PRESIDENTIAL ADDRESS: SIMPLE EXPERIMENTAL CANCER RESEARCH

Millard C. Marsh, Springville, New York

Appears on page 181 of this number of The American Journal of Cancer.

BENIGN GLANDULAR BRONCHOGENIC TUMORS

Louis H. Clerf and Baxter L. Crawford (by invitation), Philadelphia

ABSTRACT

In a series of bronchial neoplasms a number were encountered with definite tumors producing bronchial obstruction. From the biopsy studies these were considered to be malignant, but subsequent developments have proved them to be clinically benign. It would appear that this type of growth is a distinct entity and that by careful study of the clinical and bronchoscopic aspects, as well as the histologic structure of the growth, a majority can be recognized and differentiated from carcinoma.

A group of 16 cases has been studied, 8 in males and 8 in females. Five of the patients were between twenty-one and twenty-seven years of age; one was sixty-one; 9 were over forty. The growth commonly occurred in one of the large bronchi. In 5 instances it was in the right bronchus; in 11 in the left. In 9 a lower lobe bronchus was involved.

The growth is essentially sessile, being attached quite firmly to the bronchial wall by a broad base. It does not infiltrate the bronchial wall nor is there fixation of the bronchus, so commonly seen in carcinoma. The surface, which is usually covered by bronchial mucosa, may be ulcerated, dependent upon the extent of the associated inflammation and infection.

Certain histologic characteristics may be recognized from properly prepared and carefully studied biopsy material. The cell type varies, but the growth is usually composed of a columnar or transitional type of epithelium which frequently forms acini and a pseudo-roseate arrangement. The cells are often degenerated and distorted, with pyknotic changes in the nuclei resulting from pressure and inflammation. The bronchial mucosa usually covers the growth without any evidence of connection between the epithelium of the mucosa and that of the growth. The structure of many of these lesions suggests a mucous gland origin.

In a few of the cases where the growth could not be removed bronchoscopically observation was continued for a period of many years. The growth remained within the bronchus and did not infiltrate the surrounding tissue. It produced bronchial obstruction and associated pulmonary suppuration.

It is often impossible, from the histologic structure alone, to differentiate between this benign tumor and carcinoma, but when the clinical and bronchoscopic manifestations are also considered its benign nature should be recognized. Because of the clinical be-
behavior of these cases and the peculiar histologic structure of the growths, we consider that they constitute a definite clinical entity. We do not believe that these tumors should be classified as simple adenomas, but that some descriptive term, as "benign glandular bronchogenic tumor," is probably preferable.

Discussion

Dr. Carl V. Weller (Ann Arbor): I am much interested in this group of cases because of my own recent experience with a similar case. I see great difficulty in diagnosing this neoplasm because of the variety of cell types presented. In my own case I did not hesitate to make a diagnosis of carcinoma on a very small biopsy specimen removed bronchoscopically. A pneumonectomy was done and the gross specimen showed clearly that the neoplasm could have been completely removed endobronchially. I am glad to say that the patient survived the operation, which was unnecessarily severe for the nature of the neoplasm. How is the pathologist to recognize these growths when they present such a varied histopathology?

Dr. James Ewing (New York): Through the courtesy of Dr. Clerf I have had an opportunity to look over all his sections, and have been much impressed. He refers to a rather compact, somewhat variable group of tumors of the lung which must be clearly separated from the malignant bronchial and epidermoid types of pulmonary carcinoma. As the last speaker has said, the structure varies a great deal. The last two or three of Dr. Clerf's cases I would have classed as benign adenoma. They are very cellular, but they show an orderly arrangement with small cell groups and few mitoses, and they have the appearance of fairly benign tumors. Others are distinctly adenocarcinomatous, and some of them seem to show distinct infiltration with cellular stroma. Their location is also characteristic. Dr. Clerf has the great good fortune to be working in a highly organized bronchoscopic clinic where he sees great numbers of cases of this group.

Dr. Clerf is to be congratulated on the success of operations for these localized tumors. I do not think, however, that his report on their radiosensitivity, or the capacity of modern methods of x-ray technic in their control, is to be taken as the final word. I assume, and if I am not correct I hope he will correct my impression, that he has used pretty full doses, but when he reports that these tumors show no effect whatever of radiation, we want to know what the dosage is. We have had quite a few of these tumors at our institution, and a good many of our patients have shown improvement, clinical, radiologic, and bronchoscopic, under modern x-ray technic, so that I think the best method of treatment is still to be decided. Of course, in the hands of experts all the tumors that can be removed should be. One of Dr. Clerf's cases showed a limitation of a broad polypoid tumor to the wall of the bronchus at the end of ten years. That is a condition which must be radioresistant, but the fact that it had not extended in so long a period indicates that the roentgen treatment had considerable effect.

Dr. Clerf: I am interested in securing Dr. Ewing's opinion concerning this neoplasm. In the earlier cases we leaned rather too heavily on the pathologist's opinion based on examination of tissue removed bronchoscopically. As a result certain of these cases of presumably malignant neoplasms responded to treatment that could hardly be considered adequate for carcinoma. We now appreciate the necessity for correlation of the endoscopic appearances with the pathologist's report. On the basis of experience gained in approximately fifteen cases, I am of the opinion that clinically these tumors are benign, although the microscopic appearances do not always warrant this conclusion.

Significance of Variations in the Morphology of Sarcomas Produced by 1: 2: 5: 6 Dibenzanthracene

Otto F. Krebsiel and Cushman D. Haagensen, New York

PROCEEDINGS

Discussion

Dr. Shields Warren (Boston): I think Dr. Haagensen is to be congratulated on this histological study. I am interested to know whether he has succeeded in transplanting any of the tumors, especially the fibrosarcomas, whether they have held true to their histological type in the transplants, and also whether in the earlier stages of tumor development the medium in which the dibenzanthracene has been applied is an important factor in the histological picture.

Dr. C. C. Little (Bar Harbor): I would like to ask Dr. Haagensen if he used uniform genetic materials, or whether this experiment represented a number of mice in which the reaction and the different type of tumor may in some degree reflect a different biological constitution.

Dr. Haagensen: In answer to Dr. Little, we used several types of rats but only one type of mice, the Marsh strain, and we have found, in transplanting the tumors in mice, that they grow much better in the stock in which the tumor arose. Several different types of rats were used, but not a great many of each, so that I think we are not justified in drawing conclusions here.

In answer to Dr. Warren, we have been trying to obtain very early tumors, but have not been fortunate enough to do so. All those we have seen have been large enough to be recognized easily as sarcomas.

The melting point of the paraffin was just low enough so that it would solidify.

THE VALUE OF THE MACRONUCLEOLUS IN THE CANCER PROBLEM

William Carpenter MacCarty, Rochester, Minn.

To appear in THE AMERICAN JOURNAL OF CANCER.

PRIMARY CARCINOMA OF THE LUNG APPEARING IN THE APEX

George E. Marcil (by invitation), Philadelphia

Appears on page 137 of this number of THE AMERICAN JOURNAL OF CANCER.

Discussion

Dr. Baxter C. Crawford (Philadelphia): I had the opportunity of studying this tumor of Dr. Marcil's, and it seemed to me that it should be excluded from the group of so-called pulmonary sulcus tumors, that it is a typical case of carcinoma of the lung, the diagnosis being arrived at by exclusion. There was extensive tumor involvement of the upper lobe, and while there was nothing characteristic about the growth to identify it, we are justified in concluding, by a process of exclusion, that it is a primary carcinoma of the lung appearing in the apex.

Dr. Joseph MacFarland (Philadelphia): It seems to me that there is some confusion here between what Pancoast described as a primary sulcus tumor and this tumor of Dr. Marcil's. Dr. Pancoast was kind enough to show me his material. The characteristic feature of the superior sulcus tumor is that there is no cancer of the lung. In the specimen which Pancoast presented to me for examination, there was a tumor above the lung, descending to and subsequently invading the pleura, apparently from the neck, and composed entirely of large sheets or squamous epithelium with prickle cells and occasional pearly bodies. The conclusion to which we came was that it was probably one of the neck tumors, related to the branchiogenic carcinoma, and might have had its origin in the precervical sinus.

PROPERTIES OF THE PURIFIED CHICKEN TUMOR AGENT

Albert Claude, New York

To appear in THE AMERICAN JOURNAL OF CANCER.
Discussion

Dr. Jacob Furth (New York): I would like to ask Dr. Claude whether he has compared the activity of his preparations by determining the concentration of the virus, that is, the smallest amount that will produce the disease. His charts show that activity was tested by determining the size of the tumors produced. The size of a tumor that a given agent will produce depends not only on the concentration of the virus, but also on the presence of various substances in the inoculum.

Dr. M. J. Sittenfield (New York): I would like to ask Dr. Claude if he has arrived at a conclusion as to the nature of the real tumor-producing factor of the Rous chicken filtrate. As I understand it, it is still possible after concentration and purification of the filtrate to produce tumors with the remaining 3 per cent of solid matter, consisting of protein and phospholipoids. In view of this I am particularly interested to know if Dr. Claude has any notion whether we are dealing with an extrinsic or an intrinsic, chemical or other factor which is accountable for the tumor principle in the residue of the Rous chicken filtrate.

Dr. Claude: According to our experience the tumor-producing power of chicken tumor extracts, especially when Berkefeld filtrates are used, decreases rapidly with dilution. As a rule, both the size of the tumor and the percentage of "takes" give a fair approximation of the activity of the material. When greater activity was suspected we resorted to dilution. The relative tumor-producing power was determined by inoculation of the various fractions into the skin of the same bird. By this method, early development of the tumor may be detected and accurate measurements may be secured.

As regards Dr. Sittenfield's question, I am sorry that I can not offer a satisfactory answer. By successive fractionation the tumor agent has been purified so that about 95 per cent of the inactive products associated with it are eliminated. The chief constituents of the remaining active fraction seem to be a protein and phospholipoids. Here again we may be dealing with some impurities carried over with the agent. It is quite possible that, with the concentration available in the extracts, the detection of the agent cannot be accomplished with our present chemical methods of analysis. Our study of ultraviolet absorption shows that no correlation can be established between the tumor-producing activity of the extracts and the absorption curve, thus suggesting that the sensitivity of this test may also be inadequate. For the moment, chemical analysis alone does not give any definite information as to the true nature or origin of the chicken tumor agent.

A STUDY OF THE ENZYME CONTENT OF A PARENCHYMATOUS ADENOCARCINOMA OF THE PANCREAS AND A COMPARISON WITH THE NORMAL HUMAN PANCREAS

Kanematsu Sugiura, George T. Pack, and Fred W. Stewart, New York

To appear in THE AMERICAN JOURNAL OF CANCER.

Discussion

Dr. E. T. Bell (Minneapolis): I would like to know if Dr. Stewart means that tumor of the pancreas contains more insulin per unit volume than normal pancreas. He points out that the proteolytic action is about the same, but we are interested to know how much insulin there is in these carcinomas of the pancreas. An islet-cell adenoma produces more insulin than a corresponding volume of normal islet tissue. The hyperinsulinism can hardly be due to a quantitative increase in the amount of islet tissue.

Dr. Stewart: The tumor described was not an islet-cell carcinoma of the pancreas, but a purely parenchymatous tumor, and insulin determinations were not made.

EXPERIMENTAL TERATOMA TESTIS IN THE FOWL AND THE RELATION OF GONAD-STIMULATING HORMONES TO ITS PRODUCTION

Halsey J. Bagg, New York

Appears on page 69 of this number of THE AMERICAN JOURNAL OF CANCER.
**Discussion**

*Dr. George A. Wyeth (New York)*: I should like to know Dr. Bagg's method of preparing the anterior pituitary hormone. It has been my experience in its preparation by vacuum distillation that if the temperature exceeds 70° C., the growth hormone is destroyed.

*Dr. Baxter L. Crawford*: I should like to ask if any of these tumors have metastasized.

*Dr. Bagg*: No metastasis has been noted.

In reply to Dr. Wyeth, the Bugbee-Simond-Grimes method of preparing the hormone was used.

**DEVELOPMENT OF MULTIPLE TUMORS, PART III: RESULTS OF INGESTION OF CARCINOGENIC AGENTS. PRELIMINARY REPORT**

*M. C. Reinhard and (by invitation) C. F. Cundee, Buffalo*

To appear in *The American Journal of Cancer.*

**ON THE ACTION OF DINITRO COMPOUNDS ON CELL DIVISION**

*G. H. A. Clowes and (by invitation) M. E. Kralh, Indianapolis*

**ABSTRACT**

It has been found that 4–6 dinitro-o-cresol (DNC) and other dinitro compounds are capable at optimum concentrations of raising the respiration of sea urchin eggs to from four to six-fold the normal figure. At the optimum concentration for respiration the division of fertilized eggs is already markedly retarded and at higher concentrations entirely suppressed, but such eggs when returned to sea water, even after two or three hours' exposure to inhibiting concentrations of DNC, continue division in a normal manner and at a normal rate. At appropriate concentrations the stimulating action of DNC on respiration may be exactly balanced by the inhibiting action of cyanide, but the effect of these two agents on cell division is not antagonistic but additive. Eggs which have been exposed to an inhibiting concentration of DNC prior to the first division proceed for the most part to the early prophase, at which point they lie quiescent as long as they are kept in the DNC solution. If at the time of exposure to DNC the prophase of the first division cycle has already been passed, the eggs tend to proceed to the early prophase of the second division cycle, at which point they remain blocked so long as they are exposed to the DNC solution. Similar blocks in early prophase are noted in subsequent division cycles. The eggs so blocked in division are characterized by possessing a nucleus which is spherical in form and has an intact membrane, but the chromosomes are easily recognized and fully as large and as clearly stained as are the chromosomes in prophase of normal eggs after the rupture of the nuclear membrane has already occurred. A similar tendency to a block in the early prophase is observed when cyanide is used in inhibiting but non-toxic concentrations.

**Discussion**

*Dr. Stanley P. Reimann (Philadelphia)*: To the chemist, dissolution of the nuclear membrane means at least a dissolution of the bonds that hold amino acids together. Naturally, it means much more, but this may be regarded as a working guess. The building-up of chromosomes means synthesis of at least amino acids and protein material. It has been shown that oxygen tension and hydrogen-ion concentration play a part in the test tube in protein re-synthesis. Presumably, therefore, these two factors have something to do, also, with protein re-synthesis inside of nuclei whereby chromatin material is built up into chromosomes. If acids are produced, the sulphur equilibrium definitely enters the picture, since it is more stable in acid than alkaline media. Since mitosis with its rearrangement of structures is a dynamic affair, the chemical processes
entering into the procedure must also be extremely labile and sensitive. Voegtlin has shown that the sulphur equilibrium plays a part in protein re-synthesis. We now know that somehow the sulphhydryl group has a share in mitosis. It is therefore a fair enough problem to attempt to correlate Dr. Clowes' work on the action of dinitro compounds on cell division with sulphur equilibrium.

Dr. Clowes: I agree in general with Dr. Reimann's remarks, though I did not have time to go into this vast question. Our results fit in very well with those of Voegtlin, who has given special attention to the sulphhydryl group. His work on the nuclei of ameba appears to indicate that the sulphhydryl group plays a significant rôle in the protein syntheses that presumably precede division. Our work on the influence of organic acids on cell division goes back to the studies of Homer Smith and myself on the influence of CO₂ tension on cell division in sea urchin eggs. It should be definitely recognized that any acid nuclear division-blocking effect resulting from the use of dinitro compounds is not attributable to the direct action of these compounds, since they are from one thousand to ten thousand times as effective in blocking cell divisions as are the corresponding cresols or phenols, but rather to the influence exerted on certain metabolic processes.

AN INTERSTITIAL-CELL ADENOMA OF THE TESTIS WITH HYPERGENITALISM

C. A. Stewart (by invitation) and E. T. Bell, Minneapolis

Appears on page 144 of this number of THE AMERICAN JOURNAL OF CANCER.

LIPOSARCOMA OF THE KIDNEY

James S. McCartney and (by invitation) H. M. N. Wynne, Minneapolis

Appears on page 151 of this number of THE AMERICAN JOURNAL OF CANCER.

DIBENZANTHRACENE REACTIONS IN CONTROLLED STRAINS OF MICE

Charles F. Branch, Boston

Appears on page 110 of this number of THE AMERICAN JOURNAL OF CANCER.

Discussion

Dr. Clara J. Lynch (New York): It is interesting that these strain differences have been found after painting with dibenzanthracene. We have compared strains of mice as to their susceptibility to tumors in the skin and lung as a result of painting with tar, and have one strain which gave a high rate of lung tumors but a low incidence of tumors in the skin, another strain in which the organ susceptibilities are reversed, and a third which yields a high percentage of both types of tumor. There seems to be no correlation between the susceptibilities of the two organs. In one strain highly susceptible to skin tumors squamous-cell carcinoma of the stomach has also occurred.

Dr. David Seeof (Montreal): I should like to ask if the C57 strain showed any spontaneous tumors.

Dr. Cushman D. Haagensen (New York): May I ask the average age of the female mice in Dr. Branch's cancer strains? A similar situation occurred a number of years ago at the Crocker Institute. Marsh’s strain, which is a high-cancer strain, had been brought to the Institute, and no tumors were obtained. This seemed to us very curious, so we attempted to determine whether or not some extrinsic factor was concerned. A new sample of the strain was obtained, and the mice were divided into groups which were given different types of diet and kept under different living conditions. Under all of these different régimes the mice developed tumors, if they lived long enough. We therefore assumed that the mice of the original sample of the strain did not develop tumors because they did not live long enough to reach the cancer age.

Dr. Branch: To answer Dr. Seeof, the C57 mice did not have spontaneous tumors.
In reply to Dr. Haagensen's question, we used no mice under four months of age. Dr. Little suggested that a possible reason for our paucity of spontaneous tumors was that our mice did not live long enough. He suggested that we let our breeding females live eighteen to twenty months. We have tried this, having about 100 breeding females two years old, in whom the incidence of spontaneous breast tumors is practically nil.

Immunity to Transplantable Leukemia in Mice

C. P. Rhoads, New York

To appear later.

Leukemia of Mice and Chickens as a Neoplastic Disease

Jacob Firth, New York

Appears as part of a paper on Relation of Leukemia of Animals to Leukemia of Man, by J. Firth, H. W. Ferris, and P. Reznikoff: J. A. M. A. 105: 1824, 1935.

Genetic Aspects of Mouse Leukemia

E. C. MacDowell, Cold Spring Harbor, New York

Appears on page 85 of this number of The American Journal of Cancer.

Clinical Manifestations and Treatment of Leukemia

Lloyd F. Craver (by invitation), New York

Appears on page 124 of this number of The American Journal of Cancer.

Acute Leukemia with Remissions

Henry Jackson, Jr., Boston

Abstract

Acute leukemia is usually regarded as a disease which, from its incipiency, progresses relentlessly and with but insignificant remissions to a fatal termination in a matter of weeks or at most a few months. The nature of the condition is uncertain. Some would ally it to the infections. In the minds of others it more closely resembles a neoplastic disease. In any event, the steady progression of its course is regarded as rather characteristic and indeed to a certain extent diagnostic.

Yet in certain instances complete remissions, from both the clinical and hematological point of view, do occur. From a careful study of such cases we may derive information concerning the diagnosis and prognosis of the disease.

I. R., a thirty-nine-year-old man, was admitted to the hospital on Nov. 9 with a history of intermittent fever of three weeks' duration. The previous day he had passed a moderate quantity of blood by rectum. On entrance he was profoundly prostrated and sweating profusely. The gums were swollen and bled easily. The spleen was palpable three Angers below the ribs, and a large ecchymosis was present on the left thigh. The red cell count was 3,500,000 per c.mm., the hemoglobin 70 per cent (S), and the white blood cell count 3,500 per c.mm. Platelets were absent. The white blood cells were entirely stem-cells—blasts of the earliest type. The temperature was 103° F. The diagnosis seemed clearly to be acute leukemia.

1 From the Thorndike Memorial Laboratory, 2nd and 4th Medical Services (Harvard); the Mallory Institute of Pathology, Boston City Hospital; the Department of Medicine and the Collis P. Huntington Memorial Hospital, Harvard University.
For several days the patient’s clinical condition grew worse. The red blood cell count fell to 2,500,000 per c.mm. Then a sudden and dramatic change took place. The temperature became normal. Bleeding from the mucous membranes ceased and the spleen receded. In the meantime the white blood cell count fell to 1,000 per c.mm., without any change in the differential count and then suddenly rose to 55,000 with the appearance of progressively more and more mature cells of the granular series. The platelets returned to a normal figure. Following this change the white blood cell count again fell to 1,000 per c.mm., only to rise more slowly to a normal figure as the differential count became progressively more and more normal, until a month after admission no abnormality whatsoever in the white blood cell series could be detected. In the meantime the red cell count had gradually risen to a normal figure and the patient was in all respects clinically well.

For over five months the patient remained well. Neither clinically nor hematologically was there the slightest evidence of leukemia, either acute or chronic.

Suddenly and without warning the original symptoms returned in late April. Once more the white blood cell picture was that of a typical acute leukemia. Anemia developed rapidly, the temperature rose, bleeding recurred, and the patient died six months after his remission started. The sternal bone marrow showed the typical picture of acute leukemia.

Quite similar was the case of a three-year-old girl for whose history I am indebted to Dr. Louis K. Diamond of the Children’s Hospital, Boston. She was admitted to the hospital with a history of bleeding gums of three weeks’ duration. Her temperature was 105° F. The white blood cell count was 3,100 per c.mm., and the differential count showed 91 per cent stem cells. The platelets were markedly reduced and the red cell count was 2,300,000 per c.mm. As in the first case, the white blood cell count fell rapidly, reaching 600 per c.mm. The differential count remained unchanged. The blood picture became rapidly more and more normal and for two months the child showed no signs either clinically or hematologically of leukemia. Yet at the end of that period the characteristic picture suddenly returned and the patient died with an unquestionable diagnosis of acute leukemia.

Almost precisely similar were the cases of N. B., eight years of age, and G. W., four years of age.

In each of these instances, therefore, there were initial signs and symptoms usually regarded as pathognomonic of acute leukemia. In each there was a complete and prolonged remission of months’ duration. In each the initial signs and symptoms returned with dramatic suddenness and death ensued.

No conclusions can be drawn from these observations. They are offered merely as a chapter in the natural history of acute leukemia. The relation of the first attack to the second must remain problematic. Was the first illness due to infection which paved the way for the development of true leukemia? Were the patients always “leukemic,” the outward and visible signs being merely suppressed? Or may the true disease have true remissions? What is the relation of agranulocytes to the extreme leukopenic stage seen in all these cases? These questions must for the present remain unanswered. We learn, however, that complete remissions in what appears to be acute leukemia may occasionally occur and that our prognosis must always be guarded, even for months.

Discussion of papers by Drs. Rhoads, Furth, MacDowell, Craver, and Jackson

Dr. James Ewing (New York): I wish to make a single generalization about these five papers. It seems to me that to the general pathologist the most striking fact about leukemia is the very wide variety of conditions in which the phenomenon which bears this name is observed. The most striking group of cases is the one just mentioned by Dr. Jackson, occurring chiefly in children, in whom there is an acute infectious process in the nasopharynx, tonsil, or gums, with a high fever and a leukemic blood picture, a very rapid course, and death in a month or two, or else a remission with a recurrence of the symptoms and death with the typical subacute leukemic blood picture and changes in the tissues of a leukemic type. However, in some of these cases the patient does not die, but recovers, and we speak of a transient leukemic blood picture, and wonder whether we are dealing with the same disease.
During the Spanish War when the troops came back from Cuba many were suffering from a type of typhoid fever which had been passed rapidly from one individual to another, and had attained great virulence. The disease ran eight to ten days, was highly febrile, extremely toxic, with a great growth of lymph nodes throughout the body, and often a very distinct blood picture of lymphatic leukemia.

About 1910 I reported a case of acute lymphatic tuberculosis with purpura hemorrhagica which was proved to be due to a generalized infection with tubercle bacilli. The patient had a typical leukemic blood picture. He died within four months with characteristic leukemic symptoms.

A common clinical condition with a leukemic blood picture, generally fatal, is that which involves necrosis of bone either in the extremities, the sinuses, or maxilla. There is often a myelocytic reaction instead of the ordinary leukocytosis, which has a very unfavorable prognosis. These cases show the changes of subacute lymphatic or myelocytic leukemia.

In the Sloane Maternity Hospital many years ago I encountered a few cases of puerperal infection in which, after a period of weeks, or sometimes months, the patients went on to a progressive anemia; the blood picture then changed and death occurred with the changes of lymphatic or myelocytic leukemia. I think the first case of proved acute myelocytic leukemia was published from that group of cases.

In a few cases of pneumonia there is an extreme leukocytosis and a marked change toward the leukemic picture.

In 1895 I examined the blood picture in diphtheria at Willard Parker Hospital and encountered four cases of diphtheria in children in which the white cell count reached 150,000 to 200,000 with 95 per cent lymphocytes. All these patients died.

We could run over the group of myelogenous infections in which there is a pronounced leukemic picture in the blood, with lesions in the body which cannot be distinguished from any other type of leukemia.

A high proportion of cases of chronic leukemia give a history of pre-existing infections disease, mild or severe. Considering the cell type, we have the lymphocytic type, the myelocytic, the monocytic, and the plasma-cell; we have flooding of the blood stream with various tumor cells. Recently there has been reported a case of polynuclear leukocytic leukemia, in which a high total count was made up of polynuclear leukocytes, and finally there are the transitional types. The cell types thus vary enormously.

Consider the general pathological anatomy. The disease follows Hodgkin's disease and that very variable group of lymphoid sarcomas which Dr. Craver has emphasized. It follows mycosis fungoides and the acute and chronic infectious diseases. There is no time to review the scope of the pathological anatomy, but any pathologist who has had any experience in the study of these cases knows that we have often a very varied picture which is extremely difficult to interpret.

What are the conclusions? What is leukemia? The only conclusion I can reach is that it is a symptom-complex produced by a great variety of agents, running a great variety of courses. It has, unfortunately, a very uniform tendency to prove fatal. This point of view is important to the discussion when we consider the leukemias in the lower animals. Have they anything to do with our human problem? I am inclined to think not. They may, however, reveal principles which may be transferable to man, but I do not think there is any ground for assuming that the disease studied in chickens and mice is identical in origin with any form of human leukemia. Yet among human leukemias there may possibly be some virus disease.

Finally, I would ask the experimentalists if they consider, in the course of their work in the transfer of cells from one animal to another, that they may introduce into the picture agents which are not active under normal conditions, and may not exist in human cases? It seems to me the whole subject requires a more general point of view, that we are dealing here not with a single disease, but with a symptom-complex, arising under a great variety of conditions, caused by a great many exciting factors, but bringing into action certain intrinsic properties of the cells. That does not exclude the possibility that there are forms of the disease in man which may be comparable to the disease in the lower animals.
Dr. Fred W. Stewart: Unfortunately the student of human pathology has no basis for the discussion of papers such as those of Drs. Furth and MacDowell. The nature of the material is not reproducible in present methods of investigation of human leukemias. We cannot control the genetic make-up of our patients, nor do we study a transmitted disease. On the whole, I am rather loath to draw conclusions from Dr. Furth's work. It seems to me that he is studying leukemia by using the mouse as a sort of culture medium for transplanted cells and that one should be wary of endeavoring to explain the complexities of human leukemic or lymphosarcomatous reactions merely by reference to such experiments. On the other hand, I find in Dr. MacDowell's studies a rich field for experimentation on the factors of realization, as Nicholson would call them, in mouse leukemia. Such experiments might find their application in the human field. I find little satisfaction in trying to determine whether or not human leukemia is a neoplasm, nor do I believe this distinction very important. In human cases the criteria of neoplasia have to be applied to the varying manifestations of individual cases or to phases of individual cases, rather than to the disease as a whole. Some have them, others do not, and the neoplastic quality is scarcely a fixed property.

Dr. E. B. Krumbhaar (Philadelphia): Since Ellermann first established in 1908 that leukemia could be transmitted in fowls by cell-free filtrates, the experimental study of the leukoses has attained such proportions that doubtless we shall have to have a subgroup of “leukocytologists” before long! I can not aspire to join that particular group, so that I shall confine my remarks to some applications of the experimental studies to the human disease. First, I would like to add my opinion to Dr. Ewing's statement that we must take these experimental studies of the transmissible forms, interesting as they are, with more than a grain of caution as regards the human disease. It is well known that the same disease pictures can be produced in different species by different disease processes; as a single instance, consider the infectious pernicious anemia of horses. I think, however, that we can satisfactorily apply many features of the experimental studies, in an analogous way at least, to the human disease. As regards the various instances of high blood counts (including lymphocytes) of which Dr. Ewing spoke, it seems to me that they can be quite satisfactorily and simply dismissed as “leukemoid” blood pictures, a convenient term which I coined some years ago for such conditions. This over-emphasis on the peripheral blood picture reminds me of a story I heard recently about Türek, the great German hematologist. When he was asked about some tissue changes in a certain blood disease, he drew himself up and said, “Sir, I am a peripheral hematologist!” I think, also, as Dr. Ewing suggested, that the tissue changes in the various forms and stages of the human disease have been neglected. The very tedious study that the inaccessible bone marrow requires (with the different cytological pictures in various bones at different marrow levels, different ages, etc., that Custer has so well brought out) offers obvious explanations for such neglect.

While the dangers of applying the results of experimental studies too closely to the problem in man are recognized, still they offer satisfactory explanations for certain problems. One difficulty, for instance, that has puzzled the students of the human disease is the marked clinical difference between the acute and chronic forms. Some people even go so far as to claim that the acute forms are infectious and the chronic forms neoplastic. In animal studies I understand that it is possible to get all gradations between the two, or even some symptoms of the acute form and some of the chronic, in the same individual, which makes it easier for us to believe what I have always felt it was not difficult to believe, that these differences are largely of a secondary nature. The tissue changes are similar in the two forms, and the characteristic cells in the blood are essentially alike, though of different maturity, and from the same stem; the questions of fever, prostration, hemorrhage, changes in the erythrocytes and platelets, etc., are of only secondary importance as regards the nature of the disease. It is rather different from the condition in Hodgkin's disease, where the tissue picture does not, to my mind, at least, resemble a neoplasm, so that it seems easy to look upon the leukemic group as neoplastic, and still favor an infectious origin for Hodgkin's disease.

In the same way animal studies are useful in showing very satisfactorily that, there at least, no essential difference exists between leukemia and lymphosarcoma and leukosarcoma. Here we have added human evidence, as we know that leukosarcoma, although
rare, does exist as an intermediate stage between the leukemias and lymphosarcoma, making it easier to assume that these conditions are at least related. We can not forget that the great majority of clinical cases show quite different pictures in leukemia and lymphosarcoma; but Dr. Furth’s animal strains also showed great differences. As I recall, some showed a marked tendency toward leukemia and others toward lymphosarcoma, but in the same strain some of the recipients might show both pictures, so that it becomes easier to reconcile ourselves to the idea that the disease in man, if not identical, is very closely related to the transmissible forms.

If I may turn to the clinical side, I would like to add very briefly a few more unusual clinical pictures. I recall a necropsy done a few weeks ago in an individual dying with the terminal blood picture and tissue findings of myeloid leukemia; yet that patient had been studied for two to three years before death without signs that could be recognized as leukemia. The onset was different from any which has been mentioned so far: a long-continued anemia, thrombopenia, hemorrhages and hematemesis on one occasion, and an increase of monocytes. That picture went on for some two years until finally, just a few months before death, a typical leukemic picture became manifest.

I recall, also, a case seen a number of years ago that fulfilled the criteria for Banti’s disease, nebulous though they may be. The spleen was removed by Dr. Deaver with that diagnosis; the patient showed much improvement, lasting for eighteen months, at the end of which time a fulminating type of leukemia appeared. Death occurred with the blood picture and tissue changes of leukemia. Did the patient first have Banti’s disease, and later happen to have leukemia, or did he have leukemia all along?

Dr. Bauer talked with us recently about a case at the Pennsylvania Hospital with an unusual onset. The history was typical of pneumonia: exposure in an underfed individual followed by chills and fever, pulmonary signs, neutrophilic leukopenia, vomiting, and bloody sputum. This went on to a fulminating type of leukemia, again with the tissue changes of leukemia and death in a few months. The exposure here seems to be very closely connected with the onset of the disease. Was the ground already laid for leukemia, and the exposure coincidental, or is exposure one of the stimuli which may initiate the disease? About such questions we are still in the dark.

You may have seen an account by Rössler in the Münchener Medizinische Wochenchrift (82: 217, 1935) of a man who received a blow over the pubis. A few weeks after the local signs of trauma had disappeared, he became acutely sick, with persistent priapism and a leukocyte count of 357,000, 30 per cent myelocytes. It is hard in this instance not to connect the trauma with the onset of the disease, and yet we are still so much in the dark that we have to leave these questions unanswered. I think one can say with some justice that Naegeli’s statement as regards human leukemia, that we are in a condition of stalemate, is still true. I for one, however, would be willing to vote for its neoplastic nature at least as the best working hypothesis at present, on account of the close analogies with the experimental neoplastic disease.

Dr. Harry C. Schmeisser (Memphis): I reported a study on Spontaneous and Experimental Leukemia of the Fowl in the J. Exper. Med. 22: 820-838, 1915. The spontaneous case was of the myeloid type. From this animal, the disease was transmitted into the fifth generation. A total of 105 animals was used in conducting many different types of experiments. Of this number, 22 developed leukemia. This paper was confined to a report of the simple transmission of the disease by the intravenous or intraperitoneal injection of an organic emulsion. Of the 40 chickens thus inoculated, 13 developed leukemia. The clinical picture and changes produced in blood and organs were analogous to those which occur in human leukemia. This confirmed the work of Ellerman and Bang, who first successfully transmitted the disease. Although not mentioned in this report, myelomata in the skin about the head occurred in at least one fowl to which the leukemia had been transmitted. This is of interest in relation to Dr. Furth’s paper in which he considered leukemia of chickens as a neoplastic disease.

Note: Papers were also presented by Dr. Douglas A. MacFadyen of New York, on The Degree of Inhibition of Transplantable Mouse Tumors, and by Dr. Helen Woodard and Dr. Gray H. Twombly of New York, on A Preliminary Study of Serum Phosphatase in Bone Tumors. These will not be published.