B. Moore criticises a paper recently published by us² in which we had occasion to comment on some previous work by himself and certain of his colleagues. We had hoped that our comments were sufficiently intelligible to obviate the necessity for further explanation, but Professor Moore is evidently of a different opinion and has published a lengthy "criticism" in answer to our remarks.

In the first place we feel it incumbent upon us to point out that Professor Moore misquotes the title of our paper more than once in his criticisms and so, doubtless unintentionally, conveys to his readers an entirely erroneous impression as to its scope. Our paper was entitled, "A Study of the Variation in the Secretion of Hydrochloric Acid in the Gastric Contents of Mice and Rats as Compared with the Human Subject in Cancer," *not*, as Professor Moore puts it, "On the Acidity of the Gastric Contents of Mice and Rats with Transplanted Tumours and also of a Number of Cases in Man." The difference is vital, for although as a matter of fact in all our experiments we made determinations of the total acidity we did not profess to regard that series of estimations as of any great importance, but merely as having a subsidiary interest in connexion with the entirely independent determinations of physiologically active hydrochloric acid (and incidentally of free hydrochloric acid) which constituted the main object of our research.

Professor Moore next quotes a statement of ours to the effect that the *conclusions* at which we have arrived contradict or materially modify those arrived at by himself and others, and adds as a criticism of this statement that he desires no better confirmation of his *results* than is given in our table when using his methods "which are those established by many previous observers." Here again he conveys a somewhat erroneous impression, for although our conclusions, in certain respects, greatly differ from those of Professor Moore we have nowhere disputed his results, nor his well-known ability as a chemist, nor the accuracy of the methyl-acetate process as employed by him for estimating the free hydrochloric acid in the gastric contents. But inasmuch as in his first paper³ he finds as an average in 12 cases of cancer 0.0039 per cent. of free hydrochloric acid in the gastric contents, while in his second paper⁴ he finds as an average of 13 cases of cancer 0.0515 per cent., or nearly 13 times as much, and in the same paper demonstrates an average of 0.063 per cent. in 20

non-malignant cases, we pointed out as an obvious inference that no stress can be laid on, nor deduction of any kind be drawn from, such widely divergent results. This conclusion, moreover, applies equally to the work of Dr. A. S. Morton Palmer⁵ who finds, as an average of 14 cases, 0.0217 per cent. of free hydrochloric acid and to our own average of 0.0407 per cent. in 13 cases of cancer, although attention may be called to the fact that our average agrees fairly well with that recorded in Professor Moore's second paper.

As an explanation of the causes of these differences in the amounts of free hydrochloric acid found in the gastric contents the simplest appears to be, as we suggested, either dilution of the test meals with water during withdrawal or the varying intervals (from an hour to two hours) at which the test meals were withdrawn; but Professor Moore indignantly repudiates the first suggestion and disputes the second, notwithstanding his own statements as to variation in time of withdrawal. He is even inclined to be sarcastic at our expense and refers in his criticism to "the enormous difficulty experienced by Copeman and Hake" in the withdrawal of the test meals. This is not quite fair comment on his part, for in our paper (p. 456) we discuss this matter at length and show that we relied on experts at the Middlesex and Westminster Hospitals and at the Cancer Hospital, Brompton, as regards administration and withdrawal of the test meals, and we point out that it was owing to the remarkable variation of results in the estimations of both free and physiologically active hydrochloric acid that we made special inquiries and found that water had been added in certain cases owing to the difficulty experienced by the experts themselves. We further point out that only by great insistence and by special arrangement with Mr. C. H. Leaf and his house surgeon (Mr. Allan) at the Cancer Hospital were we able to obtain undiluted test meals, and we actually quote Mr. Allan, who informed us that "where test meals had been given, two out of three cases had to be abandoned owing to the impossibility of inducing the withdrawal of the fluid from the stomach of the patient." Moreover, Dr. Morton Palmer himself calls particular attention to the importance of avoiding the use of water in the withdrawal. We are of opinion that not a few interesting instances of absence or marked diminution of free hydrochloric acid in the gastric contents, recently so frequently recorded, may not improbably owe their origin to a neglect of this vital rule, so strongly insisted on by Ewald, who originally suggested this aid to diagnosis.

In the face of the wide divergences in the percentage of "free" hydrochloric acid in the gastric contents found by Professor Moore and others, above quoted, and for other reasons specially discussed in our paper, it seemed to us more logical to estimate what has been termed the "physiologically active" hydrochloric acid, and we are of opinion that Lüttke in the first instance, and Dr. W. H. Willcox later, have made out an incontrovertible case for this procedure. Both of these workers regarded the estimation of free hydrochloric acid as involving a distinct fallacy and it is therefore somewhat surprising to find Professor Moore quoting Dr. Willcox's paper⁶ in support of his own views, since in this particular paper Dr. Willcox is at great pains to expose the fallacy above alluded to, and we have referred to the point in our paper. Moreover, Dr. Willcox has not altered his views, since in a paper published in THE LANCET⁷ in 1908 he says:—

As I have pointed out, it is absurd to draw a deduction between free HCl and HCl combined with proteid; therefore the presence or absence of free HCl is of no value as evidence. The important question is, "What is the amount of active HCl present?"

Here it is obvious, in fact, that Professor Moore and ourselves join issue, for in his criticism of our paper he calls "physiologically active" hydrochloric acid "a misnomer" and considers that the method "shows something quite different from hydrochloric acid in any active form." We think that it is neither necessary to repeat the lengthy arguments already put forward by us in support of our view of the question, nor does it serve any useful purpose, inasmuch as Professor Moore refuses to recognise the value of the estimations in the face of reliable scientific authority. To emphasise the apparent uselessness of pursuing the argument Professor

¹ Bio-chemical Journal, vol. iii., No. 10, 1908.

² Proceedings of the Royal Society, B. vol. lxxx., 1908. A preliminary note on our investigations appeared in THE LANCET of Nov. 10th, 1906, p. 1276.

³ Proceedings of the Royal Society, March, 1905.

⁴ Bio-chemical Journal, May, 1906.

⁵ Guy's Hospital Reports, 1906.

⁶ THE LANCET, June 10th, 1905, p. 1566.

⁷ THE LANCET, July 25th, 1908, p. 221.

Moore even goes so far as to designate our physiologically active hydrochloric acid estimations as "peculiarly absurd," and takes up what seems to us an even more untenable position in saying, "nor does it matter that the acid so combined may previously have been free."

There are some other minor details of our paper which are discussed at some length by Professor Moore to which we must briefly reply. Thus Professor Moore makes a great point of the fact that in several of the test meals from cancer cases quoted by us, the total acidity to phenol-phthalein was less than the physiologically active hydrochloric acid determined by the Volhard process. As a matter of fact the differences are not so great as he would imply. Our average total acidity for 13 cases of cancer is 0.1636 per cent., while the average physiologically active hydrochloric acid is 0.1626 per cent. There is here no question of a base firmly attached to chlorine, as Professor Moore suggests, the explanation being sufficiently simple—viz., that whereas the physiologically active hydrochloric acid determinations are absolute from the point of view of chemical accuracy, the determination of total acidity to phenol-phthalein is admittedly approximate. We arrested the titrations at the point at which the first pink tinge showed itself. Another drop or two of the soda solution, causing a stronger colour reaction, would have brought these two determinations into line, for as a matter of fact the majority of the differences

are represented by 0.2 cubic centimetre $\frac{N}{10}$ soda or 0.02 cubic centimetre normal soda solution. As previously stated, we have never laid any stress on these total acidity determinations, and the physiologically active hydrochloric acid determinations are quite independent of them and entirely reliable. The rather larger differences in our case of cancer of the bile-duct and in the normal case cannot so easily be accounted for, but the facts remain; and, moreover, it is evident that the same condition obtains in both of these cases, although the one is malignant and the other normal. We have no doubt that, even assuming the presence of hydrochloric acid neutralised by organic bases, the acid combined with these must at some previous moment have been free, hence to say that such combined hydrochloric acid is "as inactive as chloride of sodium" is not accurate in any sense.

As regards our Günsburg results (which, by the way, agree fairly well with those of our methyl-acetate determinations), Professor Moore argues that inasmuch as the free hydrochloric acid (Günsburg) is greater in the normal case, this is a further confirmation of his original conclusions. Up to a point this may appear to be the case, but it is a begging of the question, since, as already demonstrated by others as well as by Professor Moore himself, the "free" hydrochloric acid, whether in the normal stomach or in malignant or non-malignant disease, is a constantly varying quantity, but the physiologically active hydrochloric acid represents the total hydrochloric acid present in the stomach at and during the time of digestion. The same argument obviously applies to the methyl-acetate determinations.

With regard to the Möner-Sjöqvist estimations of free and organically combined hydrochloric acid, we cannot agree with Professor Moore that this method is better than the Volhard process used for the same estimations. We have shown conclusively⁸ that in the Volhard method there is no danger of loss of sodium chloride on charring, and this is further confirmed by Willcox. Our Möner-Sjöqvist determinations usually agreed fairly closely with the Volhard determinations, but in some instances they were much less. The loss in certain cases we explained as due to the condition of the test meal, the presence of mucus-like material preventing the complete contact of the barium carbonate, and hence a loss of hydrochloric acid occurred on evaporation. For this reason alone, indeed, the Möner-Sjöqvist method must be considered as inferior to the Volhard method, in which the chlorine is precipitated as the insoluble silver chloride in the presence of nitric acid in the cold, hence avoiding the possibility of loss.

Finally, we may note that Professor Moore states that he and his co-workers did not claim any diagnostic value for their results, but on p. 156 of their original paper⁹ this diagnostic value is certainly implied, and Professor Moore must himself be aware that this was the general impression conveyed, since soon after the publication of the paper it

became, for a time, at any rate, a rather generally utilised routine method among a large number of medical men to estimate the free hydrochloric acid in gastric contents, more especially by the Günsburg reaction, with a view to the possible diagnosis of cancer. Not only has Professor Moore's work been appraised as of diagnostic value in cancer in man, but it has also led to the therapeutic administration of hydrochloric acid in this disease, and a whole edifice of hypotheses on the cause and nature of cancer has been built upon it. It was only in his second paper¹⁰ that he does distinctly state that the "presence or absence of free hydrochloric acid cannot be regarded as a diagnostic sign of any great value." This statement was obviously necessary in the face of his subsequent results in the further estimations in malignant and non-malignant cases to which we have referred above.

Indeed, notwithstanding this disclaimer Professor Moore still appears to attach a certain amount of diagnostic value to the determination of free hydrochloric acid, for in the paper now under discussion¹¹ he finally summarises his conclusions as follows: "The depression (of free hydrochloric acid) is particularly well-marked in cases of cancer." And again: "It is at present indeterminate whether the greater drop in cancer cases is due to the greater degree of cachexia and general ill-health in such cases or whether it is due to something specific in cancer;" although in his concluding paragraph he states that as there are exceptions to the rule of depression, and because it may occur in other conditions than cancer, its absence or diminution "cannot be taken as a diagnostic sign of any great value." What exact deductions are to be drawn from such mutually destructive statements we, at least, are unable to say. But since in physiological as in all scientific work clearness of conception is of the highest importance we prefer to abide by our original standpoint—viz., that whatever the diagnostic signs of malignant disease may be, they are not to be found either in an absence or marked diminution of "free" or even of physiologically active hydrochloric acid in the gastric contents. On the contrary, the determinations of physiologically active hydrochloric acid made by us would seem to convey the interesting interpretation that in mice and rats with "transplanted" or with spontaneous tumours this constituent is not only not diminished, but is, for the most part, present in slight excess above the normal. In human beings suffering from cancer it seems quite probable that a similar condition obtains in some cases, and that the physiologically active hydrochloric acid is not materially diminished in a large number of others.

It seems, indeed, somewhat hopeless to continue this discussion in view of the fact that in addition to his rejection of physiologically active hydrochloric acid as an entity, and his strongly expressed objections to our methods (for all of which we have ample authority), Professor Moore even disputes the fact that the mice experimented on were "cancer" mice, and also the statement enunciated by the Imperial Cancer Research Fund, based on an extensive series of statistics, that cachexia is by no means a necessarily constant accompaniment of malignant disease. These are matters entirely outside the province of a purely chemical discussion. That mice, in common with all mammals, suffer from cancer is now the reasoned conclusion not only of workers in this country but also of pathological authorities abroad. The attendance of Professor Moore, either at the recent meetings of the Pathological Society of Great Britain and Ireland, or the German Pathological Society, or the Pathological Section of the Royal Society of Medicine, would, we think, have convinced him how little weight can attach to his *ex cathedra* statements on the subject. At the same time he would have learned how great is the importance which pathologists attach to the experimental study of cancer in mice and rats, and also that the results obtained thereby, whether through investigating the digestive processes or otherwise, are now recognised as having important bearings upon the study of cancer in man. In our opinion it is not improbable that the more exact chemical investigations which can be made on animals bearing experimental cancer will lead to results of greater permanency than can be obtained in the presence of the many uncontrollable factors inseparable from similar investigations in man.

⁸ See note, p. 446, in our Royal Society paper.

⁹ Proceedings of the Royal Society, March, 1905.

¹⁰ Bio-chemical Journal, May, 1906.

¹¹ Bio-chemical Journal, vol. iii., No. 10, 1908.