# THE AMERICAN JOURNAL OF PATHOLOGY

VOLUME XXXI MARCH-APRIL, 1955 NUMBER 2

## PATHOLOGY OF HEMORRHAGIC FEVER

### A COMPARISON OF THE FINDINGS—1951 AND 1952 *

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Hemorrhagic fever first appeared in United States troops in Korea in 1951. Patients were treated in many hospitals, and methods of treatment varied considerably, but included the liberal use of intravenous fluids. The pathologic findings in 61 fatal cases were reported at the end of 1951,[1,2] and it was concluded that three features were prominent and characteristic: hemorrhage, particularly in the renal medulla, right atrium, and gastrointestinal submucosa; a peculiar type of necrosis of the renal medulla, anterior lobe of the pituitary body, adrenal gland, and, occasionally, islands of Langerhans; and a mononuclear cellular infiltration of the myocardium, pancreas, spleen, and liver. The abnormal physiologic processes were not entirely understood but shock caused many of the deaths during the early stages of the disease and thereafter renal failure was the important cause of death.

In 1952, a special center was established in Korea for the treatment of patients with hemorrhagic fever. They were brought to this hospital by helicopter to avoid the trauma and delay of road transportation. Emphasis was placed on fluid restriction to give a slightly negative balance. Concentration in one hospital of physicians, nurses, and corpsmen experienced in the treatment of this disease resulted in a considerable improvement in the general medical care. The laboratory facilities made available permitted close observation of electrolyte changes. In addition, highly trained investigators studied the physiologic changes and evaluated various forms of therapy. Fundamental concepts not previously clearly recognized were examined.

Possibly because of the changes in treatment, the frequency and severity of certain lesions differed in 1952 from those observed in

* Received for publication, June 22, 1954.

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1951. The present report attempts a comparison of these differences in fatal cases during the 2 years and presents new interpretations of clinicopathologic findings.

## Materials and Methods

The 406th Medical General Laboratory in Tokyo received necropsy material from 71 patients dying of hemorrhagic fever in 1951, and from 50 in 1952. Six* of the 1951 cases had insufficient clinical information and were dropped from the study. This report is, therefore, based on 115 fatal cases of hemorrhagic fever. The pathologic changes observed in 39 patients who died at the Hemorrhagic Fever Center in 1952 have recently been described.[3]

In 1952, as in 1951, most of the fatalities occurred in Korea and the necropsies were performed at the Hemorrhagic Fever Center. Stained sections and fixed tissues were studied at the First Medical Field Laboratory in Korea and were reviewed at the 406th Medical General Laboratory. Protocols were much more complete in 1952 than in 1951, permitting more accurate clinicopathologic correlation. The same general procedures and special staining techniques used in 1951,[1,2] plus the Schiff periodic acid and the Feulgen stains, were applied as indicated to the 1952 material.

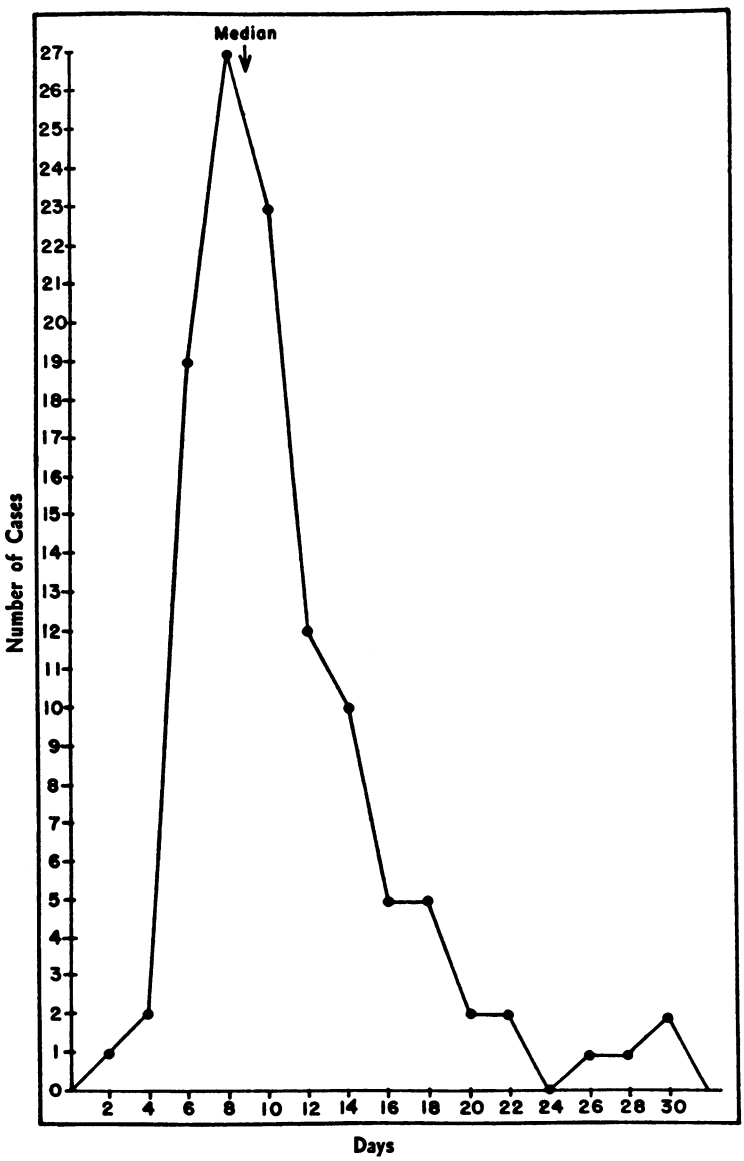
In the 1951 reports[1,2] the significance of the different clinical stages was not fully appreciated. Correlation of cause of death with variations in organ weights and histologic changes was based either on an arbitrary duration of disease (7-day intervals) or not related to the duration of disease at all. For purposes of the present report, all necropsy protocols and histologic sections from both years were reviewed in the order received and evaluated according to the clinical stage of the disease at the time of death. The sections of heart and kidney were then re-studied in the new order.

## Basis for Clinicopathologic Correlations

One of the significant concepts resulting from the study of hemorrhagic fever in 1952 was the division of the disease into fairly well defined stages of fever, hypotension or shock, oliguria, diuresis, and recovery.[4-6] The signs and symptoms during the febrile and hypotensive stages appeared to be due to a circulating toxic agent and consisted of high fever, circulatory collapse, a leukemoid blood reaction, and various hemorrhagic phenomena. Patients dying at this time had severe shock which did not respond to therapy. Death during the oliguric and diuretic stages resulted from renal failure, pulmonary

* Duration of disease was: unknown, 4, 7, 8, 8, and 11 days, respectively.

edema, pulmonary suppuration, cerebral hemorrhage, or a combination of these. The relation between the early hypotension and the late acute renal failure was not apparent since patients showing little or no evidence of shock nevertheless developed renal involvement.[7] So




Text-fig. 1. Duration of disease for 111 fatal cases, 1951 and 1952.

uniform was the renal involvement that urinary changes were required to confirm the clinical diagnosis of hemorrhagic fever, and typical kidney changes were found in all fatal cases at necropsy.

The following criteria were used in determining the clinical stage of the disease at the time of death: hypotensive, if spontaneous return of the blood pressure to normal or to hypertensive levels had not occurred; oliguric, if, in addition to decreased urinary output, the blood pressure had been maintained at normal or hypertensive levels for at least 24 hours even though hypotension had recurred as a terminal event; diuretic, if 2 or more liters of urine were excreted during a 24-hour period regardless of the subsequent recurrence of oliguria or shock.

## Data for Comparison of Disease in 1951 and in 1952

It was the general clinical impression that hemorrhagic fever had not changed in character, severity, or clinical findings during the 2 years of the study. The average and median duration of disease in fatal cases did not differ significantly in 1951 and 1952. The largest number of deaths occurred on the 8th day of disease, the median on the 9th day of disease, and 76 per cent of the fatalities occurred before the 13th day of disease (Text-fig. 1). During both years of the study the average interval between onset of disease and hospitalization for all patients who died was 3.6 days. When broken down by stage of

Table I

*Available Information on Interval Between Onset of Disease and Hospitalization*

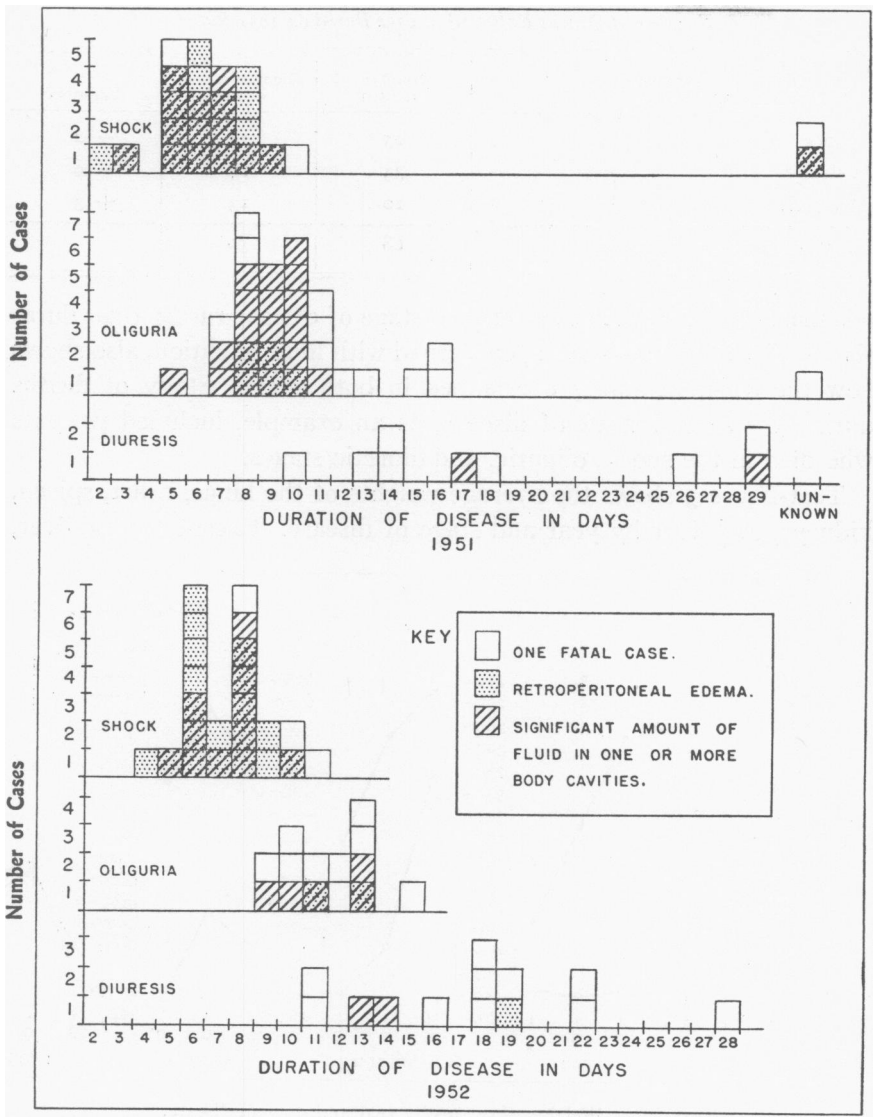
| Stage of disease at time of death | 1951 | | 1952 | |
|---|---|---|---|---|
| | Average no. of days | Deaths | Average no. of days | Deaths |
| Shock | 3.15 | 20 | 3.50 | 22 |
| Oliguric | 3.92 | 26 | 4.0 | 13 |
| Diuretic | 4.12 | 8 | 3.45 | 11 |
| Totals | | 54 | | 46 |

disease (Table I), it was evident that delay in hospitalization after the onset of symptoms was not responsible for any difference in the case fatality rate in the 2 years.

During the fall epidemic of 1951 (beginning September 12), 876 cases of hemorrhagic fever were reported with a case fatality rate of 6.4 per cent.* During 1952, there were 1,067 reported cases of hemor-

* The first American experience with hemorrhagic fever during the spring and summer of 1951 was associated with a high case fatality rate. In retrospect, it is believed that this resulted from inadequate knowledge of the disease and non-diagnosis of many mild cases. Subsequently, beginning with the fall epidemic of 1951, medical officers were on the alert and suspected the presence of the disease in all patients showing unusual symptoms. For this reason, the comparison of case fatality rates is based on the reports for the second half of 1951 rather than on the reports for the entire year.

rhagic fever, with a case fatality rate of 4.9 per cent.[8] A difference in the number of deaths in the oliguric phase between the 2 years became evident when the expected mortality rate by stage of disease based on the 1951 fall epidemic experience was applied to the 1952 experience (Table II). Since it is the current belief that restriction of fluids de-




**Text-fig. 2. Fluid retention and stage of disease at time of death by year and duration.**

creases the fatality rate in acute renal failure, it appeared that the fluid restriction program instituted in 1952 decreased the case fatality rate in the oliguric stage of hemorrhagic fever.

## Gross and Microscopic Changes at Necropsy

When fatal cases were studied by clinical stages of disease, it was realized that the duration of the different stages varied considerably among patients. Therefore, study of cases by arbitrary duration peri-

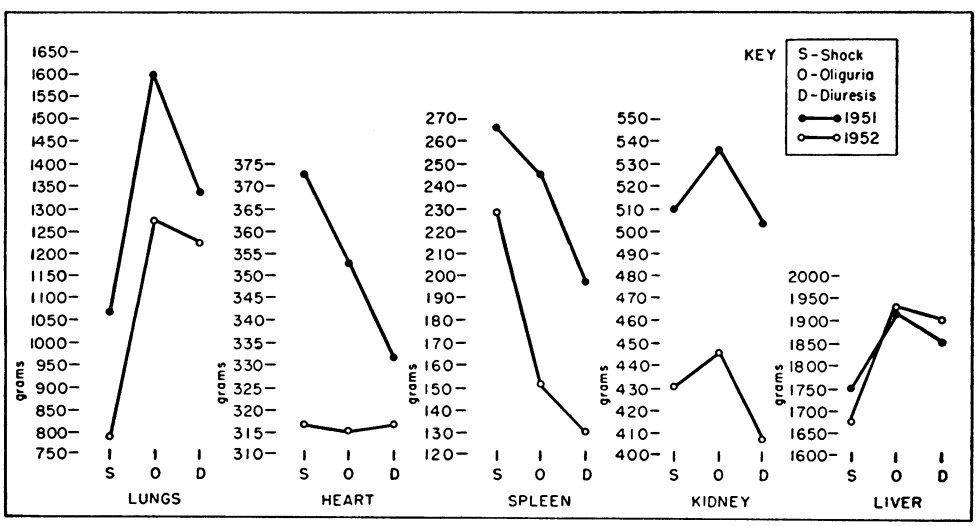
Table II

*Number of Deaths Expected in 1952 Based on 1951 Rates*

| Stage of disease at time of death | Number expected | Number which occurred | Variation |
|---|---|---|---|
| Shock | 25 | 23 | − 2 |
| Oliguric | 33 | 14 | −19 |
| Diuretic | 10 | 13 | + 3 |
| Totals | 68 | 50 | |

ods masked those changes related to stage of disease rather than duration of disease. Text-figure 2, concerned with fluid retention, also shows how the different stages overlapped in both years. Study of deaths during the second week of disease, as an example, included patients who died in the shock, oliguric, and diuretic stages.

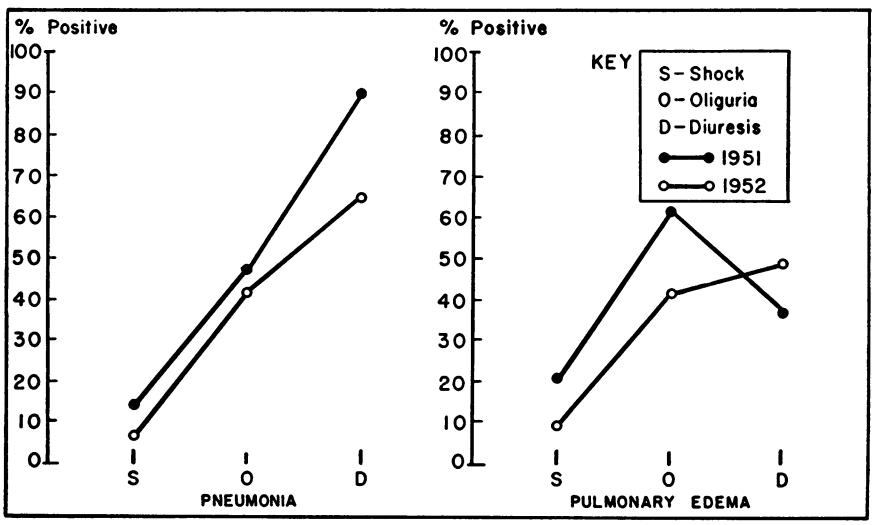
Text-figure 3 shows the average weights of the lungs, heart, spleen, kidneys, and liver by year and stage of disease. Except for the liver,




Text-fig. 3. Weights of organs by year and stage of disease.

these organs were consistently heavier in 1951 than in 1952 when compared by stage of disease and, with the exception of the heart, the weights of these organs increased or decreased in both years almost in the same proportion in the different stages of disease. The average

of the available estimated body weights of 46 patients in 1951 was 160¼ lbs. and of 46 patients in 1952 was 153 lbs., indicating that differences in organ weights probably were not due to differences in




Text-fig. 4. Presence of pneumonia and pulmonary edema (microscopic examination) by year and stage of disease.

the weights of the patients. In each year, 7 patients were Orientals.

*Lungs.* The increase in the average weight of the lungs in the oliguric and diuretic stages was due to the occurrence of pulmonary edema and pneumonia. The presence of either or both was recorded when the lung sections were studied microscopically (Text-fig. 4). In the diuretic stage, the effect of the decreased incidence of pulmonary edema on the weight of the lungs was not entirely balanced by the increased

TABLE III

*Average Severity of Pneumonia as Seen Histologically by Year and Stage of Disease*

| | Shock | | Oliguria | | Diuresis | |
|---|---|---|---|---|---|---|
| | 1951 | 1952 | 1951 | 1952 | 1951 | 1952 |
| Number of patients | 16 | 16 | 25 | 9 | 9 | 10 |
| Average severity of pneumonia | 0.33 | 0.17 | 0.95 | 1.82 | 1.89 | 2.27 |

incidence of pneumonia. Pneumonia occurred less frequently in 1952, but, when present, it was more severe than in 1951 (Table III). The severity of pneumonia was graded histologically* on a 1 to 4 basis,

* Histologic grading of the various tissues was accomplished by judging the degree of involvement in tissue sections from each patient in the group and dividing the sum of the grades for each group by the number of patients in each group. The factor resulting from this manipulation was considered the average severity of involvement.

grade 1 being small foci of bronchopneumonia, grade 3 being diffuse consolidation involving almost the entire section, and grade 4 being diffuse consolidation with suppuration.

During 1951, no cases of pulmonary suppuration were found. In 1952, 9 of the 27 patients who died in the diuretic or oliguric stages of the disease had suppurative pulmonary lesions at necropsy. There was no correlation between the presence or absence of pulmonary suppuration and use of cortisone or ACTH.

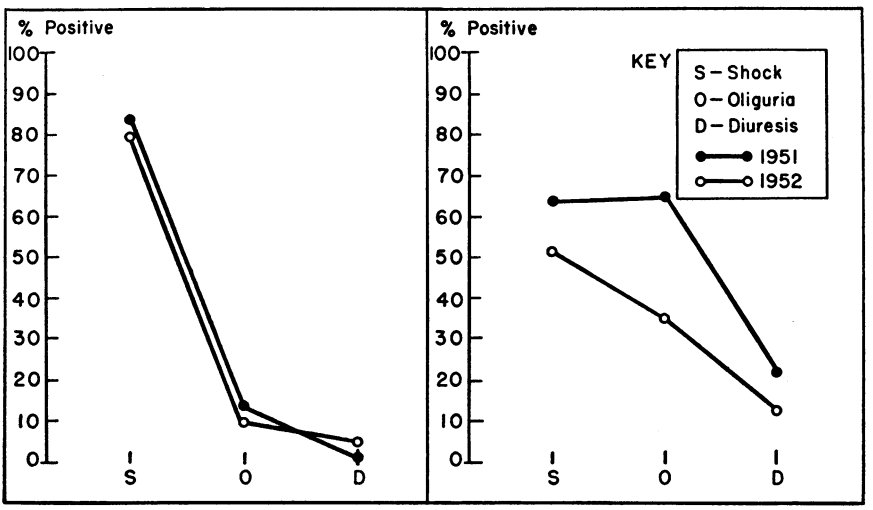
*Heart.* In 1951, the weight of the heart was increased in the shock stage, decreasing progressively in later stages, while in 1952 the average heart weight was normal in all stages.

*Body Fluids.* The presence of retroperitoneal edema is shown by cases in Text-figure 2 and by percentage in Text-figure 5a. There was little difference in the frequency of retroperitoneal edema in the 2 years and not all patients dying in shock had retroperitoneal edema. The presence of significant abnormal amounts of free fluid in one or more of the three body cavities (more than 25 ml. in the pericardial sac and more than 100 ml. in the pleural or peritoneal spaces) is also shown by cases in Text-figure 2 and by percentage in Text-figure 5b. Free fluid in body cavities was found more frequently in 1951 than in 1952 and in both years persisted in the oliguric and diuretic stages. Infrequently, pleural effusion was due to pneumonia.

### *Microscopic Examination*

*Heart.* When the cardiac sections were reviewed, it was realized that certain mild changes described in 1951 were present so frequently and were so unusual as to be almost diagnostic. In addition to the "hemorrhage" observed in all cases in the right atrium, there was a mild infiltration of cells into an edematous layer immediately beneath the intact and unaltered endothelium of the endocardium (Figs. 1 and 2). The infiltrate consisted principally of various mononuclear cells, including plasma cells and Anitschkow's myocytes, occasionally mast cells and eosinophils and, rarely, polymorphonuclear leukocytes. Such infiltrates, generally only a few cell layers thick, were found in all chambers, on occasion in the valves, and could be traced from the endocardium between muscle bundles into the interstitial tissue. Similar infiltrates frequently were found about small vessels, but nowhere were they consistently associated with an endothelial or intravascular reaction. Infiltrates, consisting of collections of a few mononuclear cells, were sometimes found beneath the endothelium of the aorta and coronary arteries. Special stains have failed to reveal inclusion bodies or rickettsia in these cells. There was little variation in the incidence

of these findings between 1951 and 1952, but in both years these changes were progressively less prominent and less frequent after the shock stage (Table IV). Some of the myocardial infiltrate found in




Text-fig. 5a. Presence of retroperitoneal edema by year and stage of disease.

Text-fig. 5b. Presence of free fluid in body cavities by year and stage of disease.

patients dying in the oliguric and diuretic stages may have been related to hyperkalemia, azotemia, and/or pulmonary infection.

In the edematous subendothelial layer of the right atrium the red blood cells frequently were massed so that cell outlines could not be

TABLE IV

*Percentage of Cases Showing Cardiac Changes by Stage of Disease, 1951 and 1952 Combined*

| Histologic findings | Shock (39 cases) | Oliguria (32 cases) | Diuresis (17 cases) |
|---|---|---|---|
| | % | % | % |
| Subendocardial edema | 100 | 82 | 53 |
| Subendocardial infiltrate | 97 | 78 | 65 |
| Myocardial infiltrate | 64 | 63 | 41 |

distinguished, while in the atrial myocardium pooling of blood was not frequent, the erythrocytes usually being diffusely distributed, almost in a mosaic pattern. Even in the cases of longest duration, no cellular reaction to the extravasated blood was found, iron stains were negative, and pigment-bearing phagocytes could not be found in either the myocardium or the epicardial fat. In the heart and in other areas of hemorrhage, considerable variation in the size of erythrocytes was observed. Extremely small red blood cells often were seen. Monroe

and Strauss[9] described similar changes, believed they resulted from fragmentation of larger cells without loss of pigment, and interpreted this as evidence of mechanical red blood cell destruction.

*Kidney.* Although necrotic renal lesions were much less frequent and severe in 1952, the fundamental changes described in 1951 were consistently found. Changes in the cortex generally were not prominent in cases of short duration. In cases of longer duration, tubules, principally distal convoluted tubules, tended to be dilated and to contain casts consisting of precipitated protein, desquamated cells, and material resembling hemoglobin pigment. Such sections showed mild edema of the interstitial tissue. A rough estimate of the duration of disease could be made, based on these changes.

In 2 cases, one from each year, there was necrosis involving the cortex as well as the medulla. Both were of long duration, 22 and 26 days respectively. Both had severe medullary necrosis. The areas of necrosis in the cortex were wedge-shaped, sharply demarcated, and typical of anemic renal infarcts, but no evidence of vascular occlusion could be found.

When the corticomedullary "hemorrhage" was re-examined, it was realized that hemorrhage resulting from rupture or loss of continuity of a vessel was rarely, if ever, present. In cases of short duration (5 days or less), engorged, dilated, but still recognizable vascular channels were seen. Thereafter, in many areas, although distinct vascular channels were not found and tubules were separated by fields of red blood cells (Fig. 3), special stains showed very delicate fibers lying among the red blood cells, suggesting an extremely dilated sinusoidal pattern. In some patients, including many dying in the diuretic phase, there was less congestion. In such cases, the interstitial tissue of the corticomedullary area was edematous and contained separated red blood cells.

Even in cases of long duration, there was little, if any, evidence of red blood cell destruction, although it appeared that hemorrhage was present very early in the disease and in most patients. It is now believed that these hemorrhages represent vascular engorgement and diapedesis of red blood cells rather than hemorrhage from ruptured vessels and that the lack of evidence of red blood cell destruction is related to the mechanism which produces these changes. Obstruction to the venous return by occlusion of renal vessels, the usual cause of these changes, has not been demonstrated. A few sections did show an infiltration of mononuclear cells in the walls of renal veins; in three sections, veins in the peripelvic fat showed thrombophlebitis. An attempt was made to tabulate vascular infiltrative changes but this was

not reliable because lesions could sometimes be found in cases from which a large number of kidney sections were available and not in those with but a few sections or in those not containing adequate portions of renal medulla.

In most cases, there was clearly recognizable tubular necrosis in the medulla (Fig. 4). When the involvement was more severe, groups of ghost-like tubules were seen lying sometimes in an area of congestion, but more frequently in an area of edematous acellular stroma. Such areas resembled anemic infarcts and sometimes were so extensive as to involve the entire pyramid (Fig. 5). There was a gradual transition from involvement of individual tubules to areas of definitely recognizable necrosis. For the purpose of this report, the criteria for focal necrosis were made more strict and only definitely recognizable necrotic areas involving interstitial tissue as well as tubules were tabulated. Table V shows both the incidence and severity of this lesion by

TABLE V

*Incidence and Average Severity of Medullary Necrosis by Year and Stage of Disease*

| | Shock | | Oliguria | | Diuresis | |
|---|---|---|---|---|---|---|
| | 1951 | 1952 | 1951 | 1952 | 1951 | 1952 |
| Number of cases | 20 | 23 | 27 | 14 | 9 | 13 |
| Necrosis present | 25% | 4% | 52% | 36% | 67% | 23% |
| Average severity of necrosis | 0.45 | 0.04 | 1.48 | 0.71 | 2.11 | 0.62 |

year and stage of disease, as graded in the histologic sections on a 1 to 4 basis. It is apparent that there was appreciably less focal necrosis in the medulla in the 1952 cases than in the 1951 cases.

No correlation could be found between the presence or absence of medullary necrosis and shock, retroperitoneal edema, fluid in body cavities, pneumonia, the use of vasopressor drugs, or the use of ACTH or cortisone. Some patients with little hypotension throughout the course of their disease had medullary necrosis while others did not. Some patients who survived severe shock, only to die in a later stage, had necrosis, while others did not. Necrosis appeared to be related to duration of disease but there were exceptions to this. In 1951 necrosis appeared in some cases of short duration (6 days) and was absent (17 days) or mild (29 days) in cases of long duration. In 1952, necrosis was not seen in cases of less than 10 days' or more than 22 days' duration.

*Pituitary Body.* The presence and severity of foci of necrosis in the anterior lobe of the pituitary body appeared related to the stage of disease at the time of death (Table VI). Approximately 58 per cent

of patients who died in the shock stage had pituitary necrosis and this was generally mild. All patients who died in the oliguric stage had pituitary necrosis which was frequently severe. In the diuretic stage, 17 of 18 patients had some degree of necrosis, but often, especially in the 1952 cases, this was so slight as to involve only a few cells. Table VI shows the degree of involvement based on a 1 plus to 4 plus scale

TABLE VI

*Necrosis of Anterior Lobe of Pituitary Body by Year and Stage of Disease*

| | Shock | | Oliguria | | Diuresis | |
|---|---|---|---|---|---|---|
| | 1951 | 1952 | 1951 | 1952 | 1951 | 1952 |
| Number of cases | 17 | 19 | 21 | 9 | 6 | 12 |
| Necrosis present | 53% | 63% | 100% | 100% | 100% | 92% |
| Average severity of necrosis | 1.2 | 1.0 | 3.1 | 2.9 | 2.5 | 1.9 |

as seen in histologic sections. Despite this evidence of frequent involvement of the pituitary body, it has not been demonstrated that pituitary insufficiency plays an important rôle in this disease.

*Adrenal Gland.* Table VII presents in a similar manner the data dealing with adrenal necrosis. The degree of histologic involvement was based on a scale of 1 to 4, with grade 4 representing necrosis of

TABLE VII

*Necrosis of Adrenal Gland by Year and Stage of Disease*

| | Shock | | Oliguria | | Diuresis | |
|---|---|---|---|---|---|---|
| | 1951 | 1952 | 1951 | 1952 | 1951 | 1952 |
| Number of cases | 20 | 22 | 29 | 13 | 8 | 13 |
| Necrosis present | 15% | 23% | 35% | 0% | 0% | 15% |
| Average severity of necrosis | 0.5 | 0.6 | 1.1 | 0 | 0 | 0.4 |

half an adrenal section, the most severe degree seen. Comparison of the 2 years showed a considerable difference in the degree and frequency of adrenal necrosis in the oliguric and diuretic stages.

*Liver.* Midzonal necrosis was noted in 24 cases with only 12 being of more than minimal degree. No correlation could be determined for stage of disease and there was an equal number each year.

*Gastrointestinal Tract.* In the esophagus, a mononuclear infiltrate of varying degree, associated in some cases with actual ulceration, was seen in most sections. These, however, were too few to permit study by stage of disease or by year.

Very little difference could be noted in gastrointestinal congestion when examined by year and stage of disease. It was frequently pres-

ent and often intense in all stages, but it was limited to the most superficial portion of the mucosa. In a few early cases, there was congestion at the base of the mucosa with edema of the area usually congested in later stages.

## Discussion

There were two major differences in the treatment of patients in 1952, as compared to 1951. First was the better general medical care resulting from the concentration of patients in one hospital with treatment by physicians, nurses, and corpsmen experienced with the disease. Second was the emphasis placed on fluid restriction. The decrease in the average weight of organs and free fluid in body cavities in the 1952 series as compared to the 1951 series (Text-figs. 2 and 5b) was at least in part due to the fluid restriction program. Since the major decrease in mortality in 1952 occurred in the oliguric stage (Table II), it appeared that when hemorrhagic fever was treated as acute renal failure, some patients were saved and others were carried to the diuretic stage before succumbing.

Characteristic renal and cardiac changes were observed in necropsies of patients who had been ill for only a short time before death, indicating that the tissue damaging agent was active during the first few days of the disease. Clinical studies showed that the renal damage occurred early and in some ways resembled so-called lower nephron nephrosis which often follows a renal insult of short duration. Because the cellular reaction in the heart tended to be less intense when the disease was of long duration and because the hemorrhages and the infarct-like necrotic foci in the various organs of the same patient appeared to be of the same age, it was suspected that the agent causing tissue damage was active only during the first few days of the disease and that the processes seen in patients with disease of longer duration represented tissue reaction to previous injury. This concept was supported by the Russian reports[10] that the etiologic agent of hemorrhagic fever could be transmitted by blood and urine obtained only from patients who had been ill for less than 6 days.

The diversity of organs involved, the widespread vascular reaction, the cellular changes in the heart, and the peculiar type of hemorrhage in many organs suggested the presence of a circulating vascular toxin. Since, in most non-fatal cases, recovery was complete by all clinical criteria, it was concluded that the vascular changes were reversible and that hemorrhages were resorbed. One patient who died of acute hepatitis 3 months after recovery from a typical moderately severe attack of hemorrhagic fever had no evidence of damage resulting from the latter disease.

Because the foci of necrosis in the kidneys and pituitary and adrenal glands resembled infarcts and were usually associated with areas of hemorrhage, vascular dysfunction and anoxia were considered to be the more likely cause for focal necrosis than the direct action of a toxin. The cause of hemorrhage apparently was not the cause of necrosis since necrosis was never found in the right atrium. The changes in the renal tubules likewise appeared secondary to vascular changes and resultant local anoxia. Although the renal lesion of hemorrhagic fever might, therefore, be considered a form of so-called lower nephron nephrosis,[11] the hemorrhage at the corticomedullary junction in hemorrhagic fever was much more severe than the congestion in the same area in lower nephron nephrosis; infarct-like areas of necrosis have not been described in lower nephron nephrosis; and the focal interstitial infiltrates and granulomas found in that syndrome have not been observed in hemorrhagic fever.

The pituitary and adrenal changes did not appear to be an essential factor in the pathogenesis of the disease because they were not always present, patients showed no consistent response to ACTH and/or cortisone, and no case of pituitary cachexia has been reported among patients who recovered from the disease.

Moderate to severe retroperitoneal edema was present at necropsy in approximately 75 per cent of patients who died in the hypotensive phase of the disease. The remaining 25 per cent had little or no retroperitoneal edema. Fluid in other areas such as periorbital and subcutaneous tissues and large muscle groups, and free fluid in body cavities were not always present. It therefore appeared that, in some patients, escape of fluid from the vascular compartment was not essential for the development of the hypotensive phase. However, it was evident that in the majority of patients such fluid loss was frequent, sometimes massive, and, if not the primary cause of shock, contributed to and increased its effect on organ function.[12]

Retroperitoneal edema was rarely found in patients dying in the oliguric and diuretic stages although free fluid was often present in the body cavities. Clinical studies[13-16] showed that hemoconcentration and decreased circulating blood volume were present in many of these patients during the hypotensive phase and were quickly reversed with recovery from hypotension. It was, therefore, suspected that these patients had had retroperitoneal edema during the hypotensive phase and that the fluid had been rapidly resorbed. Because a few patients who died after recovery from shock showed retroperitoneal edema at necropsy and because a few patients had a low circulating blood vol-

ume in the post-hypotensive phase, it appeared that the resorption of retroperitoneal fluid was not necessary for recovery from the hypotensive phase.

Although previously present, the signs and symptoms of progressive renal failure did not become prominent until the patient recovered from the hypotensive phase of the disease. During the oliguric and diuretic phases some patients died because of renal failure with or without detectable electrolyte abnormality, some died of complications such as hemorrhage, pneumonia, and pulmonary abscess, and some died of severe acute pulmonary edema. The pneumonia showed no unusual features except for the large number with suppuration in 1952, apparently due to aspiration. In both years, but particularly in 1951, pulmonary edema was a frequent terminal event and appeared to be caused by the rapid return of large amounts of fluid to the vascular compartment rather than to cardiac failure.[12]

## Summary

A comparative study has been made of the pathologic findings in patients dying of hemorrhagic fever in 1951 and 1952. There is evidence that the changes were similar in both years, but of a different degree of severity. It is suggested that these differences were related to differences in therapy rather than to a change in the character of the disease itself. It is suspected that fluid restriction and treatment as for acute renal failure were the important therapeutic changes and that a decrease in the number of deaths in the oliguric stage resulted from this approach.

It is believed that a toxin is elaborated and is active only during the early course of the disease. During this time there is evidence of widespread capillary and endothelial damage and apparently all subsequent manifestations of this disease are the result of this damage.

Re-evaluation of cardiac lesions indicates that an almost pathognomonic picture is present, especially in cases of short duration. The important feature is a mild subendothelial mononuclear cell infiltration.

Re-evaluation of the renal lesions indicates that hemorrhage due to loss of continuity of blood vessels was not present. It is believed that the so-called hemorrhage represents extreme congestion and dilatation of corticomedullary vessels with diapedesis of red blood cells. Diapedesis of red blood cells is also suggested as the mechanism of the hemorrhage in the right atrium.

Re-examination of the foci of necrosis in the kidneys and the pitui-

tary and adrenal glands suggests that these were the result of anoxic changes rather than due to the direct action of the etiologic agent or a toxin.

The recognized and controversial fluid balance changes were discussed. On the basis of the necropsy studies it is believed that in fatal cases these are severe, important, but secondary changes. Until the etiologic agent and a specific therapy are discovered, they will remain as significant problems in the management of this disease.

## REFERENCES

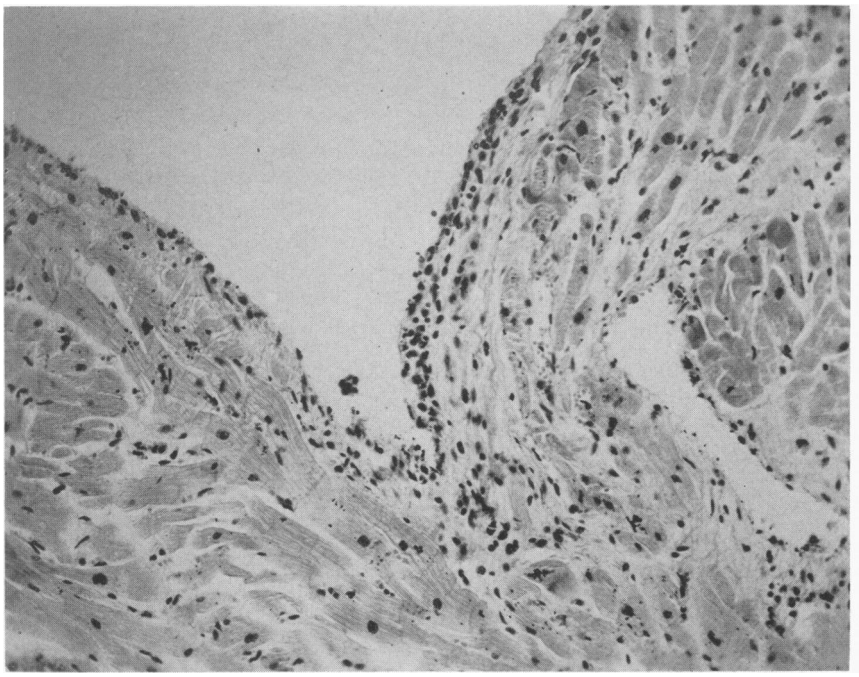

1. Steer, A., and Hullinghorst, R. L. Epidemic Hemorrhagic Fever. In: Karsner, H. T. (ed.) The 1951 Year Book of Pathology and Clinical Pathology. Year Book Publishers, Chicago, 1951, pp. 7–14.
2. Hullinghorst, R. L., and Steer, A. Pathology of epidemic hemorrhagic fever. *Ann. Int. Med.*, 1953, **38**, 77–101.
3. Lukes, R. J. The pathology of thirty-nine fatal cases of epidemic hemorrhagic fever. *Am. J. Med.*, 1954, **16**, 639–650.
4. Barbero, G. J.; Katz, S.; Kraus, H., and Leedham, C. L. Clinical and laboratory study of thirty-one patients with hemorrhagic fever. *A. M. A. Arch. Int. Med.*, 1953, **91**, 177–196.
5. Katz, S.; Leedham, C. L., and Kessler, W. H. Medical management of hemorrhagic fever. *J. A. M. A.*, 1952, **150**, 1363–1366.
6. Sheedy, J. A.; Froeb, H. F.; Batson, H. A.; Conley, C. C.; Murphy, J. P.; Hunter, R. B.; Cugell, D. W.; Giles, R. B.; Bershadsky, S. C.; Vester, J. W., and Yoe, R. H. The clinical course of epidemic hemorrhagic fever. *Am. J. Med.*, 1954, **16**, 619–628.
7. Froeb, H. F., and McDowell, M. E. Renal function in epidemic hemorrhagic fever. *Am. J. Med.*, 1954, **16**, 671–676.
8. Epidemiologic data, Surgeon Eighth Army, Korea.
9. Monroe, W. M., and Strauss, A. F. Intravascular hemolysis; a morphologic study of schizocytes in thrombotic purpura and other diseases. *South. M. J.*, 1953, **46**, 837–842.
10. Mayer, C. F. Epidemic hemorrhagic fever, a collective study of the literature (preliminary draft). Army Medical Library, Washington, D.C., 1951.
11. Lucké, B. Lower nephron nephrosis. (The renal lesions of the crush syndrome, of burns, transfusions, and other conditions affecting the lower segments of the nephrons.) *Mil. Surgeon*, 1946, **99**, 371–396.
12. Earle, D. P. Analysis of sequential physiologic derangements in epidemic hemorrhagic fever; with a commentary on management. *Am. J. Med.*, 1954, **16**, 690–709.
13. McDowell, M. E., and Furth, F. W. Body Water Compartment Studies in Hemorrhagic Fever. Special Report to Commission on Hemorrhagic Fever, Army Medical Service Graduate School, Washington 12, D.C., 1952.
14. Furth, F. W. Observations on the hemostatic defect in epidemic hemorrhagic fever. *Am. J. Med.*, 1954, **16**, 651–653.
15. Giles, R. B., and Langdon, E. A. Blood volume in epidemic hemorrhagic fever. *Am. J. Med.*, 1954, **16**, 654–661.
16. Hunter, R. B.; Yoe, R. H., and Knoblock, E. C. Electrolyte abnormalities in epidemic hemorrhagic fever. *Am. J. Med.*, 1954, **16**, 677–682.

[ *Illustrations follow* ]

## LEGENDS FOR FIGURES

FIG. 1. Section from right ventricle showing subendocardial infiltrate and edema, mild myocarditis, and mild infiltrate beneath endothelium of a vein. Death on seventh day of disease in shock stage. Hematoxylin and eosin stain. × 160. (Armed Forces Institute of Pathology negative 53–23475.)

FIG. 2. Another field from the same section as that from which Figure 1 was taken, showing in greater detail the infiltrate and edema beneath the intact endothelium. Hematoxylin and eosin stain. × 555. (A.F.I.P. negative 53–23476.)



1

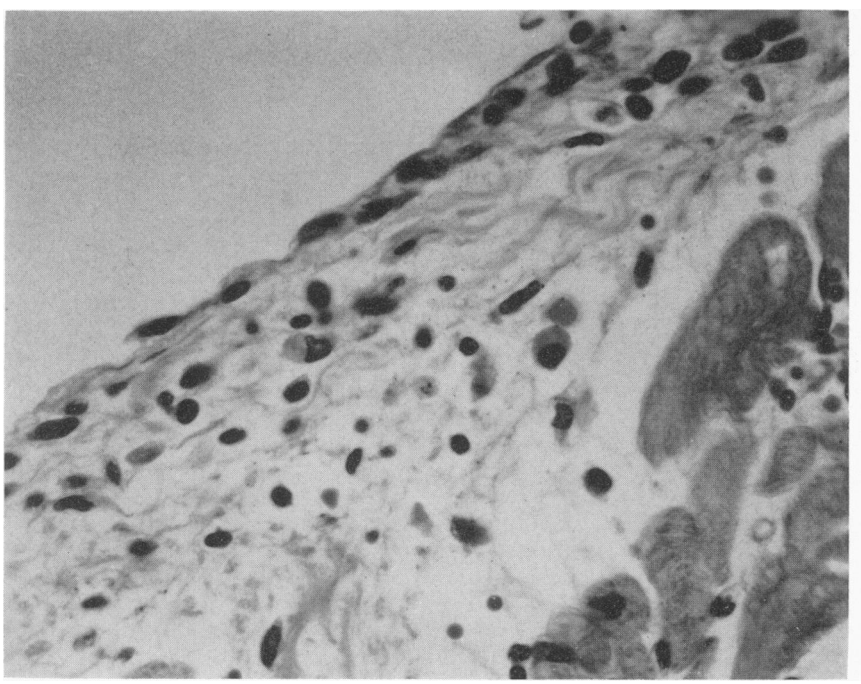


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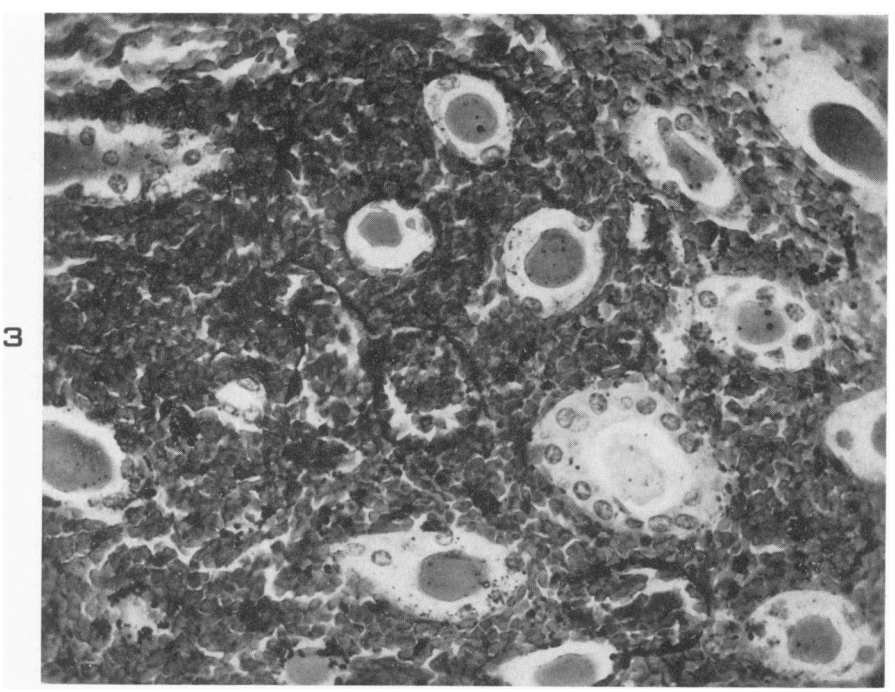
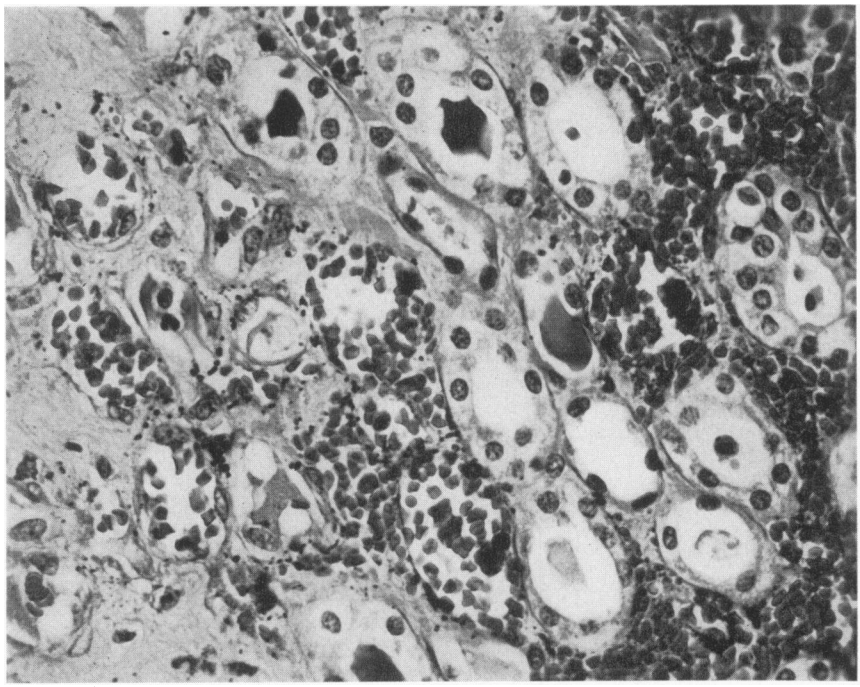
FIG. 3. Section from kidney at the corticomedullary junction, showing extreme engorgement, tubular casts, and tubular epithelial changes. Death on eleventh day of disease in shock stage. Hematoxylin and eosin stain. × 395. (A.F.I.P. negative 53–23489.)

FIG. 4. Section from a kidney at the corticomedullary junction showing congestion, tubular necrosis, and casts. Death on eighth day of disease in shock stage. Hematoxylin and eosin stain. × 400. (A.F.I.P. negative 53–23488.)

FIG. 5. Section from kidney at the corticomedullary junction and medulla showing congestion and large infarct-like area of necrosis. Death on 26th day of disease in diuretic stage. Hematoxylin and eosin stain. × 48. (A.F.I.P. negative 53–23490.)





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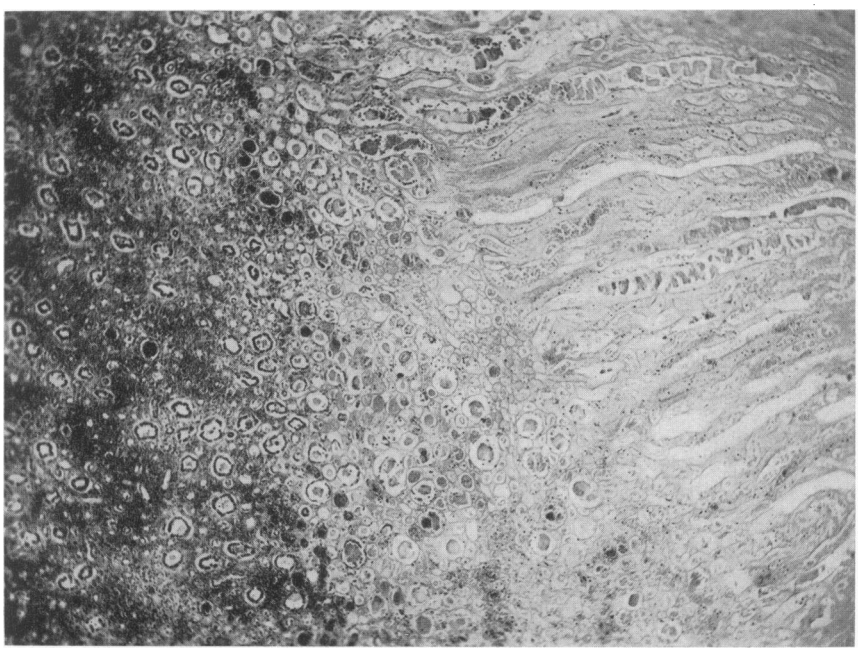

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