INFECTIOUS FELINE AGRANULOCYTOSIS *

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Infectious feline agranulocytosis is a disease of the domestic cat characterized by leukopenia and pronounced neutropenia. The condition was first described by Lawrence and Syverton in 1938,[1] when it was reported that the evidence suggested a filterable virus as the etiological agent. Since then the viral etiology has been satisfactorily established as a part of an extensive study of the disease which is being carried out at the University of Rochester. The object of the present communication is to present in detail the hematological findings, together with a brief description of the clinical and pathological aspects of the disorder. The clinical features have been described previously.[1] Since an adequate description of the pathological picture of the identical disease has been made by Hammon and Enders,[2] our description of the pathology, which is for the most part confirmatory, is brief. A detailed presentation will be made later of the bacteriological observations, which include the viral studies, methods of transmission and host range.

The data which are used in this report have been collected from observations made on 113 animals suffering from this disease.

CLINICAL COURSE

The clinical course is in all essentials the same as that reported in our previous communication. A typical animal appears well for 5 or 6 days after exposure to the infectious agent. We have been unable to elicit any tell-tale symptom during this period of incubation. Following the incubation period the stage of clinical disease is gradual in its onset and variable in its manifestations. Infected cats may appear entirely well, or occasionally suffer a

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slight impairment of appetite. Other animals become listless, assume a recumbent position and refuse all food, usually from the 6th to the 9th day. Vomiting, diarrhea, and nasal and ocular discharges may occur irregularly. Death may intervene at any time after the animal refuses food. In some instances, in fact in many, this may occur before listlessness and weakness develop. It is not at all uncommon to leave an animal in apparent good condition and find it dead upon returning a few hours later. Oral or perianal lesions have never been noted. Enlargement of the peripheral lymph nodes has not occurred. If recovery is to take place, it usually begins after 2 to 4 days of the disease. The first clinical evidence for this is ingestion of food by the cat. Once the animal begins to eat, one can be fairly sure of eventual recovery. The period of recovery usually requires only 5 or 6 days.

Pyrexia: Fever is not a prominent symptom. Sixteen animals were carefully observed with reference to pyrexia. To establish the limits of temperature variability within this group of 16 cats, the rectal temperature for each cat was recorded on 10 of the 18 days that constituted the period of isolation, or control period. Based on these 160 readings, the mean temperature was 38.5° C. Following inoculation, temperature readings were made daily. Of these 16 animals, 6 had fever (a temperature above 39.4° C. was arbitrarily accepted as indicating fever) 1 day before the height of the disease and 10 had no fever at this time. Observations were made on only 12 of these animals at the height of the disease; 6 were found to have fever, and 6 to have no fever.

Weight: The disease is too acute and too short in duration for much loss of weight to occur. Of 11 cats with the disease, 5 showed no loss of weight, 4 showed a loss of 114 to 228 gm., and 2, a loss of only 57 gm.

Mortality: The experiments which have been conducted justify only a tentative statement as to the percentage of animals that succumb to the disease. We do know, from the number of animals that have died, that the mortality is quite high. Thus, of 110 animals with the disease, 51 died, 33 were killed * and 26 recovered. If one assumes that the mortality rate would have been the same for the 33 sacrificed animals as for the others, 22 of these animals

* Throughout these experiments ether was used as the lethal agent and for all operative procedures.

would have died. Therefore, 73 out of 110 cats with the disease would have succumbed, giving a mortality rate of 66 per cent.

The Blood

The White Blood Cell Picture

Detailed white blood cell studies were made on 83 cats with the disease. In addition, a sufficient number of white blood cell counts were made on the other 30 cats to establish the presence of leuko-

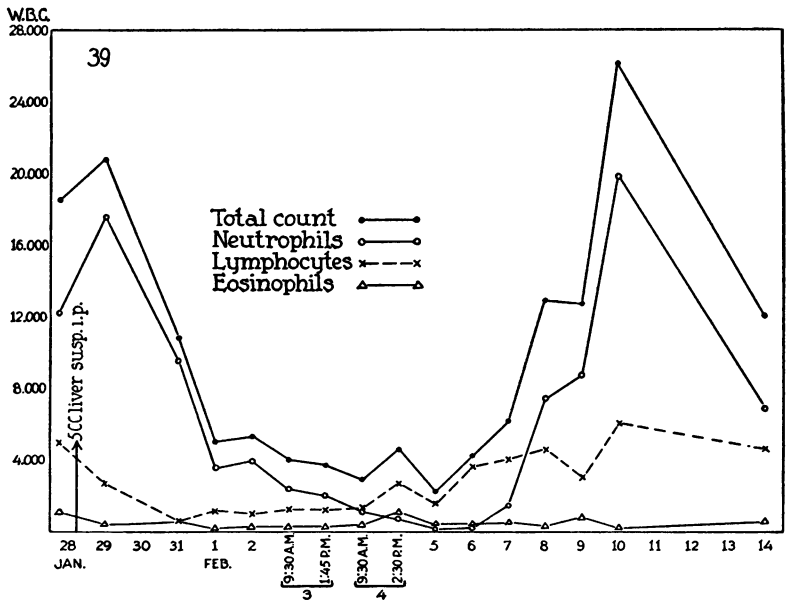

Chart 1. White blood cell findings in a cat of the "gradually declining type."

penia and neutropenia. Sixty-three of the 83 cats studied had only one or a few counts made prior to known exposure to the infectious agent. Counts were made on these animals repeatedly thereafter until death occurred or until recovery was under way.

The additional 20 cats were studied as follows: 18 had white blood cell counts and differential counts at 1 to 3-day intervals for 18 or 19 days prior to exposure; the other 2 had the same observations made at 2 or 3-day intervals (except for a single 5-day period) for 48 days prior to exposure. Following exposure, 16 of these cats had daily white blood cell studies until death occurred,

until they were killed at the height of the disease, or until they returned to normal. The remaining 4 animals of this group of 20 had essentially the same studies following exposure to the infecting organism, the only difference being that blood studies were omitted for a few days.

The animals all fell into two groups on the basis of the type of response shown by the white blood cells. We have designated these

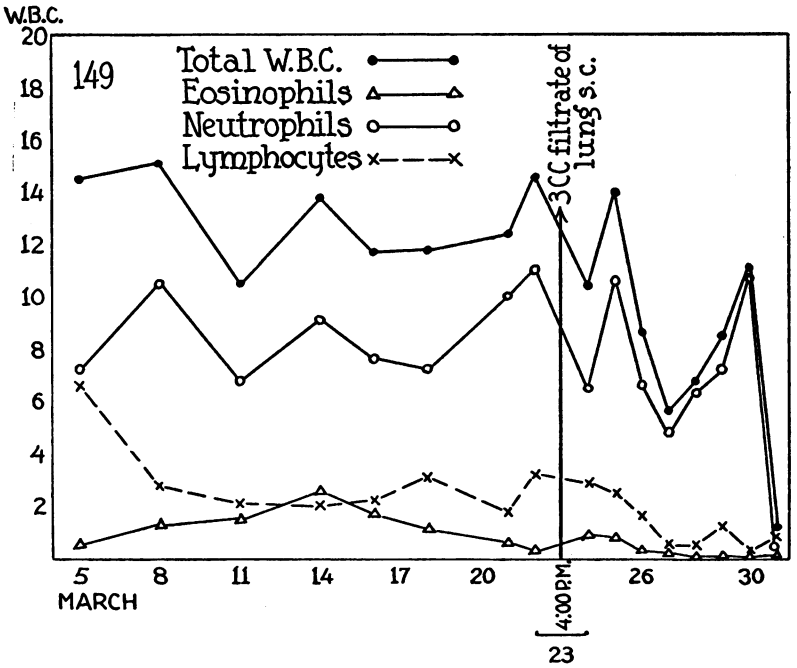

CHART 2. White blood cell findings in a cat of the "precipitously declining type."

groups as the "gradually declining" and the "precipitously declining." In the former group the total number of the white blood cells and the absolute number of the neutrophils gradually diminish from a few days after exposure to the infectious agent until the height of the disease. A typical response of this sort is shown in Chart 1. In the latter group, the precipitously declining, the total white blood cell count may diminish but little, if any, for the first 5, 6 or 7 days. The percentage of neutrophils rises, however, so that the absolute number of neutrophils approaches more and more closely the total number of the white blood cells. When

the point is reached where the neutrophils constitute almost all of the white blood cells (on the 5th to the 7th day usually), there is a sudden precipitous drop in the total number of the white blood cells, the number going to zero in some instances. A typical response of this sort is shown in Chart 2. Of the 83 animals used in this analysis, 42 had the gradual curve and 41 the precipitous. The mortality was much higher in the latter group.

Total Number of White Blood Cells: The average total white blood cell count for 113 cats at the height of the disease was 1350 per cmm., as compared with our normal of 15,000 per cmm. (average of 826 counts in 100 animals). Of the 113 animals, 22 had total white blood cell counts from 0 to 200 per cmm., whereas 19 animals had counts above 3000 per cmm. A total count as high as 6400 was found in only a single animal.

Differential Count

Neutrophils: The most marked abnormality in the blood picture was found in the differential count. The neutrophils were more markedly affected than any of the other white blood cells. At one time during the course of the disease 80 of the 113 animals used in this report had from 0 to 200 neutrophils in their peripheral blood. At the height of the disease 30 of these 80 had no neutrophils in their peripheral blood; 37 had less than 11 per cent, and only 6 had more than 60 per cent. Of the latter 6, all had a definite leukopenia, 1 having only 500 cells per cmm. The distribution of animals with reference to the absolute number of neutrophils is shown in Chart 3, while Chart 4 gives the findings with reference to the percentage of neutrophils at the height of the disease. These data show clearly the marked effect which the infection has on the neutrophils.

Lymphocytes: The total number of the lymphocytes was generally diminished at the height of the disease, as one would expect with such a pronounced leukopenia. In the majority of instances, however, there was a relative increase in the lymphocytes, the percentage being high in the differential count. Thus, 90 of 111 animals had more than 50 per cent of lymphocytes in the peripheral blood at the height of the disease, while only 5 of these cats had above 3000 lymphocytes per cmm. These cells appeared normal in every respect. While the relative percentage of lymphocytes

was generally increased at the height of the disease, it was usual in the precipitously declining group of animals to have both the percental and the absolute number of these cells fall just prior to the height of the disease. Furthermore, in both groups of animals, *i.e.* the gradually declining and precipitously declining, an absolute lymphopenia was demonstrable during the greater part of the incubation period. (This observation is in agreement with the re-

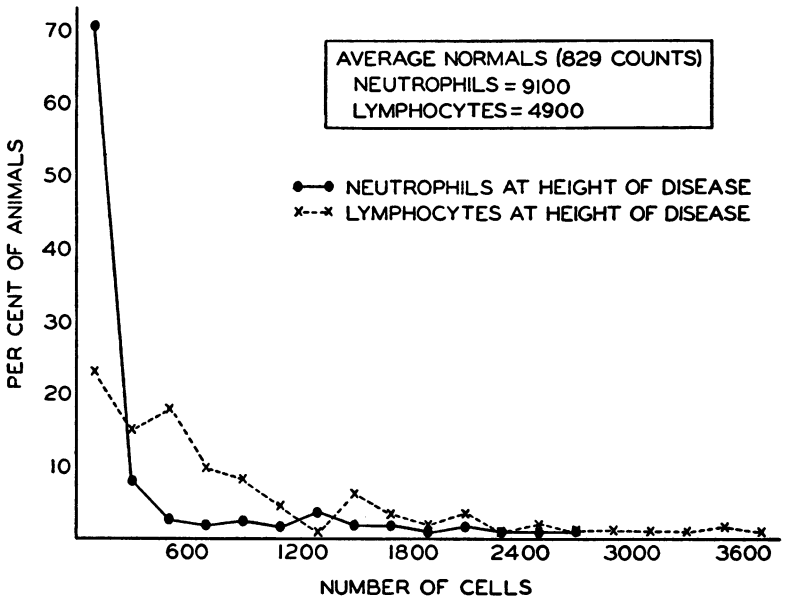

CHART 3. Curves showing the distribution of animals with regard to the number of neutrophils and lymphocytes.

sults Plum [3] has reported for human agranulocytosis secondary to the ingestion of amidopyrine.) In a few instances a definite lymphocytosis was observed during the period of recovery. In Charts 3 and 4 the distribution of the animals with reference to the total number and the per cent of lymphocytes at the height of the disease is plotted.

Eosinophils, Basophils and Monocytes: No consistent changes were noted with reference to these cells. The impression was gained at times that the eosinophils were increased at the height of the disease, but analysis did not bear this out. The average percentage of eosinophils in 20 animals at the height of the dis-

ease was 13 per cent, as compared to an average figure of 9 for the same animals prior to inoculation. In isolated instances the percentage of eosinophils was quite high (as much as 80 per cent).

"Stab" Cells: The "stab" cell proved to be an important part of the white blood cell picture in these animals. Normal cats only rarely showed "stab" forms in the peripheral blood. In the typi-

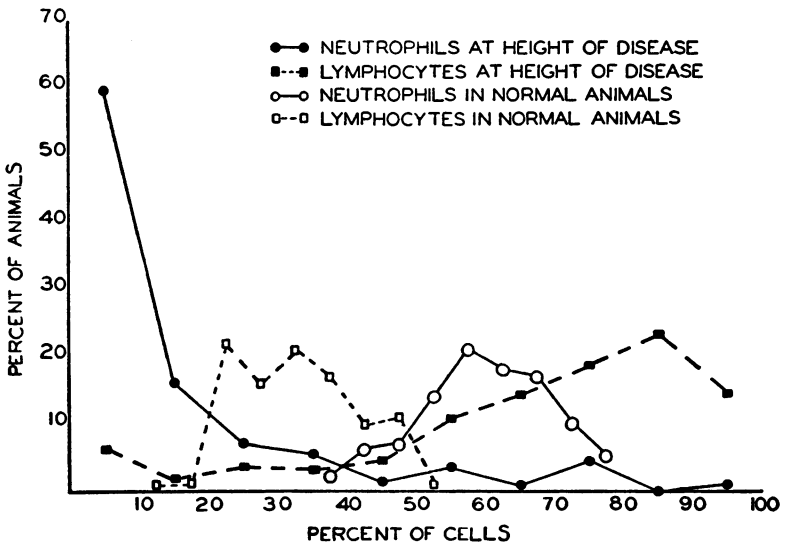

CHART 4. Curves showing the distribution of animals with regard to the percentage of neutrophils and lymphocytes. For comparison, curves are shown for values obtained for these cells in counts on 100 normal animals.

cal animal with the disease an increased number of "stabs" occurred on the day before the height of the disease or at the height. The increase was usually slight in amount. With recovery, however, a pronounced increase in the number of these cells occurred. In some instances there were over 30 per cent of "stab" forms. This marked "shift to the left" persisted for 4 or 5 days.

The Red Blood Cell Picture

Determinations of the total number of red blood cells in the peripheral blood of 21 cats were made prior to the active stage of the disease and during its height. Fifty-nine red blood cell counts

were made prior to the height of the disease and 23 counts during the height of the disease. The average figure for the total number of red blood cells before the height of the disease was 7,140,000 per cmm., as compared with 6,880,000 per cmm. at its height. On 9 of the 21 cats repeated red blood cell counts and hemoglobin determinations were made prior to the height of the disease in order to reveal any changes which might otherwise be masked by the general average. Identical results were obtained. An occasional animal showed lower counts at the height of the disease than in the pre-exposure period. On the same 9 animals observations were begun at the following time intervals before the height of the disease: 10 days (1 animal); 11 days (2); 13 days (2); 14 days (1); 15 days (2); and 32 days (1). The lowest number of determinations prior to the height of the disease was 3 and the greatest was 23, the average being between 7 and 8. These observations were continued throughout the height of the disease and during recovery. We have satisfactory studies on only 3 animals during the period of recovery. Two of these animals were studied until the 8th day and 1 until the 11th day following the height of the disease. A slight tendency for the hemoglobin and red blood cell values to drop at the height of the disease or during the early days of recovery was observed, but the change was not great enough to be of significance. Slightly more nucleated red blood cells were noted in the peripheral blood of cats with the disease (particularly in the recovery period) than in normal cats. Otherwise, there were no changes in the red blood cell picture. In summary, slight evidence of anemia was found in a study of the peripheral blood.

Pathological Examination

Autopsies were performed on 45 animals. In the majority of instances the animals were killed when at the height of the disease, or else were autopsied a very short while after death. Grossly the organs showed little that was abnormal. In the lungs of some of the animals small hemorrhagic areas were apparent, but this was an inconstant finding. The small intestine, from about 12 inches below the pylorus to the ileocecal valve, was sometimes moderately injected. There were no other abnormalities to be seen in the gross.

Sections were obtained from 41 of the autopsied diseased animals in addition to those obtained from normal animals for purposes of control. The following tissues were prepared for histological study: heart, lung, liver, gall-bladder, bile ducts, spleen, kidney, kidney pelvis, ureter, urethra, urinary bladder, adrenal, pancreas, lymph node, esophagus, stomach, duodenum, ileum, jejunum, colon, bone marrow (humerus, femur, vertebrae and ribs), nervous tissue (including various areas in brain and cord), parotid gland, submaxillary gland, testicle, epididymis and tonsil. The histological changes characteristic of their infection with the virus were: necrobiosis, as evidenced by cells in various stages of degeneration; proliferation, as shown by the extensive increase in the reticular cells, and by hypertrophy of inclusion-bearing cells; and the formation of intranuclear inclusion bodies.

The most significant feature of the histopathological picture was the presence of intranuclear inclusion bodies (Cowdry's type A). These inclusion bodies were found only in sites where one could attribute the pathological alterations to the specific infection. They were typically acidophilic and were variable in size, shape and structure. In their internal structure they ranged from compact, rather homogeneous and well organized bodies to loosely dispersed, discrete granules. In nuclei with inclusion bodies there was an accompanying margination to the nuclear membranes of both the nucleolus and the chromatin network, resulting in a clear space or "halo" around the inclusion body. The inclusion-bearing cells varied in size from normal to greatly hypertrophied and vesiculated cells. Inclusion bodies were found only in the epithelial cells of the gastro-intestinal mucosa, in reticular cells of the lymphoid tissue (intestine, lymph nodes, spleen and tonsils), and in the alveolar epithelium of the bronchial mucous glands.

Significant histopathological changes were limited to the hematopoietic system and to the gastro-intestinal tract. The remaining tissues were essentially normal. It was noted that the neutrophils were absent or markedly diminished in the lungs and the liver.

Spleen

Thirteen sections from 13 animals were examined. The capsule was intact. The follicles were less prominent than in normal animals. There was considerable proliferation of the reticuloendo-

thelial tissue throughout the organ. In most instances the reticular cells in the germinal centers were increased in number. At times this picture was markedly abnormal, and at others there were only slight alterations. The stroma appeared normal. There were no neutrophils and no megakaryocytes. Furthermore, there was no phagocytosis of red blood cells or pigment except in a single instance where it was slight. In a few sections extensive hemorrhage was present, but in most of them hemorrhage was conspicuously absent. A microphotograph of the spleen at a low magnification (× 100), showing typical changes, is reproduced in Figure 14.

Lymph Nodes

Forty-five sections from 16 animals were examined. The general architecture was retained. The capsule was intact. The most striking change was the marked hyperplasia of the reticuloendothelial cells. This was particularly prominent in the medullary portion of the node. Many of the germinal centers appeared to be replaced by reticuloendothelial cells, but, in each node, considerable numbers of immature lymphoid cells were found. Lymphocytes were most numerous about the cortical portions of the lymph nodes where they did not appear to be appreciably decreased in numbers. An occasional observation was the presence of neutrophils among the hyperplastic reticulum in the central portions of the node. In a few of the specimens there was marked phagocytosis of hemoglobin by the reticuloendothelial cells. The changes that occur in lymph nodes are shown in Figure 13.

Gastro-Intestinal Tract

Seventy-one sections, taken at several levels from each division of the gastro-intestinal tract, were obtained from 10 cats. With the exception of sections removed from the esophagus, every section yielded evidence for a specific viral infection, as shown by the presence of Type A (Cowdry) intranuclear inclusion bodies in the epithelial cells of the mucosa (Fig. 18). The distribution of inclusion bodies was highly variable, ranging from one or two in an entire histopathological section to a score within a single high power field. The further histopathological changes, which were largely confined to the lateral and basilar portions of the

villi, varied from hypertrophy of the individual cells with questionable circumferential mononuclear invasion to complete necrosis and, in certain instances, sloughing of both villous and acinar epithelium. In no instance was the involvement of the gastro-intestinal tract extensive or of a grossly ulcerative nature. On the contrary, the lesions were characteristically minimal in extent and were limited to the mucosa and lymphoid tissue. Irrespective of the extent of the involvement, the architectural pattern characteristic of the gastro-intestinal mucosa was maintained. The changes in the mucosal epithelium varied from animal to animal and even in the same animal. On study, one of four pictures, or any combination of them, might be presented. Epithelial cells that were: (1) *normal*, except for a very occasional cell with an intranuclear inclusion body; (2) *flattened and pyknotic*, either individually or in groups; (3) *necrotized*, both *in situ* and lying in the glandular lumens; and (4) *sloughed*, leaving the denuded basilar membrane behind. The cellular invasion that accompanied the epithelial derangement consisted mainly of mononuclear cells. Occasional clumps of polymorphonuclear cells were present, however, and these cells persisted in the necrotic portions, even though the peripheral blood had been entirely depleted of polymorphonuclear cells.

Esophagus: No histopathological changes were present.

Stomach: The only apparent abnormality in the fundus was limited to an occasional intranuclear inclusion body. In the pylorus, however, the damage to the epithelium was quite extensive with denudation and flattening of the cells.

Small Intestine: Although scattered lesions were present throughout, the involvement of the mucosa appeared to be more consistent and extensive toward the iliac portion of the intestine. In every animal examined, the sections from the ileum showed more extensive involvement than any other region of the intestine.

Colon: The colon showed much less involvement than the small intestine. When microscopic changes were encountered they were largely confined to the proximal portion of the colon with only slight evidence for the infectious process in the distal portions. In certain instances the histopathology in the proximal portion of the colon closely simulated that of the lower ileum.

For control purposes 17 sections from 5 normal cats were

carefully studied. In none were inclusion bodies or other changes characteristic for the disease found.

Central Nervous System

No abnormalities were noted on gross examination of the central nervous system, either *in situ* or after removal from the body, in the group of 7 animals killed at the height of the disease, or in the group of 3 normal animals which were killed for control purposes. The brains and cords of all of the animals were studied. In the diseased group microscopic study of 134 sections, representing every division of the central nervous system, failed to reveal any abnormality that could be ascribed to infection with the virus of infectious feline agranulocytosis. No cytoplasmic or intranuclear (either Type A or B) inclusion bodies were present. A similar study of 40 sections from the 3 normal animals also failed to reveal any abnormalities.

The Bone Marrow

The bone marrow was studied in detail, for the clinical picture pointed to this organ as the principal point of attack by the infectious agent. On gross examination the marrow appeared to be fatty and aplastic, or normal. (We agree with Custer [4] that little significance can be attached to the gross appearance of the marrow.)

For histopathological study specimens were fixed in Zenker's fluid (plus 5 per cent acetic acid), decalcified and embedded in paraffin for sectioning. The sections were stained with hematoxylin and eosin. Our studies may be divided as follows:

Group I: Observations on the bone marrow of animals killed at the height of the disease.

Group II: Observations on bone marrow biopsied from individual animals at different stages of the disease.

Group III: Observations on the bone marrow of animals killed at various periods during recovery.

Group IV: Differential counts on smears made from suspensions of bone marrow removed from animals at various stages of the disease.

Group I: In the 1st group, bone marrow was studied from 17 cats killed at the height of the disease. From 14 of the 17 animals,

marrow was obtained from the following bones: vertebra, rib, femur and humerus. Each of the animals yielded bone marrow with essentially the same cellular picture. The myeloid series of cells was most markedly affected. The almost complete lack of differentiation was characteristic and resulted in one predominant type of myeloid cell, probably the myeloblast type. These cells had much the same characteristics as those described by Custer.[4] The nuclei were large, vesicular, and lacking in specific granulation. Usually they contained one or more large nucleoli. The number of mitotic figures was not abnormal. There were no juvenile, stab or segmented forms in most of the specimens. The erythroid elements persisted more than the myeloid and in some animals were abundant. The megakaryocytes were undiminished in number and normal in appearance. Even with extensive hypoplasia, there was a definite sprinkling of megakaryocytes. Extensive congestion was evident in all of the bone marrow sections. Eosinophils were present in smaller or larger numbers. In a single animal the majority of the cells in the vertebral marrow were eosinophils. In a specimen from another animal a lymphoid follicle was present. The histopathological changes that typify the reaction of the bone marrow in cats at the height of the disease are illustrated in Figures 9–12. In these microphotographs it may be seen that the characteristic type of cellular reaction persists even when there are extensive quantitative differences in the total number of cells present.

Group II: Serial biopsies of the femoral or humeral marrow were performed on 6 cats at various stages of the disease. Marrow was obtained on three occasions from 5 of the cats and only twice from the remaining animal. The day of the biopsy in relation to the height of the disease and the findings are recorded below.

Two days before height of disease. A single specimen revealed many typically undifferentiated cells, a fair number of later myeloid cells and scattered erythroid cells. The cellular picture was similar to that for marrow in the stage of recovery.

One day before height of disease. The salient observation in two specimens was the absence of practically all late myeloid forms. The myeloid series was represented almost entirely by undifferentiated cells. There were many erythroid cells. Mod-

erate numbers of megakaryocytes and eosinophils were seen. There were a few mitotic figures.

Height of disease. The picture was identical with that given for the autopsied animals, *i.e.* most of the cells present were undifferentiated cells of the myeloid series and erythroid cells.

1st day of recovery. Two specimens showed a tremendous increase in the number of cells in the marrow as compared with the number at the height of the disease. The great majority were undifferentiated myeloid cells but there was some beginning differentiation into stab forms. Mitotic figures were noted frequently. There were few erythroid cells. Few to moderate numbers of megakaryocytes were seen.

2nd day of recovery. Three specimens were studied. The cells were present in normal or increased numbers. The differentiation of the myeloid cells had advanced so that more of the late forms were seen. Mitotic figures were frequent (up to three per oil immersion field). Erythroid cells appeared normal, as did megakaryocytes. A few eosinophils were present.

4th day of recovery. Three specimens were studied. The striking part of the picture at this stage was the large number of cells. These showed well marked differentiation into late myeloid forms, but there were still a good many undifferentiated cells. Frequent mitotic figures (up to five per oil immersion field) were found. Normal numbers of erythroid cells and megakaryocytes were present.

Group III: In addition to the serial bone marrow biopsies, 6 animals in various periods of recovery were killed for specimens of marrow from the vertebra, rib, femur and humerus. The findings were similar to those recorded for the serial specimens. In Figures 1–8, microphotographs in both low and high magnifications, are the bone marrow of the normal cat (1 and 2); bone marrow of a cat at the height of the disease (3 and 4); bone marrow of the same animal on the 1st day of recovery (5 and 6); and bone marrow of this animal on the 4th day of recovery (7 and 8).

Group IV: For differential counts, specimens of marrow were obtained from the humerus or the femur 2 and 1 day before the height of the disease; at the height of the disease; and 1, 2, 3 and 4 days after the height of the disease. The marrow was macerated in human blood serum to yield suspensions for making smears on

TABLE I

Average Differential Marrow Counts (Per Cent)

	Normal	2 days before height	1 day before height	Height of disease	1st day of recovery	2nd day of recovery	3rd day of recovery	4th day of recovery
Number of counts	13	1	2	13	4	5	1	5
Eosinophils	1.5	0.8	2.9	4.2	0.6	2.0	0.0	0.8
Myeloblasts	1.3	1.8	2.4	1.8	3.3	2.9	3.0	2.0
Promyelocytes	7.6	3.2	4.8	2.5	8.9	5.9	8.8	6.2
Myelocytes	4.6	0.8	3.2	2.7	5.2	8.3	3.0	5.6
Juveniles	9.8	3.8	1.2	0.5	8.1	11.0	4.2	17.2
Stabs	13.4	17.6	2.0	0.6	7.8	13.9	11.2	20.1
Segments	5.3	6.8	0.5	0.2	0.6	1.6	3.4	4.1
Total myeloid cells	43.5	34.8	17.0	12.5	34.5	45.6	33.6	56.0
Lymphocytes	7.8	2.0	3.8	8.9	4.5	2.0	2.6	2.0
Plasma cells	0.3	0.4	0.3	0.17	0.2	0.2	0.0	0.1
Megaloblasts	0.7	1.2	0.7	0.9	0.7	0.24	0.0	0.5
Erythroblasts	6.3	15.0	12.8	6.1	3.4	3.8	5.0	7.4
Normoblasts	8.3	11.4	10.3	5.4	6.4	6.6	2.4	6.1
Total erythroid cells	15.3	27.6	23.8	12.4	10.5	10.6	7.4	14.0
Unclassified cells	6.2	9.6	7.8	3.4	4.9	2.5	4.8	2.2
Degenerated cells	26.3	25.6	47.3	62.6	45.8	39.3	51.6	25.6
Erythroid myeloid ratio	0.35	0.8	1.4	1.0	0.3	0.23	0.22	0.25

glass slides. After fixation the smears were stained with Wright's stain or occasionally with the oxydase stain. Of the 44 preparations that were stained with Wright's stain, 13 represented marrow from normal animals and 31 marrow from sick animals.

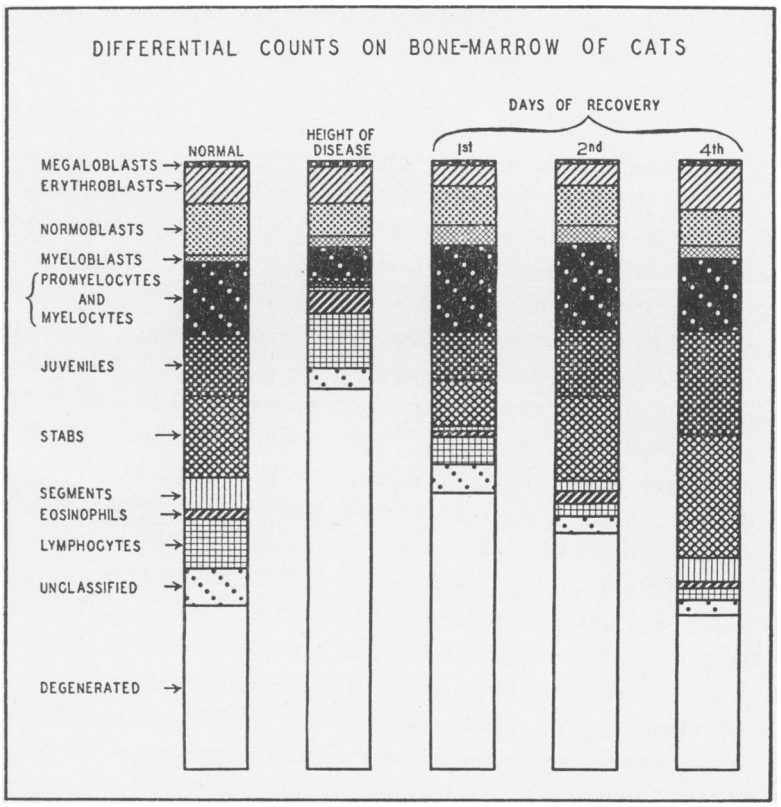

CHART 5. Graphic representation of differential bone marrow counts. The marked diminution at the height of the disease in the percentage of myeloid cells, particularly the juveniles, stabs and segments, is in striking contrast to almost normal percentages of erythroid cells. Note that there is a very rapid return of the myeloid cells during the recovery phase.

Differential counts were made of the nucleated cells in each of these preparations, 500 cells being counted in each instance. The results of these differential counts are shown in Table I and in Chart 5. In brief, the principal finding was a marked diminution in juveniles, stabs and segments at the height of the disease. The

eosinophils were slightly increased at this time. Following the height of the disease there was a pronounced increase in the number of late myeloid cells until on the 4th day they were present in greater than normal numbers. The erythroid cells showed no constant variation and usually were present in normal numbers at each stage of the disease. In summary, it may be said that the differential counts yielded results that agree with those obtained from a study of the fixed stained sections.

Discussion

The results of the present studies indicate that there are many points of similarity between infectious feline agranulocytosis and human agranulocytosis. The white blood cell picture in the feline disease simulates that seen in the human disease. In both conditions there are sudden drops in the total white blood cell count and in the number of neutrophils. These changes result in a relative increase in the number of lymphocytes. (See Chart 4 which illustrates the relative lymphocytosis.)* The marked "shift to the left," which occurred regularly in the feline disease during the phase of recovery, has been noted repeatedly in man. Moreover, the absence of thrombopenia and the inappreciable anemia parallel the human malady.

A satisfactory comparison of the white blood cell changes in the pre-agranulocytic stage of the human malady with those in the preclinical period of the feline disease cannot be made since most of the human cases have been studied mainly after the development of pronounced neutropenia. Stephens and Lawrence [5] have studied in this laboratory a woman with cyclical agranulocytosis and in her case there was no antecedent lymphopenia. However, this represented an unusual type of the disease and the white blood cell responses may have been different from those in the usual case of agranulocytosis. The best opportunity for comparison is afforded by patients in whom the disorder has been produced a second time by the readministration of amidopyrine. Plum [3] has made a detailed study of seven patients of this type. Qualitatively the changes reported by him are of the same type as we have noted during this period in the cat. There is this dif-

* This chart also serves to contradict Hammon and Enders' statement that there is no constant relative increase in the number of lymphocytes.

ference: whereas he found a marked rise in the lymphocytes at the time of the primary marked fall in granulocytes, we found the rise in the lymphocytes to be inconstant and further it did not occur until the recovery phase had developed.

The cytological picture of the bone marrow is also essentially similar to that which has been reported for human agranulocytosis. Thus, the erythroid cells are not affected in the human disease. Similarly, in the feline disease these cells are present in normal percentages. Noteworthy is the fact that foci of erythroid cells were readily detected. It is probable, however, that the absolute number of erythroid cells in the bone marrow is reduced when the bone marrow is markedly hypoplastic.

No systematic study in human agranulocytosis has been made of the changes in the bone marrow which develop during successive stages of the disease. It has been possible to make such observations in the feline infection. We believe that our findings may throw light on the widely divergent descriptions of bone marrow from cases of human agranulocytosis. A most remarkable and regular finding is the rapidity with which changes have been observed to occur in the bone marrow. Two days before the height of the disease some diminution is detectable in the differentiation of the myeloid cells. This progresses until at the height of the disease there is no differentiation of the myeloid cells, all being early forms. At this stage there is usually a hypoplasia, but, in some of the animals, the number of cells may not be diminished appreciably. On the 1st day of recovery differentiation of the myeloid cells can be detected and within 4 days there is marked differentiation with an abundance of neutrophils, stabs and juveniles. In the light of the rapidity with which these changes occur it is easy to understand why one report states that the bone marrow in human agranulocytosis is aplastic, and another that the bone marrow contains a normal number of cells. In fact, one wonders why there is even as much uniformity in the literature as there is, if such changes occur as rapidly in man as they have been observed in the cat. The observations of Rohr [6] and Plum [3] bear out this opinion. With a realization that such sudden rapid changes in cell content and cell types do occur, it becomes immediately apparent that the results of a single study of the bone marrow should not be accepted as diagnostically con-

clusive. The fact that only a small portion of marrow is removed from a single isolated area in the usual biopsy emphasizes this statement.

With the exception of the involvement of the gastro-intestinal tract in the feline disease, the other pathological changes resemble those reported for the human condition. As points of contrast, however, the absence of oral and perianal lesions in the feline infection may be mentioned. Furthermore, the duration of the acute phase in the cat is less than in the human. There is probably a marked difference in etiology as well. The feline disease is caused by a virus, whereas the most likely explanation for the human malady is that it is the result of a chemical intoxication. Generalized blood stream infections by secondary invaders may occur in both diseases, probably as the result of the lowered resistance of the host.

By the foregoing comparison of an experimental agranulocytosis of known etiology, as it occurs in the feline host, with the disease as it has been observed in humans, we do not presume, of course, to imply that the two are the same. On the contrary, we wish to emphasize that they are not. Nevertheless, the similarity of the clinical and pathological pictures in the two hosts suggests that widely different agents may instigate similar reactions. Thus, the agranulocytosis itself may be regarded as a symptom, like fever, purpura, and so on, which are produced by a variety of agents. To make clear our line of thought we may refer to an analogous situation — the frequency with which lead encephalitis, an intoxication, simulates a viral encephalitis, an infection. This is due to the fact that the elements of the central nervous system can respond to injury in only a limited number of ways. Thus, while amidopyrine, sulfanilamide and other chemical compounds hold the foremost place in any consideration of the etiology of the human disease, it is by no means impossible that the responsible factor may be any one of a variety of other agents, such as a yet unrecognized virus or filterable agent.

Moderate leukopenia is present in most viral infections. In so far as we know, hog cholera is the only viral disease with a blood picture that even resembles that of feline agranulocytosis. The peripheral blood picture in hog cholera was described by Lewis and Shope,[7] but they did not report the pathological changes in

the various organs. It is only possible, therefore, to compare the peripheral blood picture in the two infections.

What explanation is there for the leukopenia and profound neutropenia of the feline disease? The neutrophils are known to disappear from the peripheral blood stream extraordinarily rapidly. Within a few hours a normal percentage of neutrophils may be supplanted by complete absence of neutrophils. We have seen this happen repeatedly. Such rapid disappearance cannot be explained on the basis of bone marrow insufficiency alone, for if this were the sole mechanism at work there would be a gradual diminution in the number of neutrophils, the older ones going first and then the younger ones. While the exact life of the neutrophil is not known, it has been estimated as from 3 to 5 days.[8,9] Accordingly, if bone marrow insufficiency were the responsible factor, one would expect the cells to take this long to disappear. Aside from the failure of regeneration in the bone marrow, it is suggested, therefore, that a toxic substance is produced which may destroy neutrophils in much the same way as antineutrophilic serum.[10] Furthermore, there is evidence which indicates that such direct destruction does occur in the human. In fact, Fitz-hugh [11] has suggested such a possibility. It would seem, therefore, that a combination of at least two mechanisms may be held responsible for the leukopenia and neutropenia. These are, first, hypoplasia and maturation arrest of the myeloid cells in the bone marrow; and, second, direct destruction of neutrophilic leukocytes in the peripheral circulation by an, as yet, hypothetical toxic agent.

It is interesting that the platelets remain in normal abundance. This is what the findings in the bone marrow would lead one to expect, since megakaryocytes were found wherever there were marrow cells. In the light of Howell and Donahue's [12] idea that large numbers of platelets are made in the lungs of cats, our findings are the more readily explained, for we discovered no abnormalities in the pulmonary tissues.

The absence of significant anemia may be explained in two ways. First, the remaining marrow cells were observed to include a normal percentage of red cell progenitors. Thus, appreciable numbers of these cells remain in practically every instance, even though the total numbers of erythroid cells may actually be diminished when there is a pronounced hypoplasia of the marrow.

Second, the duration of the illness is too short to result in marked anemia on the basis of a cessation in the manufacture of red blood cells. Certainly this is true if we can assume that the average period of survival for red blood cells of the cat is similar to that of dog and man, *i.e.*, from 100 to 120 days.[13, 14, 15]

SUMMARY

The clinical, hematological and pathological aspects of a recently discovered viral infection of cats, which we have named infectious feline agranulocytosis, are described. The disease is characterized by marked leukopenia and neutropenia in the absence of thrombopenia and appreciable anemia.

The histopathological changes are directly attributable to viral activity, as evidenced by intranuclear inclusion bodies (Type A, Cowdry), necrobiosis and proliferation. The most pronounced abnormalities have been found in the hematopoietic tissues and in the intestinal mucosa.

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DESCRIPTION OF PLATES

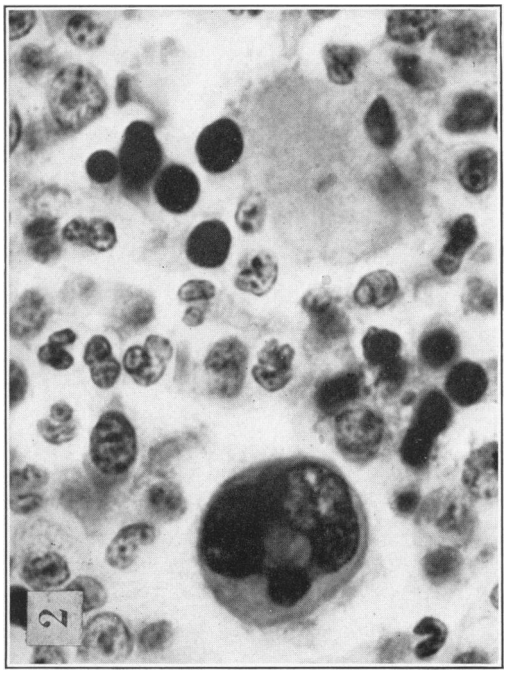
PLATE 68

FIG. 1. Bone marrow from the humerus of a normal cat. × 100.

FIG. 2. High magnification of bone marrow from the humerus of the same normal cat. Note the wide variety of cells. × 1500.

FIG. 3. Femoral bone marrow of Cat 285 at the height of the disease. Note the marked hypoplasia of the specimen. × 100.

FIG. 4. High magnification of area from Figure 3. Note the undifferentiated cells with large vesicular nuclei. × 1500.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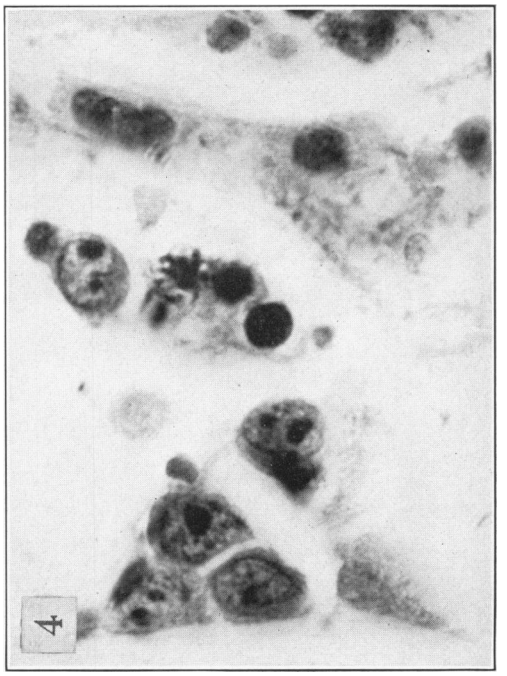
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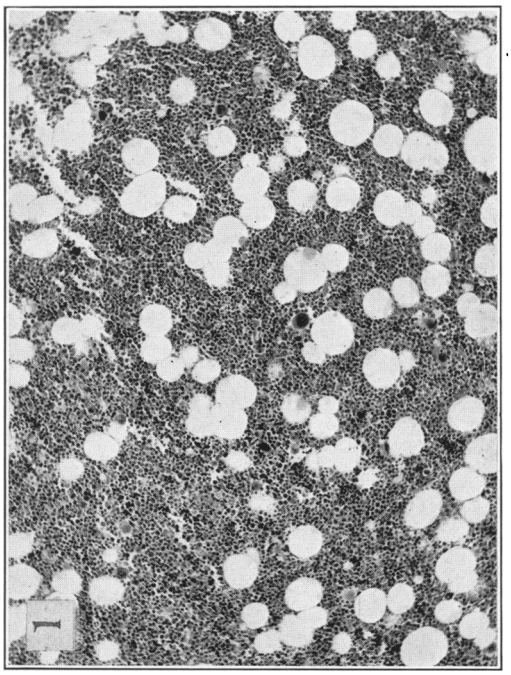
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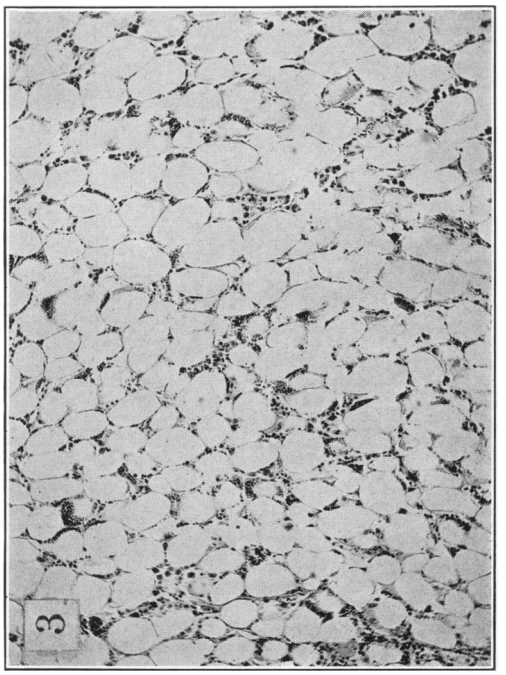
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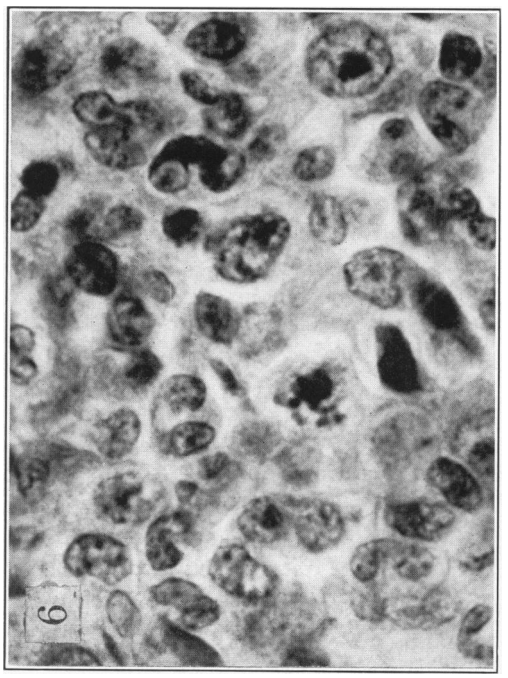
PLATE 69

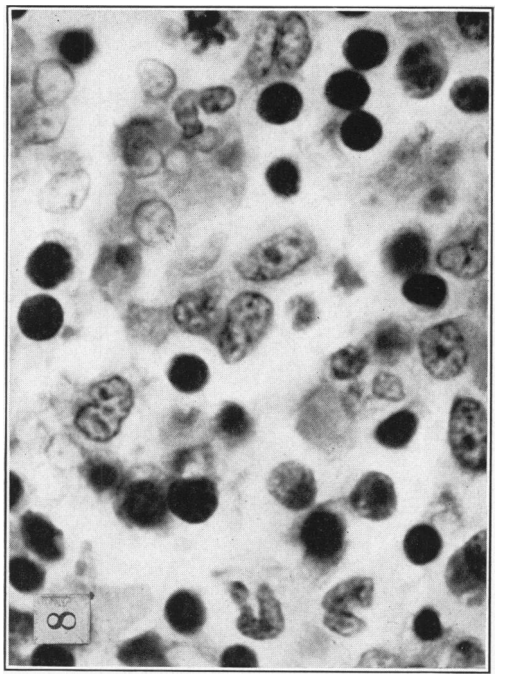
FIG. 5. Femoral bone marrow of Cat 285 on the 1st day of recovery. Note the presence of distinctly more cells. × 100.

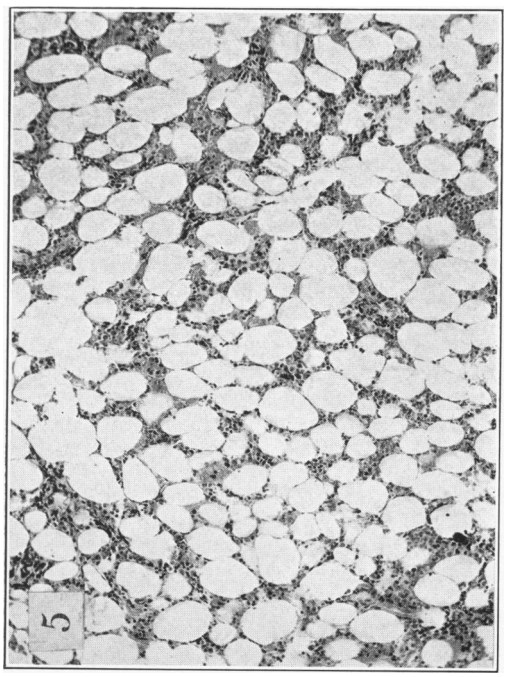
FIG. 6. High magnification of area from Figure 5. Many undifferentiated cells are still present but a few neutrophils can be seen. × 1500.

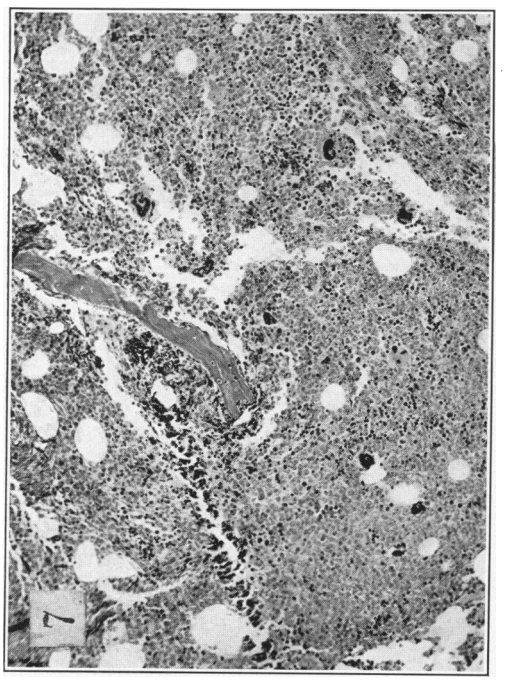
FIG. 7. Humeral bone marrow of Cat 285 on the 4th day of recovery. Note the presence of numerous cells — if anything, more than in the normal specimen. × 100.

FIG. 8. High magnification of an area from Figure 7. Undifferentiated cells are still present but the general cellular picture is approaching the normal. × 1500.









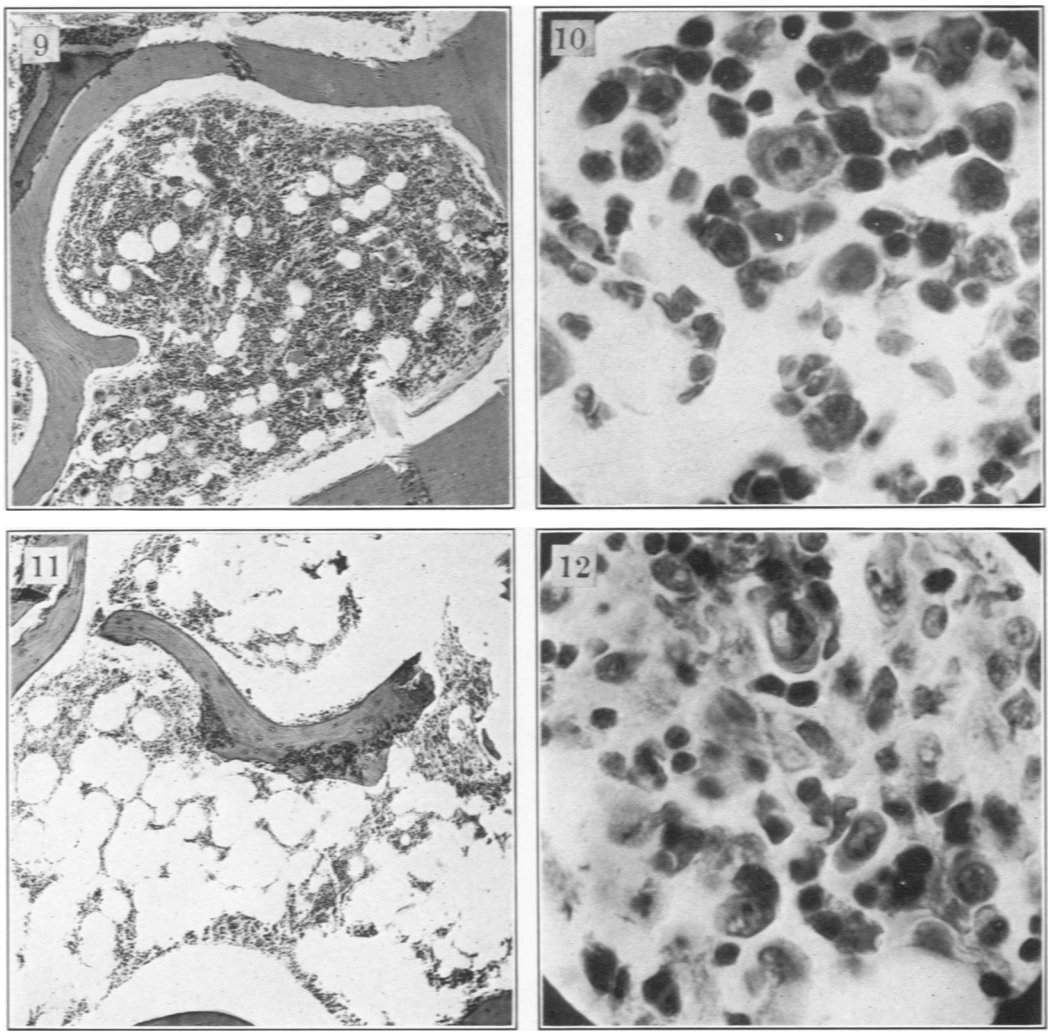
Lawrence, Syverton, Shaw and Smith

Infectious Feline Agranulocytosis

PLATE 70

FIGS. 9 and 10. Low (× 100) and high (× 1500) magnification of the vertebral bone marrow of Cat 77 at the height of the disease. Note the large number of cells present. The myeloid cells are for the most part undifferentiated. Many erythroid cells were found in this specimen.

FIGS. 11 and 12. Low (× 100) and high (× 1500) magnification of the vertebral bone marrow of Cat 55 at the height of the disease. This specimen shows marked myeloid hypoplasia. The qualitative changes in the cells are of the same character as those in Figures 9 and 10.

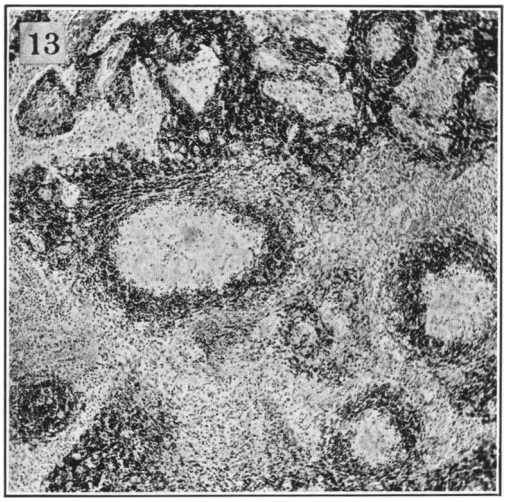


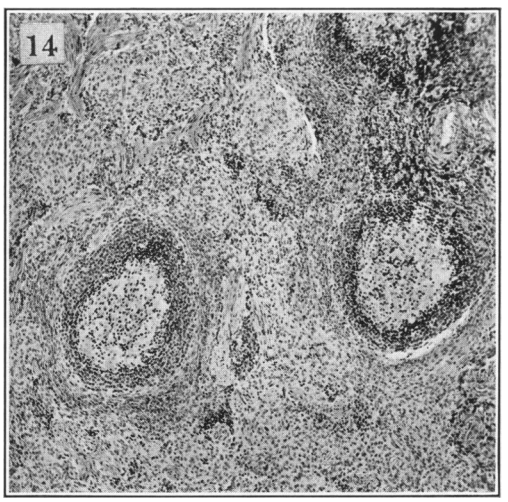
Lawrence, Syverton, Shaw and Smith Infectious Feline Agranulocytosis

PLATE 71

FIG. 13. Lymph node from Cat 54 at the height of the disease. Note the marked proliferation of the reticuloendothelial tissue. × 100.

FIG. 14. Spleen from Cat 54. This shows marked proliferation of the reticuloendothelium also. × 100.





Lawrence, Syverton, Shaw and Smith Infectious Feline Agranulocytosis

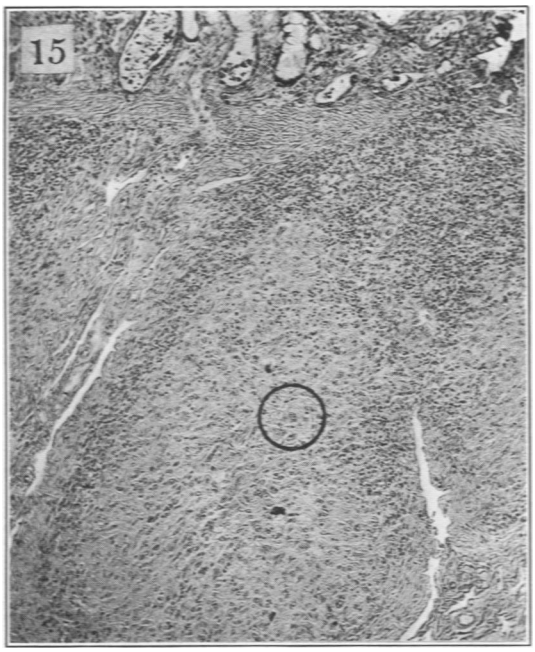
PLATE 72

FIG. 15. Low magnification of the wall of the terminal ileum of Cat 389. A large hyperplastic lymph node with its germinal center largely replaced by reticuloendothelial cells is shown. × 100.

FIG. 16. High magnification of the area within the circle in the germinal center of the lymph node shown in Figure 15. Four intranuclear inclusion bodies are shown, as indicated by arrows. × 1500.

FIG. 17. Low magnification of the terminal ileum of Cat 389. × 100.

FIG. 18. High magnification of the area within the circle in Figure 17. Three intranuclear inclusion bodies are shown, as indicated by arrows. × 970.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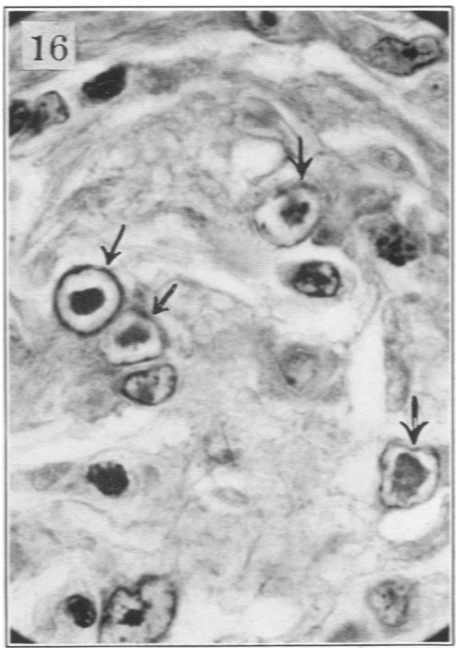
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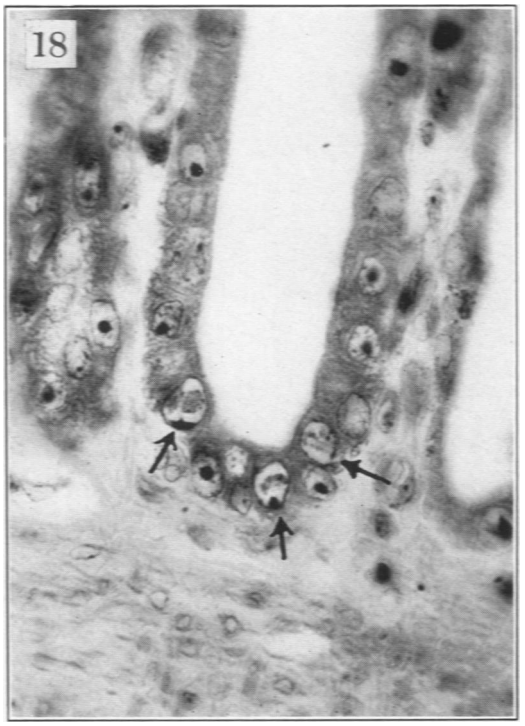
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