LIGATION OF THE HEPATIC ARTERIES AND HISTOLGICAL CHANGES OF THE LIVER IN DOGS

by

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CONTENTS

I. INTRODUCTION

In 1951, RIENHOFF et al. and BERMAN et al. reported on cases of liver cirrhosis to which ligation of the hepatic arteries was applied with good results. Since then this new therapeutic treatment has been performed successively by many surgeons. Some of them advocate that this form of treatment is remarkably effective, but others assert that it should not be put into practice for the moment, not only because it is not always effective, but also because the method of the selection of patients is at fault. However, if the mechanism of development of necrosis after the ligation of the hepatic arteries, and the theoretical background of this treatment are to be thoroughly studied, this new treatment of ligating the hepatic arteries in portal cirrhosis of the liver will gain much credit because it implies at least an effort toward improving liver function. Some of the experiments that motivated RIENHOFF, BERMAN and others to apply this method to men were the accomplishments made by MARKOWITZ et al. as well as the liver perfusion experiment made by HERRICK. MARKOWITZ proved that liver necrosis, the greatest of dangers to occur after the ligation of the hepatic arteries, could often be prevented by penicillin which is used for about seven days after the ligation. This finding has been verified by many investigators. MARKOWITZ concluded that penicillin prevents necrosis by inhibiting the growth of anerobes normally present in adult dogs and probably the production of lethal enzymes, such as lecithinase. On the other hand, GLINDLAY

et al. and FRASER et al. emphasized the significance of ischemic necrosis of the liver which appears after the occlusion of the hepatic artery.

I once reported on the results of experimental studies on the problem of ligation of the hepatic arteries and arterial collateral circulation, chiefly using colored plastics. Now, I have tried to study the histological changes of the liver after the ligation of hepatic arteries, with special reference to administration of penicillin.

Ⅱ. METHODS OF EXPERIMENT

About 90 healthy adult dogs were used. Chiefly the common hepatic, the gastroduodenal and the right gastric arteries (abbreviated to the hepatic 3 arteries in the following pages) were cut under the double ligations, and postoperative histological changes were followed up: that is, microscopic observations were performed on the tissue specimens taken from the liver at exploratory laparotomy, at the time of sacrifice, or immediately after natural death: above all, in some cases, specimens were successively taken at short intervals after the ligation with much care to do them as little damage as possible. To avoid artificial influences, the tissue specimens were taken not using mass ligature, but cutting the tissue with a sharp razor at a stroke, and then fixed in formalin and stained chiefly by Hematoxlin and Eosin.

Ⅲ. RESULTS OF EXPERIMENT

After the ligation of the hepatic 3 arteries the liver showed marked changes which exclusively led to massive necrosis. Previously URABE and others in our clinic followed up macroscopic changes in the liver after the ligation of the hepatic 3 arteries, and obtained the following results: immediately after the ligation there appears in the liver a diffuse congestion-like state which gradually begins to show a tendency to be localized about 3 hours after the ligation. After 12 hours the localization gets more marked, and the localized areas usually overlap the favorite sites of liver necrosis after the ligation of the hepatic artery. Under administration of antibiotics, although the liver goes half-way through much the same process of changes as observed above, localization of congested areas is more marked and limited. In my study, therefore, histological examinations were made on those areas where the congestion was expected to occur or really existed.

A. Cases given no antibiotics.

1) Follow-up findings.

On 3 dogs observations were made by repeating laparotomy 7 to 9 times from immediately after the ligation of the hepatic arteries with the following results.

5 minutes after the ligation: Grossly, the whole liver presents a reddish livid tone, with a moderate degree of congestion already seen in some of the portal spaces and sinusoids.

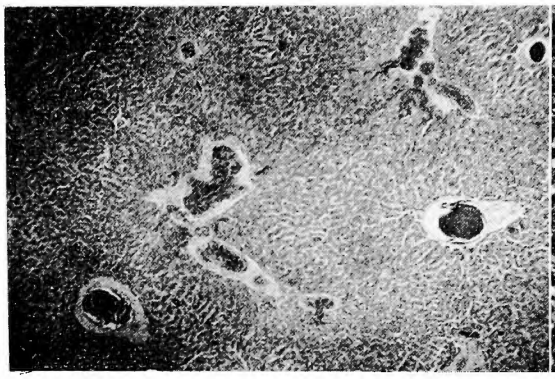
After 30 minutes: No particularly marked changes are yet seen. Blood cells increase in some of the portal spaces and sinusoids, and in some areas of the parenchyma there is a tendency to hemorrhage (Fig. 1). The ink tone observed diffusely on the liver surface is yet to be easily dispersed by pressing it with fingers.

After 1 hour: Peripheral portal branches are seen full of blood cells and therefore going tortuously. In the interstitial spaces and occasionally peripheral parts of lobules, hemorrhage and

Table 1. Summary of Cases of Histological Study.

antibiotics	Penicillin-untreated	Penidillin treated						
survival or daeth	Died of massive liver necrosis				Survived			
ligation method / Time after ligation	Ligation of hepatic 3 Arteries		Ligation of hepatic 2 arteries	Ligation of hepatic 4 arteries	Ligation of Com. hep artery	Ligation of hep. 3 arteries	Ligation of hep. 2 arteries	Ligation of hep. 4 arteries
< 1 hs	No.54 (v101 v102)	No.36				v11 v13		
1～ 3 hs	No.44							
3～ 9 hs	No.60	No.62				No.37		
9～15 hs	No.64	No.65				No.38		
15～24 hs	No.24 No.26 No.35 No.39 No.5 No.6 No.12 No.19 v39	No.18 No.40 v16				No.30	No.41	
24～36 hs	(No.8 No.25 No.27 No.29 No.31 No.32) v6	No.11	v69 v70			No.10		
36～48 hs	No.2 No.4 No.17			No.73		No.7	v40	
2～ 3 ds		v13 v14	v35 v68	No.111		No.14 No.16		
3～ 4 ds		v30		No.131 v71		No.28	v75	
4～ 7 ds		No.15 v11				No.21 No.22	v76	
7～10 ds						v22	v114	v74
10～14 ds		v02				No.20 v5 v19		(v114)
14～17 ds						v10 v20		(v40) v60 v120
17～21 ds						v21 v23 v36		v75 (v76)
21～30 ds			No.72			v18 v31 v46		
1～ 3 Ms						v6		
3< Ms					No.13 v15	v01		
Total 87	25	13	5	4	2	27	4	7
		22			40			

Note : 1) The sign } means Cases followed up 2) Killed cases given in parentheses 3) See the previous report for the ligation methods



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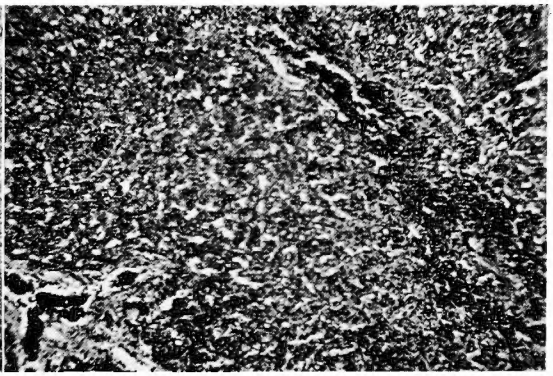

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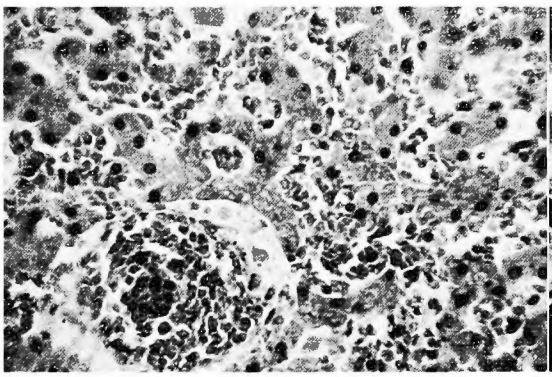

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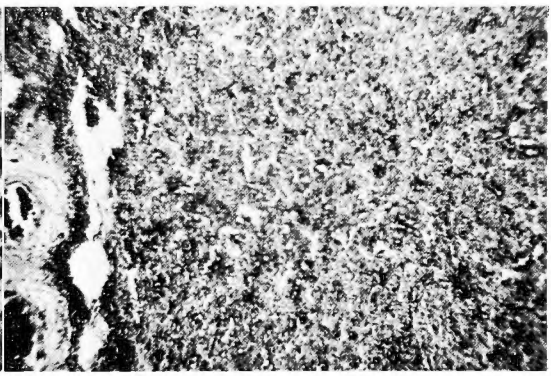

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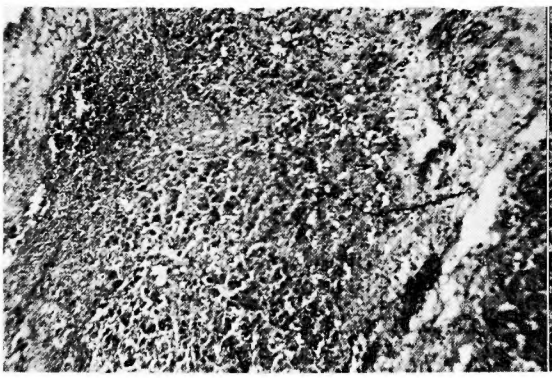

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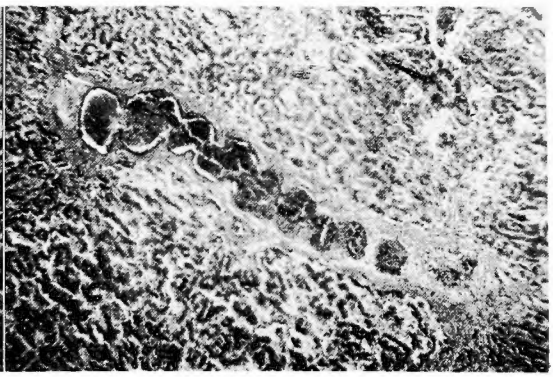

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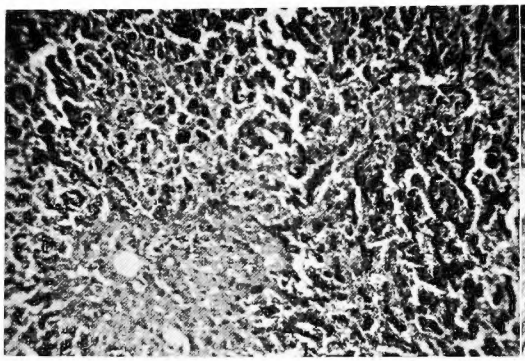

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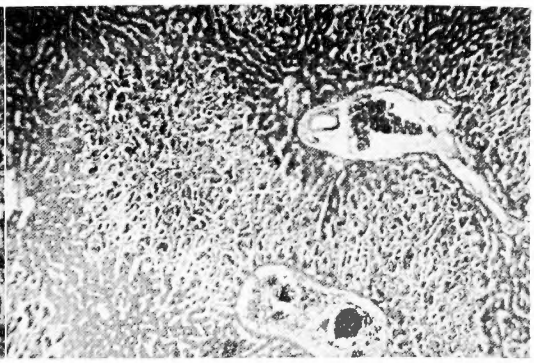

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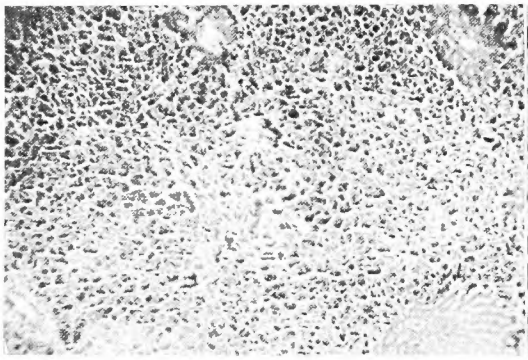

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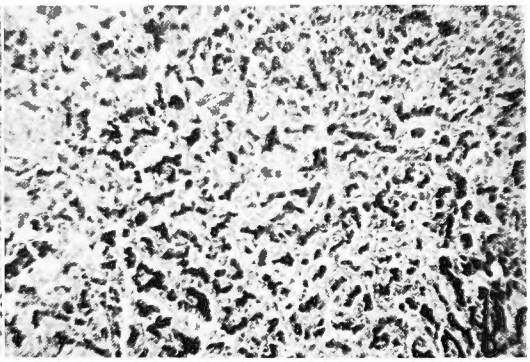


Fig. 10 No.64 10×10

Favorite Sites of Liver Necrosis

Fig. 11 No.36 4×15

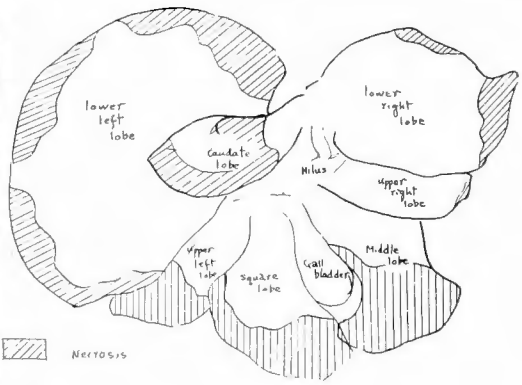


Fig. 11′

small round cell infiltration appear here and there (Fig. 2). Grossly, the findings are much the same as those obtined 30 minutes after the ligation, but there are colored freckles seen scattered here and there in the periphery of the middle, and in the caudate lobe, etc.

After 3 hours: The congestion presents in sinusoids, central veins and portal spaces become still more marked (Fig. 3), partially with hemorrhage in interstitial spaces (Fig. 4). The colored freckles, apparently caused by congestion and grossly observed on the liver surface, can no longer be dispersed by finger press microscopically, However, no marked parenchymal damage is yet observed even in areas where changes have occurred, except for a slight tendency to nuclear pycnosis.

After 6 hours: About this time degeneration of some parenchymal cells begins. (Fig. 5) Both the portal venous and the hepatic venous radicles show themselves markedly congested and dilated and going tortuously (Fig. 6). In some parts of the liver there are hemorrhagic foci and cell infiltration in the parenchyma.

After 9 hours: The changes mentioned above get still more remarkable, with a high degree of centrilobular congestion, atrophy of hepatic cords, cloudiness of parenchymal cells and nuclear pycnosis, (Fig. 7) ···a marked tendency to necrobiosis of the parenchymal cells.

After 12 hours: Much the same findings as those after 9 hours are observed. To focus our observation on a single lobule, the damaged area spreads more wider than before, extending from the central part of the lobule to the middle and further to the peripheral part of it, with a clear picture of necrobiosis. The peripheral portions of the lobule which adjoins the portal space still present a picture of almost normal tissue (Fig. 8).

After 15 hours: The changes become still more marked, with atrophy or complete dissociation and decomposition of cell cords (Figs. 9, 10). But the portions where changes are less than elsewhere remain around the portal spaces like islets. Neither necrosis nor decomposition of interstitial spaces are yet recognized.

The 3 dogs died between 16 and 17 hours after the ligation of the hepatic 3 arteries, and until their death no bacteria could be found on microscopic examination.

The changes of color macroscopically observed on the liver surface became irreversible about 3 hours after the ligation, and microscopically, degeneration of parenchymal cells begins chiefly in the periphery of the liver lobes after the 3rd postoperative hour, always preceded by a high degree of congestion of both the portal and the hepatic veins.

2) Findings immediately after death.

Ligation of the hepatic 3 arteries without administration of antibiotics is fatal to the animal operated on. About 20 dogs, thus operated on, were examined at laparotomy immediately after death. The findings are briefly as follows:

Survival hours: The shortest was 17 hours and the longest 44 hours, with a mean of about 28 hours. These figures agree with those reported by many investigators. In the present experiment, no case survived longer than 48 hours.

Appearance of liver: At autopsy, in the peritoneal cavity an accumulation of a moderate amount of light dark reddish, foul-smelling ascites was found. The entire surface of the liver was found more or less tinged with a dirty reddish livid color, involving some well-demarcated areas of a green purple color. In some cases, it presented a yellow tone suggestive of fatty degeneration. Moreover, necrosis or necrobiosis was observed in the periphery or the greater part of the liver.

Favorite sites of liver necrosis: Necrotic changes were most likely to occur in the edges of the middle lobe, in the quadrate and caudate lobes and in the periphery of the left superior and inferior lobes, whereas the right lobe showed

comparatively less changes (Fig. 11). Seeing that congestion always preceded parenchymal necrosis, this difference between the lobes may be attributed to the following facts: (1) in terms of the anatomical relation of the outflow passage of hepatic blood, that is, the hepatic vein, the right lobe is comparatively near the inferior caval vein; (2) the inflow of portal blood is supposed to be going on more favorably in the right lobes than in any other lobes; in other words, the portal circulation of the right lobe can be kept comparatively undisturbed after the ligation of the hepatic artery. However, there was no case whose right lobe suffered no changes at all.

Areas of severe necrotic changes were grossly well-demarcated from comparatively normal areas, but microscopically, the former more or less alternated with the latter (Fig. 12). In those areas which were only slightly damaged, no marked changes were observed except for congestion of potal and hepatic veins, or a slight degree of centrilobular atrophy of cell cords. On the other hand, those severely damaged areas presented a picture of central necrobiosis or necrosis. Those lobules which suffered severe centrilobular changes alternated with those which suffered only slight changes.

Centrilobular necrobiosis developed into necrosis extending from the middle to the peripheral parts of lobules, leaving only the islet-like areas, where the changes were found to be comparatively slight, around the portal spaces. As time further went on, those greatly changed lobules were fused together, presenting patterns like a map, and finally turning into massive necrosis (Fig. 13). In some cases, those necrotic areas had marked foci of hemorrhage (Fig. 14), around which was seen cell infiltration as a vital reaction (Fig. 15). Seldom, however, were leucocytes found in the necrotic areas. Even in the case where micro-abscesses developed, infiltration of leucocytes was not found in the degenerated areas surrounding the micro-abscesses (Fig. 16).

Concerning the growth of bacteria, I recognized massive grouping of large-sized bacilli in the liver in only those dogs which were examined a long interval after death, or those which died after long survival ··· because the necrotic area in them had been considerably limited (Fig. 17). These bacilli were Gram-positive and may be supposed to be anerobes for the time being, as many predecessors have asserted. A number of such bacilli were observed in the parenchyma which had become necrotic to a considerable degree, and in the adjacent portal and hepatic veins, and sometimes in the surrounding areas of necrobiosis (Fig. 18). But in those areas of the same section which were near the normal portion showing a slight degree of cell degeneration, no bacilli were found.

Furthermore, in one case which was examined a considerable period after death, large vacuoles as well as bacilli were observed in some parts of a markedly necrotic area, and it is assumed that these vacuoles had been produced by the growth of anerobic bacteria (Fig. 19). It may be added here that a liver containing such vacuoles, that is, a "foamy liver" was not found in those cases examined immediately after death, or in those examined at probative laparotomy.

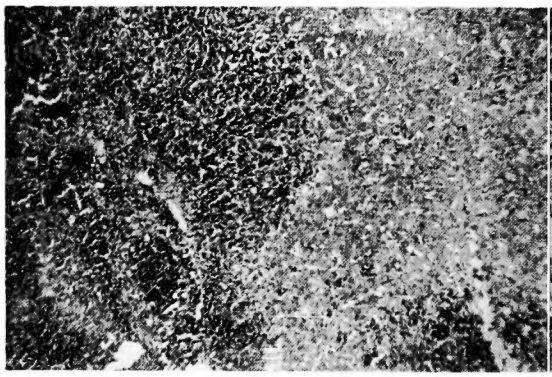
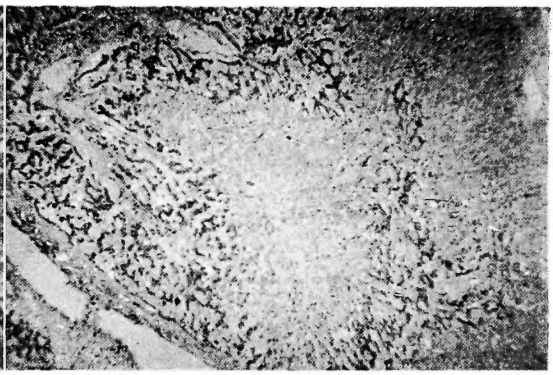


Fig. 12 No.36 4×15



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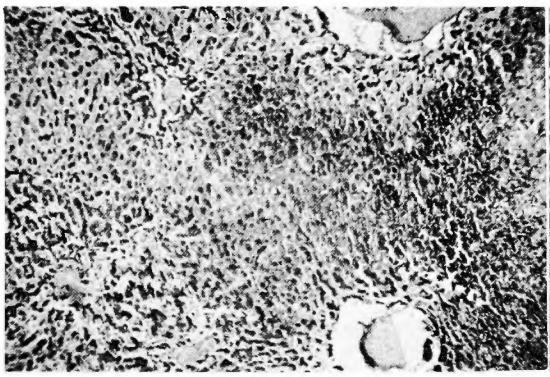

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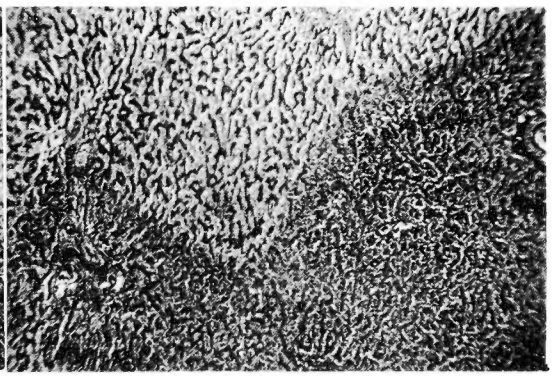

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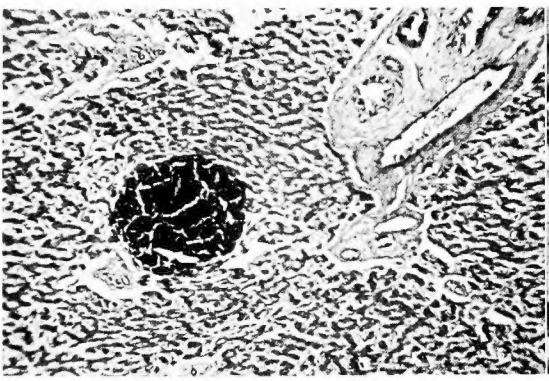

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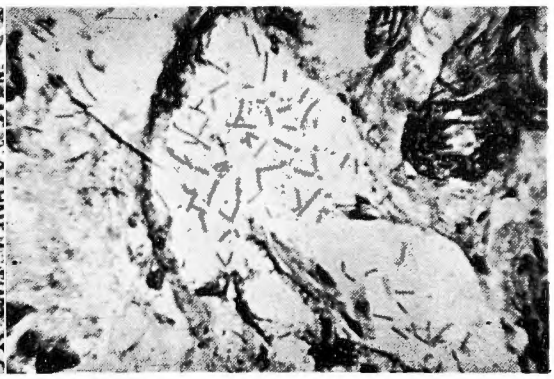


Fig. 17 No.25 40×15

In some subcapsular portions of the liver, there were sometimes observed small hemorrhagic spots, concentric round cell infiltration or cocci-infection, which may have been caused by the damage done at the time of operation.

From the above results no hasty conclusion should be drawn, but it may be safely said that the proliferation of anerobic bacteria is not the direct cause of necrosis, but rather that it is not until necrosis has been fully developed that the explosive growth of bacteria takes place. On the other hand, parenchymal degeneration is always preceded by a high degree of hepatic venous and portal venous congestion, and it is the very stagnation of blood flow caused by such congestion that makes the area necrotic.

B. Cases that died in spite of administration of antibiotics.

1) Follow-up findings.

Three dogs underwent the ligation of the hepatic 3 arteries, with 300,000 units of penicillin given immediately after the ligation and then 6 hours after it, and postoperative successive changes of the liver were followed up in the same way as was previously stated. The details of the course of events will not be given here, except that as time passed, the histological pictures showed much the same changes as were mentioned above, until massive necrosis was finally resulted. In other words, so far as those dogs that died are concerned, administration of antibiotics made no great difference in the postoperative course of events.

2) Findings immediately after death.

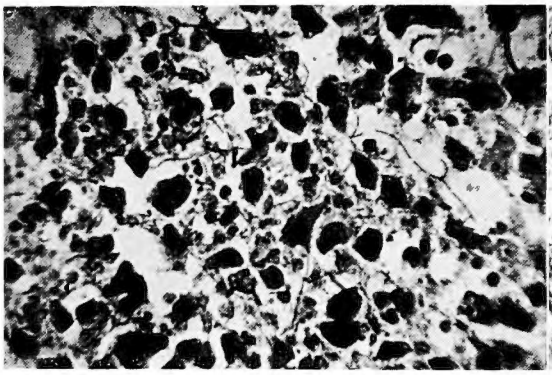
Ten dogs belong to this group. The time of survival from the ligation until death caused by necrosis ranged from the shortest 16 hours to the longest 10 and a half days, with a mean of 80 hours. These are longer than when no antibiotics were given. However, in any of these cases, centrilobular or diffuse necrobiosis or necrosis was more or less observed, though the degrees varied from case to case and from lobe to lobe, and the course of events proceeded in quite the same way as when no antibiotics were given, except for the difference in times when necrobiotic changes took place.

C. Cases which could survive due to administration of antibiotics.

After the ligation, macroscopically, the whole liver temporarily assumed a tinge of diffuse congestion, which presently showed a tendency to localize and faded away.

After 6 hours no macroscopic changes had yet been present, but in some areas of the histological picture, only congestion of sinusoids and enlargement, congestion and winding of portal venous radicles were observed, both to a slight degree (Fig. 20). The caudate lobes of some dogs, however, presented such comparatively great changes of the parenchyma as sometimes amounted to necrobiosis (Fig. 21).

After 12 hours: Grossly, even in those areas where localization of the change was marked, a clear picture of parenchymal necrobiosis was yet to be seen, but there was a slight tendency to degeneration. In these areas enlargement and congestion of sinusoids, a slight degree of atrophy of cell cords (Fig. 22), and a slight degree of hemorrhage or cell infiltration in the interstitial spaces were observed (Fig. 23).



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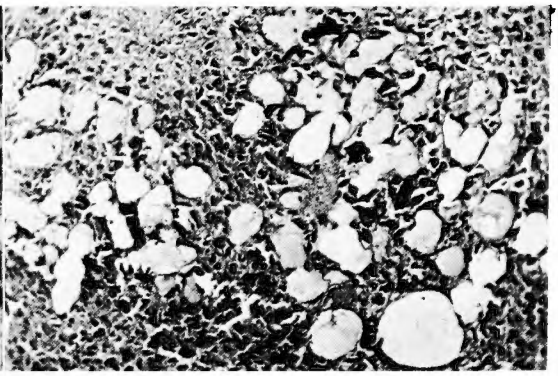

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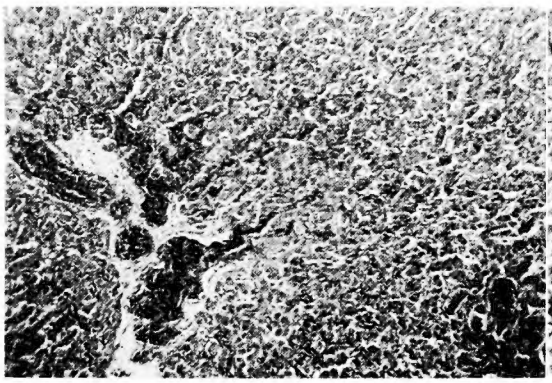

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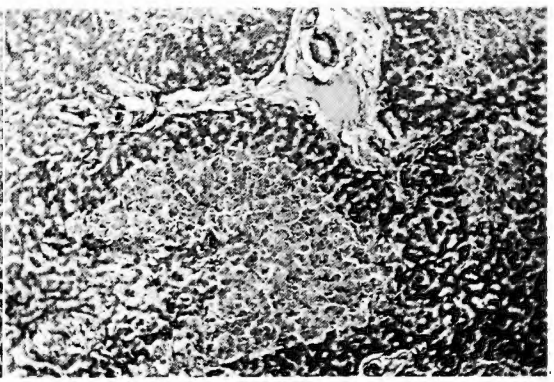

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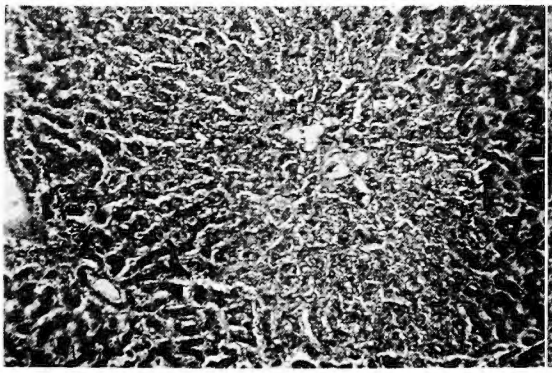

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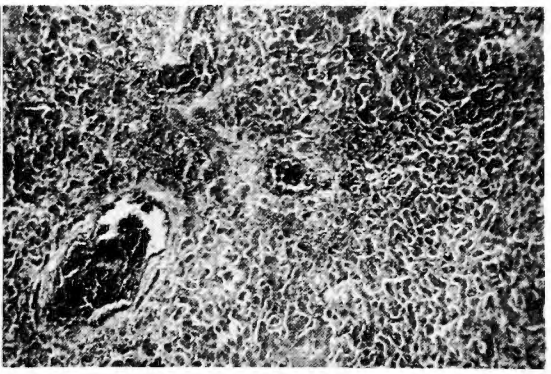

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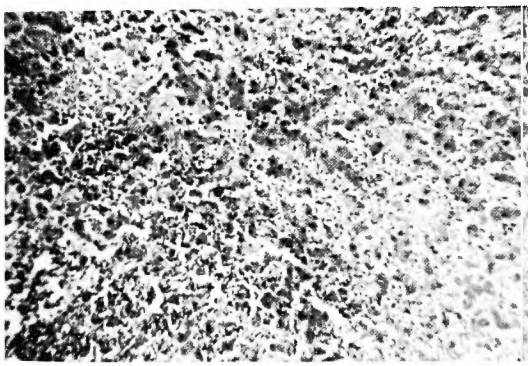

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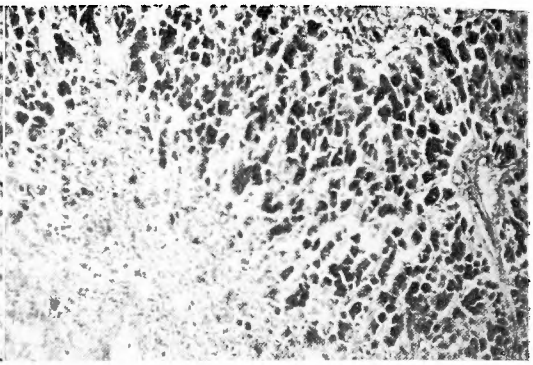

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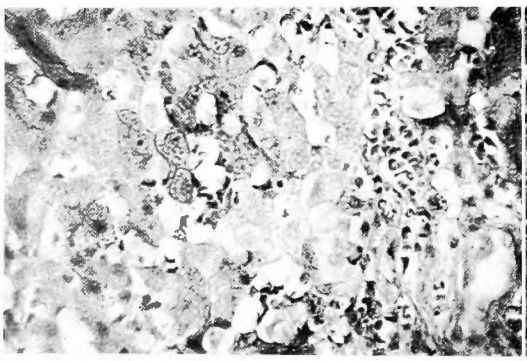
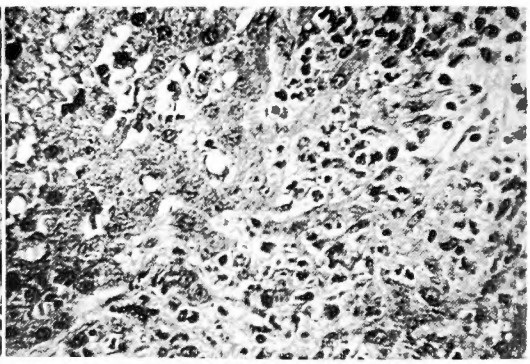


Fig. 26 V 40 40×10



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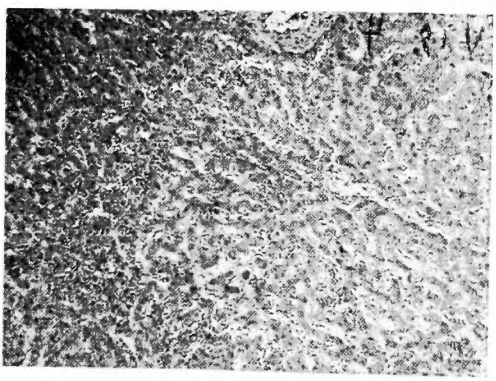

Fig. 28 V. 19 10×10

After 24 hours: Grossly, the diffuse color change which was seen immediately after the ligation of the hepatic artery disappeared completely, except for some clearly localized changes. In these areas comparatively marked histological changes were seen; cell cords had become atrophic due to severe centrilobular congestion, some of them having been dissociated (Fig. 24), and parenchymal cells had become necrobiotic or necrotic. In these areas the interstitial spaces, too, had a considerably high degree of changes (Fig. 25). As a whole, however, these areas having such changes were limited in space, and the other greater part of the liver suffered very little changes. Thereafter, as time went on, the courses of the histological changes each dogs took varied from case to case. So it was difficult to point out definitely how many hours had to be passed for what degree of change and localization to occur. However, not a single case has been encountered without having any changes at all from immediately after the ligation to about a week after that. About 2 weeks after the ligation, when the survival of the dog had become definite, the changes had been restored almost to normal, macroscopically or microscopically.

On the other hand, even in those small areas where the changes remained unhealed, hepatic cells themselves showed a tendency to regeneration (Fig. 26), although there still remained a disturbed arrangement, a slight degree of atrophy of hepatic cell cords and cicatrial changes or what suggested a secondary infection (Fig. 27). Moreover, peripheral portal spaces or sinusoids had no marked congestion any longer (Fig. 28). This may imply that in all portions of the liver, the portal circulation had already been restored to normal.

Ⅳ. SUMMARY AND DISCUSSION

In 1909, Wolbach and Saiki found anerobic bacilli present in the liver of normal dogs. Since then Ellis, Dragstedt, Manson, Mason and many other investigators have confirmed this fact, saying that these bacilli could cause hepatic autolysis after the ligation of the hepatic arteries. In 1949, Markowitz and others reported that penicillin remarkably prevented the development of necrosis after the ligation of the hepatic arteries, and explained that this was because penicillin suppressed the growth of bacteria. They thought that interruption of hepatic arterial supply brought about an anoxic condition of the liver, under which anerobes present there proliferated extraordinarily to cause necrosis. Again, Tanturi et al. putting emphasis on this growth of anerobes, said α-toxin produced by these anerobes, that is, Lecithinase, was the real cause of death. Supplementing the accomplishments by Tanturi et al. by culturing bacteria in sections of the liver or the blood taken after the ligation of the hepatic arteries, Chau and others concluded that death after the ligation was caused by an overwhelming infection by such anerobic bacteria.

Since then many workers have confirmed the effectiveness of antibiotics in saving dogs from death after the ligation of the hepatic arteries. Most of them used antibiotics for several successive days, but Chau and others reported on cases in which even a single dose of 300,000 units of penicillin was enough. What is more, Urabe

in our clinic reported that much the same results as were obtained by MARKOWITZ et al. could be obtained by only a single dose of 100,000 units of penicillin given immediately after the ligation. It is quite doubtful, however, whether such a small amount of penicillin could suppress such an explosive growth of anerobes in spite of the persistence of anoxic condition.

On the other hand, GLINDLAY and others reported on cases where death was caused by ischemic necrosis despite penicillin therapy, although they admitted such an effect of penicillin on bacteria. FRASER and others emphasized the presence of necrosis without infection, as well as with infection, for they observed that in spite of postoperative administration of large doses of penicillin which had completely suppressed the growth of anerobes in some cases, many dogs died of ischemic necrosis. And many others pointed out arterial collaterals as an important factor in the matter. Again, even TANTURI et al. said that some portions of the area of necrosis was not always be considered to be of an acute inflammatory type. YAMABE in our clinic measured values of Lecithinase-C activity and stated that in some cases even areas of necrosis could be Lecithinase-negative, which indirectly proves the presence of anoxic necrosis without the growth of bacteria.

My previous experiment verified that the fate of the dog after the ligation of the hepatic arteries did not depend upon whether or not arterial collaterals remained postoperatively. In the present study, which is also related to the above problem, histological changes of the liver after the ligation of the hepatic arteries were followed up. Though based only on the findings of histological pictures, the impression was gained that anerobic bacteria grew explosively on the area of anoxic necrosis not before but after the necrosis had been completed. On the other hand, it was found that degeneration of the parencyma was always preceded by a high degree of congestion of the portal and hepatic venous systems, and it was assumed that the very stagnation of blood flow due to such congestion put the area in a more anoxic state, which led to parenchmal degeneration and finally to anoxic necrosis.

Some investigators, such as POPPER et al. and TANTURI et al. reported that in those dogs which survived due to penicillin therapy no hepatic cell degeneration was found. Whereas others like GLINDLAY et al. said that penicillin could not protect the liver against all lesions caused by the stagnation of the hepatic arteries, for the dogs with their hepatic arteries ligated showed serious symptoms for a certain period after the ligation in spite of penicillin therapy. In this report, I have tried to follow up the histological changes of the liver after the ligation of the hepatic arteries in those dogs with or without administration of penicillin. It was found that so far as those dogs which died are concerned, there was no difference in the course of events resulting in necrosis between those dogs given penicillin and those given no penicillin, except in the time relationship; and that even in those dogs which survived due to penicillin therapy, the liver tissue had been more or less damaged within at least 1 week after the ligation to such an extent as to become, in some cases, completely necrotic. When localization of the damaged areas took place early and remarkably, and when the proportion of the necrotic area against the normal one was small, the dog was able to survive with the lesions which had

become scarred and had disappeared, or had been replaced by regenerating cells. In short, in normal dogs the interruption of arterial supply to the liver necessarily causes hepatic circulation impediment, which results in parenchymal degeneration of a greater or lesser degree. And even if the dogs can survive the lesion, they cannot escape serious, though partial, hepatic cell degeneration.

V. CONCLUSION

In the present study, changes in the histological pictures of the liver after hepatic arterial interruption were followed up. The results obtained are;

(1) Degeneration of the parenchymal cells becomes marked about 3 hours after the ligation, ending in necrosis.

(2) The parenchymal degeneration is always preceded by a high degree of congestion in the portal and hepatic venous systems, inducing anoxia and finally necrosis in the liver.

(3) Growth of anerobic bacteria is not the direct cause of liver necrosis, but the result of it ··· an explosive growth of anerobic bacteria takes place in the necrotic area due to anoxia.

(4) In those dogs which died, whether they were given penicillin or not, there was no difference in the process of histological changes leading to necrosis. Even in those dogs which could survive, some degree of parenchymal degeneration was also shown. The fate of the dogs depended upon the time and degree of localization of the damaged area.

In concluding my report, I wish to express my deepest gratitude to Dr. Chisato Araki, professor of Kyoto Univ. and Dr. Ichio Honjo, ex-assist. professor of the same and present professor of Kanazawa Univ. for their kind, continuous guidance, encouragement and supervision. Pertaining to histological findings, I am greatly indebted to Dr. Yoshihiro Hamajima, assist. professor of the Pathological Division, Kyoto Univ. Medical School for his kind guidance.

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和 文 抄 録

肝動脈遮断と肝の組織学的変化（実験的研究）

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肝への動脈血をほゞ完全に遮断した後，抗生物質を使用するとしないとに依つて，肝壊死による犬の死亡率に著明な違いを生ずる．私は先の論文に於て，動脈性副血行路の残存が，肝動脈血遮断後の犬の生死に何等関係を持たないことを実証したが，今回は本問題とも関連して，約90匹の犬に就いて，動脈血遮断直後より時間の経過に従つて肝の組織学的変化の推移を調査し，若干の知見を得たのでその概略を報告する．

1) 肝動脈血遮断直後より肝を肉眼的に観察すると遮断後肝は全体的に色調を変じ藍色を帯びる．この色調の変化は遮断後3時間目位いより漸次消褪する一方次第に限局化の傾向を示し，これは12時間後には更に著明となる．然もこの限局性著色斑の発生部は，所謂肝壊死の好発部位とよく一致する．この点を組織学的に時間を追つて追究すると，この一見藍色を呈する箇所には，静脈洞の拡大鬱血，並びに門脈枝の蛇行鬱血を証明し得，又遮断後3時間目頃からは，之等の部分に限局した実質的細胞の変性が始まり，更にこの変化は時間の進展と共に高度となつて，12時間後にあつては，或部分は相当明瞭な中心性死生乃至壊死像を示し，更にこれは遂には瀰漫性の壊死へと進展する．(尚こゝで壊死の所謂好発部位について私見を加えた．)

2) 壊死性変化の強い部分と比較的正常に近い部分との境界は，同一の肝葉に於ても肉眼的には明瞭に区別される．然し組織像には両者間に多少の移行が見られる．即ち，変化の軽い部分では遮断後相当時間を経ても単に門脈静脈系の鬱血，軽度の中心性索萎縮が見られる他著変なく，一方変化の強い部分にあつてはす

べて中心性死生乃至壊死像を呈し，この中心性変化の強い小葉が変化の軽いものとの間に互に入り組んでいる．この中心性死生は更に小葉中間部から周辺部に及ぶ壊死へと進展し，更に，僅かに間質周囲に比較的変化の軽い実質を島状に残すのみとなり，更に相隣れる変化した小葉が融合して地図状に拡大し，遂には広汎な壊死へと発展する．

3) 壊死に陥つた部分の周囲には，生活反応としての細胞浸潤帯を見ることもあるが，然し白血球が壊死領域に入つているものは甚だ稀であつて，又或る例に於ては，かゝる非感染性と思われる壊死巣を母地として，之に細菌感染が続発したかの組織像を認めた．更に所謂嫌気性菌の発現は，死後に時間をおいて観察したもの，或は肝の一部に著明な壊死巣を持ちながら，限局化が比較的高度であつた為死亡の遅れたものに於てのみ，その壊死巣内に集中的に認められ，更に附近の門静脈腔内，或は時に隣接の死生の部分にも菌体を見出しうるが，同一切片内であつても未だ死生に至らない変化の軽い部分には顕微鏡的には発見出来なかつた．以上から即断は許されないにしても，菌体の発育は，それが直接肝壊死発生の原因ではなく，むしろ壊死巣を発育の培地として之に続発するものと考えられる．

4) 実質細胞の変性には常に門・静脈系の強い鬱血が先行しており，かゝる鬱血に依る血行の停滞こそがその局所に乏酸素環境を齎らし，やがては該部を壊死に到らしめる原因となるものと考えられる．（従つて所謂 Ishemic Necsosis なる言葉は適当ではなく，鬱血に基く Anoxic Necrosis と称すべきであろう．）

5) 術後にペニシリンを投与した場合は，犬の死亡率を著明に低下せしめ得はするが，ペニシリン使用の有無に拘らず，死亡するものはその組織変化に於て全く同様の過程を辿つて遂には広汎な肝壊死に達し，単にその時間的経過を異にするだけである．一方ペニシリン投与に依り生存し得た例に於ても，少くとも遮断後の1週間前後に到る間に，常に若干の組織障害は免れ得ず，或る部分ではそれは完全な実質壊死にまで発展する．唯，該部の限局化が早期に，且つ著明に行われ，又その肝全体に占める割合が比較的少範囲にとゞまれば，他の要素の恢復と共にその犬は生存し得，その生存がほゞ確定的となる2週間目前後に於ては，既に障害された部分も瘢痕として消失し，或は再生細胞に依つて置き換えられることを知つた．何れにしても正常犬に於ては肝への動脈血供給を遮断すれば，抗生物質を使用すると否とに拘らず肝には常に循環障害に基く実質障害が多少とも発生し，夫等の生死の岐路となるものは，その限局化の時期と程度である．

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