

CHAPTER 15

THERAPEUTIC APPROACH TO CANCER

ONE OF THE ULTIMATE AIMS of our research has been to try to utilize in cancer the knowledge obtained from investigations of the general problems of pathology and therapy. Encouraged by the results of biologically guided therapy in many other conditions, we have applied it to the treatment of malignancy.

As we have mentioned before, differences between animal cancers, both experimental and spontaneous, and human cancers represent one reason why an agent, however good its results in animals, may not apply to human malignancy. Another factor, conduct of treatment, is no less important. The main characteristic of our therapeutic approach resides in the fact that treatment is continuously guided by data representing the actual condition of the subject. At least for the moment, it appears impossible to recognize, through suitable tests, the patterns present in animals so as to apply them to guided therapy. Therefore, we have been obliged to do our therapeutic research in humans, reserving animal studies for limited problems. This situation had led us to emphasize, always, the experimental nature of our therapeutic efforts in humans. Although we started with desperate terminal cases, frank immediate subjective and objective benefits, even though temporary, were obtained frequently enough to encourage us to go on. Together with the above mentioned considerations, they seemed to justify the continuation of therapeutic research in human patients. We will try to review as objectively as possible the results obtained with therapeutic methods and agents evolved over the years.

In 1927, a 33-year old woman with typical preterminal cancer of the stomach came under our care. In the highly emaciated patient, a hard,

irregular mass filling the entire epigaster was palpable. Radiological examination indicated a prepyloric gastric tumor. Laparotomy showed an inoperable tumor of the stomach, with the omentum and lymphatic glands greatly involved and evidence of multiple peritoneal and liver metastases. In view of the patient's general condition and the fact that the pylorus was only partially obstructed, no surgical procedure was performed other than biopsy of one of the metastases in the omentum. The biopsy showed an adenocarcinoma Grade III of gastric origin. Treatment was not prescribed.

I saw the patient two years later in apparently good health. Clinical and radiological examination at that time showed no tumor. The patient attested to receiving no treatment. At the time of the operation she had been two months' pregnant. We had attributed her amenorrhea at that time to the advanced cachectic condition. She had given birth at term to a normal girl. Hers was one of those cases usually catalogued as "spontaneous remission."

Since then, I have analyzed many of the published observations of cases of so-called "spontaneous remission" of cancer always to find a turning point that coincided with the intervention of some event usually considered to have no possible significance for malignancy. The fact that such events have not induced similar changes in other cancer patients has made them seem unimportant to many investigators.

While not regarding them as the only cause of favorable changes, we have not eliminated the possibility that such events may have a contributory role. We must recognize that, if such events in themselves appear to be powerless to change the course of cancer, they may intervene in conjunction with, and potentiate, another factor also powerless in itself to induce a change.

It was with this concept in mind that we reviewed the case of the woman with stomach cancer. We considered the possible effects of two factors which apparently intervened concomitantly: pregnancy and surgery. We then began a series of experiments.

Ehrlich mammary carcinoma was grafted in two groups of female mice, one pregnant and the other not. In each group, half of the mice were kept as controls while the other half was submitted to a sham surgical procedure consisting of a laparotomy in which multiple ligatures were performed. Growth of the tumors and survival times were noted. Compared with non-operated, nonpregnant mice serving as controls, both the pregnant mice and the surgically treated mice showed a slowing down in the evolution of cancer lesions. It was in the group of mice, both pregnant and surgically treated, that a temporary arrest in tumor evolution was seen. In some ani-

imals even temporary regression was noted; in 1/20 the tumor regressed entirely.

Placenta Extracts

These experiments led us to try an extract obtained from placenta autolysates which, in our opinion at the time, would reproduce, up to a point, some of the conditions present in these experiments. Human placentas were autolyzed by being maintained from several hours to a few days at 37° C, and an alcoholic extract was obtained. The alcohol was eliminated through distillation in vacuum. The residue proved non-toxic in animals and was injected intramuscularly in some terminal cancer cases.

Impressive results were observed in the first cases. Pain was markedly diminished and, in some instances, disappeared entirely. Objective changes in the tumors could be noted. While only temporary results were seen for most of these cases, for some the results appeared to last a long time. Their number would exclude pure coincidence.

Mr. H. B., 56 years old, came under our care with a cancer involving more than half of the right part of the tongue. Multiple large submaxillar and cervical gland metastases were present, two of them being approximately 8 cm. in diameter. The mouth lesion was very painful and bled occasionally; there was moderate pain in the ganglionic metastases. A biopsy performed at a much earlier stage had shown a squamous carcinoma. Considered inoperable, the subject had not received any treatment except for pain palliation.

We administered daily intramuscular injections of 5 cc. of the placenta extract. Except for a limited local reaction at the site of injection, no disagreeable effects were seen. On the contrary, after each injection, the pain in the tongue was reduced for a few hours. It disappeared entirely after one week of treatment. During the second week of treatment, the tumor of the tongue, as well as the metastases, began to decrease in size. The local reaction at the site of the injections increased, however, to such an extent that we were obliged to stop treatment after 5 weeks. In spite of this, the lesions continued to decrease so that the tongue tumor was no longer palpable after two months. At that time, the gland metastases were reduced to approximately one and a half centimeters in diameter. The patient's general condition was much improved and he gained weight. In another month, except for a scar on the tongue, no other pathology could be found. We followed this case without treatment for another year and a half during which time there was no recurrence. After that, the patient left town and we were unable to reestablish contact with him.



Mrs. B. A., 44 years old, came under our care with a massive tumor filling the entire vagina. The condition had been diagnosed 8 months previously as carcinoma of the cervix which had invaded the parametria and was propagating toward the vagina. A biopsy made at that time indicated squamous carcinoma Grade III. As the patient was considered inoperable and refused any other treatment, only sedation was prescribed. When we examined her, the tumor was protruding from the vagina as a hard mass. Rectal examination revealed invasion of the entire recto-vaginal wall. The patient received a daily injection of the placenta extract preparation for 45 days, after which she interrupted the treatment. The pain had been entirely controlled in less than a week, but no other changes had been observed.

She returned three months later, having received no treatment in the interval. Examination revealed complete disappearance of the vaginal tumor, with the cervix entirely replaced by soft scar tissue. We followed this case for two years, during which no further treatment was given and the patient showed no recurrence.

Mr. A. N., 40 years old had an extensive cancer of the cheek, with massive ulceration resulting in a large communication between oral cavity and exterior. Occasionally small hemorrhagic episodes were experienced. The patient had had several courses of radium therapy. When he came under our care, he had multiple lesions, and several biopsies performed at that time revealed active carcinoma in all lesions tested. The patient received intramuscular injections of 5 cc. of the placenta extract preparation daily for 17 days. A massive hemorrhage occurred at this point, treatment was stopped, and he went home without further medication. When the patient returned three months later, scar tissue covered all areas where the tumor had been seen previously. Clinically no trace of tumor could be found. In a few months, the patient's condition was good enough to allow his surgeon to attempt a skin graft to cover the big opening in the cheek. This was not successful. The graft from the skin of the neck unfortunately underwent necrosis.

In several other cases, similar subjective and objective changes were observed with use of the same alcoholic extract of human placenta autolysates. During this time, we attempted to substitute cow placenta, utilizing both fetal and maternal parts, which are easily separable in the cow. In a relatively small number of cases in which these products were used, we could see no differences in the influence of placenta extract according to origin. Poorer results were obtained with extracts using fresh placenta in-

stead of the autolysate. However, certain interesting clinical results indicated that fresh placenta still has a capacity to influence what can be considered to be the normal course of cancer. The following case is an example.

Mrs. C., 54 years old, had a tumor of the rectum which was considered inoperable. Only a colostomy was performed. Pain was slight and no other treatment was instituted. Several months after the colostomy, the patient came under our care. At that time, the tumor filled the entire rectal ampulla. Treatment with the fresh cow placenta alcoholic extract was started, using intramuscular injections of 5 cc. daily. After less than a month of treatment, the tumor diminished in size, leaving a small passage for the examining finger. After another month and a half, the tumor had entirely disappeared and the rectal ampulla was wide open. Proctoscopic examination showed only normal mucosa. This case was followed for two and a half years with no evidence of recurrence. Thereafter, because of the war, we lost touch with her.

In spite of such results in a few cases however, extracts of fresh placenta were judged to be much less effective in general than extracts of placenta autolysates.

At the beginning of our research, still unaware of the dualism intervening in cancer pathogenesis, we observed a series of cases in which the placenta preparations in general produced undesirable results, such as increase in pain intensity. Furthermore, when used in higher doses over a longer period of time, it induced new pains which clearly increased with each subsequent injection. For a while, this fact made us limit the use of the product to only those patients showing favorable responses in pain, until we could find an explanation for these paradoxical results.

With the progress of our research and recognition of dualism in the pathogenesis of pain, we limited the use of the placenta extracts to patients with an acid pattern of pain. This improved the subjective and objective results, and reduced the cases in which undesirable effects occurred. In over 100 terminal patients treated with this preparation between 1935 and 1938 in different hospitals in Paris, objective improvement was observed in 20%. In a few, tumors disappeared. Acid pattern pain was relieved. In many of these cases, however, after a period in which the tumor decreased in size, or even clinically disappeared, it started to grow again and could not be influenced by further treatment. Furthermore, when the dose was increased, other pathological manifestations appeared. The following cases are examples.

Mrs. B. B., 42 years old, came under our care with severe pain result-



ing from a widely ulcerated cancer of the cervix involving the parametria and the vagina. 5 cc. of the cow placenta extract was administered daily and the patient remained without pain for almost three weeks, after which time the pain returned. An increase in dosage—to two injections of 5 cc. daily and then to two injections of 10 cc. daily—resulted not only in an increase in pain but also caused the appearance of an abundant watery vaginal discharge. In a few days this reached several liters a day. Despite the fact that we stopped treatment, the exudate continued to increase. At one point, it amounted to 8 liters in 24 hours. The very concentrated urine was reduced to less than 200 cc. in 24 hours. The patient died in ten days in spite of all attempts to stop the excessive secretion.

Mrs. G. L., 48 years old, had a radical mastectomy for a left breast adenocarcinoma. A rapidly growing local recurrence was seen 6 months later. The patient came under our care with an ulcerated tumor occupying the entire left half of the chest. Administration of 5 cc. of cow placenta extract for two weeks not only increased the burning sensation present but caused the appearance of an abnormally abundant watery exudate. As is often true in such cases, an infection with *B. pyocyaneus* was seen. A clear fluid was observed surging in drops from the ulcerated lesion. By weighing the dressing, the amount excreted was measured and found to exceed 10 kilos a day. Despite use of saline infusions, calcium preparations, vitamin C in high doses, atropine, and other measures, the patient expired in less than a week. The appearance of such complications, the frequent changes toward alkaline patterns of pain, and the increase of intensity of alkaline pattern pain, made us reduce and ultimately stop use of these placenta extracts in spite of some good results obtained.

Cod Liver Oil Fatty Acids and Sterols

At the same time, progress in our research had led us to recognize, in addition to dualism in the pathogenesis of many manifestations, the special role played by lipids. In 1938, we began to use two groups of antagonistic lipids, fatty acids and sterols. We started with a mixture of fatty acids prepared from cod liver oil for one group and with cholesterol for the other. Later we utilized only the polyunsaturated members from the group of cod liver oil fatty acids.

Fatty acids were administered intramuscularly in oily solutions or in gelatinous capsules by mouth. As with administration of placenta extract, the immediate effect was favorable on pain of an acid pattern, and adverse on alkaline pain. In both cases, the effect occurred in a few minutes. Therapeutic attempts with fatty acids were consequently limited to patients with

an acid pattern pain and with this restriction, pain was efficiently controlled. We used the effect upon pain as a criterion, and we discontinued treatment in any case in which fatty acids induced or increased pain.

Subsequently, along with the effect upon pain, we used urinary pH and specific gravity as criteria for treatment with fatty acids. A persistent high urinary pH and a low specific gravity were indications for the use of these substances. In addition to the control of severe pain, interesting objective changes occurred. Unfortunately, most of them were only temporary. The following two examples taken from a group of 15 similar cases are illustrative.

L. B., 66 years old, had cancer of the right lung for which he had received only symptomatic treatment. For more than a month the patient had complained of pain in the right chest, with increasing breathing difficulty. Chest X-ray examination revealed a tumor of the right lung extending from the mediastinum into the medium lobe. A diagnosis of bronchogenic cancer was made. Subsequent X-ray examinations showed rapid growth with several tumors in the upper lobe and in the left lung. The general condition was rapidly and progressively deteriorating, the dyspnea and pain increasing. Two months after first symptoms, the patient was bedridden.

When the patient came under our care a few weeks later, he was dyspneic, slightly cyanotic, had persistent cough, was extremely fatigued and in almost continuous pain. By this time, we had started to use urinary specific gravity and pH as criteria for the recognition of the offbalance present. Because of low specific gravity and high urinary pH, the patient was given oral treatment with cod liver oil fatty acids. Gelatinous capsules containing 0.25 gm. of the fatty acid mixture were used in a starting dose of 0.5 gm. a day, and were increased progressively to 1.5 gm. a day. The patient made an impressive gain in a few days of treatment. The pain disappeared entirely, as did the dyspnea. The cough also almost disappeared in a few days, and in two weeks the patient was able to get out of bed. The improvement continued, and in less than two months, the patient was even able to go horse-back riding. Radiologically, the tumors also showed progressive regression. We continued the treatment with a relatively high dosage—2 grams of cod liver oil fatty acids daily—for a total of two months, with evidence of continued improvement. Then, suddenly, symptoms of pulmonary congestion became apparent and the general condition rapidly became worse. Urine analyses now showed a high specific gravity and a low pH. In spite of discontinuing the medication, the patient was back in bed with increasing dyspnea. He died two weeks later with symptoms of pulmonary edema.

Mrs. D. A., 68 years old, had a cancer of the left breast for which she had undergone a radical mastectomy four years previously. Pathological examination of the lesion had shown an adenocarcinoma Grade IV, with ganglionic involvement. When the patient came under our care she was bedridden with a diagnosis of multiple bone metastases. Radiological examination showed multiple osteolytic lesions in the pelvis, femur, lower spine, ribs and skull. We instituted treatment with cod liver oily fatty acids in gelatine capsules. The dose was progressively increased, by 0.25 gm. increments, until it reached 3 grams a day. Ortho-phosphoric acid was added orally in doses of $\frac{1}{4}$ cc. of a 50% solution given in water in order to control the pain which appeared after administration of the capsules and was of an alkaline pattern. Improvement began in a few days and continued so satisfactorily that in less than six weeks the patient was up and about. Five months later, with bone lesions healed, the patient went home. I saw her in 1941, almost two and a half years later, during which time no treatment had been given. When examined at that time, she appeared in excellent condition. Subsequently, because of the war, I lost contact with her.

The increase of pain, and especially the frequent appearance of pain of an alkaline pattern after extended treatment, considerably limited the use of these cod liver oil fatty acid preparations. Furthermore, an inconsistency in objective changes was seen even when administration was guided by the acid or alkaline character of the pain. In most patients, favorable objective changes were only temporary.

During this research, we observed a very favorable response in some cases of hemorrhage, especially of the long-term oozing type, treated with these preparations. Bleeding usually stopped after one injection of 1 cc. of a 10% solution of unsaturated members of cod liver oil fatty acids. We still use this preparation for this purpose, as mentioned previously.

Among the group of lipids opposed to fatty acids, we first used cholesterol with the intention of trying to influence pain having an alkaline pattern. The effect was much less impressive than that obtained with fatty acids in pain of acid pattern. In some cases, objective changes also were observed although they were less frequent and less profound than those seen with the fatty acid preparations. Cholesterol alone never produced total clinical disappearance of tumors.

Acid Lipidic Fractions and Unsaponifiable

The development of the concept of dualistic pathogenic intervention of two groups of lipids led us to a treatment employing these two types of lipid constituents of the body chosen according to the character of the

manifestations. We obtained from different organic sources the insaponifiable fraction as well as the acid lipid fraction. Human placenta was widely employed. The two preparations, acid lipid and insaponifiable fraction, were used until 1943 on about 200 patients (in France, and Mexico). Some good subjective and objective results were observed. The subjective changes were most impressive. Frequently, an injection of only 1 cc. of the human placenta acid lipid preparation (5% in oil) controlled pain in a few minutes, with relief lasting for hours or sometimes even days. With the same preparation, alkaline pain increased after only a few minutes and sometimes became unbearable. In cases treated with placenta acid preparation, using acid pain pattern as a criterion, we observed some significant objective changes.

Mrs. B. B., 54 years old, with a papillary adenocarcinoma of the ovary and multiple peritoneal metastases found during exploratory laparotomy, had rapidly reproducing ascites. The patient required repeated paracenteses at short intervals. In the month just prior to coming under our care, it had been necessary to tap her once a week or even every five days. Treatment with acid lipids of placenta was instituted, with daily injections, first of 1 cc. and then of 2 cc. of the 5% oil solution. In less than two weeks, the pain was controlled and much less fluid accumulated. The patient had two more paracenteses at two and three week intervals, after which fluid no longer was a problem. The multiple tumor masses, which were very easily felt through the skin after each paracentesis, were seen to decrease rapidly and disappeared in about two and a half months of treatment. After four months, treatment was discontinued and no recurrence was seen during the three years we followed this patient.

We saw Mrs. L. S. N., 73 years old, in 1942 in a subcomatous state, with deep jaundice and with a history of primary tumor of the stomach and multiple big metastatic lesions of the liver. Her condition, which had started a few months earlier, was getting rapidly worse. When we examined her, the liver was occupying the abdomen until the pubis, and practically each of the individual metastatic tumors present at the surface of the liver was easily palpable through the thin abdominal wall.

Guided by the urine analyses—with a high pH and a low oxiredution index—we started with a treatment with 10% solution in oil of a human placenta lipoacid preparation. The doses were increased according to the analyses until they reached 3 injections daily of 2 cc. each. The patient improved, and in less than a week she was conscious again. Her condition continued to improve for more than a month when a rapid change for the worse took place. As the analyses at this time showed the opposite offbal-

ance present, the treatment was changed. In addition to infusions with glucose and saline, glycerol in a dose of 8 drops daily with 20 drops of coramine was given. Again the response was impressively good. The general condition improved rapidly and in less than a month, the patient was out of bed and started to take care of her home. By this time, the jaundice had almost completely disappeared, although the liver remained almost of the same dimension. The patient continued to take glycerol for more than 6 months, leading an absolutely normal life. It took almost one year for the liver to come back to normal dimensions. The patient remained in perfect health for the next 9 years. Several coronary occlusions led to her death at the age of 83, from a myocardial infarction. She showed no objective or subjective signs of recurrence of either her stomach or liver condition.

Unfortunately, uncontrollable changes toward rapid tumor growth ultimately occurred in most cases treated with placenta acid lipids despite favorable objective changes at the beginning of treatment.

Clinical use of the insaponifiable fraction preparations supported observations made in animals, indicating the importance of other factors for obtaining favorable changes in tumors. With the insaponifiable fractions of placenta, marked clinical effects could be obtained only when the condition of the patient permitted the treatment to be continued for a long time. Temporary regression or even clinical disappearance was effected in several cases, only to have the tumors start growing again, this time beyond control by the medication. Even at this point, it was obvious that favorable influence with these two antagonistic groups of lipids was dependent on using the lipid which corresponded to the pattern present. It became increasingly evident that changes in the pattern occurred during treatment. Administration of acid lipidic and insaponifiable fractions induced unfavorable responses in patients with tumors in which a predominance of the same lipids was indicated by analyses. Pain increased and unfavorable changes occurred in the evolution of the disease. For example:

Mrs. A. D., a 42-year-old woman, operated on for an adenocarcinoma of the breast 18 months prior to coming under our care, presented a few skin lesions near the operation scar. Radiological study revealed a few small osteolytic lesions in two ribs, and one in the skull. The analytical data showed low urinary pH, high specific gravity and high chloride index, indicating an offbalance which we attributed to predominance of fatty acids. Treatment with 2 injections daily of 1 cc. of a 5% oily solution of the insaponifiable fraction of placenta was started. This was later increased to 2 cc. twice a day. The patient left the city for a summer vacation and took the medication with her. Disregarding our instructions that treatment must

be guided by further analysis, she continued it without interruption for four weeks, despite a rapid change in her condition and a constant increase in the pain after each injection. When we saw her again a month later, all the analyses had changed markedly, indicating the appearance of an opposite offbalance. Clinically, the condition also had changed. The skin was extensively involved in the vicinity of the operative scar and multiple, rapidly growing metastases were seen all over. Radiological study showed extensive new lesions in many bones. The condition had progressed in one month in a manner never seen before in any patient and we had to relate it to continued use of medication after a change in the offbalance. This change was similar to that seen in animals with massive administration of the insaponifiable lipidic preparation. Switching to placenta acid lipid preparations quickly changed the evolution of the condition in this patient. Pain was controlled and for three months the condition seemed arrested. In spite of treatment, however, it started to evolve rapidly again after that and the patient died five months following her return from vacation.

Similar deleterious effects were seen with acid lipid preparations obtained from organs when their administration apparently was at variance with the pattern present.

W. S., 56 years old, had a carcinoma of the cheek mucous membrane which led to wide perforation. Biopsy of the edges of the ulceration showed squamous cancerous tissue. Based upon the urine analysis, which indicated low specific gravity and high pH, treatment consisted of two daily injections of 1 cc. of the acid lipid fraction of placenta in a 5% solution in oil. As the patient was treated on an ambulatory basis, he was advised to see us in a few days. He continued the treatment without any control for two weeks. When next seen, a marked gelatinous edema of the tissues surrounding the ulceration was found and the patient complained of severe pain. Biopsy at this time revealed, in addition to interstitial edema, a high vacuolization of the cancerous cells which had not been seen in the biopsy done the day prior to beginning treatment. The pain became unbearable a few minutes after each injection. These local changes were accompanied by a marked deterioration of the general condition, the patient complaining of a sensation of weakness. The unfavorable changes which occurred in only two weeks were very impressive.

Favorable results were obtained even in terminal cases with these fraction preparations. In some cases, arrest or disappearance of tumors was noted. In most cases, however, these effects were only temporary. After being arrested for months or even years by these lipid preparations, some tumors began to grow and to become painful and could not be as readily

controlled again by the same preparation. In a small number of patients, about 3% of the group of 200 treated with these preparations, the favorable results could be maintained over a number of years.

Even with the relatively strict guidance of therapy by the analyses available at the time, results were not always favorable. We attributed this both to the agents used for therapy and the criteria employed for recognition of offbalances. For a long time, research was devoted to developing means to permit better recognition of offbalances and to ascertain the value of the various analyses used as criteria for the conduct of treatment. Each new urine or blood test was investigated as a criterion for the group of lipids to be administered. This led to better results in controlling pain, improving the general condition and even in objective changes in tumors.

However, the temporary character of the effects obtained with lipids derived from normal organs appeared more and more evident in long-term appraisal of results. We changed from human placenta to other sources for both acid and insaponifiable fractions. We prepared and used lipids from different organs of cow, pig, fish, and chicken. We also used mollusks, chicken embryos, molds and even microbes, as well as milk and eggs as source for these lipids. In one group of investigations, we even tried to use lipids of the organ from which the tumor derived. Most of these preparations satisfactorily controlled pain, and in some cases, good results were seen in the growth of tumors.

The following observation concerns a case treated with the lipoacids of human blood.

A. M., a 56-year-old man, was referred to us by his physician with a diagnosis of cancer of the rectum. Difficulty in defecation, mucosanguinolent discharges, and pain in the rectal region had been increasing in the three months prior to the diagnosis. Examination had revealed a tumor of a cauliflower type, starting at about 4 cm. from the anal orifice and almost entirely filling the rectal ampulla. A biopsy had shown it to be an adenocarcinoma, Grade III. The patient had refused surgical intervention because, years before, a minor operation on his right hand had led to local infection followed by amputation of the hand.

At the time he was referred to us, his main complaints were pain in the rectum, radiating to the left leg, and tenesmus with frequent mucosanguinolent discharges. We employed daily injections of 1 cc. of a 5% oily solution of the acid lipidic fraction obtained from human blood. The treatment was continued for six weeks, the injection being given daily during the first two weeks and twice a week thereafter. After one week, the pain and tenesmus disappeared and there was a decrease in the mucosanguinol-

ent discharge. There was also an obvious decrease in the size of the tumor. In less than a month the tumor regressed to one-fourth its original size; in six weeks, digital and proctoscopic examination showed no clinical tumor. A whitish scar could be observed in the posterior wall of the rectum. Thereafter, the condition of the patient was followed indirectly through reports from his physician. There was no tumor recurrence in spite of the fact that he received no further treatment. He died six years later from an acute paratyphoid infection.

Our clinical experience provided ample evidence that the preparations rich in polyunsaturated fatty acids would influence pain as well as the growth and evolution of human cancers. Using the same amounts of poly-ethenic fatty acids prepared from various sources, no differences in effects could be noted. The effect upon tumors in all instances was relatively limited.

Our next effort was to try fatty acids unlike those found in the organism. They included norbixine—the monomethyl ester of the bicarboxylic acid, bixine—which we used in a group of patients between 1938 and 1940. With urinary specific gravity and pH as criteria, daily doses of from 1 mgr. to 100 mgr. were administered to 30 preterminal and terminal patients with patterns corresponding to predominance of sterols. Even with small doses, the changes toward a predominance of fatty acids were impressive. Superficial, massive tumors were often seen to melt away within a few days, usually leaving ulceration in their place. This rapid change of a massive tumor into an ulcerated one, however, usually was followed by a manifest deterioration of the general condition. With this preparation, once the offbalance was changed from the original to the opposite type, attempts to control the new offbalance were usually unsuccessful. This led us to discontinue its use at this time in spite of the rapid and intensive changes it induced in tumors.

Groups of Agents

Parallel to these researches on fatty acids, the use of agents with positive polar groups also underwent changes. As previously mentioned, it appeared increasingly clear that no single agent could be effective in itself if an offbalance corresponding to predominance of fatty acids was present. Quite early in this research it could be observed that the simultaneous use of two agents from the same group appeared to be a better procedure than using either agent alone. In a limited number of patients treated with single agents, without impressive clinical changes, better effects were obtained when combinations were tried. Although it was difficult to ascertain in

individual cases that favorable effects were due exclusively to change in medication, the following cases are interesting.

A. Ch., a 53-year-old woman, had a radical mastectomy for an adenocarcinoma of the right breast with axillar and supra clavicular ganglionic involvement. Almost two years later—during the three months immediately prior to the time we first saw her—she showed rapidly developing multiple metastases for which only symptomatic treatment was applied. Along with multiple bone metastases, and a recent pathological fracture of the inferior third of the right femur, there were liver metastases and a right pleural effusion for which she had been tapped three times. When she came under our care, she complained especially of pain in the lower back caused by lumbar and sacrum metastases. Her condition was considered terminal so that the surgeon did not think it advisable even to apply traction for the fracture of the femur. It was under these conditions that we started to treat her with two injections a day of 1 cc. of a 5% solution in oil of the insaponifiable fraction of human placenta. Except for the unexpected survival of the patient, no apparent change was seen after two weeks of treatment. The pain, pleural effusion and general condition remained the same.

The treatment was changed to 5 drops of glycerol three times a day, and the dosage was progressively increased to 15 drops of glycerol t.i.d. After ten days without change, Coramine in doses of 15 drops was given when necessary to control the typical alkaline pain. After another week there was still no change. The pain remained almost the same, except for a decrease in intensity immediately following administration of Coramine. When all three substances were given concomitantly—the insaponifiable fraction by injection and glycerol and coramine orally—the situation changed impressively. Within a few hours, pain disappeared completely, and within one week other manifestations had totally changed. The pleural effusion, for which the patient had been tapped regularly each week or every 6 days, disappeared. The fracture which, until then, had appeared entirely inactive, showed a consolidation so rapid that in less than two weeks a solid callus was present. In three weeks the patient was out of bed on crutches. X-ray pictures taken two months after the change in medication showed most of the osteolytic lesions replaced by new bone tissue and the fracture replaced by an abnormally solid callus. There was no fluid in the pleura. All treatment, except the glycerol, was discontinued after another three months when, at the start of the war, the patient left Paris. We heard that she continued in good health without further treatment for three more years, at the end of which time she developed a recurrence, with liver metastases, and died shortly thereafter.

M. R., a 58-year old woman, the wife of a professor of gynecology, had an ulceration of the cervix two years before coming under our care. Biopsy had revealed squamous carcinoma, Grade III. After local treatment with radium, she underwent total hysterectomy. Six months before we saw her, she developed multiple abdominal metastases for which only symptomatic treatment was prescribed. When she came under our care, she had a distended abdomen in which masses of various dimensions were easily palpable. Besides several large tumors, two of them about 15-20 cm. in diameter, there were many smaller ones which gave the distended abdomen a very irregular appearance. The abdominal pain, her generally poor condition, as well as severe edema of the legs, kept the patient bedridden. She showed a high urinary specific gravity and low pH, and treatment consisting of a daily injection of 2 cc. of a 2.5% solution of cholesterol in oil was prescribed. When no subjective or objective changes were seen in three weeks, the treatment was changed to 10 drops of glycerol orally, three times a day, for another three weeks. There was still no obvious change.

After another three week period, this time without treatment, during which her general condition deteriorated, mixed treatment with cholesterol and glycerol was started. The patient now made a sudden remarkable recovery. The edema of the legs disappeared rapidly and in less than a month the tumors were no longer palpable. The abdomen, however, continued to be distended, but instead of the previous irregularity with multiple well-delineated tumors, a single huge mass was recognized. It filled practically the entire abdomen. We made the diagnosis of a large ovarian cyst which had probably been present before but had been obscured by the multiple tumors. The patient was operated on three months later and the cyst was removed. Not only were no tumors found in the abdomen, but there were no adhesions which the surgeon had feared. White patches were seen at the sites previously occupied by the tumors. There were no recurrences during several years of follow-up, after which we lost track of the patient.

Similar results were obtained during the following years, indicating the value of mixed therapy. We made it our standard clinical treatment except when the pharmacodynamic effect of a specific agent was being investigated.

As an example of the objective changes obtained through mixed treatment for type D offbalance, we give an abbreviated form of the following observation.

Miss S., 39 years of age, came under our care with bone metastases from an adenocarcinoma of the breast, for which she had a radical mastectomy 1½ years previously. At admission in very severe pain, besides other multiple bone metastases, she showed especially a marked destruction



FIG. 154. Arterioposterior view of the chest of patient S at time of admission showing an osteolytic process in the 6th and 9th left ribs.



FIG. 155. Arterioposterior view of the chest of patient S 5 months later, with the appearance of the new bones replacing the part of the ribs previously destroyed.

of the 6th and 9th left ribs. (*Fig. 154*) The analyses showed an offbalance type D and consequently she was treated with butanol and glycerol. The patient showed rapid changes not only in her subjective feeling, but also objectively. *Fig. 155* shows the rib osteolytic lesions healed and the missing bone replaced by new bone.

In general, however, in spite of some favorable cases, the results were not satisfactory. Even in patients in whom tumors regressed and disappeared, recurrences were seen anywhere from a few months to several years after discontinuation of treatment. By prolonging treatment over a period of years, the period of improvement was lengthened in some cases. Still, all too often the response to treatment was only temporary.

Mercaptans

Other substances with lipoidic character but with a polar group different from the carboxyl were tested. Mercaptans, as lipoids with a thiolic negative polar group, were used. In 1942, we started to study the therapeutic effect of ethyl mercaptan injected intramuscularly, in a 10% solution in oil. (326)

Use of ethyl mercaptan had to be limited to subjects with an offbalance corresponding to a predominance of sterols. Although only a few patients were treated because of the offensive odor, the results were satisfactory as indicated by the following case histories.

F. C.—This patient, at the age of 66, had a small carcinoma of the tip of the tongue resected at Columbia Presbyterian Hospital on May 6, 1941. At the same time, a second carcinoma of the left lateral border of the tongue was found infiltrating into the deeper portions. This lesion was treated with radium needles with a total dose of 2500 mg. hours. In September 1941, a prophylactic left radical neck dissection was performed. The patient was well for 8 months thereafter, and then began to experience soreness in the region of the scar on the lateral side of the tongue.

In August 1942, 16 months after the tumor had been irradiated, the patient came under our care. At the juncture of the anterior and middle third of the left lateral border of the tongue, there was an induration of 2/1 cm. in dimension with an ulceration of 1/0.5 cm. covered by necrotic tissue. The indurated base was especially developed anteriorly to the ulcerated lesion. There was no evidence of recurrence at the scar of the tip of the tongue nor at the left side of the neck. The latter lesion was very tender. A Wassermann analysis was negative. Biopsy of the edge of the ulcerated tumor revealed squamous cell epithelioma.

The patient was treated with placental acid lipid fraction for the first

week without any subjective or objective change. The treatment was changed and the patient received 1 cc. of a 10% solution of ethyl mercaptan in oil intramuscularly, three times a day. The dose was increased after three days to 2 cc., three times a day. By the end of one week under this treatment, pain had disappeared, although there was still some burning sensation. The appearance of the lesion was unchanged. The treatment was continued. By the end of the second week, the edema was reduced, and after another week of the same treatment, the induration was gone. After one month of treatment with ethyl mercaptan, epithelization of the lesion was noted. The treatment was discontinued. The lesion appeared completely healed, without induration, burning sensation or pain, less than a week later. The patient has remained without treatment since, and there has been no recurrence in the last 18 years. Three years ago, the patient had a basal carcinoma of the skin of the nose, which responded well to local treatment with radium in Mexico.

Mrs. L. F.—In June 1942, the patient then 50 years old, observed an induration on the right border of her tongue. Biopsy revealed a squamous cell carcinoma. After the biopsy, the lesion progressed so rapidly that it was judged inoperable. Without having received any other treatment, the patient came under our care in August 1942. At that time, the tumor had involved the right half of the tongue and multiple submaxillary and neck nodes, the biggest being 2 cm. in diameter. The lesion was extremely painful. Urine analyses showed low specific gravity and high pH and the patient was treated with 10% ethyl mercaptan in vegetable oil. We started with three $\frac{1}{2}$ cc. injections daily. The dose was progressively increased until it reached 6 cc. daily. The pain disappeared entirely in less than a week.

Treatment was continued for only $3\frac{1}{2}$ weeks at which time there was a marked improvement in the tongue lesion and lymph nodes. Except for an inflammatory reaction at the site of injection, no side effects were seen. A month after the start of treatment, the lesions had completely disappeared. No treatment has been given since. The patient is still well today, free of recurrence, 18 years after treatment with ethyl mercaptan.

H. A.—In May 1942, at the age of 52, the patient developed hematuria, pyuria and tenesmus. In June 1942 an infiltrating tumor of the right side of the trigone was revealed by cystoscopy and cystogram. The patient came under our care at the end of August 1942. Having high urinary specific gravity, he was treated first with insaponifiable fraction of placenta, receiving 1 cc. of a 5% preparation in oil three times a day. Hematuria and the other symptoms increased under the treatment which was then changed to ethyl mercaptan, 10% solution in oil, starting with $\frac{1}{2}$ cc. three

times a day. The dose was progressively increased to 3 cc., three times a day by the tenth day. Hematuria decreased in the first 48 hours and ceased completely on the fourth day. Other symptoms disappeared. The treatment was continued with this dose for another 2½ weeks. Disappearance of the tumor was seen in follow-up cystograms. Without further treatment, the patient remained well until the beginning of 1955, 12½ years later, when a recurrence of the tumor of the bladder was noted. Being in Mexico, he did not receive treatment by this method and died from generalized carcinomatosis after 9 months. (*Figs. 156 and 157*)



FIG. 156. Cystogram of patient H.A. before treatment.

Similar favorable results were obtained for other patients with patterns corresponding to sterol predominance. We treated only three patients with patterns indicating fatty acid predominance. The use of ethyl mercaptan in these cases caused an exacerbation of symptoms and rapid deterioration of the general condition.

The odor of ethyl mercaptan was so offensive that its use posed insurmountable problems. Patients were forced to be social recluses and it was practically impossible to get nurses to administer the injections because of persistence of the odor on skin and clothes. We had many complaints that the odor of the medication polluted the atmosphere of a large area for

a long time. Obligated to discontinue its use, we sought other preparations containing thiol groups or bivalent sulfur that we hoped would have similar biological effects.

We investigated a large number of such substances in animals. Only a few were extensively studied in patients. Of the homologous series of aliphatic mercaptans, we utilized propyl, butyl and amyl mercaptans. These offered no advantage over ethyl mercaptan, being less active but hardly less offensive in odor.

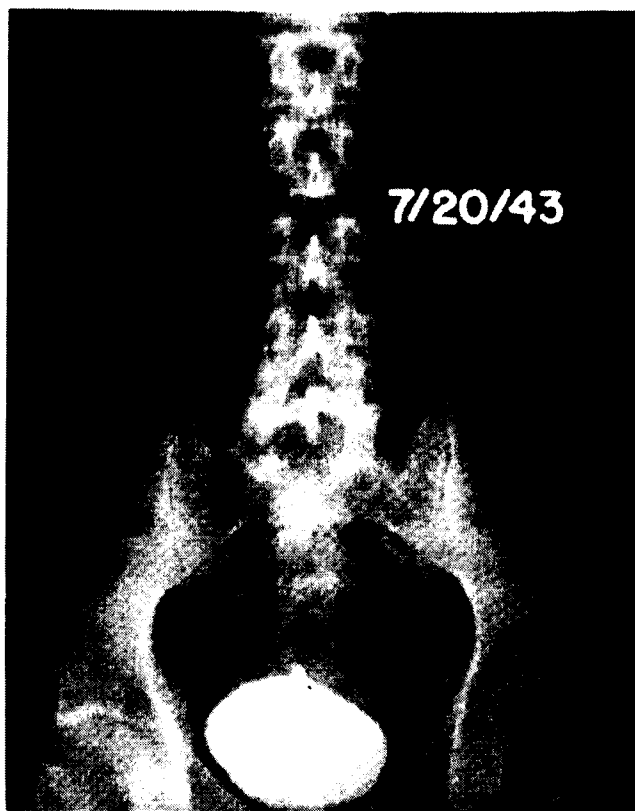


FIG. 157. Cystogram of patient H.A., after treatment with ethyl mercaptan.

Hexyl mercaptan was the first of the series that had a more bearable odor but it was definitely less active. Although objective changes in cancer were observed with its use, the tumors did not disappear as they did in some cases treated with ethyl mercaptan, and many favorable responses were only temporary.

Of the higher mercaptans, dodecyl and hexadecyl were most extensively studied. While their odor was far less objectionable, they produced less favorable results than the lower homologues. Much larger doses were required to influence pain, and even then the effects were reduced and tem-

porary. The striking results obtained with ethyl mercaptan could not be duplicated with any of the higher homologues. For this reason, we reluctantly abandoned the use of mercaptans.

Sulfurized Oil

During the years that followed, we tried to achieve results similar to those obtained with ethyl mercaptan by using other agents with bivalent sulfur. The one most commonly used was the so-called "sulfurized oil" containing fatty acid hydropersulfides, whose pharmacological characteristics have been discussed previously. Sulfurized oil's effects on pain and systemic manifestations were less impressive than those of the mercaptans but better than those of unsaturated fatty acids and their derivatives. In several cases, tumor disappearance was actually observed. Generally the clinical results were neither as consistent nor as persistent as with the mercaptans. With the use of this product alone, however, long-term favorable responses were the exception. For example:

Mr. I. G.—White male, was operated on at Maimonides Hospital in January 1950 at the age of 56. A pyloric mass was found and a subtotal gastrectomy was performed. Diagnosis of adenocarcinoma of the stomach was made. Microscopic examination showed a large area of replacement of gastric mucosa by atypical glands, with a great mass of abnormal cells invading the submucosa. These cells extended into the first part of the duodenum. There were post-operative complications with abscess formations in the wound, which were incised and drained. With new complaints of pain in the upper abdomen, and rapid loss of weight, the patient was admitted to Monticello Hospital in July 1950, and to Kings County Hospital twelve days later. He was then transferred to a nursing home with a diagnosis of terminal cancer with recurrent tumor in the upper abdomen and metastases to the chest. He remained at the nursing home for seven weeks. In September, he came under our care.

At this time, he had lost 39 lbs., and complained of extreme weakness, pain in the lower chest and upper abdominal region, and cough with hemoptoic sputum. The pain was only slightly relieved by narcotics and the general condition of the patient was considered very poor. A large mass was found occupying the entire upper abdomen; X-ray examination of the chest showed masses in the right lung. No fluid was obtained from several chest punctures.

Based on the urinary analyses, the patient was treated with a preparation of hydro-persulfide. The response was excellent. Not only was his pain rapidly relieved but the mass in the abdomen progressively decreased in



size. Evidence of lung involvement slowly disappeared in X-ray studies. After November 1950, he continued the treatment at home for over 13 months after which he resumed his old job as a millinery cutter. He had gained 55 lbs. since beginning treatment. For the past 7½ years, he has worked without interruption and there has been no clinical evidence of malignancy. The extreme condition under which the patient came into our care can explain the length of time needed for general recovery and his inability, despite disappearance of the tumoral masses within a few months, to resume his job for more than a year.

Thiosulfates

We also utilized sodium thiosulfate in many patients where symptoms such as pain, vertigo, itching, etc., could be related to a local acid pattern. In these specific cases, the results were generally satisfactory. Sodium thiosulfate was administered either orally in drops of a 10% solution in water, or parenterally in a 4% solution in water. Intramuscular and subcutaneous injections were well tolerated even when doses were as high as 10 cc. Doses as small as 10mgs. were observed to influence symptoms in certain patients. However, in some cases it was necessary to give as much as 5 gr. of the substance—125 cc. of the parenteral solution—in 24 hours to obtain any effect. In these cases there were no apparent side effects even when this dosage was continued for many days. Effects upon tumors with the use of thiosulfate alone were seen in several cases but the treatment did not produce complete disappearance and results usually were only temporary.

The use of sulfurized oil in conjunction with sodium thiosulfate has been tested in a sufficient number of cases (more than 75) to enable us to recognize that the combination produces changes in pain and systemic analysis, as well as reduction in the size of tumors, especially when given in adequate amounts over a long enough period of time. In several cases, tumors disappeared for many years following this treatment. The following are illustrative cases:

G. M.—In March 1944, this patient had an ulceration of the cervix. Biopsy showed squamous cell epithelioma, Grade III. A total hysterectomy was performed. She was treated with 3,600 mg. hours of radium in and around the cervix in April 1944. Five months later, there was evidence of local recurrence and the patient was given 1800 r. of deep X-ray therapy. In July 1945, examination revealed no evidence of disease. On October 28, 1945, the patient was examined at the Scott and White clinic in Temple, Texas, and a diagnosis of extensive metastatic carcinoma of the para-

metria was made and further deep X-ray therapy was advised. The patient refused this.

She came under our care in November 1945. She was extremely weak and showed evidence of considerable weight loss, weighing only 86 lbs. Hematuria and dysuria were the principal complaints. Multiple large tumor masses were palpable in the pelvis and extended into the abdomen above the umbilicus. The largest mass palpable, about the size of a big grapefruit, was in the right lower quadrant. The tumor was found to have invaded the bladder, too.

The treatment with which we started, t.i.d. intramuscular injections of 1 cc. of placenta fatty acids, 10% in oil, was changed after one week, in view of the preterminal condition of the patient. A hydropersulfide preparation containing 1% sulfur, and sodium thiosulfate 10% was administered orally. We started with a dose of $\frac{1}{4}$ cc. three times daily of hydropersulfide and $\frac{1}{2}$ cc. thiosulfate and increased it progressively, with amelioration of the general condition and disappearance of the hematuria. After a month, the dosage reached 3 cc. of the first and 9 cc. of the latter preparation daily. Under this treatment, the patient continuously gained strength and weight. The hematuria did not reappear.

In May 1946, she was admitted to the University of Chicago clinic. A large fixed, firm, irregular tumor mass was still present in the lower abdomen rising from the pelvis to the umbilicus. Although her general condition had improved, the patient again had urinary frequency and urgency, and cystoscopy revealed a severe cystitis and several small stones in the bladder. An intravenous pyelogram showed a right hydro-nephrosis.

The treatment with hydropersulfide and sodium thiosulfate was continued for 4 months in Chicago during which time the abdominal mass became smaller, softer, less fixed and was no longer tender. By August 1946, her weight was 136 lbs., a gain of 50 lbs. since start of treatment. The treatment was continued during 1947, although abdominal examination did not reveal any palpable masses. On rectal examination, however, the pelvis appeared to be frozen but no definite mass was felt. Cystoscopy showed severe cystitis, bladder calculi and a distorted bladder. Although she passed several stones and gravel, her urinary symptoms persisted.

In December 1948, an attempt was made in Texas to remove a bladder calculus transuretherally after lithotripsy. The bladder was perforated during this procedure and a recto-vasical fistula resulted. The patient's local physician in Texas believed that the patient was terminal, but we insisted upon This was done, and the surgeon reported that there was no evidence of any a colostomy to divert the fecal stream as an immediate first procedure.

pelvic or abdominal masses. The patient made a slow recovery. According to reports to this date, 16 years after start of treatment, no recurrence has been noted. Recently the colostomy was closed, the patient being in good condition.

Mrs. M. L.—In November 1941, at the age of 40, the patient had a left oophorectomy for a multi-loculated ovarian tumor with ascites and peritoneal implants. The pathological finding was papillary cyst adenocarcinoma of the left ovary. Without any other treatment, she remained free

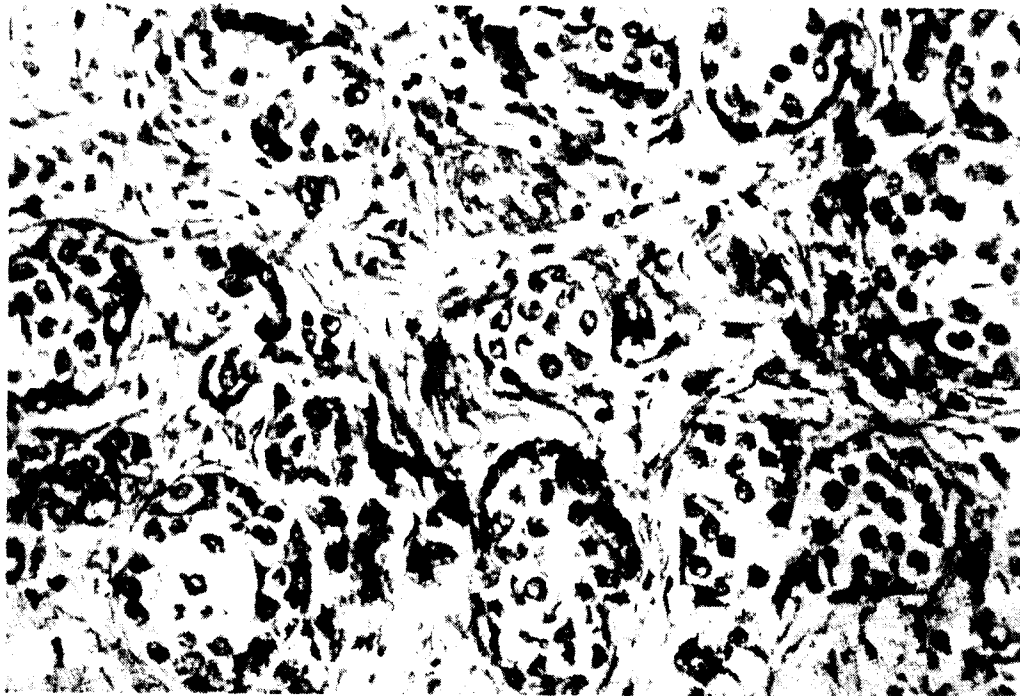


FIG. 158. Photomicrograph of lymph node from Case E.H. showing metastatic adenocarcinoma Gr III (400 x).

of symptoms until the beginning of 1945, when she started to complain of abdominal discomfort in the lower left quadrant. A mass was found at the site of operation. Growth was noted in further examinations. The patient had no treatment until December 1945, when she came under our care. On examination, a tumor of 11/6 cm. with limited mobility was found. No abdominal fluid was present at this time. She was started on amylmercaptan in doses increasing to 6 cc. daily of a 10% solution in oil. The treatment was discontinued after a week because of the odor. No manifest changes could be seen. A preparation of hydropersulfide containing 1% sulfur, in a dose of 1 cc. three times a day orally, was used. The mass in the left parameter disappeared entirely in about 2 months. She

continued with the same medication for another 14 months. There has been no recurrence to date.

Mrs. E. H.—In April 1947, at the age of 46, this patient had a right radical mastectomy. The pathological diagnosis was adenocarcinoma, Grade III, with metastases to axillary lymph nodes. (*Fig. 158*) A course of post-operative irradiation was administered. Menses had been interrupted 8 years before by a total hysterectomy and bilateral salpingo-oophorectomy.

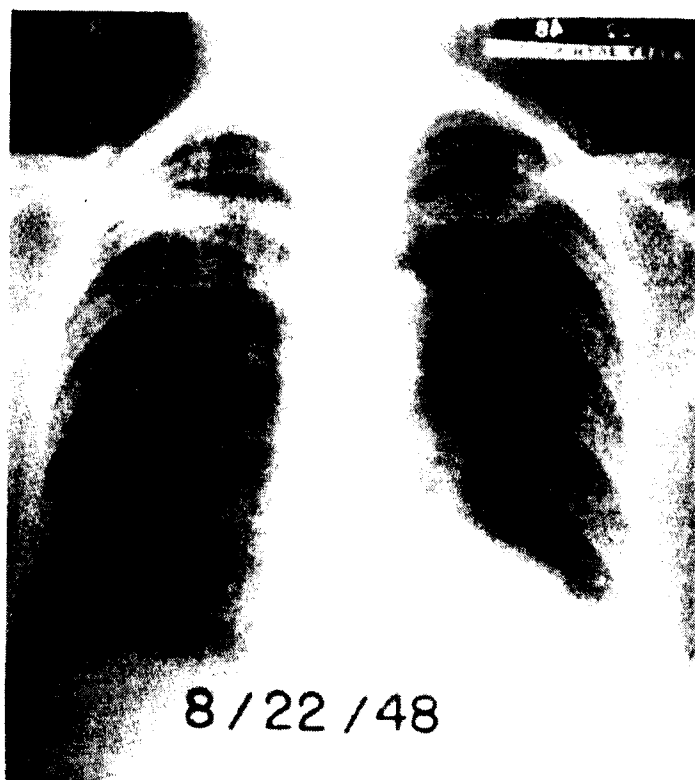


FIG. 159. Anteroposterior view of chest in Case E.H. at conclusion of testosterone and deep X-ray therapy to spine, showing destruction of medial 1/3 of left clavicle and metastatic rib lesions.

The patient was free of symptoms until July 1948, when she began to complain of back pain and difficulty in walking. X-ray examination revealed osteolytic metastatic lesions in the medial third of the left clavicle, pelvis, thoracic and lumbar vertebrae, with collapse of the ninth thoracic and third lumbar vertebrae. She was hospitalized and deep X-ray therapy was applied to the thoracic and lumbar vertebral regions and the right hip. 1800 r. being delivered to each of the three fields. A total of 600 mgm. of testosterone propionate was also administered in four weeks (50 mgm. three

times a week). Clinically, there was improvement and the patient was able to walk with the aid of a back brace and cane upon discharge. X-ray examination on August 22, 1948, at the conclusion of this period of therapy, revealed continued spread of osteolytic lesions, involving the bodies of the lower cervical, lower thoracic and lumbar vertebrae and pelvis. Numerous lesions were observed in the left ribs and in the upper thirds of both femurs. There was further destruction of the left clavicle. (*Fig. 159*)

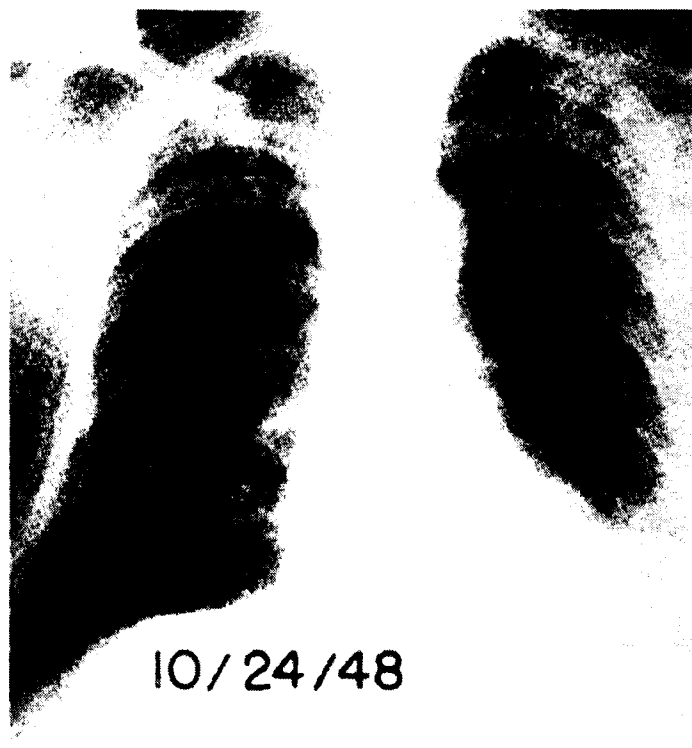


FIG. 160. Anteroposterior view of chest in Case E.H. two months after stopping testosterone and X-ray therapy, showing further involvement of medial $\frac{1}{3}$ of left clavicle.

After discharge, the patient did not receive any further X-ray therapy or testosterone. The clinical improvement lasted for only a short time, the back pain and difficulty in walking recurring within a few weeks. Radiographic examination at the end of October revealed further increase of the previously described lesions, with new areas of involvement. (*Fig. 160*)

The patient received several injections of an unknown medication at home but her condition continued to grow worse. Pain was more severe, and required increasing amounts of narcotics. The patient was confined to bed and there was evidence of increasing nerve involvement, culminating,

by the end of November, in paralysis of both lower limbs with loss of sensation below the level of the ninth thoracic vertebrae. There was no bladder or rectal dysfunction.

The patient came under our care in this condition on December 21, 1948. Pain was so severe that a body cast appeared indicated, but the orthopedic consultant considered the patient's condition too far advanced to warrant this. The urinary pH was alkaline.



FIG. 161. Lateral view of thoracic spine in Case E.H. at time of admission, showing extensive metastatic involvement of vertebrae with collapse of fifth and ninth vertebrae.

A hydropersulfide preparation with 0.5% sulfur was administered in doses ranging from several drops by mouth to 1 cc. twice a day intramuscularly. Sodium thiosulfate in a 10% aqueous solution was given at the same time by mouth, and after a few weeks a 4% solution administered intramuscularly was substituted and was given in increasing doses up to as much as 11 cc. every few hours. For a short period, colloidal sulfur was administered in doses of 100 mgm. orally every three hours.

During the first few weeks, with small oral doses of sulfur in oil and sodium thiosulfate, there was no evidence of improvement. 2 cc. doses of sodium thiosulfate provided definite pain relief for a short time after each injection and the gradual increase of the individual dose to 11 cc. over a

twelve week period gave complete pain relief. During this time, the patient's general condition improved rapidly. Motion and sensation returned to the toes, feet and finally to the whole leg. By April, the patient was able to sit out of bed. By the end of May, she was ambulatory without requiring a brace or cane. Her only complaint was a mild facial acne that developed during the course of treatment.



FIG. 162. Anteroposterior view of left shoulder region in Case E.H. four months after stopping testosterone and X-ray therapy at time of admission, showing involvement of entire left clavicle and continued spread in left seventh and eighth ribs posteriorly.

Radiographic examinations were made at the beginning of treatment and each month thereafter. At the beginning, four months after the last X-ray treatment and doses of testosterone, osteolytic metastases were observed in all the vertebrae of the cervical spine and the bodies of the lower thoracic and lumbar vertebrae, with compression fractures of the third, fifth and ninth thoracic vertebrae. The entire pelvis was involved (*Fig. 163*) and there was destruction throughout the entire length of the left clavicle, in the left acromial process, both humeri and several ribs on the left side. (*Fig. 162*) Vascular markings were moderately increased in both lung fields.



FIG. 163. Anteroposterior view of pelvis and upper 1/3 of both femurs in Case E.H. at time of admission, showing widespread osteolytic process.



FIG. 164. Lateral view of thoracic spine in Case E.H. four months after beginning of treatment, showing considerable bone regeneration in all vertebrae.

Comparison with previous films showed definite evidence of continued spread of the metastatic process.

Films in February showed no change, but in March, slight regressive changes were observed, especially in the left clavicle, left humerus and pelvis. During this time the urine became acid and remained so almost continuously. In April regressive changes were observed in the ribs, pelvis,



FIG. 165. Anteroposterior view of left shoulder region in Case E.H. four months after beginning of therapy, showing considerable repair of left clavicular and rib lesions.

femurs and left shoulder girdle. Elsewhere no further involvement was noted.

In July 1949, regressive changes were found to be continuing in all the involved bones. (*Figs. 164, 165, 166*)

At this time, all medication was discontinued and the patient returned home. In August, the patient again complained of pain in the back, right thigh and left shoulder, and had increasing trouble walking because of difficulty in moving the right leg. The urinary pH again was alkaline. Sodium thiosulfate and sulfur in oil again were administered with relief of

pain and considerable improvement in the ability to walk. A few months later the patient had a stroke from which she died in a few days.



Subjective changes and objective ones upon the tumors were obtained. We found that only minimal doses are to be used, corresponding to micrograms of sulfur and milligrams of tetralin. With these doses, no side effects were observed. When given slightly higher doses, some patients felt a sensation of weakness and also, in a few cases, of dizziness.

This agent has shown a marked influence upon the existing patterns with a special facility to induce, in most cases, an offbalance of type D at the cellular level. With higher doses, the systemic offbalance which is also influenced, can be changed back to offbalance type A only with difficulty. This fact indicates the need for reduced doses, acting almost exclusively at the cellular level. The dosage must be guided by a continuous control of the analyses, and especially by those of serum potassium for the cellular level and of urinary surface tension for the systemic. With values above 5 mEq potassium in serum (and low in blood red cells) and urinary surface tension of less than 68 dynes/cm., corresponding to a systemic offbalance of the type D, the decrease or even suppression of the medication is indicated.

We utilized the agent in cancer cases where the rapid disappearance of the tumor appeared as the capital aim. More time is needed to judge the value of those results already obtained. Among the cases treated, the following observation represents an interesting example.

B. P., 32 year old male, was operated for a wart at the right ear 2½ years before coming under our care. Pathological examination had revealed malignant melanoma. A month later, a dissection of cervical glands was made. The analyses of the obtained glands showed no cancerous cells. Two months before coming under our care, a checkup revealed a new tumor in the right side of the larynx. With the growth of the tumor, edema of the right face was also increasing. Examination showed a tumor 4 cm. in diameter on the right side of the larynx. The tumor was adherent to the skin. Laryngological examination showed the tumor protruding in the pyriform sinus. Because extensive surgery would have been necessary for the tumor removal, the patient refused such surgery. He was admitted and first treated with only limited change in the tumor. Treatment was changed to tetralin persulfides in a dose of 10 drops of a 10% solution in oil, administered 3 times a day. Under this treatment, the tumor involuted very rapidly, and practically disappeared in 3 weeks. Subjective feeling, such as dizziness, made us discontinue the administration of the preparation. The treatment was changed to epichlorohydrin and sulfur in the form of fatty acid hydropersulfides, administered in small doses. The patient has continued this treatment at home for the past 2½ years with no apparent recurrences.

Butanol, Glycerol

During the period when mercaptans and other sulfur-containing agents were being studied, attention also was centered on butanol in the group of anti-fatty acid agents. While butanol's effect upon pain and other subjective manifestations appeared evident from the beginning of its use, the influence upon tumors seemed small. Together with glycerol, however, it produced several long-lasting objective changes. Characteristically, in most of these cases recurrences appeared only after many years of normal active life during which there was no clinical manifestation of cancer. In some cases, however, there were no recurrences.

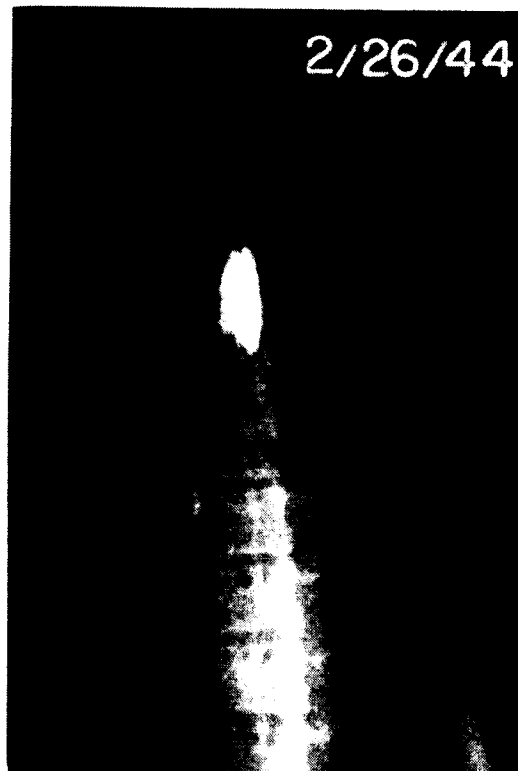


FIG. 167. Myelogram of patient M.H. showing the flow of lipiodol arrested at the level of 4-T.

Mrs. M. H.—This 45-year-old patient experienced, in June 1943, sensory and motor disturbances which progressed so rapidly that in September 1943 she presented a complete paraplegia below 4-T. She came under our care in February 1944, a paraplegic for 5½ months. The myelogram taken at that time showed complete obstruction, with the flow of lipiodol arrested within the spinal canal at the level of the 4-T. (Fig. 167)

The urine analyses showed an offbalance of the type A, and she was treated with the acid lipid fraction of human placenta, and with hydro-persulfides. The symptoms continued to progress and the pain was more severe. Following a change in the urine analyses toward the offbalance D, the treatment was changed to butanol and glycerol. The pain was controlled in a few days, and a slow regression of the paraplegia occurred. After four months of this treatment, there was complete remission and the patient was again ambulatory. The myelogram repeated at the end of November 1944, showed complete disappearance of the obstruction. (*Fig. 168*) The

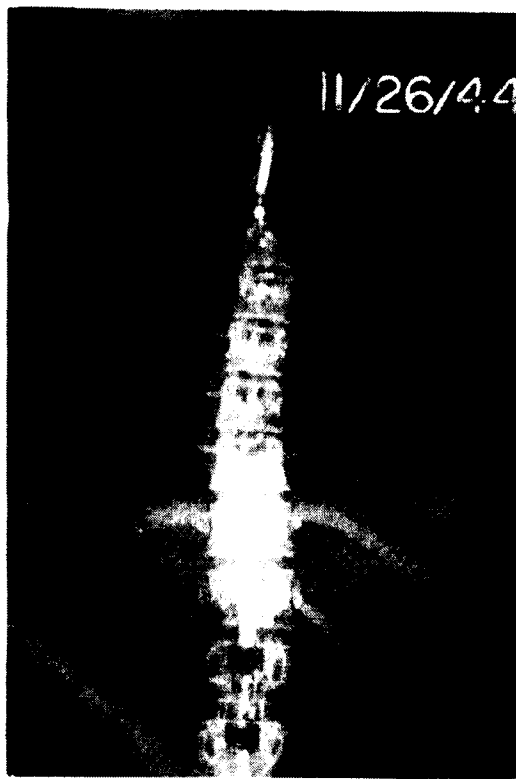


FIG. 168. Myelogram of the patient M.H., showing the complete disappearance of the obstruction.

patient remained entirely well, without treatment and free of symptoms for eleven years. We were informed that, subsequently, a recurrence appeared, followed again by paraplegia and multiple lung metastases. The patient died after four months of paraplegia.

Mr. I. H.—In 1938, at the age of 30, the patient underwent surgery for a tumor of the right parotid diagnosed as chondromyxosarcoma; in 1940, a recurrent tumor was removed and was followed this time by facial

paralysis. In 1943, another recurrence was treated surgically. In June 1945, the same procedure was repeated. Immediately after the last operation, there was still another recurrence and the tumor this time started to grow rapidly. Severe pain was only slightly relieved by narcotics. Radiotherapy was refused, in spite of the massive tumor and pain.

The patient came under our care in December 1945, with several tumors occupying the right parotid region and extending below the mandibula. He was using various narcotics with little effect. With the urinary chloride retention index, pH and specific gravity as criteria, treatment with



FIG. 169. Patient I.H. with a recurrent chondromyxosarcoma of the right parotid gland before and after treatment. The scar is from repeated previous surgical interventions.

sodium thiosulfate and hydropersulfides was started. Under this treatment, which lasted a week, the lesion appeared to be unfavorably influenced and pain increased. With the urine chloride index used as a criterion, the treatment was changed. 1 cc. of butanol 6.5% was administered orally three times a day along with 0.3 cc. of glycerol. After 4 days, the dose of butanol was increased to 2 cc. three times a day. Pain was relieved in a few days. Rapid disappearance of the tumor masses followed. The same treatment was continued for one year. Since then, the patient has been well and is enjoying good health without any recurrence as of this date. (*Fig. 169*)

E. M.—In 1935, at the age of 42, this patient had a right radical mastectomy for adenocarcinoma of the breast. In 1940, recurrent nodules appeared in the line of the scar. One of these was biopsied and showed a recurrent adenocarcinoma, Grade III. The patient was then treated with deep X-ray therapy, 3800 r. being delivered through five fields to the

especially the first, fourth and fifth bodies and transverse processes. Deposits were present throughout the sacrum, in both iliae, the right ischium, left acetabulum and upper femurs. Another series of deep X-ray treatments was used on the same areas of the spine and posterior pelvis as before, the total dose this time being 2000 r., using the same factors. There

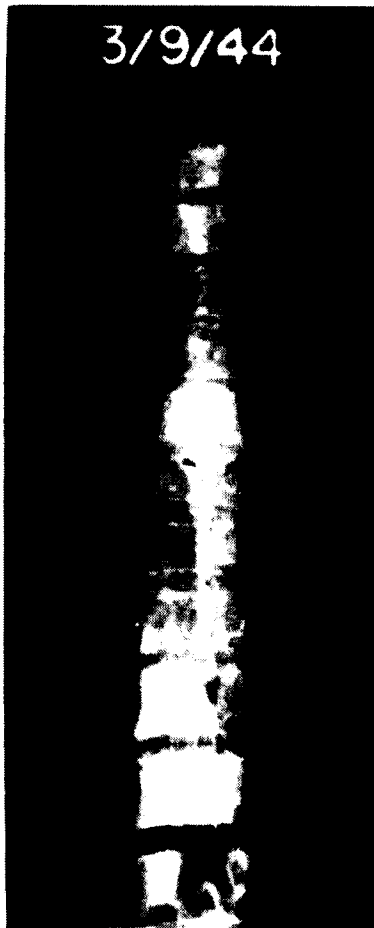


FIG. 171. Anteroposterior views of thoracic spine in Case E.M. at time of admission, showing metastatic involvement of vertebrae.



FIG. 172. Lateral view of the thoracic spine in Case E.M. at time of admission, showing metastatic involvement of vertebrae.

was again relief of pain, although the patient was kept in bed and a body brace was applied to reduce pain associated with motion and to avoid fracture.

We first saw the patient on March 9, 1944. She had moderately severe back pain, was confined to bed with a back brace, and complained of weakness. Blood pressure was 90 systolic, 60 diastolic. Operative scars of

the right chest region were well healed and there was no evidence of local recurrence of the tumor. There was no superficial lymphadenopathy. The liver area was tender to pressure on deep inspiration but the liver was not palpable. There was tenderness over most of the vertebrae with pressure. Patellar reflexes were hyperactive bilaterally. X-rays showed widespread skeletal metastases involving the dorsal and lumbar vertebrae, the sacrum and the pelvis. The lesions were predominantly osteoplastic. (*Figs. 171, 172, 173*)



FIG. 173. Anteroposterior view of pelvis in Case F.M. showing widespread metastatic involvement in fifth lumbar vertebrae, sacrum, both iliac and femurs, two months after onset of treatment.

The patient was hospitalized and treated experimentally from March 8 to December 5, 1944, a total of nine months. The substances employed were n-butyl alcohol, cholesterol and glycerin, administered singly and concurrently at different periods. n-Butyl alcohol was administered as saturated water or saline solution (7.9%) in doses of from 3 drops every two hours to 20 cc. three times a day by mouth, or from 1 to 5 cc. three times a day. 2.5% cholesterol in neutral oil solution was administered intramuscularly in doses of 1 to 8 cc. three times a day. Glycerin was employed orally in 0.5 to 1 cc. doses three times a day. Dosages of all medication were increased progressively, the aim being to bring about and maintain alkalization of the urine.

At the time of admission, the daily urine pH was almost constantly

acid. After five months of treatment, the urine became alkaline and remained so until the patient was discharged from the hospital. (*Fig. 174*)

Clinically, pain was completely relieved after about one month. The patient's appetite improved and she began to gain weight and to feel stronger. After five months, she was mobilized with a brace and showed good progress in the ability to walk.

No changes were observed in monthly X-ray studies during the first four months of treatment. In the X-rays taken in July, the fifth month, at the time of urinary pH change, a few lesions began to show areas of decreased density. These changes progressed fairly rapidly thereafter.

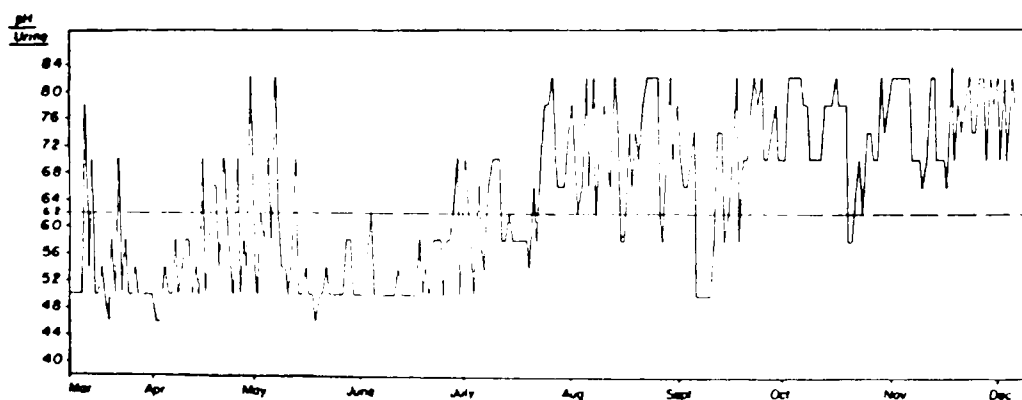


FIG. 2

FIG. 174. pH of daily morning urine specimens in Case E.M. determined colorimetrically, showing changes from acid to alkaline 5 months after the beginning of the treatment.

Following her discharge from the hospital, the patient continued to take 0.25 cc. of glycerol three times a day for another six months. All medication was discontinued after that and the patient has received no further treatment since. She returned to her old clerical position and after several years, when the X-ray changes appeared to warrant it, the brace was removed.

X-ray pictures taken fifty-seven months after beginning of the experimental treatment, (*Figs. 175, 176, 177*) no longer showed osseous pathology and indicated virtually complete restitution of normal appearing bone. The clinical condition was excellent and remained so in 1956, when we saw her. We were indirectly informed that later, in Texas, she suffered a right pleural effusion and died shortly thereafter.

M. H.—In February 1948, at the age of 18 months, this patient was admitted to the Good Samaritan Hospital in Dayton, Ohio, because of

abdominal pain. An exploratory operation revealed an obstruction caused by a tumor of the bowel that had spread to the lymph nodes throughout the abdomen. A by-passing operation was performed to relieve the obstruction. A piece of the mass and some of the involved lymph nodes were removed. The pathological diagnosis was fibro-sarcoma.

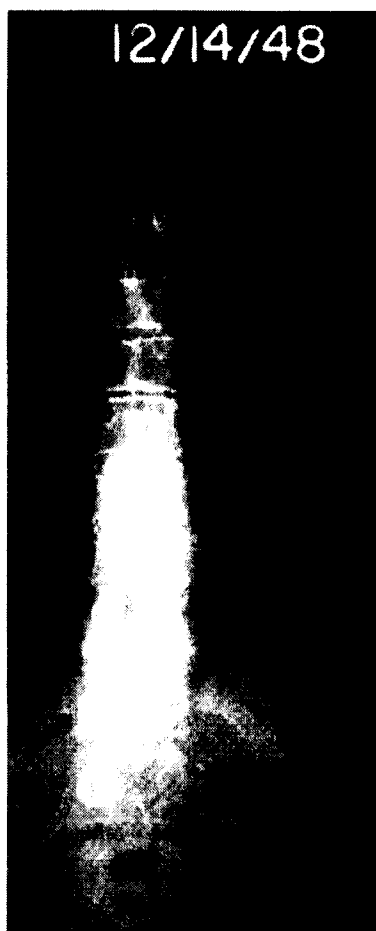


FIG. 175. Anteroposterior views of thoracic spine in Case E.M., fifty-seven months after onset of therapy, showing almost complete restitution of normal bone structure.



FIG. 176. Lateral view of thoracic spine in Case E.M., fifty-seven months after onset of therapy, showing almost complete restitution of normal bone structure.

On March 3, 1948, the patient came under our care. At that time, almost a month after surgical intervention, a mass the size of a tangerine was found in the right side of the abdomen. Based upon her analyses, the patient was treated with $\frac{1}{2}$ cc. glycerol and 2 cc. of butanol solution three times a day. She continued the same treatment without interruption for

responded. Even very large amounts of this conjugated fatty acid, well tolerated in these cases, no longer had an effect upon the tumor and its manifestations. This fading effect limited the clinical usefulness of eleostearic acid. In this respect, it appeared to resemble many other constituents or even heterogeneous agents which have therapeutic effects that fade rapidly.

We have noted previously that intervention of the adrenals is directed especially against the conjugated trienes, substances related to traumatic noxious influences. Therefore, we tried to utilize other conjugated members, some with a higher number of double bonds, in the hope that the body would not be able to efficiently fight their intervention. We obtained conjugated fatty acids with four double bonds by treating mixtures of fatty acids rich in arachidonic acid, such as salmon oil, then fractionating the mixtures through their solubility in solvents, especially acetone, at low temperatures. We also obtained the same type of compound directly from *parinarum laurinum nuces* as *parinaric acid*, a tetraconjugated acid. Conjugated pentaenic and hexaenic acids were isolated from the mixture of conjugated fatty acids obtained from salmon, sardine and cod liver oils. When these preparations were tried in patients with cancer, no apparent improvement over the results obtained with mixtures of non-conjugated fatty acid was seen.

Having in mind the plurality of levels at which they would act, and especially considering the influence exerted by methylcholanthrene upon carcinogenic activity, mixtures of fatty acids from cod liver oil, sardine oils and from normal organs and tissues were conjugated and used. While the effects on pain and systemic changes were more intense and longer lasting, the effects upon tumors were not strikingly different from those obtained with the non-conjugated isomers. Of approximately 140 cases in which these conjugated fatty acid preparations were used, 45% showed subjective changes. In 25%, objective changes occurred, including clinical disappearance of malignant tumors in a few cases. Most of these results, however, were temporary. The tumors later grew again and no longer could be controlled by administration of these lipids. In some cases, the good results persisted and the following illustrates three of these cases.

B. T., 46 years old, had a left mastectomy in 1948, for an adenocarcinoma. 1½ years after the operation, progressively increasing generalized pain appeared, with the general condition going rapidly downhill. Pain, more than the general condition, obliged her to become totally bedridden. Successive X-ray examinations showed rapidly progressing osteolytic

lesions. X-ray treatment for three regions was started with the intention to control the pain which was most severe in skull, ribs, spine, pelvis and femurs. Because of the general condition, this was discontinued after a few treatments. When the patient came under our care, she was entirely immobilized and in severe pain. X-rays revealed (*Figs. 178, 179*) multiple osteolytic metastases in skull, femur, pelvic bones, spine. In view of the analysis



FIG. 178. Lateral view of the skull of patient (B.T.) at the time of admission, showing multiple osteolytic metastases.

as a typical A offbalance, treatment with hydropersulfide and conjugated fatty acids was instituted.

In her case we saw a peculiar form of response encountered also in several other subjects, and which we considered in general as corresponding to as a favorable response. During the treatment, while pain in general was relieved, one lesion was seen to become progressively more painful. It remained severely painful for 2-3 days after which the pain disappeared. The same change was seen to occur successively in one lesion after another with the same temporary increase of pain until it became very severe, followed by disappearance after 2-3 days. Not only did the pain fail to return in the same lesion, but usually the lesion was seen to involute after such a change.

With this kind of treatment the patient made a very rapid recovery and was out of bed in less than two months. The radiological changes, although showing progressive repair of the osteolytic lesions, took more time to be completed. Fig. 181 shows the healing of the bone metastases in progress, while Figs. 180 and 182 the results after almost 2 years. The patient



FIG. 179. Anteroposterior view of the pelvis and upper parts of the femurs of the patient (B.T.) showing multiple osteolytic metastases.

resumed normal life for 3 years after which recurrences appeared on skin, lung and liver. These responded less favorably to the same treatment. The patient left our care and died a few months later.

Mrs. S. T., 47 years old, came under our care in a subcomatous state, 2½ years after a left breast mastectomy for an adenocarcinoma. For three months before, the patient complained of generalized pains and especially of severe headaches, and for a month had symptoms of diabetes insipidus.

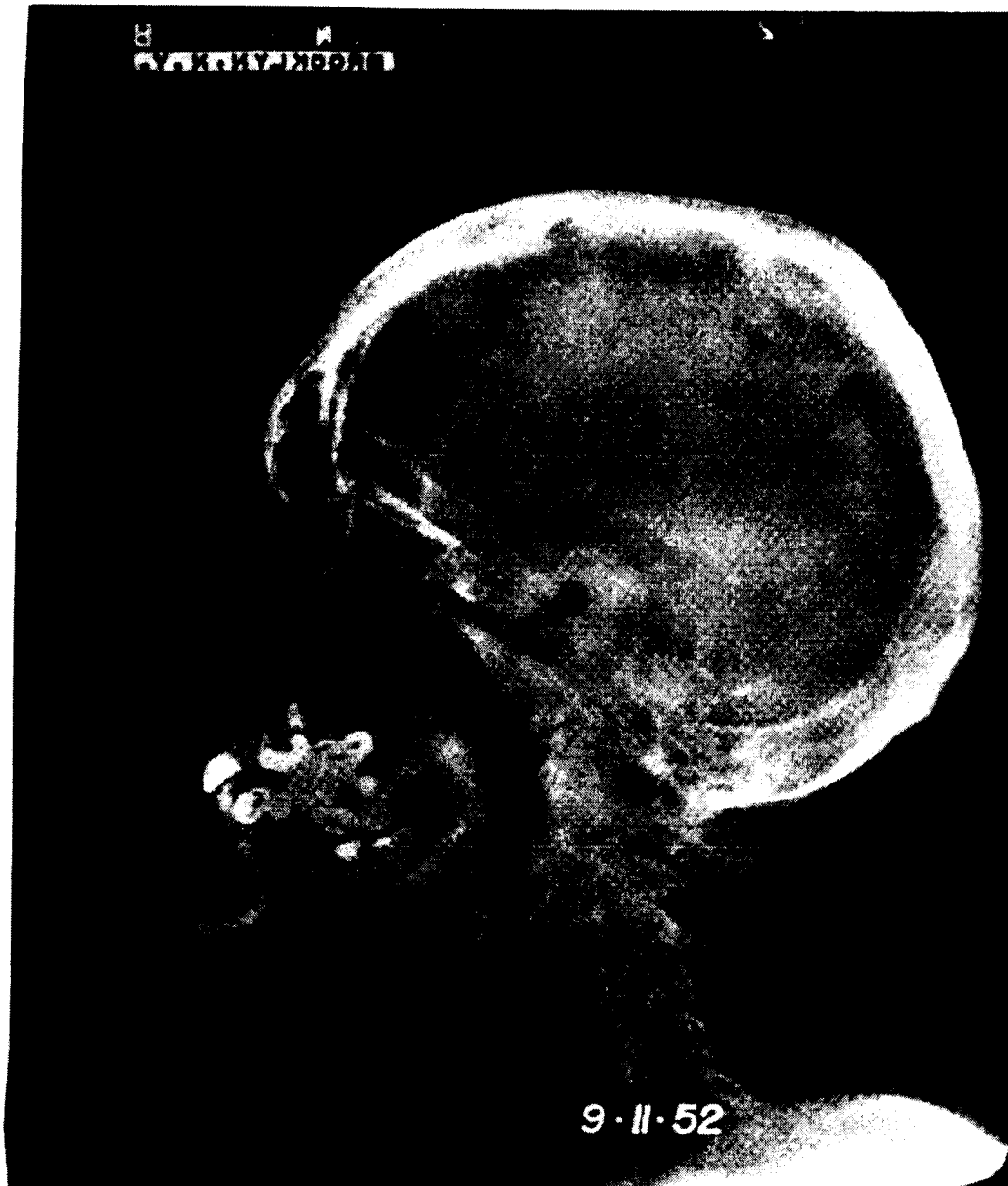


FIG. 180. Lateral view of the skull of patient (B.T.) after 22 months of treatment. Most of the lesions have disappeared.

An X-ray examination of the skull, made prior to her admission (*Fig. 183*) showed extensive skull metastases with an advanced destruction of the clinoid bones.

Because of the diabetes insipidus, the urine analyses could not furnish the needed indication for the treatment and we recurred, therefore, to the number of blood leucocytes and to the body temperature, as tests able to

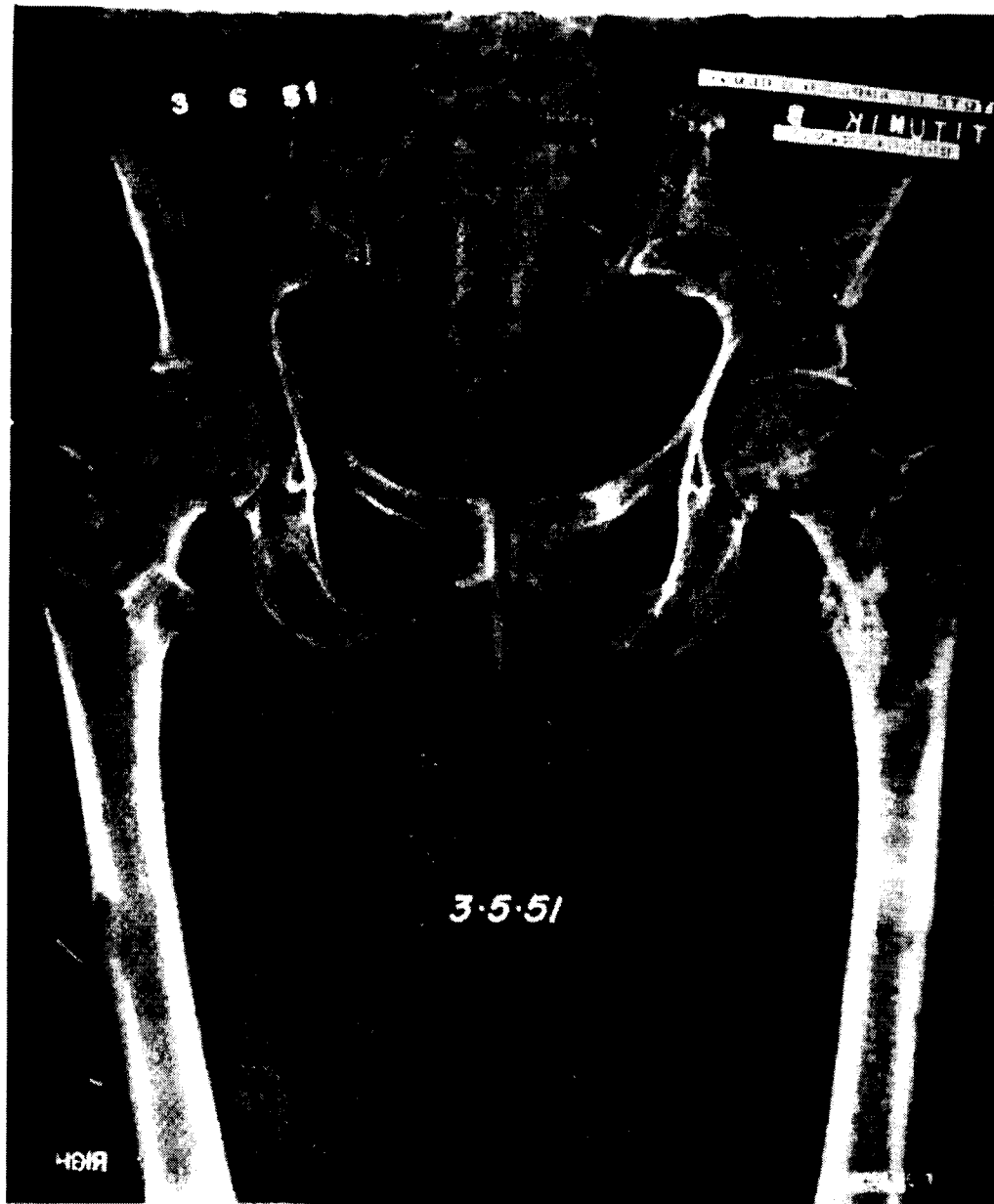


FIG. 181. Anteroposterior view of the pelvis and femurs of patient (B.T.) after four months of treatment, showing the lesions decreasing.

indicate the existing offbalance. With 14,500 leucocytes and a constant temperature of above 98.6°F, we considered the offbalance to be of the type A and administered conjugated fatty acids obtained from cod liver oil, and sodium thiosulfate together with posterior pituitary hormone for her diabetes insipidus. Probably due largely also to her electrolytic balance the patient regained consciousness and made a rapid recovery. In less than

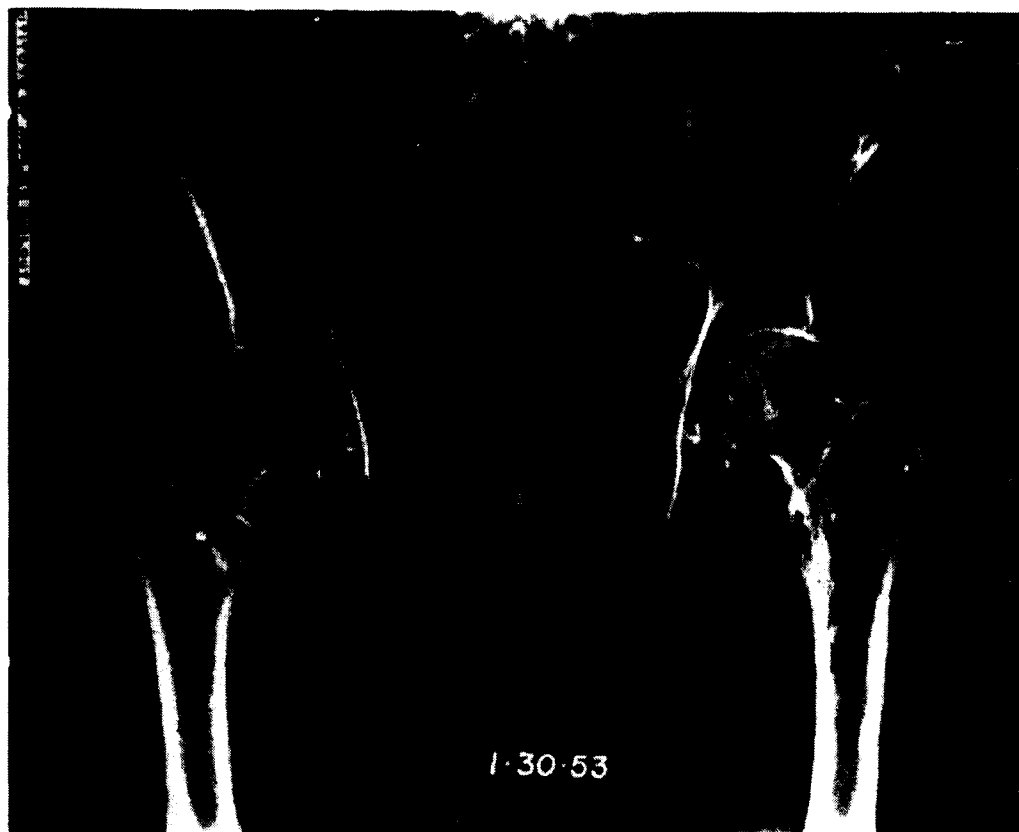


FIG. 182. Anteroposterior view of the pelvis and femurs of patient (B.T.) 2 years later, showing most of the lesions disappeared.

two weeks she was out of bed and resumed a normal life. She continued with the same treatment on an ambulatory basis. An X-ray examination four months later showed a manifest healing of the previous lesions. (*Fig. 184*)

After another four months however, without any recurrence of her malignancy the diabetes insipidus could not be adequately controlled. She refused hospitalization and left our care. She died a short time later with symptoms of electrolytic offbalance.

Mr. L. N., 64 years old, had a long history of vesical troubles, with

biopsies showing cancerous lesions. In spite of repeated fulgurations, the vesical tumors grew rapidly with constant hematuria and tenesmus. Three months before coming under our care, the patient suffered severe pains in the left groin which X-ray examination showed to be due to a bone metastatic lesion. Fig. 185 depicts the lesions upon admission. The analyses showed an offbalance type A, and a treatment with conjugated fatty acid obtained from cod liver oil and sodium thiosulfate was instituted. The pain disappeared in a few days, as did the hematuria and dysuria. The patient continued to improve. An X-ray examination, four months after treatment was started, showed the appearance of a callus at the place of the bone metastases. (Fig. 168) The patient continued the treatment for a few more months after which time we lost track of him.

Heterogeneous Agents

Because of the organism's defense against the fatty acids with which it comes in contact under normal and abnormal conditions, more hetero-

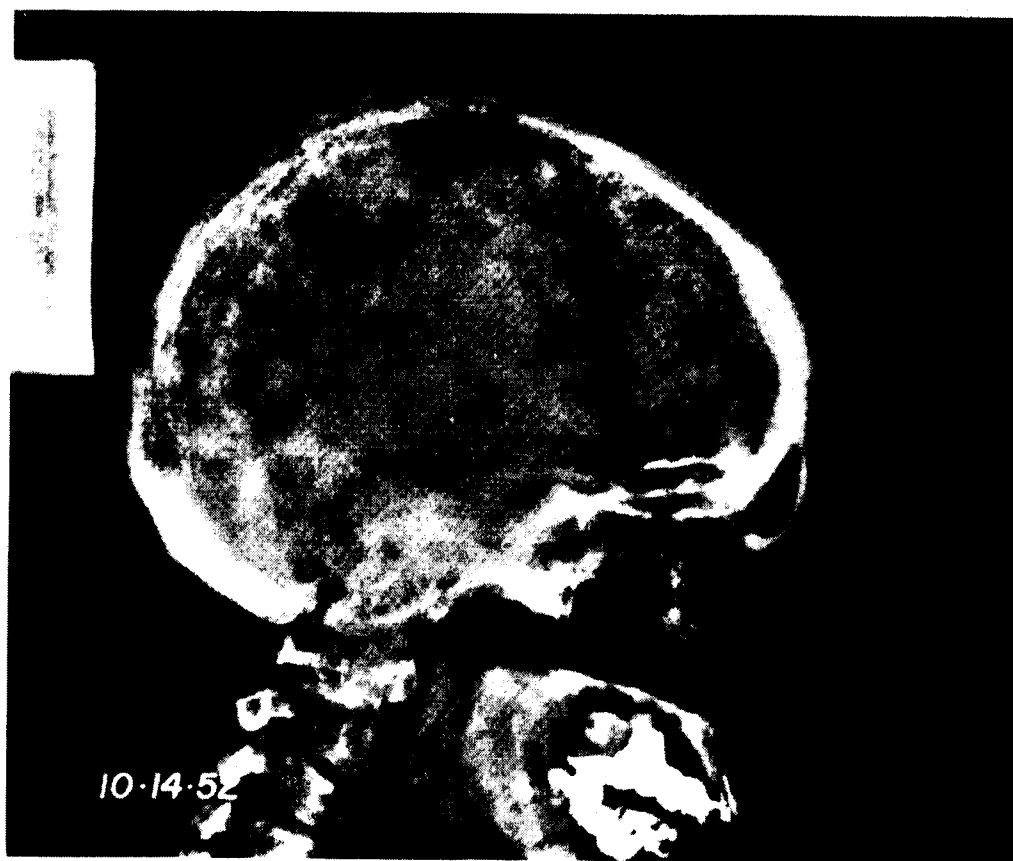


FIG. 183. Lateral view of the skull of patient (S.T.) showing multiple osteolytic processes.

geneous agents were sought. We first resorted to the alpha hydroxy fatty acids. Isolated members and mixtures of the acids, after being prepared and tested for toxicity in animals, were used in patients. We have discussed previously the striking and specific effect obtained upon lymphosarcoma in C_3H mice with alpha hydroxy caprylic acid. Although we were not able to account for this effect, we did attempt to determine whether the acid would have a similar favorable influence upon human lymphomas, especially

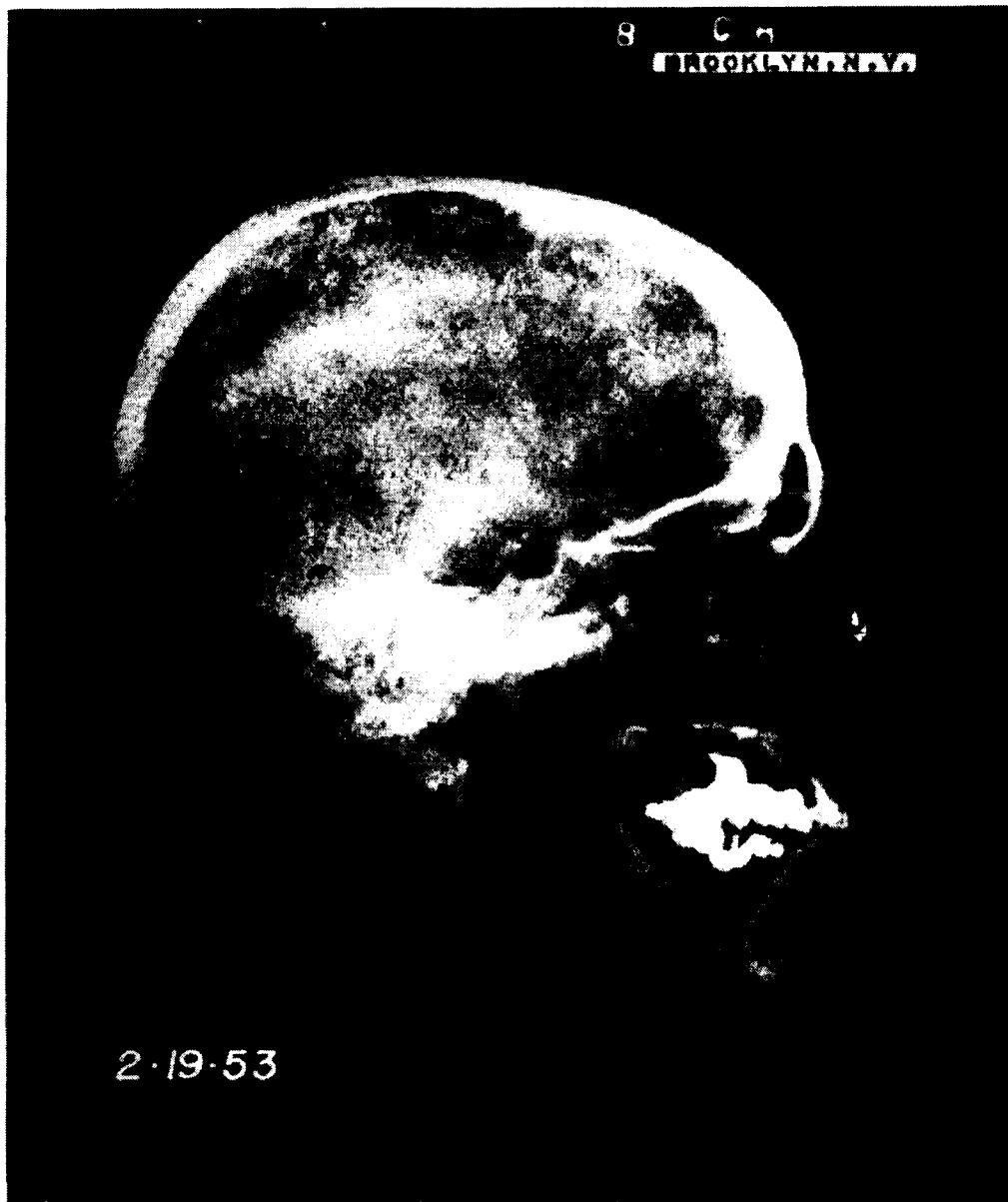


FIG. 184. Lateral view of the skull of patient (S.T.) showing most of the lesions disappeared.

Hodgkins' disease. Several patients with Hodgkins' disease were treated by oral administration of preparations of alpha hydroxy fatty acids from caproic to stearic acids, or with mixtures of them. Only in a few subjects were very limited effects, such as a small decrease in the lesions, observed. Changes were not considered to exceed those known to occur spontaneously in such cases. These effects were inferior to those obtained with the



Parallel to these efforts to find new agents for patients with the one type of offbalance, other agents for use against the opposite type of offbalance were investigated.

Sterols and nonsaponifiable fractions were treated in various ways to obtain heterogeneous substances not found in living organisms. We used heat at 300°C or ultraviolet light, according to the procedures employed by Roffo, in order to induce changes in sterols which would tend, accord-



FIG. 186. Anteroposterior view of the pelvis of patient of Fig. 185, 4 months later, showing the healing of the lesion.

ing to him (198) to make them carcinogenic. We considered these heat or ultraviolet treated sterols and nonsaponifiable fractions to represent abnormal lipoids. They were administered in oily solutions to animals and to a few patients with advanced malignancies. Injected intramuscularly daily for a few weeks, they induced no undesirable results. Their effects upon pain and systemic changes were not significantly different from those of corresponding untreated preparations. The studies of other changes in cancer patients treated with these preparations do not allow any conclusions to be drawn at this time.

We prepared and studied various sulfurized fatty acids, of which the conjugated were used on a broad scale in therapeutic trials. Clinically, these sulfurized fatty acids produced marked results in several cases, but did not constitute a significant advance over sulfurized oil in which sulfur was bound to triglycerides rather than to free fatty acids.

In the search for more active thiolipoids, we prepared several products, one of which, methylthioglycolate, was given a broad clinical trial. Although it produced some interesting objective results, they were neither sufficiently intense nor consistently reproducible nor persistent enough to make methylthioglycolate a distinct advance over the other sulfur preparations used. The compound also had the disadvantage of disagreeable odor although it is not as obnoxious as the mercaptans. As a result, we abandoned the use of this substance after a year of clinical experiments.

Of 131 patients treated with methylthioglycolate, 39—or 30% showed subjective changes and 19—or 15%, also showed objective positive changes.

Another synthetic thiolipoid, hexylthionic acid, was utilized in a few clinical cases. Only a small number of patients showed objective clinical results and these were neither consistent nor persistent enough to warrant using this substance for further research. While the results obtained with agents other than mercaptans having a thiol polar group were interesting, these compounds had too little influence upon tumors, especially in cases where the pattern indicated persistent predominance of sterols.

Selenium Preparations

We have previously noted the considerations which led us to study lipoidic compounds containing bivalent selenium. The compound used in clinical research was hexyldiselenide, a lipoid with an -Se-Se- as a polar group. Oily solutions in various concentrations were given by subcutaneous or intramuscular injection. Doses as low as 4 micrograms or as high as 400 milligrams were employed several times a day. For oral administration, capsules containing the product in solution in hydrogenated oil in amounts from 4 micrograms to 100 milligrams were employed. A short time before the experimental therapeutic use of selenium compounds, the means of recognizing the existing offbalance were implemented with the sulfhydryl index, a measure of urinary elimination of the sulfhydryl group.

Despite negative results in animal tumors, hexyldiselenide was used clinically in the hope that, with treatment guided by the data furnished by urinalyses, satisfactory results could be obtained. The sulfhydryl index served, at the beginning of this study as the principal indication for the administration of the selenium compound. Later we used urinary surface



tension as the criterion, and lately we have used the changes in serum and total blood potassium. In general, we administered the medication only if the sulfhydryl index was below 1.5, the surface tension above 68. A marked influence upon the tumor itself was seen in a relatively high proportion of cases. The results also are of theoretical interest since the compound had less influence upon symptoms at the tissue level, such as pain, or at the systemic level, and more on those at the cellular level. The effect on pain was slow to appear, often requiring days. But once relief of pain was achieved, it persisted for a long time, in contrast to the brief effect produced by other agents such as thiosulfate or hydropersulfides acting directly at the tissue level. Primarily because hexyldiselenide alters the pattern present at the cellular level, it must be emphasized that determining proper dosage at least in the beginning, appeared more difficult than for any other substance with which we have had experience.

At the beginning, we used doses in the range of 10-80 mg. but in a number of cases a persistent change to the opposite pattern occurred after one or two doses. This led to the utilization of smaller and smaller doses in order to avoid too rapid change to the opposite pattern. Also with small doses, we hoped to limit the therapeutic response to the cellular level only. We decreased the daily dose to 5 mg., then to 1 mg. and eventually even to micrograms. With these small amounts, the immediate clinical effects seemed to be almost entirely limited to the cellular level. The changes in pain and the systemic pattern were minimal. The choice of dose to be given was determined in the second part of this research primarily by urinary surface tension. It was observed that microgram doses may influence lesions without changing the values of the other analyses corresponding to the systemic level.

The clinical results obtained with the use of hexyldiselenide in humans warrants detailed consideration. Good results were obtained with greater consistency after the problem of dosage was resolved and the relationship to urinary analyses was established. Important objective changes could be achieved by using urinary analyses as a guide for dosage, as illustrated by the following cases.

A. B., 68 years old, male. In October 1949, the patient had an amputation of the left leg at the hip-joint performed at the Memorial Hospital because of a tumor of the femur. The pathological diagnosis was sarcoma. He was well until July 1955 when he began to cough and have recurrent episodes of hemoptysis. X-ray examination revealed right pleural effusion and infiltration of the right lower lobe. He was readmitted to Memorial Hospital in October 1955 and thoracentesis revealed bloody fluid. Bron-



choscopy showed partial narrowing of the right lower lobe bronchus. Examination of pleural fluid and bronchial washing by the Papanicolau method showed cells that were suspicious for malignant disease, but not conclusive. It could not be determined whether a primary lung cancer or metastatic sarcoma was present. An exploratory thoracotomy was advised but refused by the patient, who signed himself out.



FIG. 187. Anteroposterior view of chest in Case (A.B.) at time of admission showing the presence of a mass in the lower part of the right hemithorax.

Two weeks later, he came under our care and has been an ambulatory patient since then. His chest pain had been considerably relieved with the thoracentesis and there was no bleeding. He complained of distress and tightness in the chest as well as perspiration at night. A physical examination revealed dullness in the lower right hemithorax below the seventh rib. Blood pressure was 208/165. X-ray examination revealed a large round mass occupying the right lower lobe. (*Fig. 187*)

Urinalyses showed a low surface tension, low specific gravity, high pH and low sulfhydryl excretion. Hexyldiselenide was chosen as the only chemotherapeutic agent. Treatment was started with a tenth of a milligram

twice a day, and was increased gradually to half a milligram twice a day. Chest pain and hemoptysis decreased in the following weeks. The general condition improved. He felt better and had no cough. X-rays a month and a half later showed that the right lower lobe mass was slightly smaller in size.

In January 1956, a striking reduction in size and density of the lower right lobe mass was seen. It was now about 60% as big as a month before.



FIG. 188. Anteroposterior view of the chest of the patient A.B. after ten months of treatment with hexyldiselenide.

At the beginning of February, the mass in the right lower lobe was almost entirely gone. The interlobular thickening of the left lower lung still persisted. In April, further clearing of the right lower lobe was seen. (*Fig. 188*) The patient received treatment with hexyldiselenide for a few more months. He continued in excellent condition without further treatment for the next three years. At the end of that time, there was a recurrence of pain and the mass in the right lower lobe reappeared and grew rapidly. Treatment with hexyldiselenide was resumed. The pain disappeared again within a short time, and the tumor again regressed.

I. A.—This 58-year-old patient had diabetes beginning at the age of 30. It was controlled by insulin. At 35, he had rheumatic fever and remained in bed for 6 months. Angina developed at 53. In January 1956, he was awakened by a pain in the right side of the abdomen. The pain continued to be severe for months and the patient lost weight. Barium enema revealed nothing. He entered Jewish Hospital in Brooklyn with jaundice in April 1956. Upon operation, the gall bladder was found enlarged to twice its normal size and the common duct was dilated. With a finger inserted through the foramen of Winslow, a hard, stony mass involving the head, body and most of the tail of the pancreas, was felt. The tumor involved almost the entire pancreas. The lymph node of the common duct was enlarged. The liver showed no evidence of metastases. The general condition of the patient, in spite of the extensive involvement of almost the entire pancreas, did not justify a total pancreatectomy. Therefore, a palliative surgical procedure was done. The gall bladder was anastomosed to the jejunum.

The post-operative course was good. No other treatment was prescribed. When the patient came under our care at the end of May 1956, the jaundice had disappeared but the pain was the same as it had been before operation. A mass occupying the upper abdomen was felt. Treatment was started with a dose of 30 micrograms of hexyldiselenide a day. This dose was increased later to 300 micrograms a day. The abdominal discomfort lessened; pain in the upper abdomen disappeared. The patient remained on this treatment until 1957 when epichlorohydrin was added to the hexyldiselenide. With the mixed treatment, the patient continued to improve and the tumor, which had been palpable in the upper abdomen, disappeared after a few months. Except for diarrhea, which occurs from time to time, the patient has made a very good recovery. He has continued on hexyldiselenide and epichlorohydrin and, at present, four years later, is in good general condition. No tumor can be felt and he is at his regular job.

C. M., 52 years old, male. In 1946, the left breast of this patient was removed because of a malignant tumor. In 1947, the right breast was removed but the tumor proved to be benign. In 1954, the patient, showing blood in the urine, was admitted to the Presbyterian Medical Center where a right kidney tumor was diagnosed. In February 1955, the patient underwent surgery. A tumor of the right kidney with extensive lymph node involvement above and below the renal vessels was found. A simple nephrectomy was performed, the lymph nodes being considered inoperable. The pathological report revealed "clear cell carcinoma of the kidney with ex-

tension into the renal vessels and surrounding tissue." There was no evidence of pulmonary or other metastases.

The patient did not undergo any treatment at this time and felt well until September 1955, when he experienced increased fatigue, flatulence, slight pain in the right kidney region, and some abdominal pressure. No abdominal mass or lymph node involvement was found. He was treated with hexyldiselenide, starting with 200 micrograms a day. This dose was increased progressively until it reached 2½ milligrams a day.

Under this treatment, most of the patient's pain disappeared and no palpable mass could be found. The patient continued treatment, with the same dose, until October 1957, when epichlorohydrin was added. At first, with the new medication, the patient was more tired and there was a noticeable increase in perspiration. However, after a short time, he continued to improve. At present, he is still taking 15 milligrams of epichlorohydrin, and 100 micrograms of hexyldiselenide daily. He feels well, continues normal work, and no tumor is palpable now four and a half years since the beginning of the treatment.

W. H.—In March 1954, at the age of 11, this boy had the first of three brain operations at the Jersey City Medical Center. He had complained of persistent headaches for about a year. A brain tumor was removed and on pathological examination, was first thought to be benign, but later proved to be malignant (spongio-blastoma). By August of 1954, his symptoms recurred and a swelling appeared in the area of the scar. At the second operation, it was possible to remove only a part of the recurrent tumor. In November 1954, local swelling and headaches returned. X-ray treatments failed to give relief and a third operation was performed, but only a piece of tumor was removed. It showed the same pathology.

He came under our care May 3, 1955, and was treated, because of low sulfhydryl urinary index, with hexyldiselenide, in dosages ranging from 300 micrograms to 1 milligram per day. This treatment was continued for one year. He has done remarkably well since. He has had no headaches, is more alert and less drowsy than at any time since he first became ill. There has been no evidence of recurrence. Since treatment, there has been a definite reduction in involuntary movements of his head, extremities and body, which appear to have been related to the tumor growth. There have been no abnormal manifestations to date, five years since the beginning of the treatment. The patient goes to school and engages in all the activities of a normal boy of his age.

Mrs. A. L.—This patient first noted a lump in her neck in the summer of 1953 when she was 26 years old. In February 1954, a second lump

appeared. Surgery was performed at the Ottawa Civic Hospital. The pathological examination showed a cancer of the thyroid (papillary adenocarcinoma). It involved both sides of the gland and many of the lymph nodes. The entire thyroid gland was removed and bilateral lymph node dissection was done in two stages. Since the surgeon felt that he had not removed all the affected areas, the patient received deep neck X-ray therapy following the operation. However, by July 1954, a new mass developed on the right side of the neck and this was removed in November. The pathological examination proving it to be the same type of tumor.

The patient was first seen by us on January 10, 1955. Although it was only two months since the last operation, there were several recurrent tumor masses in the lateral right side of the back of the neck, as well as infiltrations into the area of the last operative wound. The patient was treated with hexyldiselenide, in doses ranging from 300 micrograms to 1 milligram daily. Under this treatment, the masses progressively decreased and, after 3 months, disappeared. She continued the treatment for another six months. Now, after 5½ years, she is feeling well, has had no recurrences, and is carrying on her usual activities as a housewife and mother.

Hexyldiselenide, although it produces impressive results, very often is not of itself able to provide enduring benefit. Many other patients have had recurrences, some in spite of impressive first results and continuation of treatment as shown in the following observation. J. D., 10 years old, came under our care in a preterminal state, after an exploratory laparotomy revealing an extensive carcinoma of the liver. (*Fig. 189*) The response to hexyldeselenide treatment was impressive with the patient making a perfect recovery. His liver which had filled the abdomen, returned to normal dimensions. The patient continued a normal life for 2 years when, in spite of the continuation of the treatment, generalized recurrences appeared. These could no longer be controlled.

Tetralin Perselenide

The good effects obtained with persulfides on one hand, and with selenium on the other, have led us to investigate the corresponding compound—tetraline perselenide. With its low toxicity, the compound was administered to humans in which the destruction of the tumor appeared the immediate aim. The effect upon pain was good although not immediate, the same as for the systemic level. It was at the cellular levels where these were the most manifest. Research with this agent is still in progress and for the moment the influence exerted upon the tumors seems to be very fa-

vorable. Similar good results were obtained with naphthalene perselenide and other similar preparations of aromatic hydrocarbons.

Parallel to studies with synthetic negative lipoids, synthetic positive lipoids were investigated. The problem was quite different because of the fundamental differences in biological roles of the two antagonistic groups. Among negative lipoids we singled out an effect against sterol predominance and a destructive activity through the induction of rapid cellular aging.

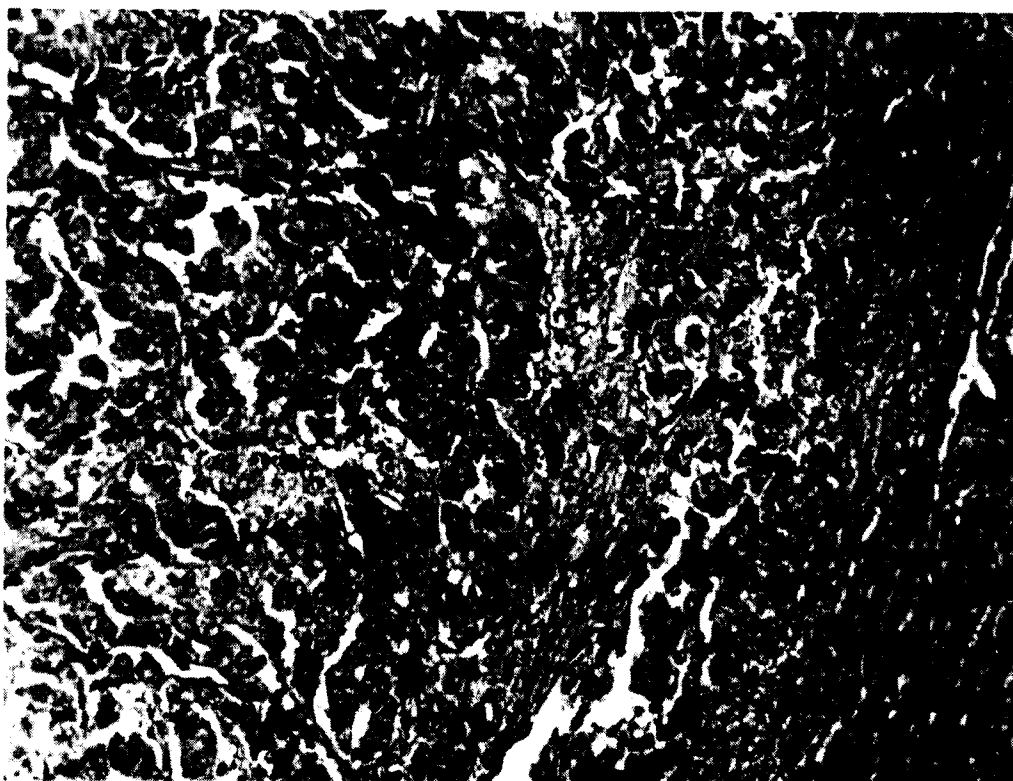


Fig. 189. Photomicrograph of a liver biopsy of patient J.D.

Among the positive lipoids, we sought agents able to correct the noxious effects induced by fatty acids. As noted previously, this led to a search in one group of experiments for substances with higher specificity for binding particular fatty acids and in other experiments for substances with broad spectrum acting against acid lipids in general. We have discussed previously the pharmacodynamic characteristics of many of these synthetic positive lipoids. Clinical results have improved with the development not only of new substances but also of new means of recognizing the pattern present and of following the changes that take place. We have mentioned the results

obtained with butanol, the first of this group of synthetic lipids with positive character to be used in humans.

Butanol was unable by itself to influence the growth of tumors, although it was effective in controlling pain of an alkaline pattern. This beneficial effect upon pain was still more manifest for other aliphatic alcohols, and especially for heptanol. In high doses, however, heptanol probably acts beyond the tissue level. Besides influencing pain, it induces severe edema and changes in the evolution of the tumor. It has little influence at the systemic level upon hemorrhage, even with high doses. For tumors with offbalance of type D, a mixed treatment appeared indicated. The use of heptanol-butanol, however, was not fully satisfactory although it has been employed in some cases with good clinical results.

During the progress of this research, it became increasingly important to have an accurate knowledge of the existing offbalance, and of the adequate use of the available therapeutic agents. The following observations show how the results obtained by the treatment are a function of the correct application of this concept of guided chemotherapy.

M. S.—This 52 year old woman started to lose weight in September 1953 and her abdomen became very distended several months later. An exploratory laparotomy was done in July 1954 at Brooklyn Hospital and revealed a large mass in the lower abdomen with metastases. A lymph node biopsy was performed and showed lymphosarcoma. (*Fig. 190*) Subsequently, she had 36 X-ray treatments, followed by another course of 12 X-rays, the last in December 1954. She felt relatively well until the first week in February when abdominal pains recurred. A mass in the middle abdomen, the size of a large grapefruit, could be felt.

Under treatment with sterols, the tumor first increased slightly in size so that by the middle of April, it extended, filling up the entire left side of the abdomen. At the end of the month, the pain became stronger while the abdominal mass remained unchanged. The patient was treated, according to her analyses, with 1 mgm. of hexyldiselenide daily. The tumor became much reduced in size. Pain recurred at intervals and, although only a small mass was still palpable after 1½ years of treatment, the patient's general condition started to deteriorate at that point. Analyses then revealed a change in the pattern present. The treatment was changed to a mixture of higher alcohols—octanol, heptanol and polyconjugated alcohols. The tumor rapidly regressed and, at the beginning of 1957, the mass had entirely disappeared. She continued in good general condition until August 1957 when she had a coronary occlusion. At present, two years later, the



patient is in good general condition and without any sign of recurrence of the tumor.

In this case, the first treatment with sterols, using urinary pH as a criterion, brought some subjective improvement but this could also be considered to be the result of the radiation. The improvement was transitory and the appearance of more symptoms, probably reflected the waning effect of radiation. The change to hexyldiselenide brought improvement but could

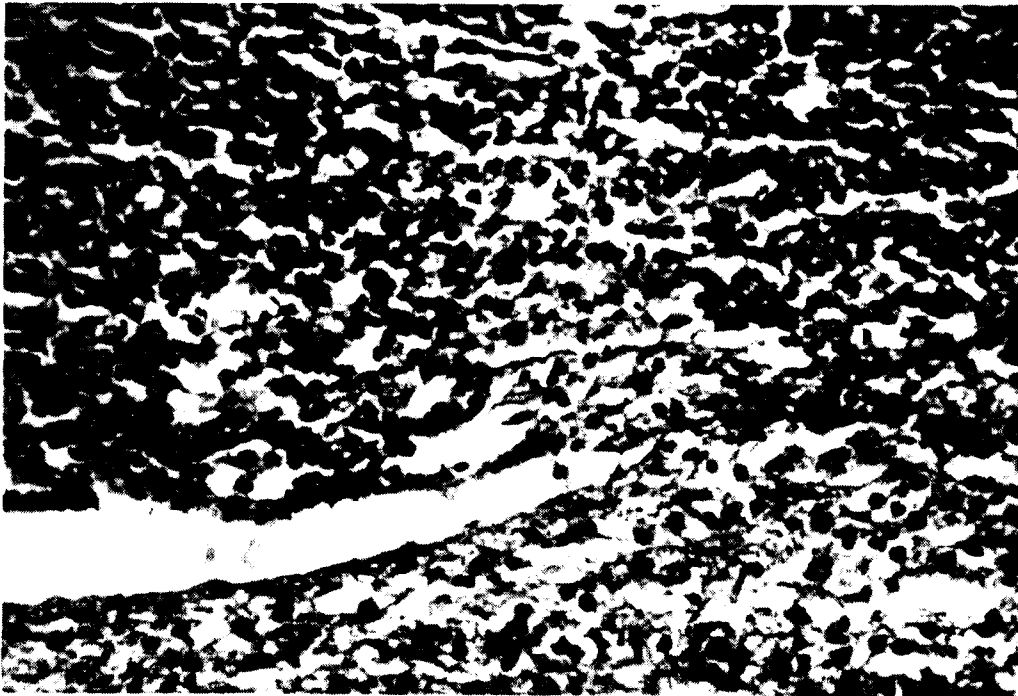


FIG. 190. Photomicrograph of a lymph node of patient M.S. showing a lymphosarcoma.

not entirely control the condition. It was with higher alcohols that important objective as well as subjective changes were achieved. The tumor decreased rapidly. Interruption of treatment, due to the cardiac condition, did not seem to influence the favorable progress of the condition.

M. B.—Toward the end of 1950, at the age of 45, the patient began to complain of right lower quadrant and intermittent left upper quadrant pain. She discovered an abdominal mass by herself. In February 1951, an exploratory laparotomy was performed at Lenox Hill Hospital with the following findings: "Situated in the left side of the pelvis, a huge cystic structure the size of a football was found. The superior wall of this mass was attached to the mesentery of the loop of the small bowel. The anterior

cyst was attached to the posterior leaf of the broad ligament and contained the left ovary. On the ovary and within the wall of the cyst were several papillomatous structures. On the right side of the pelvis was another cystic mass containing a greenish turbid fluid. This cyst contained the right tube and ovary and on its walls were several papillomatous projections. The parietal peritoneum, the liver and omentum were studded with tumor implants and several sections of bowel were matted together by the same tumoral tissue. Biopsy specimens were obtained from several areas."

The gross pathological diagnosis was papillary carcinoma of the ovary with metastases to peritoneum, liver, intestines and duodenum. The report on the frozen section was malignant. Microscopic examination confirmed the diagnosis given at the time of the operation and revealed a fibroid fatty tissue extensively infiltrated by a malignant neoplasm of epithelial origin.

The patient came under our care 11 days after her operation. The abdominal mass was palpable, rising from the pelvis to a level slightly above the umbilicus. Vaginal examination revealed large cystic masses filling both fornices and cul-de-sac. The pelvic structures were partially fixed. The urinary specimen showed a pH between 7.4 and 7.8 and the surface tension was 68 to 71 dynes/centimeter. Treatment was instituted with a mixture of conjugated fatty acids, derived from cod liver oils, and a preparation of hydropersulfides as well as sodium thiosulfate. The first preparation was administered intramuscularly in a 5% oil solution in doses of from 2 to 4 cc. daily. The sulfur preparation (corresponding to 0.5% sulfur) and 10% solution of thiosulfate were administered in doses ranging up to 6 cc. daily. The treatment was continued without change for 1 year and 8 months. The abdominal mass was found somewhat smaller a month after starting treatment. A month later, a surgeon's report showed that the tumor was about $\frac{1}{3}$ the size at the time of operation. After several months, no mass could be felt on abdominal and vaginal examination. After twenty months, the treatment was discontinued for one year. At the conclusion of this period, the patient began to relapse and a cystic mass in the cul-de-sac, palpable under finger examination, was found. Treatment with the same medications as before was instituted but did not change the dimension of the recurring tumor. Despite treatment, the tumor continued to grow and in April 1954, the abdomen was distended. X-ray also revealed a large liver and elevation of the right diaphragm. The patient was readmitted to Lenox Hill Hospital where a small abdominal incision revealed two masses, one above the liver and another one in the lower abdomen. Fluid reaccumulated rapidly and the patient's general condition became poor. On several occasions it was necessary to tap the subdiaphragmatic cyst and

lower abdomen separately as emergency procedures because of acute distress.

Because analyses now showed a low pH (around 5.2) and low surface tension (around 61 dynes/centimeters), and also because she had obviously failed to respond to conjugated fatty acids, treatment with butanol and nonsaponifiable lipids of intestine was instituted. By July the situation appeared to have been brought under control again. Fluid was no longer



FIG. 191. Photomicrograph of a lymph node biopsied from patient M.B. showing metastatic adenocarcinoma.

accumulating and leg edema, which had been pronounced, was gone. At the end of 1954, no masses could be felt. The subjective complaints disappeared slowly. In February 1955, the nonsaponifiable medications were replaced by heptanol and octanol. The patient continued to improve with this treatment. In March, the abdomen was a little swollen. By the end of April, a mass could be found in the abdomen just above the umbilicus. At the end of May the mass had increased and the patient was hospitalized for about three weeks. A large bloody cyst was drained. A small lymph node was biopsied and microscopic examination showed the same metastatic adenocarcinoma. (Fig. 191) The patient was put on epichlorohydrin and the mass did not grow back. She has remained on epichlorohydrin

and for four years has had no subjective discomfort. No mass can be felt in the abdomen and the patient is well now.

Radiation and Chemotherapy

Parallel to the guided chemotherapy, the idea of mixed radio- and chemotherapy has led us over the years to several tentatives. In one of them, in collaboration with Dr. L. Goldman on a larger scale, chemotherapy was added to radiotherapy. (*Note 1*) In spite of the interesting immediate results, if chemotherapy was not further pursued, the ultimate fate of the patients thus treated was no better than that of the patients who had received radiation alone. Analysis of these various attempts has permitted us, however, to establish the conditions under which such a mixed treatment would appear especially indicated. Consequently, it is the type of offbalance present which is seen to determine the relationship between the two therapies, and respectively the procedure to be followed. The same relation has permitted to define the conditions under which chemotherapy would be indicated and added to radiotherapy. It should not be forgotten that through its action upon the fatty acids, radiation represents indirectly an agent of the same group to be added as the negative lipoids.

The cases with a type A offbalance which seem to respond insufficiently to medication with agents, represent an indication for the mixed treatment. Acting in conjunction with radiation, chemotherapy has appeared especially active. Chemotherapy started before, is continued actively during radiotherapy and following radiation, for a long time, even for years. The radiation acting as an adjuvant agent is usually applied in small doses, from only several hundred r to a few thousand r, in general much below those dosages known to induce by themselves alone therapeutic effect upon tumors. In cases with type D, as the radiotherapy represents an agent increasing the actual offbalance, an added chemotherapy with positive lipoids would have the role of correcting not only the existing manifestations but of preventing some of those which would be induced by radiotherapy. It would in fact have the specific aim to permit the continuation of radiotherapy while limiting its noxious influence.

The mixed therapy has to be guided by the routine test, with frequent analyses, in view of the rapid important changes which have been seen to occur. In these cases, it appears useful to follow especially the changes of the chloride index, those of peroxides in the urine which together with the surface tension, are seen to be not only particularly influenced by radiation but able to indicate the important change in offbalance.

has been necessary to relate analytical data to changes occurring at specific levels. For example, changes in potassium in serum and red cells have been related to cellular level abnormalities; urinary surface tension changes, to metazoic; specific gravity to systemic; urinary pH and blood eosinophiles, to tissular. This has guided the choice of agents: selenium preparations, epichlorohydrin and heptanol for the cellular level; sulfurized hydronaphthalenes, lipoacids, unsaponifiable fractions and glycerol for the tissue level; magnesium and sodium thiosulfates, propionic aldehyde and butanol for the organ and organism levels. Through this approach, therapy has evolved toward what we can now consider to be *biologically guided level-chemotherapy*.

The following observations show the role of these level indications in the conduct of the treatment.

F. R., in March of 1957, had a left mastectomy for an adenocarcinoma of a mammary gland. In July of 1958, she began to experience pain in the lower back and legs. In the three months prior to coming under our care, several skin nodules and some progressive difficulty in breathing was evident and there was a loss of 25 lbs. in weight. On admission, multiple skin and subcutaneous lesions, some of them measuring 3-4 cm in diameter were found, as well as 3 or 4 nodules in the right breast. The ambulant patient started treatment with selenium and epichlorohydrin. Although treatment was followed with irregularity, improvement was seen in the local lesions. In December, 1959, however, the difficulty in breathing had markedly increased and oxygen administration was needed. In less than a week her condition worsened. The treatment with more selenium and epichlorohydrin appeared unable to control the situation. She was admitted to the hospital in extreme dyspnea. The suppression of oxygen for even a few minutes was followed by convulsions. Radiological examination showed a very limited exudate especially in the right hemithorax, but multiple metastases in both lungs. All the analyses showed an offbalance of type A. Considering the condition as manifested also at the organic and systemic level, to the treatment with epichlorohydrin, acting at the cellular level, we added bixine and propionic aldehyde. The first agent was considered to act at the tissular level and the latter at the systemic level. With this treatment the patient made a very good and constant recovery. In less than two weeks it became unnecessary to use oxygen and her general improvement progressed so that 3 months after treatment was started, the patient was able to resume part of her housework. With mixed treatment—epichlorohydrin acting at

the cellular level, and bixine and propionic aldehyde at the organic and systemic level—the condition seems controlled. The pulmonary metastases seen in previous X-rays have also disappeared and all the skin nodules decreased rapidly, most of them having completely disappeared. She is at present in good state of health, doing all her own housework.

Mrs. C. H., 60 years old, came under our care two years ago with a history of lymphosarcoma with two positive biopsies of the inguinal glands, complaining especially of pain in the abdomen. On examination, inguinal, axillar and cervical glands were present, some of them 4 cm in diameter. With treatment of sodium thiosulfate and fatty acid hydropersulfides in relatively small doses, the pain was sufficiently controlled. After two months of treatment, the patient experienced extreme pain and a tumor of the head of the right humerus. In view of the local lesions with analyses which all showed an intensive offbalance of type A, the treatment was changed to epichlorohydrin and heptyldiselenide. Administering these agents in relatively high doses, it was possible to not only control the pain in a few hours, but to have the lesion disappear in less than two weeks, as did also all the abnormal glands. However, in spite of these objective very good results, the general condition became unsatisfactory, especially with marked weakness. Changes in the doses of medication or the temporary discontinuation of the medication, failed to correct it. It was only when propionic aldehyde considered to act upon the organism level was administered, that a rapid change toward a feeling of general well-being was obtained. At present, with small doses of propionic aldehyde the patient is entirely free from any subjective or objective abnormal manifestations and has been so for almost a year.

Mrs. E. R., 42 years old, had a radical mastectomy for an adenocarcinoma of the breast. After 1½ years, she experienced persistent back pain which was first diagnosed as arthritis. X-ray studies and a myelogram made at Montefiore Hospital showed two metastatic lesions at the 1st and 2nd lumbar. Surgical intervention was thought to be not indicated. X-ray therapy neither relieved the pain nor made it possible for her to leave her bed. At admission under our care, the patient was in severe pain and unable to even turn in bed, although she was still able to move her legs and their sensitivity was conserved. A treatment with heptyldiselenide, propionic aldehyde and bixine made the pain disappear and up to date the patient is leading a normal life, after having been bedridden for 8 months.

Mrs. M. McB., 62 years old, came under our care for a basocellular carcinoma of the left side of the face, near the inferior eyelid. Advised to

undergo surgery, which would enucleate the left eye, she refused the operation. A biopsy was performed (*Fig. 192*) showing the presence of a basocellular carcinoma. She was treated with hexyldiselenide and with sodium thiosulfate, and the lesion disappeared within a few weeks. No recurrence was observed during the past 6 years.

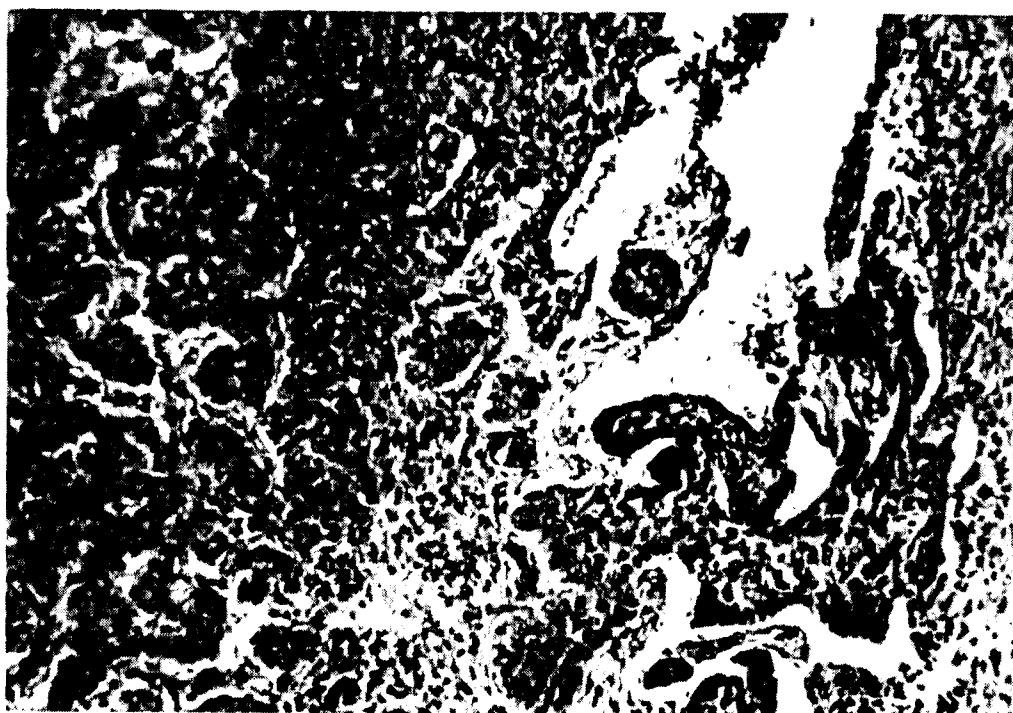


Fig. 192. Photomicrograph of the biopsy made on patient M.McB. showing a basocellular carcinoma.

Mr. G. Z., 56 years old came under our care for a lesion of the upper lip. Biopsy proved it to be a squamous cell carcinoma. (*Fig. 193*) The patient refused surgery or radiation which we advised. Following the biopsy the tumor started to grow rapidly, as seen in Fig. 194. According to the analyses, the patient was treated with fatty acid hydropersulfide. The lesion disappeared in less than 2 weeks. (*Fig. 195*) No recurrence was observed although the patient was no longer under treatment. The patient died 8 months later from a coronary occlusion.

The ability to induce changes at single specific levels has altered completely what was once a gross dualistic approach. Until recently, we had considered it inadvisable to induce therapeutic changes at a single level if offbalances were present at more than one level. With the concept of level independence, it has become part of the method to attempt to influence



FIG. 193. Patient G.Z. before treatment.

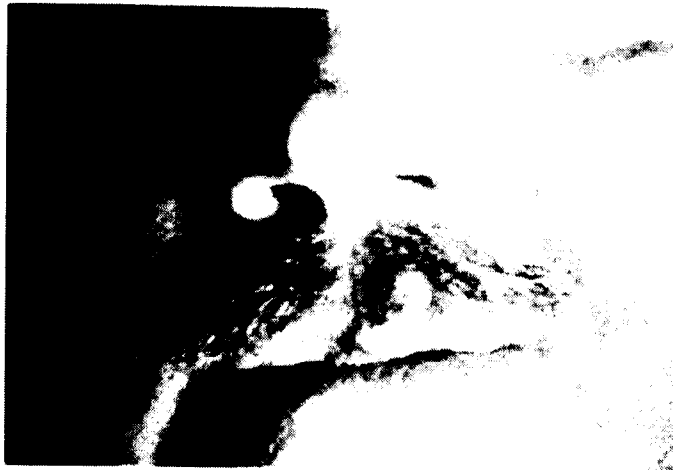


FIG. 194. The tumor grew rapidly following biopsy.



FIG. 195. Patient G.Z. after treatment.

the level in which the predominant abnormality is present rather than to induce gross changes at all levels. In cases with general offbalance A but predominant at the cellular level, therapy to induce offbalance D limited to the cellular level alone, with the metazoic remaining at offbalance A, has produced interesting objective clinical results. Similarly, good results have been obtained in cases with predominant offbalance D at the cellular level and in the metazoic compartment, with treatment directed at changing the systemic and tissular offbalance D into type A without influencing the offbalance D at the cellular level. It is interesting to note that in both types of cases the changes lead ultimately to the same overall pattern of offbalance—D for the cellular level and A for the metazoic compartment.

Level chemotherapy with selenium, heptanol, propionic aldehyde and other agents, has given highly gratifying results. It led us to the present form of treatment, with particularly good results. In a variety of tumors, some impressive because of their huge dimensions or because of their high degree of malignancy, the immediate objective response has been striking. Massive lung metastases from breast cancer, generalized abdominal metastases from colon carcinoma, bone metastases from breast or prostate, and metastatic melanoma are among the cases which have responded and we are now waiting for time to indicate whether the results have lasting value.

While we were convinced in the past of the inherent potentiality of the method in general, because of results with many different agents and criteria, we have been greatly encouraged by the most recent applications. We believe the method now provides a means of controlling a significant proportion even of preterminal and terminal cases of malignancy considered otherwise entirely beyond any hope. The particularly favorable results obtained in the cases which came under our care before the disease had progressed to advanced stages indicate that we are fully entitled to prefer this therapeutic method even for those cases where the presently used procedures might still have a chance to help.