THE PRESENT POSITION OF LEAD THERAPY IN MALIGNANT DISEASE.*

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INTRODUCTION.

At the outset it is advisable once more to express the conviction that by prevention only shall we stay the onward march of cancer. Elsewhere⁶ we have dealt with this aspect of the problem, and have indicated that success in this sphere can be accomplished only if we take into account the numerous sources of, and factors concerned in, the irritation of the human tissues that may result in the precancerous state. On the other hand, the alleviation and cure of cancer, once the disease has developed, appears not to be related to the etiology as such, but rather to the nature of the cancerous process to be arrested by all the remedial measures at our disposal. Until recently these measures have consisted almost entirely of surgical and radiological procedures, and no impression seems to have been made on the rate of increase in the mortality rate. Clearly, the mortality figures must have been reduced in direct proportion to the number of cases saved, but these have been too few in number to counterbalance the increased incidence rate of the disease, which appears in a great measure to be due to the prolongation of life in civilized communities.

In our opinion the saving of more patients stricken with the disease—often men and women in the heyday of their mental attainments and of their value to mankind—will ultimately come through chemotherapeutical or biochemotherapeutical methods. In regard to the latter, immunifacient and cytotoxic effects by means of specific biological substances were first attempted by us twenty years ago, and are still under consideration. The local treatment of malignant affections has almost, if not quite, reached standardization.

CHEMOTHERAPY IN CANCER.

Successful chemotherapy is particularly difficult even in connexion with the destruction of parasitic organisms that have gained entrance to the body, but in this direction great advances have been made during recent years. When, however, we attempt the elimination by synthetic products of certain cells developed from, and dependent on, ordinary somatic tissues—"organochemotherapy," as it is called—we are faced by many grave difficulties, and we shall probably be held up in our search for substances with a high organochemotherapeutical index until further investigations have been made concerning the functions of the reticulo-endothelial system, and in regard to the physicochemical conditions in which drugs exert their actions on living tissues. Research work along these lines is in its infancy, but nevertheless must be properly appreciated without delay.

The reasons why we adopted the metal lead as our primary constituent for the chemotherapeutical treatment of cancer have so often been stated that no further explanation is necessary.† A point of importance associated with our work is that the encouragement received from the use of crude products has been sufficient to urge us forward to seek improvements especially in the direction of organic complexes containing lead, and, in a general way, hope of ultimate success in the treatment of malignant disease by chemotherapeutical measures has been kindled in others. It is our earnest desire to foster this hope in order that many more labourers may enter this

promising field. Interest can best be promoted if we recall a few only of the encouraging developments we have witnessed during our work, and attempt to discover why we have been rewarded with a certain measure of success in the cases now described, some of which have been recorded on previous occasions.

COMBINED TREATMENT OF CANCER.

We have mentioned the utilization of all the remedial agents at our disposal in the treatment of cancer, and it is certain that no doctor, no one with humanitarian instincts, would do otherwise than place the safety and cure of his patients foremost in his mind. It will be seen, then, that not all of our patients have been treated by lead alone. Whenever practicable, we have felt it desirable to assist this treatment by the removal of as much of the growth as possible, the subsequent treatment with lead being commenced immediately. In many cases, too, we have utilized our knowledge of the augmented effect of α rays and radium acting in conjunction with lead, and of the fact that this combination may enable us to obtain satisfactory results with smaller doses of each than would be effective if either were employed alone. This, no doubt, may be open to the criticism that in those cases in which combined treatment has been practised it is impossible to say which agent has produced the beneficial result, when this has been obtained. But, even though we do regard the dictates of humanity, surely we have ample evidence in favour of the use of lead, for in a number of cases in which some preparation of this metal has alone been used recovery has followed. So, too, we now have the knowledge, not only as the result of our own observations, but also of those of Carter Wood,¹⁰ Mottram,⁷ and others,^{6, 8} that while α rays, radium, and lead may each produce a beneficial effect when used separately, an aggregate effect is secured when lead and α rays or lead and radium are applied within a short time of one another.

It will be found, therefore, that some of our cases were treated by lead alone, others by operation followed by lead, and again others by lead and α rays or radium.

INDICATIONS AND CONTRAINDICATIONS FOR TREATMENT WITH LEAD.

We have emphasized the fact that in respect of our present practice the general condition of the patient is of paramount importance. With increased experience we have come to regard the situation of the malignant neoplasm as of lesser importance, and to-day we certainly should neither exclude cancer of the lung nor malignant disease of the central nervous system.

The question of malignant disease of the liver and of a kidney is, however, more difficult, for in the general examination of the patient we lay considerable stress on the integrity of the functions of these organs. It will readily be appreciated that if either be already affected with malignant disease, or be otherwise previously damaged, there is a greatly increased risk of adding to their functional distress by the administration of lead. At any rate in such circumstances great caution is required.

It may be interesting to recall one case (248) in which there was carcinoma of the left kidney. Careful examination revealed the fact that the right kidney was absent. To have treated a patient with lead in these circumstances would have been to court disaster.

Apart from lesions in these two organs, we must also take into consideration the state of the heart and blood. Severe myocardial insufficiency necessitates the most cautious use of lead, and serious anaemia with a low red-cell count precludes the use of this substance until considerable improvement by blood transfusion or other measures has been effected. In the last place, we must also take into careful account the general condition of the patient in regard to acidosis with ketonuria and other constitutional states.

In malignant disease the progress to a fatal issue varies in different patients in a remarkable manner. In some—usually the young—the course is so rapid that the general condition of the patient appears to be little affected until the very end. In others—for the most part the aged—the disease progresses very slowly and appears to produce

* A post-graduate lecture, with lantern illustrations, delivered under the auspices of the British Empire Cancer Campaign and the Leeds and West Riding Medico-Chirurgical Society, in the Medical School, Leeds, on January 24th, 1929. This investigation was undertaken on behalf of the Liverpool Medical Research Organization.

† The chief matters of interest in this connexion were demonstrated.

no serious constitutional disturbance for a very long time. In most patients, however, the malignant process advances at a steady rate, undermining the constitution of the patient, however strong he may previously have been, and sapping his vitality, until what we describe as a condition of profound cachexia supervenes. Now it is in the presence of a state of definite cachexia that we must hold our hand. So long as the patient is in good condition, with a prospect of about six months of life, if other things are equal, treatment may be contemplated. In this matter considerable judgement and prognostic acumen are necessary.

METHODS OF TREATMENT WITH LEAD.

Dosage.—In a general way it may be said that we have tended gradually to decrease the individual doses, while aiming steadfastly at the administration of a high total quantity of lead—that is, 0.5 gram to 0.8 gram or a little more. In a number of cases we have been successful with a smaller total quantity than 0.5 gram of lead, which we believe to be the minimum amount desirable in ordinary circumstances. On the other hand, we have given nearly 1 gram of lead before obtaining a satisfactory final result. Empiricism in this matter is quite impossible; the greatest consideration and care are required if safety to the patient is to be ensured, and a successful result obtained.

Material.—For almost the entire part we have employed a suspension of metallic lead prepared by Professor Lewis and his associates, and the colloidal preparation of lead phosphate made by Professor Heilbrön and those working with him. For a time we used a suspension of lead selenide, but this appeared to be almost too stable to give good results, although it is not inert; it is, however, singularly atoxic. Lead-selenium has, however, been successfully employed by Dr. Todd of Bristol,⁹ who was the first to make and use this preparation of lead.

Administration.—Injection of the material into a vein in the arm has been by far the most common method of administration. We have, however, in a few cases, injected the preparation into an artery. Two cases of malignant disease in limbs will be mentioned in which this procedure has been practised, apparently, and so far, with promising results. We look forward to the obvious advantages and possibilities of this route in the treatment of malignant disease of the limbs, mouth, and other regions with a readily available and convenient arterial supply. In a few of our earlier cases intramuscular injections were employed. Ionization with lead of malignant ulcers is, too, a mode of attack which we have practised. We have already referred to the beneficial results that may be obtained by the application of x rays or radium at an interval of four days following the administration of lead.

Mobilization.—We apply this term to the process of bringing the lead that is stored in the body again into the circulation, from which it may be taken up by the growth, if this still be present, or excreted. Some years ago we were faced with the difficulty that in certain patients, who had received what we considered the maximum quantity of lead that could be given with safety, the neoplasm was still in existence or had recurred. It occurred to us to mobilize the lead still remaining in the body by the administration of acids or other chemical substances; and we found this possible. Sometimes stippled erythrocytes reappeared in the blood, and excretion by the urine and faeces was increased. We have, however, no direct evidence that the growth takes up the lead in these circumstances. We are at present inclined to think that the metal already attached to the tumour may be released; and in some cases (for example, patient 185 quoted below) the growth which has not entirely disappeared but is arrested may thereby be released from control and start afresh to develop. Consequently, we now hold the view that so long as any growth remains mobilization must not be practised. Indeed, this procedure should be reserved for those cases in which there has been no sign of neoplastic development for several years, and in which it is desirable that the liver and kidney functions should be normal, as in patient 77 recorded below.

There is no doubt that lead tends to be eliminated from the body in the course of time, and this itself may be a

source of anxiety in respect of the possibility of recurrence. It appears most profitable to maintain a supply of lead in the tissues until all danger of recurrence is long past, for we have observed that in such circumstances the placenta in pregnancy several years subsequently (see patients 77 and R. I. 39 described below), and therefore probably a neoplasm, is capable of taking to itself lead from that stored as the result of previous treatment.

GENERAL CHARACTER OF RESULTS.

One of the difficulties that have arisen in the general appraisal of results has been due to the different methods of tabulation adopted by various authors. Those unable to appreciate evidential values have taken the definite stand of "all or nothing"—that is, absolute cures or failures alone, in their view, are worth recording. Moreover, the primary condition attaching to all forms of scientific treatment—namely, that the method adopted shall be properly applied—has not infrequently been ignored. In this connexion it will be found that where a series of failures has been recorded the patients have been so ill that treatment could not be completed, or that the treatment was so conducted that the patients died as the result of it. Such groups of cases should be excluded from any estimation of the effect of treatment—they have no evidential value at all.

Again, it cannot be too forcefully reiterated that in the early application of any new method, however important an absolutely curative effect may be, *arrest and alleviation of the disease must equally be taken into account*; for such phenomena afford a valuable indication of the correctness of the principle of the treatment adopted, and give promise of the fruits of complete victory if the pursuit be pressed.

There is another phenomenon of great interest that has been observed by ourselves and others, concerning which we shall have more to say directly. We refer to the complete arrest or even disappearance of the growth with reappearance after a short or a considerable length of time. From this we may provisionally conclude that it is advisable to continue in a modified form the treatment over a longer period of time than previously considered necessary.

Finally, it may be suggested that in all cases in which a beneficial effect is obtained, the restoration of the natural vital processes plays a part in the result.

CERTAIN CASES TREATED WITH LEAD.*

The number of cases described under this heading are arbitrarily limited by space only, and they are merely representative of the results that may be expected if the work be properly conducted. In two or three cases we have had to accept the statement of the surgeon concerned as to the nature of the primary neoplasm; consequently we think that the interests of truth will best be served if we record the names of those connected with all the cases presented.

(A) Cases in which the Primary Growth was Treated with Lead alone.

In this group are included some cases in which the abdomen was opened to secure specimens of growth for histological examination, or the immediate relief of symptoms and physical states, such as intestinal obstruction.

1.—Female, aged 36; married; 3-para.

Diagnosis.—Carcinoma of left breast (section +) with glands in axilla. Pronounced inoperable by Professor R. E. Kelly and Mr. Frank Jeans.

Treatment.—Intravenous injections of partly colloidal lead iodide commenced on November 9th, 1920. Total quantity administered approximately 0.3 gram Pb. Severe reaction.

Subsequent History.—Now alive and well more than eight years later. Two more children; both suckled at previously diseased breast.

77.—Female, aged 27; married; 5-para.

Diagnosis.—Sarcoma small intestine (section +).

Treatment.—Intestinal anastomosis for obstruction by Professor Kelly. Growth irremovable. Intravenous injections of partly colloidal lead iodide commenced February 26th, 1923. Total quantity administered 0.45 gram Pb. Very slight reaction.

* In our forthcoming work on *Some Aspects of the Cancer Problem*, to be published by Messrs. Baillière, Tindall and Cox in the spring or early summer, the cases, here recorded very briefly, are given in more detail and are illustrated. Moreover, in this book there will be additional case records and tables, now omitted owing to exigencies of space.

Subsequent History.—Growth disappeared and, so far as original disease was concerned, patient remained well for over five years. Unfortunately she died of toxæmia of pregnancy in May, 1928.

112.—Female, aged 50; married; 2-para.

Diagnosis.—Carcinoma of liver and peritoneum (section +).

Treatment.—Paracentesis twice under the care of Professor John Hay. Exploratory laparotomy. Intravenous injections of partly colloidal lead iodide commenced August 3rd, 1923. Total quantity administered 0.345 gram Pb. No reaction.

Subsequent History.—The patient now alive and well five and a half years later.

185.—Female, aged 27; unmarried; medical student.

Diagnosis.—Retroperitoneal sarcoma (section +).

Treatment.—Exploratory laparotomy. Intravenous injections of colloidal lead commenced April 15th, 1925. Slight reaction, quick recovery. Total quantity administered 0.75 gram. No scholastic examination missed during treatment.

Subsequent History.—Now alive and well nearly four years later, though some evidence of a small arrested growth to be made out on palpation. At present holding resident hospital appointment.

R. I. 9.—Female, aged 45; unmarried.

Diagnosis.—Sarcoma of third lumbar vertebra, which was destroyed (x ray +).

Treatment.—Intravenous injections of colloidal lead commenced July 27th, 1925. Total quantity administered 0.55 gram Pb. Steady improvement. Slight reaction.

Subsequent History.—Now alive and well three and a half years later, except for occasional pain in region of deformity.

352.—Female, aged 66; unmarried.

Diagnosis.—Squamous carcinoma of larynx—left arytenoid (section +).

Treatment.—Intravenous injections of colloidal lead phosphate commenced March 8th, 1928. Total quantity administered approximately 0.5 gram Pb. Slight reaction. Gradual diminution of tumour.

Subsequent History.—Patient is alive and doing well. Last report from laryngologist—Mr. H. V. Forster—(December 10th, 1928): "The left arytenoid from which I removed a piece [previously] . . . is now pale in appearance, and in colour is similar to the right one."

R. I. 39.—Female, aged 37; married; 9-para.

Diagnosis.—Carcinoma of rectum with glands, associated with pregnancy. (No section.)

Treatment.—Exploratory laparotomy and colostomy by Mr. Kennon. Intravenous injections of colloidal lead commenced July 3rd, 1926. Total quantity administered 0.465 gram Pb. Slight reaction. Normal pregnancy and confinement.

Subsequent History.—Premature delivery April, 1928. Patient alive and well two and a half years later. No evidence of disease.

R. I. 102.—Male, aged 60.

Diagnosis.—Squamous carcinoma of floor of mouth (section +). Glands in the neck.

Treatment.—Radium (80 mg.) applied by Mr. Frank Jeans to floor of the mouth for twenty-four hours (August 18th, 1927). Intravenous injections of colloidal lead selenide commenced September 1st, 1927. Total amount administered 0.45 gram Pb. No reaction. Glands in neck gradually disappeared under treatment, and the ulcerated area in floor of mouth healed and thickening disappeared.

Subsequent History.—Patient now alive and well one and a half years later.

Comment.—Improvement and disappearance of primary growth and glands could hardly have been caused by single dose of radium.

N. H. 22.—Male, aged 69.

Diagnosis.—Carcinoma of gall bladder. (No section.)

Treatment.—Exploratory laparotomy by Mr. J. H. Rawlinson. Intravenous injections of colloidal lead commenced August 19th, 1925. Total quantity administered 0.44 gram Pb. Occasional vomiting during treatment.

Subsequent History.—Now alive and well three and a half years later. Some thickening in neighbourhood of scar.

N. H. 53.—Male, aged 59.

Diagnosis.—Carcinoma of splenic flexure of colon. (No section.)

Treatment.—Operation for obstruction by Mr. Oldham, June, 23rd, 1927. Fixed tumour size of orange; numerous glands. Anastomosis. Intravenous injections of colloidal lead commenced August 10th, 1927. Total amount administered 0.55 gram Pb. No reaction noted.

Subsequent History.—Now alive and well one and a half years later. Increased in weight 2 st. No tumour palpable.

N. H. 25.—Male, aged 42.

Diagnosis.—Carcinoma of ampulla of Vater. (No section.)

Treatment.—Gastro-enterostomy by Mr. G. C. Simpson. Intravenous injections of colloidal lead commenced June 8th, 1925. Total quantity administered 0.6 gram Pb. No reaction.

Subsequent History.—Now alive and well three and a half years later. No evidence of disease.

(B) Treatment of the Primary Growth by Incomplete Operation and the Subsequent Administration of Lead.

The following cases, in which the growth was primary, are illustrative of partial—that is, definitely incomplete—

operative procedures, as determined at operation by the recognition of malignant tissue left, or by histological examinations of pieces excised from the edge of the growth removed or from the irremovable part of the growth remaining *in situ*.

192.—Female, aged 60; married; 1-para.

Diagnosis.—Squamous carcinoma of cervix, invasion of parametrium (sections +).

Treatment.—Partial removal by abdominal route on July 18th, 1925. Intravenous injections of colloidal lead commenced August 4th, 1925. Total quantity administered 0.61 gram Pb. Malignant mass left in pelvis observed gradually to disappear. Very slight reaction.

Subsequent History.—Now alive and well three and a half years later.

221.—Female, aged 55; married; 0-para.

Diagnosis.—Carcinoma of body of uterus with three vaginal metastases (sections +).

Treatment.—Hysterectomy by Dr. R. A. Hendry, December 15th, 1924. Intravenous injections of colloidal lead commenced December 31st, 1924. Total quantity administered 0.69 gram Pb. Nodules in vagina observed gradually to disappear. Slight reaction.

Subsequent History.—Patient well for one and a half years, then evidence of regrowth in vagina. Diathermy; mobilization. Patient now well after a further lapse of one and a half years. No evidence of disease.

64.—Female, aged 47; married; 5-para.

Diagnosis.—Spheroidal carcinoma of breast, with invasion of muscle and large axillary glands (sections +).

Treatment.—Excision, December 24th, 1922. Intravenous injections of partly colloidal lead iodide commenced January 2nd, 1923. Total quantity administered 0.43 gram Pb. Mobilization. No reaction.

Subsequent History.—Now alive and well six years later.

Comment.—Operation incomplete on examination of specimen (Professor Bloodgood).

N. H. 18.—Female, aged 34; married; 0-para.

Diagnosis.—Columnar carcinoma rectum (section +).

Treatment.—Excision of rectum by Mr. G. C. Simpson, November 17th, 1924. Several adherent glands left on sacrum. Intravenous injections of colloidal lead commenced January 2nd, 1925. Total quantity administered 0.455 gram Pb. No reaction.

Subsequent History.—There has been a recto-vaginal fistula since the operation. Patient now alive and free from disease four years later.

R. I. 4.—Female, aged 52; married; 3-para.

Diagnosis.—Extensive squamous carcinoma cervix (section +).

Treatment.—Vaginal hysterectomy, September 25th, 1924. Disease left in the broad ligaments and to edge of specimen (sections +). Intravenous injections of colloidal lead commenced December 16th, 1924. Total quantity administered approximately 0.5 gram Pb. No serious reaction.

Subsequent History.—Now alive and well four years later.

R. I. 70.—Male, aged 51.

Diagnosis.—Secondary carcinoma of glands of neck (section +).

Treatment.—Operations by Mr. Woolfenden April 27th, 1926, and February 8th, 1927; growth was almost certainly left behind at the second operation. Intravenous injections of colloidal lead selenide commenced February 17th, 1927. Total amount administered 0.465 gram Pb. Slight reaction.

Subsequent History.—Now, nearly two years later, general condition good and there is no evidence of growth.

Comment.—It is hardly possible that the patient was cured by the operations, especially as the primary growth was never identified, but was probably in the mouth; which was in an unhealthy condition with papillary stomatitis.

N. H. 27.—Female, aged 37; married; 0-para.

Diagnosis.—Carcinoma of stomach (section +).

Treatment.—Operation by Mr. G. C. Simpson, November 13th, 1925—partial gastrectomy. Glands very much enlarged and hard; not removed. Intravenous injections of colloidal lead commenced December 3rd, 1925. Total quantity administered 0.45 gram Pb. Some reaction.

Subsequent History.—Patient now alive and well and free of symptoms, with gain in weight, 3 years later. No evidence of disease.

Comment.—This case obviously could not have been cured by operation alone as the involved glands were left.

(C) Cases in which Recurrence occurred after Removal of the Primary Neoplasm, and which were Subsequently Treated with Lead.

A large proportion of all cases received by us for treatment has included those in which there has been recurrence at some period after operation performed elsewhere. As we have indicated, we prefer to treat the primary growth ourselves in order that treatment may be commenced immediately after operation, rather than to treat patients in whom there is a definite recurrence. In the latter circumstances the patient is usually in poor condition, and the disease is often much more widespread than can

be recognized. These patients are difficult to cure; still we have had a number of apparent successes, a few of which are recorded below. In those cases in which a primary operation performed by others had been followed by recurrence obviously the operation cannot be taken into account as an accessory factor in the ultimate recovery of the patient.

110.—Female, aged 57; married; 5-para.

Diagnosis.—Recurrence after operation for spheroidal carcinoma of right breast (section +).

Treatment.—Excision by Mr. Battle, March, 1922; second operation by Mr. Maynard Smith, May 21st, 1923, for lump above clavicle. Further evidence of recurrence. Intravenous injections of partly colloidal lead iodide and colloidal lead commenced July 27th, 1923. Total quantity administered 0.2065 gram Pb. No reaction.

Subsequent History.—Alive and well five and a half years later.

201.—Female, aged 50; unmarried.

Diagnosis.—Scirrhus carcinoma of left breast with extensive local recurrence on chest wall, glands (section +), and left lung (x ray and aspiration).

Treatment.—Intravenous injections of colloidal lead commenced December 16th, 1925. Total quantity administered 0.7 gram Pb. Slight reaction.

Subsequent History.—The extensive disease was considerably reduced, and after two and a half years the general condition of the patient was much improved. Unfortunately she died of acute pneumonia following a chill in August, 1928.

216.—Female, aged 62; unmarried.

Diagnosis.—Recurrent spheroidal carcinoma of left breast involving rib (section +).

Treatment.—Intravenous injections of colloidal lead commenced January 13th, 1926. After 0.3 gram administered, suspension for four months. Scar tissue showed "very atypical regressing almost unrecognizable spheroidal-celled carcinoma." Further injections, making total quantity 0.575 gram Pb. Slight reaction. Later mobilization. Small recurrence removed December 6th, 1928. Radium, followed six days later by an injection, making total quantity 0.6 gram Pb. received.

Subsequent History.—Quite well at the present time.

161.—Female, aged 60; married; 1-para.

Diagnosis.—Scirrhus carcinoma of left breast (section +). Recurrence local and at root left lung (x ray, Dr. Finzi).

Treatment.—"Radical" excision by Sir Lenthal Cheate of left breast, May 12th, 1924. Intravenous injections of colloidal lead commenced August 8th, 1924. Total quantity administered 0.595 gram Pb. Severe delayed reaction after completion—vomiting for fourteen days; then complete recovery.

Subsequent History.—Believed to be now alive and well four and a half years later. Last letter received November, 1926.

169.—Female, aged 47; married; 0-para.

Diagnosis.—Scirrhus carcinoma left breast (section +). Recurrence in supraclavicular and axillary glands, and local.

Treatment.—"Radical" excision by Sir Lenthal Cheate, January, 1923. X-ray applications by the late Dr. A. Reid. Sir Lenthal Cheate discovered recurrence in August, 1924. Intravenous injections of colloidal lead commenced September 17th, 1924. Some reaction occasionally. Total quantity administered 0.6 gram Pb.

Subsequent History.—Now alive and well four and a half years later.

R. I. 51.—Male, aged 67.

Diagnosis.—Squamous carcinoma of lip (section +) with glands in the neck.

Treatment.—Excision of primary growth by Mr. Woolfenden, May 25th, 1926, and excision of glands by Mr. Nuttall, July 9th, 1926. Definite recurrence two months later: a large hard fixed mass in neck. Intravenous injections of colloidal lead commenced September 11th, 1926. Total amount administered 0.4 gram Pb. No reaction.

Subsequent History.—Now alive and well, no evidence of disease nearly two and a half years later.

(D) Treatment of the Primary Growth by Operation and the Subsequent Administration of Lead.

The next group we shall consider is that in which operation for the primary growth was performed in Liverpool, with three exceptions, and the patients treated immediately. This method has, of course, been largely employed, and the successful results are many; consequently we naturally prefer to treat cases of malignant disease ourselves from the time the diagnosis is first made. It must, of course, be admitted that in some of the patients the disease may have been entirely removed at operation. An attempt will be made to indicate the chances of this occurrence in regard to the cases described; in many it will be obvious that the prognosis subsequently to operation alone would have been very bad. Moreover, the character of the operation must be taken into account—for example, vaginal hysterectomy for cancer of the cervix, of which the first four are examples.

30.—Female, aged 31; widow; 3-para.

Diagnosis.—Squamous carcinoma of cervix (section +).

Treatment.—Amputation of cervix, October 9th, 1921. Intravenous injections of partly colloidal lead iodide commenced November 1st, 1921. Total quantity administered 0.768 gram Pb. No reaction. Subsequently vaginal hysterectomy—safety measure—December 4th, 1922; no evidence of cancer found (sections -).

Subsequent History.—Now alive and well more than seven years later.

Comment.—Operation alone might have cured this patient, but her youth made prognosis unfavourable.

139.—Female, aged 49; widow; 1-para.

Diagnosis.—Squamous carcinoma of cervix (section +).

Treatment.—Vaginal hysterectomy, February 24th, 1924. Intravenous injections of colloidal lead and partly colloidal lead iodide commenced March 7th, 1924. Total quantity administered approximately 0.3 gram Pb. No reaction.

Subsequent History.—Now alive and well nearly five years later.

Comment.—Prognosis after operation alone was unfavourable owing to the advanced stage of the disease.

155.—Female, aged 42; married; 6-para.

Diagnosis.—Squamous carcinoma of cervix (section +).

Treatment.—Vaginal hysterectomy, June 17th, 1924. Involvement of the parametrium probable. Intravenous injections of colloidal lead commenced July 9th, 1924. Total quantity administered 0.21 gram Pb. No reaction.

Subsequent History.—Now alive and well four and a half years later.

Comment.—Prognosis after operation alone would have been unfavourable. The small quantity of lead administered was due to the fact that the patient suffered with old renal damage before treatment commenced.

R. I. 82.—Female, aged 58; married; 6-para.

Diagnosis.—Extensive squamous carcinoma of cervix (section +). Mitral stenosis; hyperpiesis. Wassermann reaction +.

Treatment.—Vaginal hysterectomy, May 16th, 1927. Intravenous injections of colloidal lead selenide commenced May 26th, 1927. Total quantity administered 0.37 gram Pb. Slight reaction. Blood pressure raised.

Subsequent History.—Alive; no evidence of pelvic disease more than one and a half years later.

In view of the great malignancy of sarcoma uteri, apart from the spindle-celled variety arising in fibromyoma, the following cases are of interest.

88.—Female, aged 61; unmarried; nursing sister.

Diagnosis.—Mixed-cell sarcoma of uterus (section +) and carcinoma of right ovary (section +).

Treatment.—Abdominal panhysterectomy with removal of appendages, April 28th, 1923. Intravenous injections of partly colloidal lead iodide commenced May 8th, 1923. Total quantity administered 0.2 gram Pb. No reaction.

Subsequent History.—Now alive and well over five and a half years later.

Comment.—The small quantity of lead administered was due to the diminutive size of the patient and her frailty.

C. I. 1.—Female, aged 59; unmarried.

Diagnosis.—Large round and multinucleated celled sarcoma of the uterus (section +).

Treatment.—Panhysterectomy with right salpingo-oophorectomy, January 22nd, 1927. Intravenous injections of colloidal lead commenced February 12th, 1927. Total quantity administered 0.4 gram Pb. No reaction.

Subsequent History.—Now alive and well two years later, a period of time sufficient to state that the patient is "clinically cured" of this form of malignant disease.

The following cases of advanced carcinoma mammae with involvement of the axillary glands, in which the prognosis after operation alone would have been extremely grave, seem to be worth placing on record.

57.—Female, aged 38; married, 4-para.

Diagnosis.—Spheroidal-celled carcinoma of left breast and axillary glands (sections +).

Treatment.—"Radical" operation, November 13th, 1922. Intravenous injections of colloidal lead commenced November 21st, 1922. Total amount administered 0.578 gram Pb. No reaction. Mobilization.

Subsequent History.—Right breast excised October 27th, 1924; "chronic mastitis" (section -). Patient now alive and well six years later.

Comment.—Prognosis after operation alone very grave.

221.—Female, aged 59; widow; 0-para.

Diagnosis.—Spheroidal-celled carcinoma of left breast and axillary glands (sections +).

Treatment.—"Radical" operation, December 29th, 1925. Intravenous injections of colloidal lead commenced January 5th, 1926. Total quantity administered 0.6 gram Pb. No reaction.

Subsequent History.—Now alive and well three years later.

Comment.—Prognosis after operation alone most unfavourable.

240.—Female, aged 52; married; 2-para.

Diagnosis.—Spheroidal-celled carcinoma of right breast and axillary glands (sections +).

Treatment.—"Radical" operation, February 26th, 1926. Intravenous injections of colloidal lead commenced March 2nd, 1926.

Total quantity administered 0.685 gram Pb. Rather severe vomiting in earlier part of treatment.

Subsequent History.—Now alive and well nearly three years later.

Comment.—Prognosis after operation alone bad.

244.—Female, aged 72; unmarried.

Diagnosis.—Spheroidal-celled carcinoma of right breast and axillary glands (sections +).

Treatment.—"Radical" operation, March 15th, 1926. Intravenous injections of colloidal lead commenced March 26th, 1926. Total quantity administered 0.575 gram Pb. Some gastro-intestinal disturbance after the earlier injections, from which patient quickly recovered.

Subsequent History.—Now alive and well nearly three years later.

Comment.—Prognosis after operation alone grave.

297.—Female, aged 54; widow; 6-para.

Diagnosis.—Spheroidal-celled carcinoma of breast and axillary glands (sections +).

Treatment.—"Radical" operation, November 25th, 1926. Intravenous injections of colloidal lead and lead selenide commenced December 1st, 1926. Last dose of colloidal lead phosphate. Total quantity administered 0.555 gram Pb. No reaction.

Subsequent History.—Now alive and well over two years later.

Comment.—A very bad case. Prognosis after operation alone very bad.

The following cases, which may also be briefly recorded, are of some interest. In most the wide extent of the growth is well shown in photographs taken before treatment. They are all alive and well at the present time.

82.—Male, aged 51.

Diagnosis.—Squamous carcinoma of tongue, fauces, soft palate, glands of neck (sections +).

Treatment.—"Radical" operation, March 14th, 1923. Intravenous injections of partly colloidal lead iodide commenced March 22nd, 1923. Total quantity administered 0.56 gram Pb. No reaction. Mobilization later.

Subsequent History.—Now alive and well six years later.

Comment.—Extent, nature, and situation of disease made prognosis after operation alone extremely grave.

333.—Male, aged 68.

Diagnosis.—Squamous carcinoma of face (section +).

Treatment.—Excision with diathermy, June 26th, 1927. Intravenous injections of colloidal lead, lead selenide, and lead phosphate commenced July 3rd, 1927. Total quantity administered 0.55 gram Pb. No reaction.

Subsequent History.—Now alive and well more than one and a half years later. All spots are fast disappearing.

Comment.—Might have been cured by operation so far as the growth was concerned.

327.—Male, aged 64.

Diagnosis.—Basal-celled carcinoma of face (section +).

Treatment.—Diathermy excision May 18th, 1927. Intravenous injections of colloidal lead and lead phosphate commenced May 28th, 1927. Total quantity administered 0.33 gram Pb. No reaction.

Subsequent History.—The diathermy cautery was used on several subsequent occasions. Now alive and well, with much contracture of face, nearly two years later.

Comment.—Unlikely that operation alone would have proved successful.

R. I. 32.—Male, aged 62; medical practitioner.

Diagnosis.—Carcinoma of sigmoid (section +) with involvement of glands.

Treatment.—Excision of sigmoid and portion of adherent small bowel with some glands by Mr. Woollenden, January 22nd, 1926. Temporary colostomy. Intravenous injections of colloidal lead commenced February 3rd, 1926. Total quantity administered 0.35 gram Pb. Never any serious reaction.

Subsequent History.—Now alive and well three years later; has gained weight; no evidence of disease.

Comment.—At the operation it was considered extremely unlikely that all the numerous glands were removed.

R. I. 17.—Female, aged 23; unmarried.

Diagnosis.—Carcinoma of vulva (section +).

Treatment.—"Radical" operation, January 21st, 1926. Intravenous injections of colloidal lead commenced February 3rd, 1926. Total quantity administered 0.525 gram Pb. Never any serious reaction.

Subsequent History.—Now alive and well three years later.

Comment.—The extreme youth of the patient in connexion with cancer of the vulva must be almost unique. Prognosis would, therefore, seem to have been bad subsequent to operation only.

R. I. 21.—Female, aged 64; married; 5-para.

Diagnosis.—Epithelioma of the thigh (section +).

Treatment.—Ulcerated growth excised by Mr. Jeans, February 12th, 1926; muscle involved. Intravenous injections of colloidal lead commenced March 16th, 1926. Total amount administered 0.3 gram Pb. No reaction.

Subsequent History.—Now alive and well three years later.

Comment.—This patient may have been cured by operation alone.

R. I. 29.—Female; aged 70; unmarried.

Diagnosis.—Carcinoma of body of uterus with fibromyomata (section +).

Treatment.—Operation April 22nd, 1926; panhysterectomy with removal of appendages. Intravenous injections of colloidal lead commenced May 25th, 1926. Total quantity administered 0.425 gram Pb. Very slight reaction.

Subsequent History.—Now alive and well nearly three years later.

Comment.—This patient would in all probability have been cured by operation alone.

R. I. 100.—Male, aged 72.

Diagnosis.—Epithelioma of soft palate (section +).

Treatment.—Ulcer excised by Mr. Frank Jeans with diathermy August 19th, 1927. Intravenous injections of colloidal lead selenide commenced August 27th, 1927. Total amount administered 0.3 gram Pb. Some reaction after some injections, with oedema of ankles and cramps in legs.

Subsequent History.—Patient now alive and well one and a half years later.

Comment.—It is possible that this case was cured by operation, but the situation of the growth makes it unlikely that he was cured by such simple procedure.

R. I. 54.—Female, aged 59; married; 1-para.

Diagnosis.—Epithelioma of vulva (section +).

Treatment.—"Radical" excision of the whole of vulva including orifice of urethra, September 16th, 1926. Intravenous injections of colloidal lead commenced October 2nd, 1926. Total amount administered 0.45 gram Pb. Very slight reaction.

Subsequent History.—Now alive and well, no recurrence, nearly two and a half years later.

Comment.—The disease was so extensive that cure by operation was extremely unlikely.

N. H. 11.—Female, aged 39; married; 1-para.

Diagnosis.—Carcinoma of stomach (section +).

Treatment.—Operation by Mr. G. C. Simpson, September 26th, 1924. Growth hard, adherent to pancreas. Partial gastrectomy; gastro-enterostomy. Intravenous injections of colloidal lead commenced October 17th, 1924. Total quantity administered 0.46 gram Pb. No reaction.

Subsequent History.—Now alive and well nearly four and a half years later.

Comment.—This patient was not regarded as being curable or cured by operation alone.

N. H. 44.—Male, aged 50.

Diagnosis.—Sarcoma of cheek (section +).

Treatment.—Operation by Mr. Oldham, August 2nd, 1926 (see *Lancet*, 1928, i, 28). Intravenous injections of colloidal lead commenced October 25th, 1926. Total amount administered 0.55 gram Pb. Slight reaction.

Subsequent History.—Patient now alive and well over two years later.

N. H. 38.—Male, aged 40.

Diagnosis.—Carcinoma of colon (section +).

Treatment.—Operation by Mr. Rawlinson, May 29th, 1926. Large growth in the descending colon with abscess formation. Excision. Temporary colostomy. Later anastomosis. Intravenous injections of colloidal lead commenced June 8th, 1926. Total amount administered 0.225 gram Pb. No reaction.

Subsequent History.—Patient now alive and well two and a half years later. No sign of disease.

Comment.—It is unlikely that such an advanced case of cancer of the bowel would have been cured by operation alone.

N. H. 40.—Male, aged 61.

Diagnosis.—Carcinoma of colon (section +).

Treatment.—Operation by Mr. Monsarrat, August 3rd, 1926. Large growth in pelvic colon. No enlarged glands. Resection. Intravenous injections of colloidal lead commenced August 20th, 1926. Total amount administered 0.575 gram Pb. No reaction.

Subsequent History.—Now alive and well two and a half years later. No evidence of recurrence.

The next three cases, which are very briefly recorded, were all subjected to operation elsewhere, and were referred to us subsequently for treatment, in view of the fact that they were cases in which recurrence was expected owing to the extreme malignancy of neoplasms of these types. Histological examination was made in each case.

219.—Male, aged 47.

Diagnosis.—Melanoma of left eye (section +).

Treatment.—Operation, December 11th, 1925. Removal of eye by Sir William Lister. Intravenous injections of colloidal lead commenced January 18th, 1926. Total quantity administered 0.5 gram Pb. Slight reaction.

Subsequent History.—Patient is alive and well more than three years later.

223.—Male, aged 36.

Diagnosis.—Carcinoma of right testicle (section +).

Treatment.—Operation by Dr. Roughton, January 4th, 1926. Excision of testicle. Intravenous injections of colloidal lead commenced January 26th, 1926. Total quantity administered 0.625 gram Pb. Mobilization a year later. Slight reaction; nausea.

Subsequent History.—Now alive and well three years later.

337.—Male, aged 26.

Diagnosis.—Periosteal sarcoma of right tibia (section +).

Treatment.—Operation by Mr. Page, London, June 20th, 1927. Amputation through middle of thigh. Intravenous injections of

colloidal lead, colloidal lead selenide, and colloidal lead phosphate commenced September 2nd, 1927. Total quantity administered 0.543 gram Pb. Very slight reaction.

Subsequent History.—Now alive and well nearly one and a half years later.

(E) Treatment of Primary Neoplasm with Lead and X Rays.

Of the cases treated in this way the first two are of special interest in that regensis of the growth occurred whenever treatment with lead was suspended, and in these circumstances the x rays appeared to be ineffective until further administration of lead was practised. This is not shown in the abbreviated notes below.

133.—Male, aged 8.

Diagnosis.—Sarcoma of the scapula (section +). Involvement of axillary glands.

Treatment.—Intravenous injections of colloidal lead commenced January 29th, 1924. X-ray treatment commenced April 29th, 1924. In July an x-ray picture showed considerable improvement in the scapula. Reossification. Improvement maintained in report dated January 23rd, 1925. Treatment suspended. April 27th, 1925, regensis of tumour. Further treatment. Total quantity administered 0.2475 gram Pb. Slight reaction.

Subsequent History.—Death of patient reported June 26th, 1925. *Comment.*—It now appears that the treatment of lead should not have been suspended when so small a quantity as 0.1725 gram had been administered. The age of the patient, and the size of the child, made it difficult to decide, in view of improvement.

114.—Male, aged 18.

Diagnosis.—Round-celled sarcoma of the scapula (section +).

Treatment.—Intravenous injections of colloidal lead commenced August 10th, 1923. Rapid increase in size of tumour in next three weeks. X-ray treatment commenced. On November 16th, 1923, marked clinical improvement; maintained till end of year. Treatment suspended. March 28th, 1924, recurrence below glenoid noted. Further treatment with lead and x rays. July 3rd, 1924, improvement with reossification. Treatment again suspended. August 5th, 1924, destructive bone changes again taking place. Further treatment till December 2nd, 1924. Total quantity of lead administered 0.415 gram. Slight reaction. November 20th, 1924, report: "This patient now undoubtedly doing well. Supraclavicular and axillary swellings disappeared; the size of the scapula is almost normal."

Subsequent History.—Patient disappeared. Was reported dead, of recurrence in the spine, September 18th, 1925.

R. I. 121.—Male, aged 14.

Diagnosis.—Periosteal sarcoma of femur (no section; x-ray and clinical evidence).

Treatment.—Intravenous and intra-arterial injections of colloidal lead phosphate commenced June 11th, 1928. Total amount administered up to last injection, October 25th, 1928, 0.412 gram Pb. No reaction. Three injections (0.16 gram Pb) were given directly into femoral artery. X-ray application four days after the last three injections.

Subsequent History.—The condition of the patient is good. The tumour has decreased in size, but it is too early to state ultimate fate. So long ago as June, 1928, Professor Kelly considered the case quite hopeless, and that the duration of life could not be many weeks.

R. I. 125.—Male, aged 33.

Diagnosis.—Fixed mass carcinoma of femoral glands (section +), secondary to carcinoma of foot.

Treatment.—Intravenous and intra-arterial (femoral) injections of colloidal lead and lead aspartate commenced August 29th, 1928. Total quantity at present administered 0.46 gram Pb. Slight reaction. X rays applied four days after each of the injections of lead.

Subsequent History. Too soon for prognosis. Tumour in groin smaller, soft, and movable.

Comment.—Of interest because of arterial route employed.

N. H. 2.—Male, aged 28.

Diagnosis.—Recurrence of carcinoma of testicle (section +). Mass in groin.

Treatment.—Excision of left testicle by Mr. G. C. Simpson two years previously, followed by x-ray applications. Recurrence. Intravenous injections of colloidal lead commenced August 12th, 1924. Total quantity administered 0.265 gram Pb. No reaction.

Subsequent History.—Now alive and well four and a half years later. No evidence of disease.

140.—Male, aged 34.

Diagnosis.—Mixed-cell sarcoma of the scapula and axillary glands (section +).

Treatment.—Intravenous injections of colloidal lead commenced March 7th, 1924. After seven doses x-ray treatment begun. Eighteen x-ray applications in all in conjunction with further intravenous injections of lead. Total quantity administered 0.2 gram Pb. No reaction.

Subsequent History.—Patient is alive and well five years later.

331.—Female, aged 72; unmarried.

Diagnosis.—Lymphosarcoma of left groin.

Treatment.—Tumour excised June 24th, 1927. Intravenous injections of colloidal lead selenide and colloidal lead commenced June 28th, 1927. Recurrence noted January, 1928. Patient not seen for four months. June 12th, 1928, recurrence adherent to the femoral

artery and vein; removed with difficulty. Further course of lead phosphate injections administered together with x-ray therapy. Total quantity of lead administered approximately 0.6 gram, and five x-ray applications. No reaction to injections.

Subsequent History.—Patient has put on weight, and at the present time there is no evidence of recurrence.

R. I. 75.—Male, aged 52.

Diagnosis.—Lymphosarcoma of pharynx, roof of mouth, and cheek (section +).

Treatment.—Intravenous injections of colloidal lead commenced March 18th, 1927. Total amount administered approximately 0.6 gram Pb. No reaction. Last injection February 15th, 1928. Eight doses of x rays applied to right side of the face, and three doses applied to neck on the right side.

Subsequent History.—Now alive and well nearly two years later.

STATISTICS AND RESULTS.

In any assessment of the results of the treatment of human disease, and especially of malignant disease, we are confronted with so many variable factors—site of neoplasm, type of growth, stage of the disease, whether it be primary or secondary, the constitutional condition of the patient, the psychology and experience of the medical attendant, and the rest—that no statistical survey of grouped or general results which takes into consideration a less number than several millions of cases can be more than suggestive. So it is clear that when a practitioner, inexperienced in the method employed, fails in 25 or 50, or even 100 cases, to secure a single completely satisfactory result, as very easily may happen with a new method of treatment, it must be remembered that negative evidence of that sort can never be weighed in the balance against that which is positive.

It has seemed to us, then, that at the present time the clear enunciation of many positives in a variety of circumstances may set in motion philosophical reflection in minds trained to apprehend.

In the following table details of general interest are presented in a simple manner in order that no confusion may be created as to the results recorded, or objections raised on the score of incompleteness of information, as has happened without justification in the past,⁸ in spite of the fact that we have on several occasions^{1 2 3 4} published full statements of our methods and results, with illustrative cases.

Table of Results.

November 9th, 1920–November 9th, 1928.

1. Total number of cases treated ...	566*
2. Died of the disease before treatment could be completed ...	359
(a) Received less than 0.25 gram Pb ...	198
(b) Received more than 0.25 gram Pb, but less than 0.5 gram ...	161
3. Died of the disease after treatment concluded ...	77
4. Died of intercurrent affections, while under treatment ...	7
5. Died as result of extensive destruction of disease ...	5
6. Complete treatment refused ...	22
7. Too recent for results to be estimated ...	31
8. Believed cured, but died of other affections (1 from apoplexy, 4½ years' interval; 1 from toxæmia of pregnancy, nearly 5½ years' interval) ...	2+
9. Disease completely arrested ...	12+
10. Believed cured and treatment stopped ...	51+

* At the conference in London in July, 1928, speaking from memory, I stated that about 1,000 patients had come under our care in Liverpool. This number is a little in excess of the exact figure. Many cases additional to those given above, however, and recorded in previous tables as "died before treatment could be commenced," and a further number rejected after consultation and examination, help to bring the total of cases seen nearer to the number stated.

In any estimate of results the serious type of case for the most part treated must be clearly remembered; it may be described as consisting largely of that in which the condition was considered hopeless. Ignoring, however, any consideration of temporary benefit—amelioration of symptoms and prolongation of life, or fatal destruction of the neoplasm—it appears that we have 303 cases to consider (items 2 (b), 3, 8, 9, and 10), cases which received more than one-half of the minimum treatment advised. Seventy-seven (77) died after full treatment; consequently it might be argued that there were 65 successes as opposed to 77 failures. Moreover, we have reason to believe that at least 40 per cent. of the "too-recent" cases will terminate favourably. Nevertheless, to put our statistics in the worst possible light, we can state that there were 65 successes out of 303 cases treated—that is, 21.5 per cent. of successful results.

CONCLUSION.

In conclusion we may urge two points, the recognition of which seems to us to be of paramount importance in the consideration of the treatment of malignant disease with lead at the present time.

First, no one in his senses would care to suggest that the possession of a knife and a few instruments is all that is required for the surgical cure of cancer of the stomach. Yet some seem to think that for lead therapy in this disease all that is required is that lead shall be pumped into the veins of the sufferer. We now realize that it was not the fault of radium that it was of so little clinical use twenty years ago.

Second, the scientifically minded inquirer will not demand that a new method of treatment for cancer operating on the worst and most advanced types of cases shall give far better initial statistical results than those obtainable with other long-established and standardized forms of treatment acting on early and selected cases; but, if it should do so, those capable of appraising evidential values will appreciate the vast possibilities that await full and proper development of the method tested.

I have to thank my colleagues Dr. Leslie Cunningham, Mr. J. B. Oldham, Dr. S. B. Herd, and Dr. M. Datnow, not only for the careful way in which they have conducted the laborious task of analysing the case records and tracing the fate of the patients, but also for co-operation in the clinical work, much of which has been conducted entirely on their own initiative and responsibility.

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CHOLECYSTOGRAPHY.

AN ANALYSIS OF 137 CASES SHOWING THE RELIABILITY OF THE ORAL METHOD.

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(With Special Plate.)

I HAVE been stimulated to write this paper by the repeated inquiries of my colleagues and other members of the profession as to how much one may expect from the α -ray examination of the gall-bladder, and with special reference to what is termed the "Graham-Cole test." Up to a few years ago the radiographic examination of the gall-bladder had been most unsatisfactory, and results were so uncertain that little reliance could be placed upon them. No routine examination of the gall-bladder was carried out in hospitals, and one was rarely asked to attempt such an investigation in private practice. To the late Drs. Carman of Rochester and Robert Knox of London, Case, George, and others in America and on the Continent, is due the credit for valuable pioneer work done in connexion with the radiography of the gall-bladder by direct methods. The detection of gall-stones could be made with more certainty in those large hospitals or clinics which were heavily endowed with funds than in the smaller and less favoured institutions. Where it was possible to take a large number of films under varying conditions of tube penetration, exposure, etc., the chances of obtaining positive evidence of pathological conditions involving the gall-bladder were proportionately greater. But even in the most favourable circumstances the direct method of examination yielded only 37 per cent. of correct diagnoses. The normal gall-bladder casts no shadow in even the most technically perfect films. It was maintained, therefore, that if a shadow of the gall-bladder was shown upon a film it was an indication of pathology; that the walls were abnormally thickened, the contents of unusual density, or that multiple calculi

were present. This was probably true, and when positive shadows were obtained they were of definite diagnostic value. It was exceptional, however, to see such shadows in even the best films, and the absence of a shadow did not exclude disease, hence such a finding was of little value. The detection of gall-stones before the days of cholecystography depended upon the composition of the stones. If they contained sufficient calcium they produced well-defined shadows. Some were annular in form, depending upon the denser periphery of the stone, others cast a laminated shadow or concentric rings of dense and less dense material. Others, again, were more homogeneous and faceted. If the gall-bladder was filled with stones even of low density a faint, mottled shadow was sometimes shown. From time to time such radiographs were obtained, but were of rather rare occurrence, and were therefore looked upon more or less as curiosities.

In 1914 Cole called attention to the secondary manifestations of cholecystitis as revealed by the opaque meal, and these findings were further elaborated by George and others. Information so obtained, together with the direct visualization of stones, as already described, formed the basis for α -ray diagnosis of gall-bladder disease up to the year 1924. In February, 1924, Graham, Cole, and Copher¹ of St. Louis announced the success of their work in demonstrating the gall-bladder radiographically after the intravenous injection of tetrabromphenolphthalein. In a further communication² in 1925 these authors discuss the theory and application of this new method of examination:

"This procedure is based upon the theory that if any substance containing a metal or atoms of bromine, or iodine, can be introduced into the gall-bladder in sufficient concentration, then that organ would be made opaque to α rays. The substance must be one which can be given either by the alimentary canal or by injection. It would have to be a substance which would be excreted by the liver and carried to the gall-bladder in the bile. Moreover, the ability of the gall-bladder to concentrate its contained bile would indicate that a sufficient time must elapse before a shadow of maximal density would occur. Reasoning from these premisses, the conclusion would have to be drawn that the shadows of sharpest contrast would be obtained in normal individuals. Similarly also no shadow would be expected to appear if the liver were unable to excrete the substance in sufficient amount, if the cystic duct were occluded, or if the function of the gall-bladder were sufficiently impaired to prevent the concentration of the material."

Such is the theory of cholecystography as briefly outlined by Graham, Cole, and Copher. As the object of this paper is to demonstrate by practical statistics the reliability of cholecystography by the oral method in particular, I do not wish to lengthen my communication unduly by recounting in detail the history of its development or the chemistry of the drugs used. No paper on this subject would, however, be complete without describing the Graham-Cole technique as first practised. In January, 1925, Graham used the tetraiodo-phenolphthalein sodium salt, and claimed superiority for this over the bromine salt in that it cast a denser shadow, a smaller dose was sufficient, and the toxicity was lessened in virtue of the reduced dose.

Technique of Intravenous Method.—In 30 c.cm. of freshly distilled water 3.5 grams of the salt are dissolved. The solution after filtration is sterilized in a boiling water bath for 15 minutes. It is given intravenously in two doses, half an hour apart, in the morning before breakfast, between 7.30 and 9 o'clock. Care should be taken not to allow extravasation outside the vein, as sloughing of tissue may occur. Certain orders are given to the patient and are essential:

1. Breakfast and lunch should be omitted.
2. Protein should be omitted from the evening meal.
3. Water is allowed *ad libitum*.
4. Stomach contents should be made alkaline by frequent doses of sodium bicarbonate.

The rationale of the latter procedure is explained in an article by Cole, who found experimentally on dogs that the flow of bile into the intestines through relaxation of the sphincter of Oddi is prevented by keeping the contents of the stomach alkaline. This probably tends to promote the concentration of bile in the gall-bladder. Films are taken at four, eight, twenty-four, and thirty-two hours after injection. A normal gall-bladder will begin to cast a shadow in four hours. This will be faint, but should reveal the