THE TREATMENT OF CARCINOMA BY LEAD COLLOIDS.

BY

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As it has been my experience, and that of many who have been using the later preparations of colloidal lead prepared by the British Colloids Company and others, that considerable reaction has been met with after injection, Mr. Patterson has asked me to state the results obtained with the colloidal iodine preparation¹ with which he has been supplying me for nearly two years. Mr. Patterson has had considerable experience in the preparation of lead colloids with the Liverpool centre.

This preparation has been used by me in some sixty odd cases of malignant disease in St. Mary's Hospital, Mount Vernon Hospital, and also in private. Beyond the first batch of about half a dozen cases none have had any reaction whatsoever, and the reaction in the first cases, we thought, was probably due to some contamination of the preparation, as it had been opened and examined previous to use. Reaction never again followed the use of the colloidal iodine.

The preparation contains 0.2 per cent. of lead in the form of lead iodide. It is intended for intravenous injection, and so it is made isotonic by means of glucose, for sodium chloride would be unsuitable in the presence of lead. It contains, further, a trace of thyroid extract; the exact amount cannot be given, for the dried extract contains a varying proportion of inert matter, but it may be definitely stated to be less than 0.02 per cent. A trace of cresol is added, to act as a preservative, since glucose is present. The addition of the trace of cresol is not regarded as making the preparation sterile; it is sterile, and the cresol is added purely as a precautionary measure.

The usual course is four doses, given at four to five days' interval, with the precautionary tests for the urine, blood, and the liver efficiency, which are insisted upon by the Liverpool centre. I have given three courses at intervals to some patients, and in one I gave ten doses at weekly intervals.

This method of treatment cannot, and does not, attempt to replace operation. It is important that the growth should be removed as widely as possible, and the injections then given in the hope that they will attack any small foci which may have started in the internal organs.

The method may be used with advantage, and the results are best seen, in inoperable cases. There is every hope that, though a cure may not be brought about, the rapidity of the growth may be lessened, and at the same time it gives the patient the feeling that something is being attempted. Too many cases are brought which are past all hopes of being benefited in the smallest degree. In early cases, where operations and other procedures, such as radium and x rays, are used, the results can hardly be attributed to one agent or to one procedure, and therefore definite scientific data are very difficult to obtain.

It is too early, of course, to attempt to publish results obtained from the injection of lead, but there is no doubt that lead colloids give satisfactory results sufficiently frequently to justify hope that the growth may be retarded or may even disappear. At the same time, the limitations of this form of treatment must be realized. It is a most unsuitable form of treatment to give when the walls of a hollow viscus have been extensively invaded by the growth, because destruction of the growth means destruction of the wall of the viscus, and rapid death must follow. In certain cases, as in oesophageal strictures where a gastrostomy has been performed for cicatricial contraction of the oesophagus, this contraction has been greatly increased and the growth of a tumour brought to a standstill, so that the word "cure" may almost be used, but cure will not mean the restoration of the natural passages.

In passing, I might say that in one of my oesophageal

cases the large, hard mass of secondary glands in the neck disappeared. A second case was lost through destruction of the growth. Two large secondary masses of breast carcinoma, which had recurred on the chest wall, completely broke down during the course of injections; unfortunately, one of the masses had penetrated the chest wall, and the breaking down set up septic pneumonia in the lung to which it was adherent, and the patient died. In yet another case of breast carcinoma, where the breast had been removed and a course of treatment given, internal secondary growths broke down, and the patient died through haemorrhage, because one of the growths had invaded the wall of the splenic artery. It may some day be possible to obviate these accidents.

Growths of the solid variety or in the solid viscera, or in situations which are not vital, may be dealt with fearlessly. Patients suffering from kidney disease with albumin in the urine, or showing the extremes of anaemia, are hardly subjects for such treatment.

In conclusion, I have to thank Mr. Patterson for kindly letting me make use of his preparation in the above cases. I gladly accede to his wish that I should state the harmlessness and absence of reaction of the preparation. I have used material from one single batch for more than a year, which proves that the preparation may be considered perfectly stable.

THE COMPARATIVE VALUE OF THE "AMMONIA-COEFFICIENT" AND THE RATIO BETWEEN FREE AND AMMONIA-COMBINED ACID IN URINE.

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THE object of this communication is to consider the comparative value of two quantities which are used in the examination of urine, both of which give a valuable indication of physiological activities. The comparison was instituted with a view to determining which of these two values has the better practical diagnostic possibilities. Both quantities are ratios, and the mechanism involved in the case of one of these was outlined by us at the provincial meeting of the Children's Section of the Royal Society of Medicine held in Bristol in June, 1923,¹ and dealt with more fully subsequently.²

The first of these ratios is obtained by titrating 25 c.cm. of urine with decinormal sodium hydroxide solution, using as indicator phenolphthalein; this gives the free acid value; then to the same solution neutral formaldehyde solution is added (Folin's method), when a further titration with alkali gives the ammonia-combined acid, or ammonia.

The ratio, which we will designate R_A , is obtained by dividing the second titration by the first, and represents the ratio of ammonia to free acid present in the urine. The second ratio involves the same titrations, but in addition the nitrogen is determined by the usual hypobromite method; a ratio is obtained by comparing the nitrogen existing as ammonia with the total nitrogen from the hypobromite determination. This ratio we will call R_U . The two ratios are therefore:

$$R_A = \frac{\text{Ammonia}}{\text{Acid.}}$$

$$R_U = \frac{\text{Nitrogen as ammonia}}{\text{Total nitrogen (hypobromite).}}$$

As a practical point it will be seen that R_U requires a third determination which is by no means as accurate or simple as the ordinary titrations needed for R_A . (R_U closely corresponds with what is generally termed the "ammonia coefficient.")

The employment of ratios is of considerable importance, since the wide variations in concentrations of urine would stultify results considered singly because the quantity of

¹ The commercial manufacture of the preparation has been undertaken, under the personal supervision of Mr. Patterson, by the British Drug Houses, Ltd., Graham Street, London, N.1.

urine secreted over some period must be measured; by employing ratios valuable indications are given from examination of a single sample, especially if the specimen is selected by the method we have indicated.²

Considerable variation in concentration of urine may even affect these ratios, and for this reason results obtained from very dilute urines are not considered. This variation is a matter with which we hope to deal in a further communication.

The question might very reasonably be asked, Are these ratios merely empirical, or is there any physiological reason for their use? That is to say, have they a theoretical as well as a practical basis? For R_A there is such a basis of theory, as it indicates the effort that is being made to maintain the constant reaction of the blood, giving information of value in assessing its state and more particularly the amount of buffer salts present. The ammonia secreted may be compensatory, or in certain cases may arise from incomplete metabolism; with its source we are not immediately concerned.

With the ratio R_U there appears to be no blood mechanism which relates ammonia to urea; the urea in blood may normally vary within wide limits, and R_U may or may not be a purely fortuitous ratio depending upon the source of the excess of ammonia. The value of the ratio may really be in the numerator which happens arithmetically to be little disturbed by usual variations in the denominator.

It is interesting to note that Palmer and Henderson make use of an inverted form of R_A , but attach no special significance to it, though they find it a convenience in their pathological studies.³

Opinions differ as to the normal value for R_U ; Wells⁴ gives the proportion of nitrogen in urine in the form of ammonia as from 2 to 5 per cent., which in diabetic acidosis may rise to 10 to 25 per cent. Todd⁵ states that normally about thirty times more nitrogen is excreted as urea than ammonia, and when the ratio of urea to the ammonia nitrogen is as 10 to 1 or more, we are justified in saying that acidosis is present, but figures between 10 to 1 and 20 to 1 point to defect of the liver. Burgess⁶ gives an average value in a series of normal children of 7.04. The figures we have obtained are more in agreement with those of Burgess. There would seem to be something unsatisfactory when a ratio which is given normally in the neighbourhood of 4 (Wells and Todd) has to increase to as much as 10 before it has indicative value.

The normal value of R_A ranges up to 1.5; a value exceeding this for an early morning specimen, having a first or acid titration greater than 5 c.cm., indicates some derangement. This is in agreement with the values given by Palmer and Henderson,³ where the quantities are comparable.

To summarize briefly: Of the two ratios R_A is more accurately and readily determined, and it is definitely connected with a well established mechanism. R_U , including as it does the same numerator as R_A , must in a measure give similar indications, but is affected by a denominator which does not appear to have any definite connexion with the numerator such as is found in R_A .

Experimental.

Some fifty samples of early morning urine, presumably normal, gave the following values:

	Average.	Minimum.	Maximum.
R_A ...	1.02	0.6	1.5
R_U ...	6.6	3.4	9.0

so that in normal urines the two ratios run along fairly parallel lines. More interesting are the results of a similar comparison in cases not normal.

Case 1.—A case of cyclic vomiting in a little girl which we were fortunately able to observe also during normal health.

In normal health:

R_A ...	1.08	1.0	1.05	1.50	1.07	1.23	1.13	0.87	1.11
R_U ...	8.2	7.1	7.8	6.1	5.9	6.7	6.6	6.5	6.8

During attack and recovery:

R_A ...	4.47	4.09	1.56	0.84	1.35	1.34
R_U ...	8.9	10.4	8.0	6.4	8.7	9.3

It will be seen that whereas R_A indicates clearly a considerable derangement, R_U gives no very definite information.

Case 2.—A case of simple acetonuric vomiting. We were able to observe this patient also during normal health.

In normal health:

R_A ...	1.23	0.87	1.01	1.22	1.20	0.96
R_U ...	7.3	6.7	7.0	4.9	3.8	7.3

During attack and recovery:

R_A ...	2.10	1.75	1.88	2.0	1.21	1.40
R_U ...	9.9	9.8	4.6	5.9	7.6	8.1

Case 3.—A case similar to 2; the ratios were recorded during attack and recovery:

R_A ...	2.49	4.25	2.57	1.55
R_U ...	10.7	11.3	5.35	5.35

Case 4.—This was a case of diabetes, the patient being an adult male.

R_A ...	2.07	1.82	2.60	3.60
R_U ...	14.8	5.9	15.4	13.0

Here the ratio R_A is uniformly consistent with a marked derangement of function, but R_U fails to indicate this in one case.

Case 5.—A case of catarrhal jaundice in small girl.

R_A ...	2.13	3.36	3.25
R_U ...	15.2	17.3	14.6

Case 6.—A case of catarrhal jaundice in a girl aged 10 years.

R_A ...	1.62	2.0	2.0
R_U ...	4.4	7.1	7.5

A few cases in health and when unwell where a series of specimens of urine were not available:

	Ill.	Well.	Ill.	Well.	Ill.
R_A ...	3.54	1.29	2.22	1.36	3.62
R_U ...	14.5	6.6	8.2	4.7	15.8

It will be seen from these tables that on some occasions both ratios give similar indications, but in certain instances when R_U fails to denote any derangement R_A shows distinct abnormality—that is, R_A appears to give more generally reliable information than does R_U . As the value of these ratios is affected by taking alkalis or acids, the above results were drawn from cases where the administration of drugs containing these substances was not immediately essential in the treatment.

There still remains a considerable volume of work to be carried out upon this and similar ratios, and it would seem highly probable that by careful comparison of values obtained from various ratios it might be possible, not only to discover a derangement in physiological mechanism, but also in a measure to locate it, and we are carrying out a further investigation on the subject.

Conclusion.

Two ratios have been compared, and of the two the first—namely, the ratio of ammonia to acid present in a specimen of urine—seems to give generally better information, and has the advantage of being much more readily and quickly determined.

REFERENCES.

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THE PERINEAL AND PELVIC FLOOR MUSCLES IN THE SECOND STAGE OF LABOUR.

BY

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THE care or management of the perineum consists in the use of means for the prevention and limitation of perineal rupture in labour. It applies to the later period of the second stage, the period of perineal distension. The teaching, express and implied, that during the pains of this period the perineal muscles are in a state of contraction seems opposed to some obvious phenomena of labour. This prompted a reference to a number of books on midwifery in order to discover if the teaching were common, and in hopes of learning the evidence on which it is based.

Sixteen textbooks and manuals of midwifery, published from 1899 to 1923, were consulted. Twelve do not mention