inoperable. Every method of examination and every means of diagnosis must be exhausted.

Soon after I began to be specially interested in cancer I made a necropsy upon a case that had been diagnosed and treated and allowed to die as inoperable cancer of the uterus. At the *post-mortem* examination I found the vagina greatly distended by a huge growth which was attached to the cervix uteri by the narrowest possible pedicle. If the patient had been examined under an anaesthetic the condition of affairs would have at once been obvious, and she could have been completely cured by the most simple operation.

Technique.

In connexion with the technique of these operations, there are several points of importance. First and foremost, it must be remembered that a radical operation is not being attempted, and that methods that would be adapted to a radical operation are quite out of place. In the case of the breast, for instance, there is no necessity for wide sacrifice of skin, no reason for extensive undermining of the flaps, and often no indication for removal of the pectoral muscles.

It suffices to remove the breast with all obvious growth as far as possible. The wound is then covered in with thick, healthy flaps, which will not be penetrated easily by any growth that may have been left behind in the chest wall. Difficulties with the flaps may, of course, arise when the growth is very large or when it is in an unusual position, but this is exceptional. In breast cases I lay great stress upon thickness of the flaps, as I am convinced it is a safeguard against efflorescence of the growth later in the disease.

The same rule holds good, where possible, in dealing with other sites. For instance, in amputating a leg for inoperable sarcoma of the tibia or lower end of the femur, the line of section should be just above the growth, not necessarily at the hip-joint, for obviously it would be absurd to perform such a serious and such a crippling operation as amputation at the hip-joint for a condition in which cure is absolutely out of the question. Again, in cancer of the tongue, a simple Whitehead operation—the mortality of which is very low—is all that is indicated in those cases where radical measures are not possible. I might multiply examples; but there is no object in doing so, so long as the main principle is remembered: that what one is aiming at is the removal of a maximum amount of disease with a minimum disturbance of healthy tissues.

In all these operations there are two dangers that must be carefully guarded against. One is septic infection of the wound, and the other infection of the wound with cancer cells. The danger of septic infection arises from the fact that ulceration is usually present. Organisms permeate not only the tissues of the growth itself, but are also present in the lymphatics draining the area. It therefore follows that even if infection from the surface be avoided, it may yet arise from the organisms in the deeper tissues. When the ulceration is of small extent the application of tincture of iodine, followed by a layer of collodion, will efficiently guard against any danger arising from this source. When the ulcer is more extensive it is perhaps wiser to go over the surface with the actual cautery immediately prior to the operation. In the later stages of the operation it is well, I think, to flush very thoroughly with warm saline solution, which mechanically removes any organisms lying in the wound. Antiseptics I never use for this purpose, because I believe that they do more harm than good by lowering the vitality of the tissues. The wound should be carefully dried before it is closed, and ample drainage should be provided for.

The danger of cancer infection is more difficult to guard against, for, as my senior colleague, Mr. Charles Ryall, has pointed out, cancer cells may easily be disseminated in a wound and give rise to little deposits of secondary growth, even in stitch holes or the openings for drainage tubes. Copious flushing of the wound and the avoidance of too much handling of the tissues are probably the best means we have of reducing this danger to a minimum.

The opening of the winter session at the Leeds School of Medicine on October 1st will be marked by the delivery of an address by Professor Sherrington, F.R.S., Holt Professor of Physiology at the University of Liverpool.

THE REACTION OF THE BLOOD SERUM AS AN AID TO THE DIAGNOSIS OF CANCER.

BY

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A PAPER published by Moore and Wilson⁶ in 1906 gives the results of their estimations of the alkalinity of the blood serum of cancer patients, as compared with that of healthy persons and of patients with other diseases.

The estimations determined the reactions (1) of the serum to phenolphthalein, (2) of the serum to dimethyl,* (3) of the inorganic salts of the serum to dimethyl. The phenolphthalein results were negative, but the dimethyl results indicated a definite increase in the alkalinity of the serum of cancer patients.

Moore and Wilson were led to this research by the hypothesis which Moore and his collaborators^{4,5} had suggested to explain results obtained in previous research on the amount of free HCl in the gastric juice of patients with cancer of any part of the body. They had found that the free HCl was as definitely reduced in cancer of other parts of the body as in cancer of the stomach,† and therefore concluded that the well-known reduction in this latter condition could not be due to local causes, but might, in common with the reduction in other cases be due to "a change in the concentration in hydrogen ions in the plasma and lymph."

It is at once evident that if a definite increase in the alkalinity of the serum can be detected in persons with cancer a valuable aid to diagnosis is secured, and the present paper represents an attempt to determine whether the reaction will lend itself to clinical work. West Watson¹² has published the results of a similar attempt, and his work certainly appears to justify the hope that diagnosis may be helped. I have, however, seen no further records of work on the subject. Moore and Wilson only touched incidentally on the possible clinical value of their work.

Moore and Wilson's second method—estimation of the reaction of the whole serum to dimethyl—appeared the most simple, and therefore, if applicable, the most desirable; the third method—estimation of the reaction of the inorganic salts of the serum—involves processes of evaporation and incineration, and is therefore, *ceteris paribus*, less well adapted to clinical purposes. It still remained, however, if the selected method proved inapplicable, and it must be mentioned that Moore and Wilson had themselves noted it as, perhaps, the more accurate.

It must be remembered that physical methods are at present of little value in determining the comparative reactions of complex physiological fluids such as the serums of different persons; serum is neither measurably alkaline nor measurably acid to such methods. Methods of colour titration, at the same time, have two noticeable drawbacks: (1) The estimations are purely comparative, and no attempt can be made to determine absolute values. The turning points of the different indicators have very different relations to true neutrality, and they are even more widely separated with physiological fluids than with solutions containing free acid or alkali; blood serum is acid to phenolphthalein and alkaline to dimethyl. (2) The colour changes (with blood serum) are so gradual that it is impossible to determine any definite point of change in an ordinary titration; all that appears possible is to mix samples of serum with samples of acid or alkali of different strengths, and determine what strength of acid or alkali is needed to turn the indicator employed.

The results given in this paper make no attempt to show the absolute reactions of the given serums, but merely to show that some serums are *more alkaline* to dimethyl than others.

Technique.—Any improvement in technique is obviously of definite value; the method here described is based on that of Moore and Wilson, but contains several modifications which, I believe, increase its clinical value. I examined many cases by Moore and Wilson's method, but found definite results so difficult to obtain that I was driven to try and alter the technique.

* Dimethyl-amido-azo-benzene.

† This work has been criticized by several writers, notably by Copeman and Hake,¹ to whom Moore⁷ has replied. The latter's work has also been supported by Morton Palmer,² and others.

Collection of Blood.—The veins of the forearm are engorged, a suitable vein is chosen, and the overlying skin purified; the vein is then punctured with the needle of an antitoxin syringe, and the issuing blood collected in a small test tube of capacity about 3 c.cm. The tube is rather more than half filled and the mouth closed with a plug of cotton-wool.* It is then left in a vertical position for twenty-four hours, and afterwards centrifugalized to obtain clear serum. To avoid excessive evaporation the tubes are left in well-fitting tin boxes in a cupboard; this has been found quite sufficient, but it might be well to use close-fitting rubber stoppers.

Preparation of Acid Solutions.—A series of dilutions of normal sulphuric acid is prepared and kept in well-stoppered bottles; the dilutions run in series as follows: $\frac{N}{4}$, $\frac{N}{4.5}$, $\frac{N}{5}$, etc., to $\frac{N}{7}$, and are thus seven in number. They must be tested from time to time against sodium carbonate of known strength, and should be found to remain constant for a considerable time. When required for use, a small quantity of acid is, after shaking, poured into a watch-glass or, preferably, a small glass staining dish.

Titration.—Two drops of a 1 per cent. alcoholic solution of dimethyl are dropped on a filter paper. A small quantity of distilled water is then drawn into a capillary pipette, a bubble of air allowed to follow, and, after this, serum drawn as far as a mark about 3 cm. up the pipette; a second bubble of air is then admitted, and, finally, the particular acid solution required is drawn up to the same mark. The pipette now contains equal quantities of serum and acid and a trace of distilled water. The contents are blown out on to a porcelain slab, thoroughly mixed by aspiration, and finally blown out on to the centre of the dimethyl drop. If no pink colour appears† in the centre of the yellow drop, the process is carried out with stronger acid solution till the pink change first occurs. If, on the other hand, pink appears at the first attempt, weaker acids are used until the change is no longer obtained. The dilution which gives the first pink reaction is taken as the index; if, for instance, pink appears with $\frac{N}{5}$ acid, but not with $\frac{N}{5.5}$, the alkalinity of the serum is reckoned as equivalent to $\frac{N}{5}$ or 0.200 N.

To prevent absorption of alkali from glass, all the glass materials used are subjected to immersion in strong HCl, are afterwards thoroughly washed in distilled water, and finally dried in an oven at 110° C.

Diagram of pipette.

readings even more difficult than I had expected, and after many attempts I concluded the reactions were not sufficiently definite to justify their use in clinical work.

I therefore tried the filter paper method, using solutions

* To avoid the influence of the alkaline tides of digestion I made all my collections between the hours of 11.30 and 12.15 in the morning, the last meal having been finished about 9 o'clock.
† In order that the time relations of the various titrations may be the same, the immediate colour effect is alone considered.

of dimethyl of strengths varying from 0.001 per cent. to 2 per cent., and I finally used the strength of 1 per cent. It is clear that the use of so much indicator violates the laws of good titration, and that nothing but results can justify it. It must be borne in mind that in the present instance the results aimed at are purely comparative, and that nothing in the way of absolute determination of reaction is desired; that the 1 per cent. solution was only adopted after proper trials of other strengths (and, I may add, of other indicators); and that for present purposes a working clinical method is the main object of consideration. With these facts remembered, I believe that the results obtained by the 1 per cent. solution will justify its use, for a clear reading can nearly always be obtained.

The pipette figured in the diagram deserves a short mention; the improvements are of minor importance, but I believe that they conduce to accuracy. The diagram explains itself, and it is only necessary to say that the rubber membrane must be fairly stout; a fresh capillary tube can be slipped into the washer for each series of titrations, and a small loop of black thread affords a clearer mark than the traditional blue chalk. With this pipette the most inexpert person can control his solutions with complete ease and accuracy.

The following tables give the results so far obtained:

It will be seen that the average alkalinity of the cancer series is 0.190N, and is, therefore, appreciably higher than that of the non-malignant—that is, 0.173N. Averages, however, are of little value in attempts to diagnose individual cases.

It appears that a reading of 0.200N or over affords some presumption of the presence of cancer; and it is, in my opinion, sufficient to justify an exploratory operation in doubtful cases. It must be particularly noted that the high reading is most likely to be obtained in early cases

TABLE I.—Reaction of Blood Serum in 24 Cases of Cancer.

No.	Sex.	Age.	Diagnosis.	Alkalinity to Dimethyl.	Remarks.
1	M.	59	Cancer of axilla	0.200N	Recurrent.
2	M.	65	Cancer of larynx	0.222N	No microscope.
3	F.	50	Cancer of breast	0.200N	—
4	F.	50	Cancer of breast	0.182N	—
5	F.	43	Cancer of breast	0.200N	—
6	F.	67	Cancer of uterus (cervix)	0.200N	—
7	F.	56	Cancer of breast	0.200N	—
8	F.	30	Cancer of both breasts	0.182N	Very early.
9	F.	51	Cancer of uterus	0.182N	—
10	M.	46	Cancer of stomach	0.182N	Free HCl present in gastric juice.
11	M.	55	Cancer of jaw	0.200N	Spheroidal celled, undergoing colloid degeneration.
12	M.	67	Cancer of cervical glands	0.182N	Secondary to cancer of lip removed 12 months before.
13	F.	37	Cancer of uterus (body)	0.200N	—
14	F.	56	Cancer of stomach	0.200N	—
15	M.	70	Cancer of lip	0.200N	—
16	F.	48	Cancer of axillary glands	0.182N	Right breast 11 years previous; left breast 5 years previous. Sarcoma.
17	M.	46	Cancer of neck	0.182N	Anaemic.
18	F.	43	Cancer of left ovary	0.166N	Anaemic.
19	F.	47	Cancer of uterus (cervix)	0.200N	Very early.
20	F.	52	Cancer of breast (duct cancer)	0.166N	Anaemic.
21	M.	72	Cancer of lip	0.166N	Anaemic.
22	F.	48	Cancer of breast	0.166N	—
23	M.	48	Cancer of stomach	0.200N	No free HCl; no microscope.
24	M.	66	Cancer of rectum	0.182N	Colotomy; no microscope.

Average ... 0.190N

TABLE II.—Reaction of Blood Serum in 21 Non-Malignant Cases.

No.	Sex.	Age.	Diagnosis.	Alkalinity to Dimethyl.	Remarks.
1	M.	35	Healthy	0.165N	—
2	M.	31	Healthy	0.182N	—
3	M.	17	Varicocele	0.182N	—
4	M.	29	Varicocele	0.165N	6 days after operation, 0.156N.
5	M.	20	Varicose veins	0.182N	8 days after operation, 0.182N.
6	M.	20	Varicocele	0.165N	9 days after operation, 0.155N.
7	F.	50	Dyspepsia	0.165N	—
8	F.	47	Dyspepsia	0.182N	—
9	F.	48	Gall stones	0.182N	—
10	F.	63	Pernicious anaemia	0.166N	Haemoglobin, 25 per cent.
11	M.	50	Tuberculous hip	0.166N	—
12	M.	55	Gall stones	0.165N	—
13	M.	42	Varicose veins	0.182N	6 days after operation, 0.182N.
14	M.	27	Inguinal hernia	0.182N	—
15	F.	18	Diabetes	0.166N	Urine contains di-acetic acid and acetone.
16	F.	45	Phlebitis	0.166N	—
17	M.	40	Malaria and dysentery	0.153N	—
18	M.	36	Lipoma of back	0.182N	—
19	M.	33	Colitis	0.166N	—
20	M.	28	Appendicitis	0.182N	—
21	F.	32	Endometritis	0.181N	—

Average ... 0.173N

TABLE III.—Six Doubtful Cases.

No.	Sex.	Age.	Diagnosis.	Alkalinity to Dimethyl.	Remarks.
1	M.	52	? Cancer of oesophagus	0.182N	—
2	M.	48	? Cancer of stomach	0.200N	—
3	M.	55	Cancer of tongue and cervical glands, removed 18 months previously. No signs of recurrence	0.165N	—
4	F.	37	? Cancer of uterus	0.200N	—
5	M.	51	? Cancer of oesophagus	0.182N	—
6	M.	33	? Cancer of pancreas	0.182N	No free HCl in gastric juice

in which the general metabolism is not seriously disordered—that is to say, in precisely those cases in which the diagnosis is most likely to be obscure, and in which early operation is most likely to benefit the patient. The reaction is obviously of little value in the superficial cancers—as of the tongue and cervix uteri—when tissue can be obtained for microscopical examination. There still remains, however, the large group of deep cancers, notably of the breast, stomach, and body of the uterus.

The figures 0.200N or 0.222N appear twelve times out of twenty-four in the first table, but not once in the 21 cases of the second. It can scarcely be hoped that they will never appear in records of non-malignant cases; but I have not yet obtained them, except possibly in the two cases in the third table which give the figure 0.200N. It must be noted that the word "doubtful" signifies "still doubtful." Many of the other readings were obtained before the clinical diagnosis was certain.

The clinical evidence points to both of the two above-mentioned cases being malignant, but it would obviously be incorrect to consider them as such till the diagnosis is clear; their subsequent histories will be of some importance, and I regret that I cannot yet speak with certainty of them.

While the high figures afford some presumption of the presence of cancer, it is quite clear that low figures do

nothing whatever in the opposite direction; I believe that further work may bring a much larger proportion of cancer cases into line, but for the present any suggestion whatever of a negative diagnosis would be unjustifiable.

A careful study of Moore and Wilson's and West Watson's figures will show that they suggest similar deductions. West Watson makes a distinction between "advanced" and "inoperable" cases; such a distinction is very arbitrary and must be extremely difficult to draw, but I believe, nevertheless, that his point—that in advanced cases the increasing anaemia masks the altered reaction to dimethyl—is important. It is possible that a classification based on haemoglobin estimations may be useful; such a classification would still be very arbitrary, but it would at least be easily made.

I have purposely discussed my results very shortly, because it is clear that they are at present far too incomplete to justify definite conclusions. I hope later to have the opportunity to extend them. If the presence of a change in reaction of cancer serums to dimethyl or other indicators is confirmed, it opens up two very wide questions: (1) What is the chemical nature of the change? and (2) What is the cause—whether antecedent to, or produced by, the development of the cancer? It is impossible to do any work on the subject without considering these questions; but here, again, my views are at present too nebulous to merit quoting. For those interested in the subject it is necessary to read in full the extremely lucid and interesting papers of Professor Moore and his collaborators; suggestive facts will also be found in the writings of Grawitz,³ Mottram,⁸ and Royle.^{10, 11} The fullest bibliography that I know on the subject of estimation of the reaction of the blood on blood serum will be found in the article by Dr. Mercier Gamble² in the *Journal of Pathology* for 1906.

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SARCOMA OF THE UTERUS.

BY

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SARCOMA of the body of the uterus being a rare disease, the following notes may be of interest:

A married lady, aged 45, consulted me about excessive menstruation. She had been quite regular until about twelve months earlier, when the periods became irregular and there was an excessive loss of blood. There was no intermenstrual leucorrhoea. She appeared markedly anaemic, with a peculiar yellowish tinge, almost suggestive of pernicious anaemia. Although married for twenty years she had never been pregnant. There was no loss of flesh, and a thick layer of abdominal fat prevented detailed palpation.

Vaginal examination revealed an enlarged uterus, not, however, reaching above the pelvic brim, but feeling broader and harder than normal.

As the patient seemed so anaemic, and there were anaemic bruits over the mitral and pulmonary areas, and as she suffered agonizing pain every few weeks when semi-solid masses of maternal like blood clots were expelled from the uterus, hysterectomy was advised. I found that the temperature at night varied from 99° to 100° F. A diagnosis was made of sloughing fibroid, infecting the peritoneum and causing pain and rise of temperature.

Although the patient was in a poor state of health, removal of the uterus seemed her only chance, and she entered our nursing home, where, with the valuable help of my colleague, Dr. J. B. Hughes, I did a supravaginal amputation of the uterus. The operation proved difficult. The omentum was adherent to the fundus of the uterus and to the ovaries and Fallopian tubes.

Both tubes were inflamed and much enlarged. The uterus was about 4 in. long and 3 in. to 4 in. in width. It felt of stony hardness, and on its peritoneal surface were three hard masses as big as large peas. It extended well into the pelvic peritoneum on either side. After separating all adhesions, I first removed both tubes and ovaries, and then by strong traction on the fundus with a broad volsellum tied off the broad ligaments and uterine arteries and excised the supravaginal portion of the