THE CHEMOTHERAPY OF CANCER: I. LEAD

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Efforts to depress or combat the growth of cancer with colloidal metals have been made by numerous workers in the past. Occasional success has been reported following injections of gold, copper, selenium, and other metals. In the last decade, interest has been aroused by the brilliant researches of Blair Bell, who used compounds of lead, and compounds of this metal have received wide therapeutic trial, both here and abroad. Thus F. C. Wood, in his report before the Dallas session of the American Medical Association in 1926, was inclined to encourage their use. He and Ullmann, together with such men as Bischoff and Blatherwick, Bischoff, Maxwell, Evans, and Nuzum, were among the pioneers in this country in the development of methods and of compounds suitable for injection into man.

Following the treatment by these men of groups of patients who had cancer, it soon became apparent that, while something seemingly was accomplished, better results might be obtained by the combined use of lead and other methods of treatment. As a result of efforts along these lines, reports soon appeared of the use of lead and irradiation. Ullmann (10, 11) spoke encouragingly of such combined treatment as early as 1927. Todd (7, 8) in his early reports on the use of lead selenide stated that 80 per cent of the patients he treated were benefited, and in a report in April 1934 he advocated the use of radium and roentgen rays in conjunction with lead selenide. However, in a report of twelve well controlled cases of carcinoma of the breast in which, according to the methods reported, the patients received sufficient lead, followed at once by intensive irradiation, Aub and Smithwick voiced the opinion that not only were the results unfavorable, but that in some cases death was actually hastened.

Many other men have interested themselves in this problem. The monograph by Todd (9) summarizes the work well.

In April 1932, we reported (6) briefly our experiences with the use of lead up to that time in inoperable, apparently hopeless cases of cancer such as that illustrated in Fig. 1. We at first experimented with various compounds of lead but soon found colloidal lead phosphate

1 Submitted for publication January 26, 1935.
to be a suitable preparation. This we have continued to employ as, apparently, the most suitable therapeutic agent. In a few instances we have used colloidal lead phosphate fortified by manganese phosphate, as recommended by Kraemer, and also lead selenide. The latter two substances have not been employed intensively enough to warrant final expression of our opinion. It is our impression, however, that they offer no distinct advantages over colloidal lead phosphate. This therapeutic substance we have prepared essentially by the procedure given by Blatherwick and Ullmann. The immediate toxicity of our preparation allowed the administration of 400 to 800 mg. of lead, in the form of the phosphate, during a period of ten to fourteen days.

![Image](https://via.placeholder.com/150)

**Fig. 1. Huge, Sloughing, Squamous-cell Epithelioma of the Right Side of the Neck Treated with Lead**

This amount of lead nearly always produced lead intoxication, and was considered to constitute a course of treatment. No data have been obtained as to the concentration of lead in the circulating blood or its rate of disappearance from the circulation, although such observations might perhaps be of value and should be obtained in future investigations. Data concerning the excretion of lead in the urine have been obtained, but such findings are apparently of little significance because of the tenacity with which the body retains the administered lead salts. Obviously, only a small fraction of the heavy metal which is administered can be localized in any region of malignant tissue, since a large proportion of it is retained in the skeleton and other tissues. In a few instances, following administration of lead phosphate, when we have been able to obtain operative specimens of the cancerous growth accompanied by adherent normal tissue, the lead content of the malignant tissue was distinctly greater than that of the normal tissue. This was illustrated by the operative specimen in Case 4 (Table I). Reports in the literature are at variance as to whether or not metallic lead has any specific localizing power in malignant tissue. The fact remains, how-
Table I: Patients with Cancer Who Received Adequate Treatment with Lead and for Whom Results Were Satisfactory

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (years) and sex</th>
<th>Amount of lead given, in mg., and when</th>
<th>Lesion</th>
<th>Lead intoxication</th>
<th>Other treatment</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>44 F.</td>
<td>157.5 after amputation</td>
<td>Carcinoma of left breast, grade 3, with glandular involvement</td>
<td>Severe</td>
<td>Radical amputation, 3-30-31. Two courses of roentgen ray</td>
<td>Well: August 1934</td>
</tr>
<tr>
<td>2</td>
<td>40 F.</td>
<td>577.5 after excision</td>
<td>Carcinoma of left breast</td>
<td>Severe</td>
<td>Excision elsewhere, November 1930. Recurrence, April 1932, with excision at clinic</td>
<td>Well: June 1933</td>
</tr>
<tr>
<td>3</td>
<td>37 F.</td>
<td>277 (plus manganese) after excision</td>
<td>Fibrosarcoma of right breast with glandular involvement</td>
<td>Mild</td>
<td>Simple amputation, 5-12-33. Three courses of roentgen ray</td>
<td>Well: September 1934</td>
</tr>
<tr>
<td>4</td>
<td>51 F.</td>
<td>507, October 1932</td>
<td>Adenocarcinoma of breast, grade 3, with glandular involvement</td>
<td>Very severe</td>
<td>Radical amputation, September 1932. October 1932, courses of roentgen ray</td>
<td>Well: July 1934</td>
</tr>
<tr>
<td>5</td>
<td>27 F.</td>
<td>420, July 1932</td>
<td>Melano-epithelioma of left leg</td>
<td>Very severe</td>
<td>Excision of lesion, July 1932</td>
<td>Well: December 1934</td>
</tr>
<tr>
<td>6</td>
<td>34 M.</td>
<td>646, 1930</td>
<td>Melano-epithelioma of right foot, grade 2, with metastasis to groin</td>
<td>Very severe</td>
<td>Excision of necrotic nodes of groin after treatment</td>
<td>Well: November 1934</td>
</tr>
<tr>
<td>7</td>
<td>36 F.</td>
<td>892.5, February 1931, June 1931, May 1932</td>
<td>Epithelioma of left Bartholin's gland, grade 2</td>
<td>Very severe</td>
<td>Excision, 1924, and radium. Recurrence, February 1931</td>
<td>Well: September 1934</td>
</tr>
</tbody>
</table>

ever, that exceedingly minute amounts of lead, when present in a cancerous growth, apparently result in a destruction of the tumor. Hence the primary object behind this type of treatment is the administration of a quantity of lead sufficient to result in a lead intoxication and at the same time produce toxic effects in the tumor. In only a few instances was generalized systemic lead intoxication difficult to control.

So that careful control might be obtained in all cases, the following routine studies were adopted. Before the beginning of treatment the blood was studied from the standpoint of hemoglobin and erythrocyte content, and it was examined for basophilic stippling and to ascertain the nature of the leukocytes. Estimations of blood urea were made in all cases, combined renal function was studied, a twenty-four hour specimen of urine was examined before, and at intervals after, treatment, the lesion was photographed, and, when possible, biopsy was
Colloidal lead phosphate, 1 c.c. of which contained 3.5 mg. of lead, was administered intravenously and exceedingly slowly with a Luer syringe of 10 to 50 c.c. capacity. The initial amount injected was usually 10 c.c. If the slightest systemic reaction to this foreign material occurred, the injection was discontinued at once. In the main, however, little or no reaction occurred if injections were given slowly. Increasing amounts were given, so that a course of treatment consumed approximately two weeks.

* In February 1935, after this article was in type, abdominal metastases were discovered.
We were not able to give the lead selenide by the Luer syringe because of the frequency of thrombosis of veins. Hence, in the cases in which it was used, it was given in great dilution by the gravity method.

Since a review of the work of the years preceding January 1, 1932, suggested to us that to receive benefit from lead it seemed necessary for patients to pass through a stage of lead intoxication, during the years 1932 and 1933 we aimed to give at least 400 mg. of lead in a course, if the patient’s general condition permitted it. In some the immediate reaction was so severe that relatively small amounts could be given. To 57 of the 81 patients treated in these two years, however, more than 400 mg. were given. In 27 cases between 400 and 500 mg. were readily tolerated; in 30 cases more than 500 mg., and in one case 892 mg. were given. In 24 cases the immediate reactions were so severe or the patient’s general condition was so poor that we did not feel justified in giving the full 400 mg. The 81 patients received a total of 476 intravenous injections of lead, the average total dose administered being 440 mg.

The lesions treated included 15 carcinomas of the breast with metastatic growths (Fig. 2), 19 of the large intestine (including 2 of the colon, 3 of the cecum, 5 of the sigmoid, and 9 of the rectum), 10 of the stomach, 17 of the pelvic organs (including 3 of the cervix uteri, 3 of the ovary, 1 of the body of the uterus, 1 of Bartholin’s gland, 1 of the labia minora, and 5 so extensive that the original lesion could not be determined), 8 of the structures about the head (including 2 of the face, 1 of the antrum, 1 of the lip, 1 of the larynx, 1 of the salivary gland, 1 of the nasopharynx, and 1 of the tongue), 4 of the genito-urinary organs (including 1 of the bladder, 1 of the prostate gland, and 2 of the kidneys), 5 of the lymph nodes (metastatic from distant lesions), and 3 melano-epitheliomas of the lower extremities and 2 of the abdominal wall.

All the patients had extensive and inoperable lesions. Sixty are
known to be dead; 14 are known to be living and have been carefully examined at the clinic and found to be free of carcinoma\(^2\) two or more years after treatment. Of these 14, 7 had treatment by roentgen rays or radium, or both, in addition to the lead; 7 received only lead. The other 7 patients (Table II) have not been examined at the clinic recently; some of them may be dead, and several are known to have suffered recurrence of the neoplasm.

Table I is a review of the cases in which the patients were alive at the time of this report. It is difficult to convey the true picture of the advanced disease in these cases. Simple amputation of the breast was performed in Case 3 because it was felt that more radical surgery was not warranted. Only biopsy of the cervical nodes was done in Case 8 (Fig. 3) because of the apparently hopelessly extensive involvement.

![FIG. 3. Extensive Lesion of the Neck](image)

This patient was treated in June 1932; he was well in December 1934.

When resection was performed and lead given later, the surgeon had been unable to remove all of the cancer and had asked that lead be given as an adjunct. When lead was given, and treatment with radium and roentgen rays as well, the cases were of the type in which the radiotherapist held out little hope for satisfactory results from his treatment and combined treatment seemed indicated.

It will be noted that in Cases 2, 5, 6, 10, 11, 13, and 14 treatment by irradiation was not employed, that all patients received large amounts of lead and suffered lead intoxication, and that, as far as can be determined by any known objective examination, those patients\(^2\) are free from cancer. All the follow-up reports are the result of careful examinations at the clinic at the time recorded in Table I.

The other patients in this group received combined radiotherapy

\(^2\) Except Case 14. See Table I.
and lead. All these patients received colloidal lead phosphate, except the one in Case 6, who was also given lead selenide and those in Cases 3, 10, 14, and 20, who in addition to the lead phosphate preparation received manganese.

In Table II are listed the cases in which the patients are known to have had recurrent or metastatic lesions or from whom satisfactory reports could not be obtained by virtue of their inability to return for examination.

Case 6 (Table I) is of particular interest. The lesion in this case was huge and the lymph nodes of the groin formed a large nodular mass

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (years) and sex</th>
<th>Amount of lead given, in mg., and when</th>
<th>Lesion</th>
<th>Lead intoxication</th>
<th>Other treatment</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>F. 63</td>
<td>325.5</td>
<td>Adenocarcinoma of body of uterus, grade 4, with extension to broad ligaments and pelvic wall</td>
<td>Mild</td>
<td>Excision. Extensive treatment with roentgen rays and radium</td>
<td>Living 3 years after treatment. Not examined</td>
</tr>
<tr>
<td>16</td>
<td>F. 31, April 1932</td>
<td>273</td>
<td>Carcinoma of ovary, grade 3</td>
<td>None</td>
<td>Removal of all pelvic organs, 3-23-32</td>
<td>Living but has not been examined recently</td>
</tr>
<tr>
<td>17</td>
<td>F. 45, July 1932</td>
<td>507.5</td>
<td>Carcinoma of right breast with axillary and cervical involvement of lymph nodes</td>
<td>None</td>
<td>None</td>
<td>Living but has not been examined subsequently</td>
</tr>
<tr>
<td>18</td>
<td>M. 60, December 1932</td>
<td>409.5</td>
<td>Carcinoma of prostate gland, grade 2</td>
<td>None</td>
<td>Prostatectomy, 11-11-29</td>
<td>Living (4-29-34) but helpless owing to metastasis</td>
</tr>
<tr>
<td>19</td>
<td>M. 57, August 1933</td>
<td>490</td>
<td>Epithelioma of tongue, grade 3, with metastasis</td>
<td>Moderately severe</td>
<td>Biopsy. Roentgen rays and radium</td>
<td>Not traced</td>
</tr>
<tr>
<td>20</td>
<td>M. 46, February 1933</td>
<td>210</td>
<td>Carcinoma of pylorus, grade 4</td>
<td>Moderately severe</td>
<td>Partial gastrectomy</td>
<td>Home physician reported patient well and at work, November 1933, and May 1934; not so well August 1934</td>
</tr>
<tr>
<td>21</td>
<td>M. 30, July 1932</td>
<td>542</td>
<td>Carcinoma of stomach, grade 4, extensive glandular involvement</td>
<td>Partial gastrectomy, 6-20-32</td>
<td></td>
<td>Examination at clinic, 4-10-33, revealed recurrence of epigastric mass with jaundice</td>
</tr>
</tbody>
</table>

Table II: Patients with Cancer Who Received Adequate Amounts of Lead Who Are Known to Have Recurrent or Metastatic Lesions or from Whom Satisfactory Reports Could Not be Obtained (These Patients May be Living)
of tissue. This mass of nodes became necrotic during the course of treatment, so that very little neoplastic tissue could be found when they were excised for study. The patient received no other treatment than lead and was well four years after treatment. Granting the fact that melano-epitheliomas have been known to behave strangely under various forms of stimulation, and at times have been thought to disappear spontaneously, it still remains a fact that this one disappeared during treatment with lead.

**Summary and Comment**

This is a summary of our experiences with the use of lead in the treatment of cancer. The treatment has been applied only in cases thought to be hopeless from the standpoint of other single therapeutic agents. Lead intoxication seems necessary to produce favorable effects from the lead. Lead has an unfavorable effect on neoplastic tissue. These observations would suggest two important approaches to the treatment of cancer: (1) by providing a suitable vehicle to transfer lead into cancerous tissue by the systemic route, and (2) disturbing bodily metabolism by the introduction of a substance that will hinder the growth of cancer.

The attack on the cancer problem from the standpoint of systemic treatment is an important one. The present methods of administering lead and other allied substances do not provide the answer to the many questions about cancer. They may afford, however, a possibility for future research.

For the present, lead seems to have a field of usefulness in conjunction with surgery. When size, extent, and situation of a malignant growth make its complete removal impossible, the intravenous injection of lead seems to do something to bodily metabolism that tends toward suppression of the remaining cancer cells. Possibly the same thing would be true if cancers were treated with lead very early. The opportunity for a trial of this has not been afforded.

Reports of others and our own studies would suggest a further usefulness of lead in conjunction with radiotherapy. In this field much more intensive experimentation and trial seem warranted.

Systemic treatment with lead affords just one additional hope, but we believe a more important one than has hitherto been thought, for the control of cancer.

**Bibliography**


