A number of cases of lymphatic and myelogenous leukemia have appeared in the course of various experiments we have been conducting with Wistar rats. The animals affected were involved in several different types of investigations and had been subjected to procedures in which the only common denominator was the intragastric instillation of 30-methylcholanthrene.1

In the published reports of experiments with Wistar rats, only one case of induced leukemia has previously been recorded. This was noted by Murphy and Sturm (12) in 1941, when they observed the development of lymphatic leukemia in an animal of this strain following the accidental injection of dibenzanthracene into a lymph node. There are no cases on record of the development of spontaneous lymphatic or myelogenous leukemia in a rat of this stock.

Before 1956, leukemia had not been reported in any strain of rat. In that year, Wilens and Sproul (28) described eleven instances of myelogenous and one of lymphatic leukemia in an inbred strain of Osborne-Mendel albino rats. Two years later Rask-Nielsen (14) found, among 30 old white rats of uncertain origin, one animal with a large abdominal tumor composed of "pathological myeloblasts." Blood smears from this animal were normal except for 6 per cent of the white cells which she regarded as "immature pathological myeloblasts." Rask-Nielsen (14) was able to transfer the tumor to other rats, but at no time did "pathological myeloblasts" appear in the peripheral blood of these animals. The following year, Oberling, Guérin, and Guérin (18) reported six cases of lymphatic and three of myelogenous leukemia among 6,000 rats. These were observed only in older animals, the youngest 17–18 months of age, and the majority in animals more than 28 months old. In 1940, Arai (1) found, in a group of 500 rats of different strains, 27 animals with spontaneous tumors and noted one instance of chronic myelogenous leukemia.

Ratcliffe (15) in that same year described 273 tumors in a large colony of Wistar rats. Among these, there were two lymphoblastomas of the mediastinum, one lymphoid tumor of the thymus, and two lymphosarcomas, but none produced a leukemia. More recently, Farris and Yeakel (6) reported nine instances of reticulum-cell sarcoma in 1,000 autopsies on Wistar rats, without mention of a single case of leukemia. Similarly, Bullock and Curtis (8) found no leukemia in 78 animals with sarcoma arising in the mesenteric lymph nodes, among 489 spontaneous tumors found in 2,450 rats whose original source was apparently unknown. Although described as spontaneous tumors, it is difficult to accept them as such without reservation, since all the animals except 23 had been fed ova of Taenia crassicollis, the tapeworm of the cat, a procedure which these authors had described previously (4) as a simple method for producing sarcoma of the liver in rats.

Other efforts to produce leukemia in rats have been made. Bernard (2), using the same approach that Thomsen and Engelbreth-Holm (22) employed in fowls, was unsuccessful in his attempt to produce leukemia in rats by injecting carcinogenic tar into the bone-marrow. Storti and Storti (21) also failed after injecting 3,4-benzpyrene into the femoral bone marrow of 100 rats. Gennaro and Grazia (8) observed the development of one case of lymphatic and one of myelogenous leukemia among fifteen rats whose skin they painted with a 1 per cent solution of benzpyrene in benzene. In 1940, Ito (9) found myelogenous leukemia in one of twenty white rats, not identified as to strain, following the feeding of o-aminoazotoluene and methylene blue.

In our experiments, eight cases of leukemia appeared in a total of 59 Wistar rats under study, and a successful transfer by intraperitoneal injection of spleen emulsion was effected to two of three additional young rats from our colony.

1 Eastman Kodak Co.

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MATERIALS AND METHODS

All experiments were performed on Wistar strain albino rats grown in our own colony in which inbreeding has been carefully avoided. The cases reported here were contributed by six groups of animals, consisting of intact and castrated males and females.

Two of these groups were maintained on a calcium-free diet, two on an approximation of the "Roffo diet," and two on our colony Rockland diet. The only procedure common to all six groups was the administration of methylcholanthrene by stomach catheter (18).

EXPERIMENTS AND RESULTS

CASE 1, LYMPHATIC LEUKEMLA.—

Experimental method.—Calcium-free diet plus methylcholanthrene in castrated male.

A male rat was castrated at the age of 7 weeks and placed on the calcium-free diet recommended by Zucker (94) for the production of gastric ulceration of the antral portion of the rat's stomach. This diet was replaced for short periods with our colony Rockland diet, because young rats could not be maintained indefinitely on the calcium-free diet (17). Once the experimental diet was started, the animal received 2 mg. of methylcholanthrene dissolved in 0.5 cc. of olive oil, administered by stomach catheter (17), daily for 6 days of the week.

The animal was found dead in its cage at the age of approximately 12.5 months, after having received methylcholanthrene as described for nearly 11 months.

A blood count taken 15 days before death showed the following: R.B.C., 5,330,000; W.B.C. 38,300; differential: polymorphonuclears 8 per cent, lymphocytes 52 per cent, lymphoblasts 40 per cent, 1 nucleated R.B.C./100 W.B.C.

Bone-marrow smear showed the bone marrow to be largely replaced by lymphocytes.

Autopsy.—The significant gross findings included enlarged palpable lymph nodes in both axillary and inguinal regions, which had been noted on clinical examination 5 days before death. The abdominal lymph nodes were also enlarged, as were the nodes in the region of the thymus. The liver appeared larger than normal. The spleen was enlarged and measured 5 cm. × 1.4 cm.

Histology.—Sections of the liver showed an infiltration of rather pleomorphic hyperchromic cells, some of which resembled lymphocytes. The infiltration was diffuse throughout the sinusoids and was also present in the form of small nodules which did not have a definite architectural relationship, although most portal triads were infiltrated. The normal architecture of the spleen was destroyed by an infiltration of cells which were similar to those described in the liver. There was also a moderate degree of hemosiderosis. Sections from several lymph nodes showed complete destruction of the normal structure, with replacement of the normal cells by cells similar to those described above. The infiltration was not limited by the capsule, and the same type of cells was also present in the perinodal fat and connective tissue. A tumor mass adjacent to the undersurface of the liver proved to be the pancreas, markedly infiltrated by large numbers of cells not as pleomorphic as those found in the liver. This infiltration almost completely replaced the pancreatic tissue. A kidney section showed an extremely heavy infiltration of cells similar to those infiltrating the pancreas. The tumor cells almost completely replaced the interstitial tissue in the cortex, and the number of nephrons appeared to be reduced. The tumor cells also infiltrated the pelvic fat. The brain was infiltrated by cells similar to those already described, which were grouped in the subarachnoid space and in the adjacent brain substance. This infiltration was not pronounced. Peroxidase stain was negative in all the tissue sections in all the cases of lymphatic leukemia.

This animal died at the age of 12.5 months of lymphatic leukemia which was first detected by blood count after the animal had received methylcholanthrene for approximately 10.5 months. Since no previous blood counts had been done, it is not possible to conjecture how much earlier the leukemic state had developed.

Seven additional rats with lymphatic leukemia are included in this report. While the essential experimental details are given below, the blood counts done in the course of the study are tabulated in Table 1. Since the various tissues in these animals were infiltrated by cells that closely resembled those described in the infiltrations in Case 1 and varied only in the degree of organ involvement, the gross and histologic features have been listed in Tables 2 and 3.

CASE 2, LYMPHATIC LEUKEMIA.—

Experimental method.—Colony Rockland diet plus methylcholanthrene in spayed female.

This animal was spayed at the age of 6 weeks and placed on the methylcholanthrene schedule described in Case 1. It died, at 8 months of age, of lymphatic leukemia, after it had received methylcholanthrene for 6.5 months. Since a blood count, taken only 16 days before death, failed to show any evidence of leukemia, this result suggests that the transformation of the normal cell to the malignant cell occurred rather suddenly, as pointed out by McEndy, Boon, and Furth (11) in their studies.
with methylcholanthrene-induced leukemia in mice.

We have presented elsewhere (19) suggestive evidence that methylcholanthrene administered by stomach catheter to the lactating mother may be transferred to the offspring. We are also investigating whether the administration of the carcinogen during pregnancy will exert any influence on the offspring. In one experiment of this type, normal male and female rats were mated, and impregnation of the female was assumed to have occurred upon the finding of the vaginal mucus plug. Gastric instillation of methylcholanthrene as described for Case 1 was started when such a plug was found and continued until the day of delivery, or until the time that we could be certain pregnancy had not occurred. All animals in this group were maintained on our colony Rockland diet. The following two cases were contributed by this group.

Case 3, Lymphatic Leukemia.—

Experimental method.—Colony Rockland diet plus methylcholanthrene in intact female.

This female, at 4 months of age, was placed on the methylcholanthrene schedule for a period of 28 days. She had not become pregnant. Eighty-two days after the gastric instillation of methylcholanthrene was discontinued, the animal was found dead in its cage. No blood counts had as yet been taken.

Case 4, Lymphatic Leukemia.—

Experimental method.—Colony Rockland diet plus methylcholanthrene in intact female.

This rat, at 5 months of age, received methyl-

TABLE 1

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<tr>
<th>Case</th>
<th>Hemoglobin (per cent)</th>
<th>Days before death</th>
<th>White blood count</th>
<th>Polymorphs (per cent)</th>
<th>Lymphocytes (per cent)</th>
<th>Lymphoblasts (per cent)</th>
<th>Monocytes (per cent)</th>
<th>Eosinophils (per cent)</th>
<th>Basophils (per cent)</th>
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* Degree of enlargement indicated by + signs.

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* Degree of infiltration + to ++++.  
† N.e. = not examined.
cholanthrene for 21 days, at which time it gave birth to its litter. Six days later she killed all the newborn.

A blood count taken approximately 5.5 months after the last dose of carcinogen is shown in Table 1.

The animal was found dead in its cage just 1 month later, 200 days after completing its course of methylcholanthrene. A blood smear taken from the heart blood showed a large number of lymphoblasts. It was 1 year of age at the time of death.

Roffo (16) has reported the development of adenocarcinoma in the rat's stomach following a diet of bread and milk to which was added an equal amount of either lard, beef tallow, mutton tallow or of olive oil which had been heated to 350° C. for \( \frac{1}{2} \) hour. In the course of our studies, we attempted to repeat Roffo's conditions in two groups of rats.

The diet, No. 74, was constructed in an effort to simulate as closely as possible that used by Roffo, exact details of which could not be gleaned even though his published reports are extensive. Diet 74 had the following composition: 1,948 gm. of milk, 340 gm. of Kellogg's All Bran, and 400 gm. of white bread.

With this diet, one group of animals received methylcholanthrene in 1 cc. of unheated olive oil, on a schedule similar to that in Case 1, while the other was given methylcholanthrene in 1 cc. of heated olive oil. Each group contributed one case of lymphatic leukemia as described below.

**CASE 5, LYMPHATIC LEUKAEMIA.**

*Experimental method.*—Diet 74 plus methylcholanthrene in intact male.

This male, when 8 weeks old, was placed on experimental diet 74 with 2 mg. methylcholanthrene in 1 cc. of unheated olive oil, administered by stomach catheter, on a schedule similar to that used in Case 1.

A blood count taken 6 months after the carcinogen and diet were started is shown in Table 1. Two months later the 10-month-old animal was found dead in its cage, after having received methylcholanthrene for the last 7.5 months.

**CASE 6, LYMPHATIC LEUKAEMIA.**

*Experimental method.*—Diet 74 plus methylcholanthrene in heated olive oil in intact male.

This male rat was placed on diet 74 at 8 weeks of age, and 5 days later began to receive methylcholanthrene dissolved in olive oil that had been heated to 350° C. for \( \frac{1}{2} \) hour. A blood count (Table 1) taken 1 day before death is in sharp contrast with one taken 5.5 weeks earlier. It was sacrificed at the age of 14.5 months after having received methylcholanthrene in heated olive oil for 12.5 months.

At autopsy, after a section of spleen was taken for histologic examination, the remainder of the organ was ground with a mortar and pestle with 5 cc. of normal saline. A 1-cc. portion of suspended cells was injected intraperitoneally into each of three normal rats, 6 weeks of age, from our stock colony. Two of these transfers (Cases 6A and 6B) were successful.

Case 6A, 19 days after injection, showed enlarged inguinal, maxillary, and sublingual lymph nodes. Blood counts 6 and 19 days after the injection of the splenic cells are shown in Table 1.

The animal was sacrificed after the second count was taken.

Case 6B was sacrificed 60 days after the intraperitoneal injection of the leukemic spleen cells. The pertinent data are shown in the charts.

**CASE 7, MYELOGENOUS LEUKAEMIA.**

*Experimental method.*—Calcium-free diet plus methylcholanthrene in castrated male.

A male rat was castrated at 7 weeks of age and placed on the same diet and methylcholanthrene schedule as the animal in Case 1. It was sacrificed at 16 months of age when the peripheral blood count showed a picture compatible with that of myelogenous leukemia.

Nine months after the carcinogen was started, a small mass was palpated in the right anterior loin fold, corresponding to what we have described in a previous publication as a type B tumor (17). Three months later, a similar mass was palpated in the left anterior loin fold.

A blood count at that time was still within normal limits: R.B.C., 8,850,000; W.B.C., 10,000; differential: polymorphonuclears 27 per cent, lymphocytes 73 per cent (occasional large lymphocytes).

Six weeks later additional similar masses were palpated in each posterior axillary fold.

A blood count 2.5 months after the first count showed R.B.C., 2,590,000; W.B.C., 70,800; differential: polymorphonuclears 35 per cent, stab forms 9 per cent, myelocytes 32 per cent (15 per cent ring forms), myeloblasts 14 per cent, lymphocytes 10 per cent, 3 nucleated R.B.C./100 W.B.C.

There was an increase of granulocytes in the bone marrow based on peroxidase stain. A peroxidase stain of all tissues was positive.

*Autopsy.*—The significant gross findings were an enlarged liver and spleen, the latter measuring 6 X 1.8 cm. Two enlarged abdominal lymph nodes were also noted.

*Histology.*—Sections of liver showed an appreciable infiltration of cells of different shapes. The nuclei varied from round forms, through horseshoe shapes, to the typical lobulated nuclei of the ma-
ture polymorphonuclear leukocytes. The infiltrating cells were particularly concentrated around the portal triads, although a moderate number of similar cells could be seen in the sinusoids. The architecture of the liver was relatively undistorted. The sinusoids were dilated, but the triads were readily identified. The parenchymal cells showed granularity of the cytoplasm with some vacuolization. A moderate number of binucleated cells were observed. The architecture of the spleen was distorted, and follicles could not be recognized. The parenchyma was replaced by large numbers of cells identical in appearance to those infiltrating the liver. A moderate number of giant cells which were doubtlessly megakaryocytes were scattered throughout the section with no well defined architectural distribution. The areas around the larger bronchi in the lungs were moderately infiltrated by cells similar to those described above. In many areas there was considerable thickening and broadening of the alveolar septa. This broadening was apparently due to infiltration of the septa by cells similar to those described. The renal architecture was undistorted, and the glomeruli were normal in number and appearance. Varying degrees of parenchymatous degeneration were apparent, however, and the cells were swollen and bulged into the lumina, many of which were obliterated. The cor-
tex was lightly infiltrated by cells similar to those already described, with the greatest concentration noted around the larger arterioles. The perirenal fat was rather heavily infiltrated. The adrenal gland was infiltrated by cells beneath the capsule at one pole. There was a light scattering of similar cells in the sinusoids of the cortex. The medulla was uninvolved. Sections of lymph nodes from the vicinity of the appendix and right loin, the mesen-
teric nodes, the maxillary lymph nodes and peripancreatic nodes all showed destruction of the normal follicular architecture, although the si-
inusoids were still recognizable. The nodes consisted principally of cells similar to those infiltrat-
ing the organs previously described. The pancreas was markedly infiltrated by cells which seemed to originate in the adjacent peripancreatic nodes. Ex-
cept for this cellular infiltration, the pancreatic tissue was normal. There was no infiltration of the maxillary gland. A section of thyroid, including the trachea and surrounding muscle, had cellular infiltrations in the fat and connective tissue immediately adjacent to the glandular tissue. Peroxidase stain was positive on all the infiltrated areas of the tissues described.

This animal was 14.5 months of age and had received methylcholanthrene for slightly longer than 13 months when the leukemic state was evi-
denced in the blood count. Since a normal blood picture had been obtained approximately 2.5 months earlier, the development of myelogenous leukemia in this rat is placed between 10.5 and 13 months after the beginning of methylcholanthrene administration.

CASE 8, MYELOGENOUS LEUKEMIA.—

Experimental method.—Calcium-free diet plus methylcholanthrene in intact male.

This male, at 6.5 weeks of age, was placed on the calcium-free diet and methylcholanthrene sched-
ule identical with that used in Case 1 and was sacrificed 14 months later.

A blood count was taken approximately 10.5 months after the methylcholanthrene was started and showed: R.B.C., 6,030,000; W.B.C., 14,600; differen-
tial: polymorphonuclears, 47 per cent; eosinophils, 2 per cent; lymphocytes, 51 per cent.

Three and one-half months later, a blood count gave the following results: hemoglobin, 9.7 gm.; W.B.C., 109,800; differential: polymorphonuclears 36 per cent, stab forms 16 per cent, myelocytes 37 per cent (25 per cent ring forms), myeloblasts 3 per cent, lymphocytes 8 per cent, 2 nucleated R.B.C./100 W.B.C.

It was sacrificed the next day.

Autopsy.—The salient gross findings were an enlarged spleen, measuring 6.4 x 1.6 cm. and weighing 4.5 gm., and an enlarged liver which weighed 9.9 gm. There were no obviously enlarged lymph nodes, and the kidneys grossly appeared to be normal.

Histology.—Sections of the liver, spleen, and lungs showed an infiltration by cells similar to those described in Case 7. The kidneys, adrenal gland, and testicles were not infiltrated. A peroxi-
dase stain of all the tissues was positive.

DISCUSSION

In the material that is the basis of this report, we have seen the development of two examples of myelogenous leukemia and six of lymphatic leuk-
emia in a total of 59 Wistar rats under study.

These cases were contributed from six groups of animals on various diets in which the administra-
tion of methylcholanthrene by stomach catheter was the only procedure common to all. The length of time for which the carcinogen was administered before the leukemic state was detected ranged from approximately 1 to 14 months. In four of the eight rats, the leukemic state was suspected first from the blood count. In another animal, a blood count approximately 2 months before it died, and, in still another, a blood count 16 days before death, failed to show any diagnostic changes.

Peripheral lymph nodes were palpable clinically
in four of our animals with lymphatic leukemia. From one case of lymphatic leukemia which developed in our series, a successful transfer to two of three young Wistar rats from our stock colony was effected by the intraperitoneal injection of splenic tissue brayed in normal saline. Extensive transfer studies have been carried out subsequently and will be reported separately.

Methylcholanthrene applied percutaneously has induced and hastened the development of leukemia in mice. Thus, Kirschbaum, Strong, and Gardner (10) found that leukemia appeared earlier in a strain of mice in which spontaneous leukemia was common when methylcholanthrene was applied percutaneously. The same procedure had little effect, however, in mice with no predisposition. On the contrary, Furth and Barnes (7) were able to show that even mice of a low leukemic stock could readily be rendered leukemic by the skin application of the same carcinogen. Furthermore, McCady, Boon, and Furth (11) induced 72 cases of leukemia in mice by this method, of which 33 were lymphoid leukemia and only 2 myeloid. Of particular interest is the failure of Stewart and Lorenz (80) to find any instance of leukemia in their extensive feeding experiments with methylcholanthrene in mice.

SUMMARY

Six cases of lymphatic and two cases of myelogenous leukemia developed in a group of 59 Wistar rats under a variety of experimental conditions but in which all animals received methylcholanthrene by stomach catheter. The carcinogen was administered for periods of 1–14 months. From one case of lymphatic leukemia, the disease was transferred to two of three young colony rats by intraperitoneal injection of splenic cells suspended in normal saline.

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The Development of Lymphatic and Myelogenous Leukemia in Wistar Rats Following Gastric Instillation of Methylcholanthrene

Harry Shay, Margot Gruenstein, Halvey E. Marx, et al.

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