Original Articles

ÆTIOLOGY OF APPENDICITIS

AN EXPERIMENTAL OBSERVATION

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[This paper is a brief summary of part of a thesis submitted for the degree of M.D. (Pathology), Lucknow University.]

Introduction

APPENDICITIS is one of the commonest and not infrequently one of the most dangerous of the surgical emergencies and there is a good deal of evidence that mild attacks of inflammation of the appendix occur much more frequently than is generally supposed. Our knowledge of the exact pathology and ætiology of the disease is, however, far from complete.

Although appendicitis had been reported in the eighteenth century it received no proper recognition until 1886, when Fitz of Boston described a long series of cases, distinguished it clearly as the commonest cause of perityphlitis and gave it the name now universally adopted. Within twenty years it had attained the position of being the most common of all acute abdominal illnesses. This rapidly increasing menace in the beginning of the present century naturally drew the attention of both the pathologists and clinicians, and vague and fantastic explanations were given. Most of the evidence was clinical and co-incidental. Racial and climatic factors were blamed. The rôle of meat diet with a reduction of cellulose appeared to be a very plausible explanation to the older pathologists for the greater prevalence of the disease in the West and comparative rarity in the more vegetarian East. In fact the earliest experimental work of Wilkie (1914) on cats gave support to this hypothesis. Constipation has been looked upon with suspicion. The abnormal deformities of the appendix such as kinks and twists appeared to play a significant part in the ætiology. Various intestinal parasites, particularly *Oxyuris vermicularis*, have had many advocates in the genesis of appendicular disease.

Early in the twentieth century, with increasing interest in bacteriology, the infective theory in the causation of appendicitis was brought forward, there being two schools of thought—the hæmatogenous and enterogenous. Rosenow (1915) the pioneer of the hæmatogenous theory put forward the view that acute appendicitis was the result of the selective affinity of certain throat streptococci for the appendix. Poynton and Paine (1911) and Adrian (1901) working on the rabbit came to a similar conclusion. McMeans (1917) and more recently Williams and McLachlan (1930) however have shown that the concentration of bacterial emulsion necessary to produce lesions in the appendix was far too much to occur naturally in human beings. Patey and Whitby (1933) working on the pathology of cholecystitis found no experimental evidence to support Rosenow's theory of elective localization.

Aschoff (1932) on the other hand, by extensive studies of normal and inflamed human appendices, showed that the appendix has a special bacterial flora, the members of which are responsible for the attack; he suggested that in acute appendicitis there is an enhanced virulence of this normal flora brought about probably by stagnation of fæces within it.

Lansdown and Williams (1915) after a histological survey of inflamed appendices came to the conclusion that it was the lymph follicles in the submucosa which were the primary seat of disease in the appendix, and not the mucous membrane, thus lending support to the hæmatogenous theory. Aschoff, however, will have none of it. He has always held that appendicitis is an enterogenous infection arising on the surface of the mucosa and denies the possibility that the disease may ever be blood-borne.

Wangensteen (1937) and his co-workers have investigated the function of the human organ in appendicostomy cases and have stressed mechanical causes as responsible agents in the genesis of inflammations in the vermiform appendix.

A more recent paper on the ætiology of appendicitis is that of Wells (1937) from the Dunn School of Pathology, Oxford. From his work on animals Wells supports the enterogenous origin of the disease.

The present paper contains the experimental part of a thesis on the pathogenesis of appendicitis which was conducted both on clinical and experimental bases.

Experimental work

Observations were made on fifty adult rabbits. The rabbit is the only easily available laboratory animal which has an appendix at all comparable, both in microscopical structure and naked-eye appearance, with that of man. Also appendicitis occurring spontaneously in rabbits has been reported in the literature (Mori, as quoted by Wells, 1937). These were the main reasons for choice of the rabbit in the present investigation.

Experiments were planned to observe the changes produced in the appendices of rabbits under the following conditions :—

(*a*) Ligation of the root of the appendix by a silk thread avoiding the blood supply of the viscus.

(*b*) Ligation of the root of the appendix including the appendicular artery and vein in the ligature.

(*c*) Ligation of the root of the appendix and obstruction of the venous return by ligature of the appendicular vein.

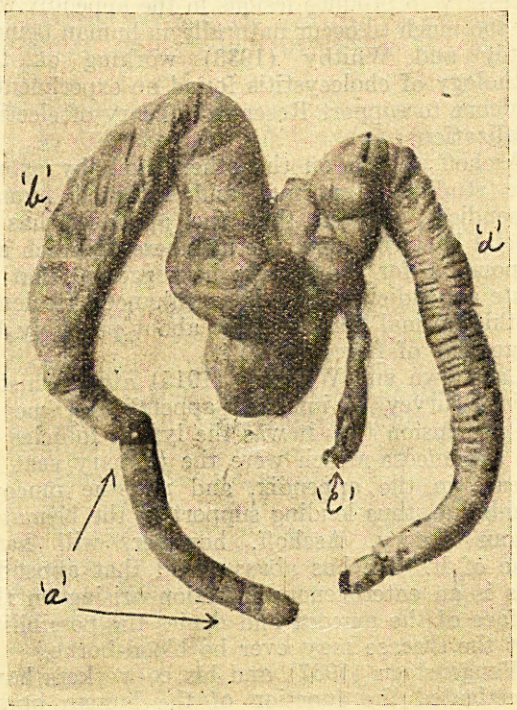


Fig. 1.—Normal appendix of rabbit *in situ*. (*a*) Appendix (3 to 4 inches). (*b*) Cæcum. (*c*) Terminal ileum. (*d*) Colon.

(*d*) Production of abnormal kinks of the appendix.

(*e*) Traumatization of the mucous membrane of the appendix by scarification with a sharp needle introduced through the tip of the intact viscus, the point of entry being subsequently sutured by catgut.

(*f*) Traumatization of mucous membrane followed by introduction of a living emulsion of streptococci into the lumen by a needle passed through the tip.

(*g*) Introduction of a foreign body in the form of glass beads or large fruit seeds into the lumen of the appendix to observe the effect of intraluminal obstruction. These were introduced into the lumen by incising the root of the appendix and suturing the wall subsequent to the introduction by catgut.

(*h*) Daily intravenous injections of emulsions of virulent streptococci isolated from the throat of patients suffering from acute tonsillitis. These injections were given daily into the marginal ear vein of the rabbit over a period of 3 to 4 weeks, unless the animal died earlier, after which the appendix was removed for histological examination.

The concentration of the bacterial suspension was estimated by the comparative opacity tube method. The doses varied between 200 and 600 millions/c.c.

Hæmolytic streptococci and *Str. viridans* were employed.

(*i*) Observations as under (*h*) in animals with appendices which had been traumatized.

Operations exposing the appendix were done with aseptic precautions and under local procaine* infiltration anæsthesia. The abdominal wound was closed in layers with catgut and sealed with collodion. The animals recovered

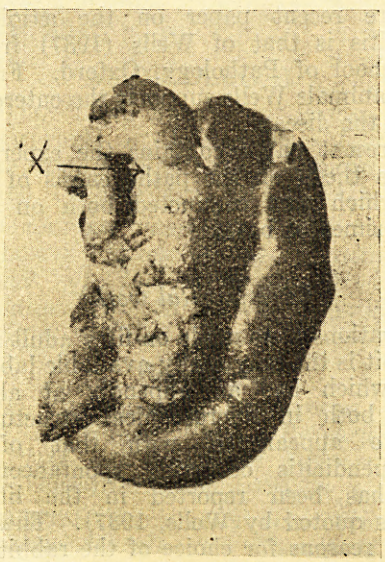


Fig. 2.

Fig. 3.

Acute appendicitis following complete obstruction by encircling ligature of root ('X'—site of ligature). Adherent and inflamed appendix in each case.

* We do not like this name which, over the telephone sounds like 'cocaine' while 'novocaine' does not. See this journal, vol. 82, p. 499.—EDITOR, *I.M.G.*

after the operations surprisingly well and operative mortality was very low. Except for two animals which developed a ventral hernia weeks to a month the appendix was removed for histological examinations, unless the animal had died already of acute appendicular inflammation

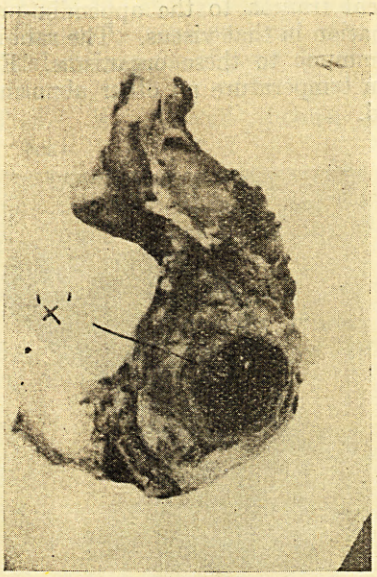


Fig. 4.

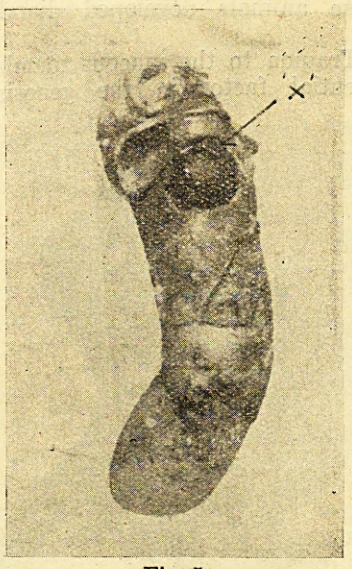


Fig. 5.

Acute appendicitis following obstruction by a large foreign body impacted in the lumen ('X'—impacted foreign body has been exposed).

the others fared very well Special procedures adopted in some experiments have been men-

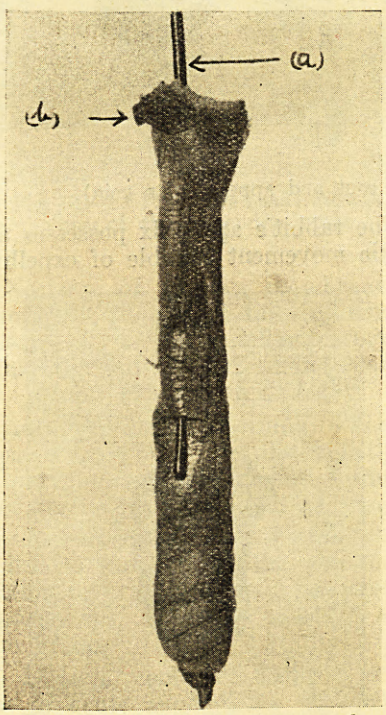


Fig. 6.—Partial obstruction of the appendix, no inflammation. (*a*) Probe shows patency of lumen. (*b*) Ligature site.

tioned already. The rectal temperature of the animals was recorded and after a period of three and peritonitis. A post-mortem examination was done on the animals which died.

Observations

(*a*) Complete obstruction of the lumen of the appendix plays the most significant rôle in the causation of acute appendicitis. The obstruction may be either by a simple ligature of the root of the appendix or by a large foreign body introduced into its lumen. All the animals died of acute appendicitis (figures 2, 3, 4 and 5).

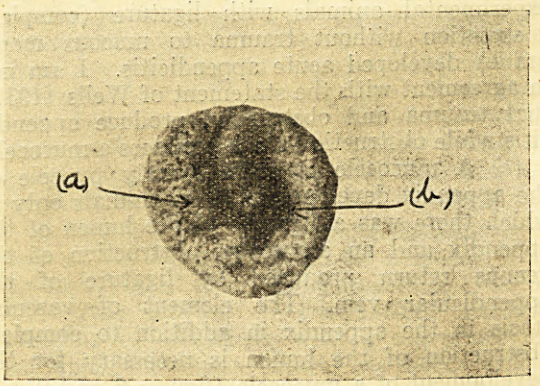


Fig. 7.—Root of appendix (figure 6) viewed end on. (*a*) Ligatured part. (*b*) Semilunar patent lumen.

(*b*) If the obstruction of the lumen was partial, in spite of a similar degree of trauma produced by the ligature, as in animals with complete obstruction of the lumen of the appendix, no inflammation followed (figures 6 and 7).

(*c*) Almost all the animals with complete ligature or obstruction showed a rising rectal temperature (104 to 105°F.).

Another significant feature observed was that all these animals developed diarrhœa before death.

(*d*) Trauma to the mucous membrane is not an essential factor in the genesis of acute appendicitis in addition to obstruction. All my experimental animals with ligature (complete obstruction without trauma to mucous membrane) developed acute appendicitis. I am not in agreement with the statement of Wells (1937) that trauma and obstruction produce appendicitis while obstruction alone produces a mucocele.

(*e*) A mucocele or more exactly pyocele of the appendix developed in those animals only in which there was a ligature of the lumen of the appendix and an associated obstruction of the venous return produced by ligature of the appendicular vein. The element of vascular stasis in the appendix in addition to complete obstruction of the lumen is necessary for the development of a mucocele (figures 8 and 9).

(*f*) Abnormal kinks or twists of the appendix cause no inflammation (figure 10).

(*g*) Trauma to the mucous membrane of the appendix by itself or with intraluminal introduction of living emulsions of *Str. hæmolyticus* or *Str. viridans*. (Doses 1,500 to 2,000 millions/c.c. from the throats of patients suffering from acute tonsillitis produce no inflammation in the rabbit's appendix.)

(*h*) Intravenous injections of living emulsions (100 to 600 millions) daily for over 30 days of the same bacteria, in normal rabbits, or those with local trauma to the appendix produce no inflammation in that viscus. The rabbit appears to be immune to these organisms. Except for a rise in temperature no other abnormality was observed.

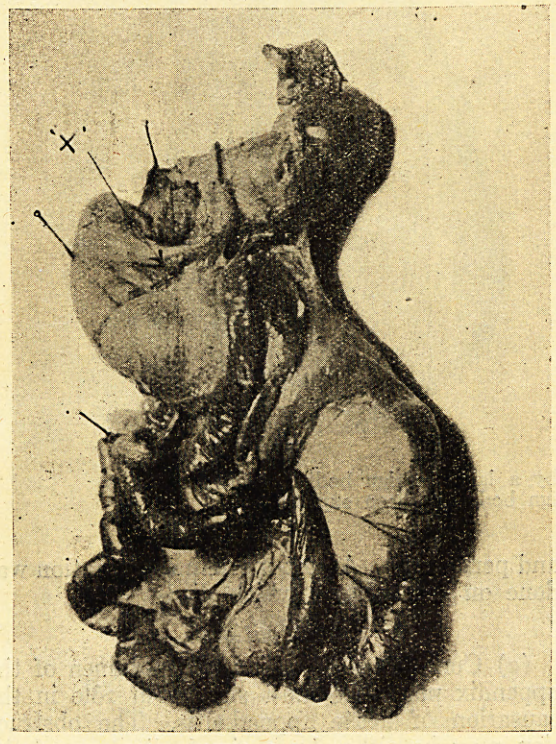


Fig. 8.

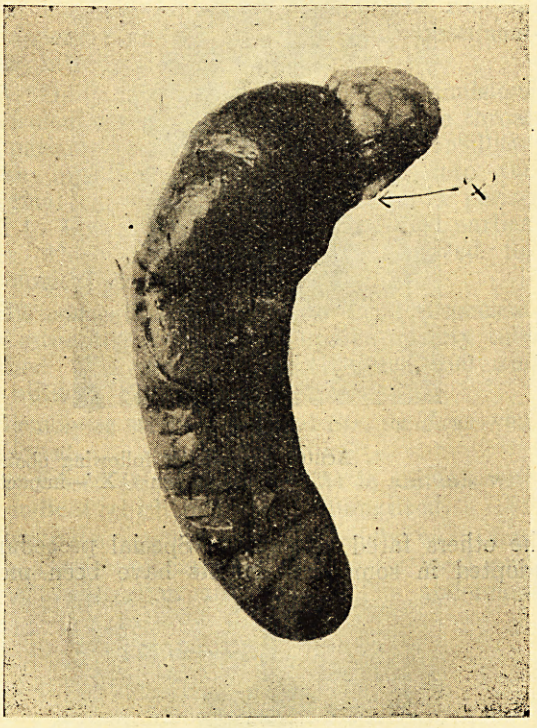


Fig. 9.

Mucocele of the appendix ('X'—site of ligature of root and appendicular vein).

(*i*) The rabbit's appendix possesses an active peristaltic movement capable of expelling small foreign bodies into the cæcum. All animals in whom the foreign body was large enough to

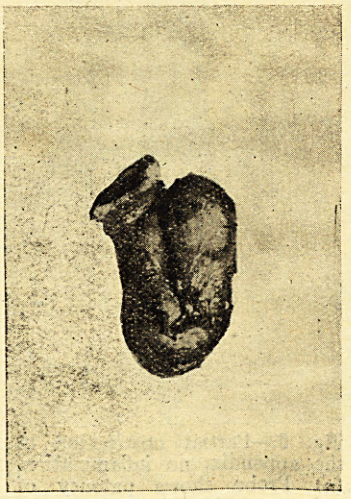


Fig. 10.—Kinked appendix.

produce complete obstruction developed acute appendicitis (figure 11).

(*j*) Histological examination of the rabbit's normal appendix shows that it resembles the human appendix except for the following histological differences (figures 12 and 13, plate XXVIII) :—

1. There is no well defined muscularis mucosæ coat.

2. The submucosa consists of a diffuse mass of lymphoid tissue without the formation of isolated lymph follicles as in the human appendix.

3. The muscle coat is a very thin layer.

(*k*) Histology of diseased rabbit's appendix resembled that of human appendicitis in the following details :—

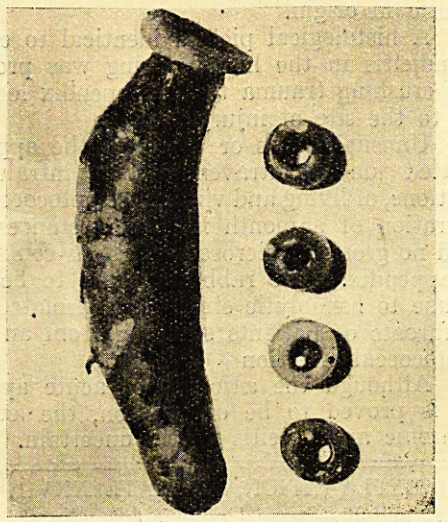


Fig. 11.—All four glass beads were passed out of the appendix lumen.

1. Necrosis of mucous membrane, atrophy of lymphoid tissue in the submucosa, and formation of a thick inflammatory exudate involving the muscle and serous coats (figures 14, 15, 16 and 17, plate XXVIII).

2. Localized crushed trauma to the appendix produces a histological picture indistinguishable from chronic appendicitis in human beings (figures 18, 19, 20, 21, 22 and 23, plate XXIX).

(*l*) The bacterial flora of the rabbit's appendix is similar to the flora in the human appendix. The following organisms were found on culture : *Ps. pyocyaneus, B. coli, B. subtilis,* and Clostridium group.

(*m*) I have come to believe that in the genesis of acute appendicitis obstruction is the all important factor, and that the enterogenous organisms of the appendix are the ones that set up inflammation.

(*n*) Although the genesis of acute appendicitis is apparent the cause of chronic appendicitis is still obscure.

Discussion

My observations, to some extent similar to those of Wells in support of the enterogenous origin of acute appendicitis as a result of obstruction, are as follows :—

1. I agree with his conclusion that, in the rabbit, injection of living bacteria, damage to the mucosa, partial cutting off of the blood supply, or partial obstruction of the lumen alone have no effect on the appendix.

2. He mentions that obstruction of the lumen of the appendix by a foreign body has no effect on the appendix. This may be true for small foreign bodies about $\frac{1}{4}$ inch in diameter but all the animals in which I introduced larger bodies, *i.e.*, over $\frac{1}{2}$ inch diameter, developed acute appendicitis with a mortality of 100 per cent.

3. Wells refers to the fact that ligature of the appendicular artery and vein and mesoappendix produces gangrene in the rabbit's appendix but this was not observed by me. There is such a profuse anastomosis among the vessels of the ileum, ascending colon and the appendix that the mere ligature of the appendicular vessels and mesoappendix is not sufficient to produce gangrene. The element of vascular occlusion was experimented on to test the ingenious hypothesis put forward by G. Ricker who advocated that appendicitis is primarily due to vascular disturbances of the organ brought about by reflex irritation of their nerves, a process akin to the 'chill' mechanism of respiratory disorders. In severe cases Ricker contended that the vascular disturbance is sufficiently intense to cause necrosis or infarction of the tissues which then become invaded by microbes from the lumen. This hypothesis as quoted by Aschoff (1932) in his book on appendicitis finds no support from my experimental results. Ligature of the vessels also includes the perivascular sympathetic nerve plexuses but in none of the animals was there any pathological response observed in the appendix. Aschoff himself, however, disagrees with such a hypothesis. He denies that a vascular disturbance is the primary lesion. He believes that such changes are secondary to a bacterial invasion of the surface of the mucosa.

4. Wells states that simple ligature of the root of the appendix produces mucocele of the appendix, and acute appendicitis follows only when the mucosa is traumatized either by crushing or scratching with a sharp needle in an appendix whose lumen has been occluded. For acute appendicitis to develop Wells emphasizes two elements, obstruction and break in mucosal barrier. My experimental results however do not agree with Wells' conclusions. I found that simple ligature of the root of the appendix alone caused acute appendicitis in 100 per cent of the animals. The factor of trauma to mucous membrane was unnecessary. I thought that a ligature may by itself damage the mucosa; and so in a set of animals I tied

the ligature very gently, but in these too the result was acute appendicitis and not mucocele.

5. I however found that of those animals whose appendix root had been ligatured, and the appendicular vessels had also been included in the ligature 60 per cent developed a distended appendix (mucocele). The contents were mucoid matter and pus cells (hence strictly speaking pyocele of appendix, a result of acute inflammation). Mucocele in the strict sense was not produced in any of the animals observed by me. Perhaps the ligature had produced obstruction only of the venous return leaving an intact arterial flow with a higher blood pressure and this caused congestion and increased secretion by the mucous glands. In order to prove this in a set of animals I tied the root of the appendix and carefully ligated the appendicular vein leaving the artery untied, and I found that the majority of these animals developed a distended appendix. Hence in my opinion the element of venous obstruction plus complete occlusion of appendix lumen is essential for the development of distended appendix resembling a mucocele. In my experiments I failed to produce giant mucoceles as stated by Wells or mucoceles in the true sense.

6. I agree with Wells that the hæmatogenous hypothesis advocated by Rosenow (1915) and by Poynton and Paine (1911) has no support from the experimental results on rabbit; at least by using doses of bacteria which would certainly be dangerous to the human subject. Extremely concentrated bacterial emulsions were not tried.

7. The hypothesis put forward by Wangensteen (1937) and his co-workers demonstrating the secretory function of the appendix is supported from my experimental results.

8. My experimental findings are in agreement with the enterogenous hypothesis advocated by Aschoff (1933) as far as the ætiology of acute appendicitis is concerned. The actual infection of the mucosa is, Aschoff holds, independent of any trauma; it occurs, for example, distal to and not in the immediate neighbourhood of a focus of obstruction. It seems to be due to an increase of virulence of the bacteria normally present in the lumen. How this increase of virulence is brought about is quite uncertain, but it depends largely on stagnation of contents. It may be pointed out here that Aschoff attributes stasis only as the all important factor and does not think that a break in mucosal barrier as contended by Wells to be necessary in the causation of acute appendicitis.

The ætiology of chronic appendicitis is still obscure. I have been unable to produce this experimentally and the literature on this subject is also very scanty. Whether this is due to enterogenous infection, or of hæmatogenous origin, one cannot say with conviction. It is this aspect of the disease that shakes the foundations of both the ardent enterogenous and rather out of date hæmatogenous schools.

Summary

1. A brief review of the various hypotheses about the ætiology of appendicitis is given.

2. Experimental observations were made on fifty young adult rabbits. The main experimental findings with illustrations are given.

3. There was no evidence found to support the hæmatogenous origin of acute appendicitis.

4. Acute appendicitis is undoubtedly due to complete obstruction of the lumen of the appendix either by a constricting ligature or large foreign body. Mucosal damage is not a necessary factor.

5. The organisms cultured from diseased appendices of rabbits were similar to those of normal appendices showing that infection is intrinsic in origin.

6. A histological picture identical to chronic appendicitis in the human being was produced by a crushing trauma to the appendix localized only to the site of injury.

7. Unusual bends or twists of the appendix, repeated daily intravenous or intraluminal injections, of living and virulent streptococci, over a duration of a month in some instances, produced no gross or microscopic lesions confined to the appendix. The rabbit appears to be quite immune to hæmolytic streptococci isolated from the throats of patients suffering from an acute streptococcal infection.

8. Although the ætiology of acute appendicitis is proved to be obstruction, the ætiology of chronic appendicitis is still uncertain.

EXPLANATION OF PLATE XXVIII

Figs. 12 and 13.—Normal rabbit's appendix.
(*a*) Mucosa.
(*b*) Submucosa.
(*c*) Muscle and serosa.

Fig. 14.—Acute appendicitis due to obstruction.
(*a*) Necrosed mucosa and atrophy of submucosa.
(*b*) Serous coat infiltrated with fibrin and leucocytes.

Fig. 15.—Acute appendicitis obstructive.

Fig. 16.—Magnified area (A), figure 15, shows necrosis and cellular infiltration of mucous membrane.

Fig. 17.—Magnified area (B), figure 15, shows polymorphonuclear infiltration of serous coat.

EXPLANATION OF PLATE XXIX

Fig. 18.—Crushed areas of appendix (X) with a hæmostat. Localized areas of chronic inflammation.

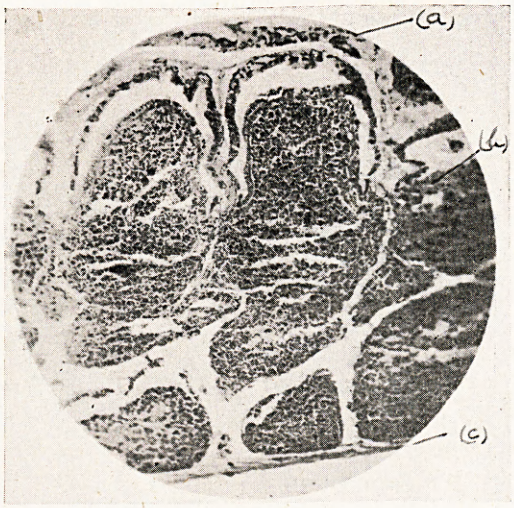
Fig. 19.—Crushed area of appendix (A) shows atrophy of mucosa, fibrosis in submucosa, muscle and serosa.

Fig. 20.—Area (1), figure 19, magnified shows atrophy of mucosa, cellularity and vascularity of submucosa, eosinophils present. (X) Submucosal vessel shows medial hyperplasia.

Fig. 21.—Area (2), figure 19, shows fibrosis and cellularity of submucosa. (X) Submucosal vessel shows medial hyperplasia.

Fig. 22.—Area (3), figure 19, shows fibrosis, cellularity of serous and muscle coats.

Fig. 23.—Normal serous and muscle coats in comparison.



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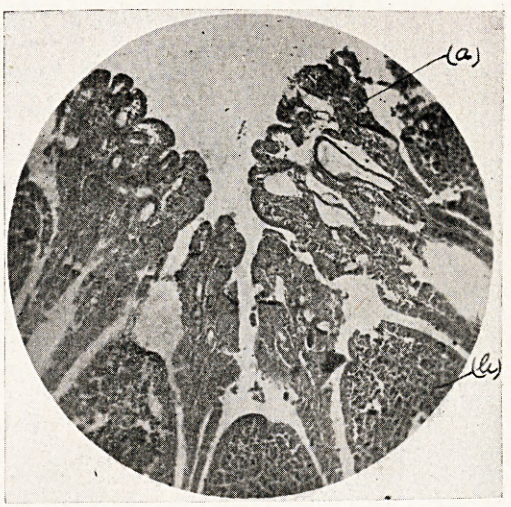
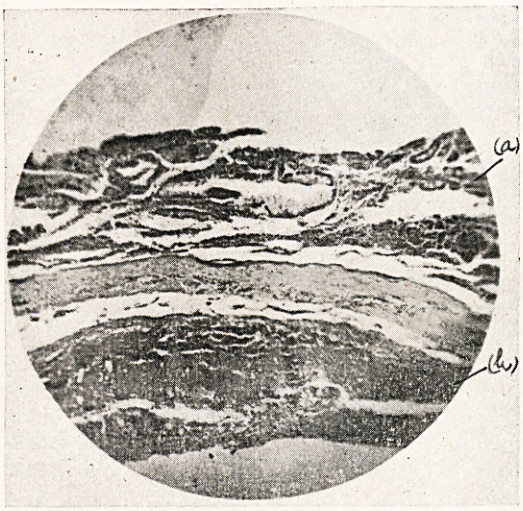


Fig. 13



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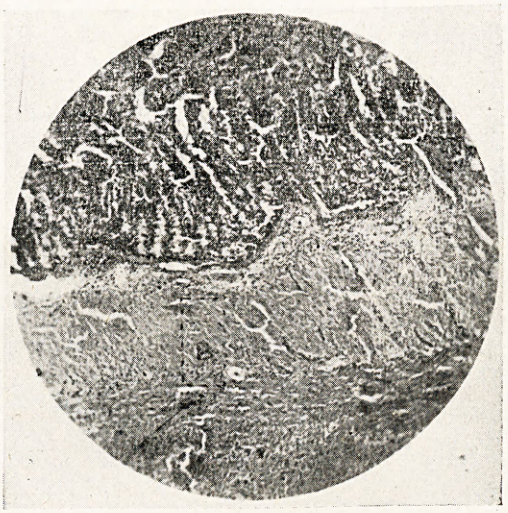

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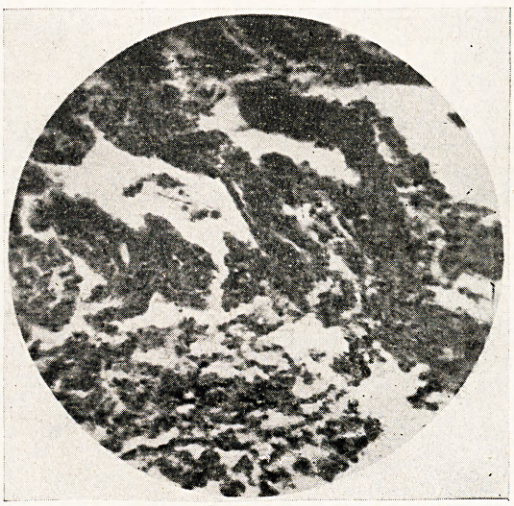

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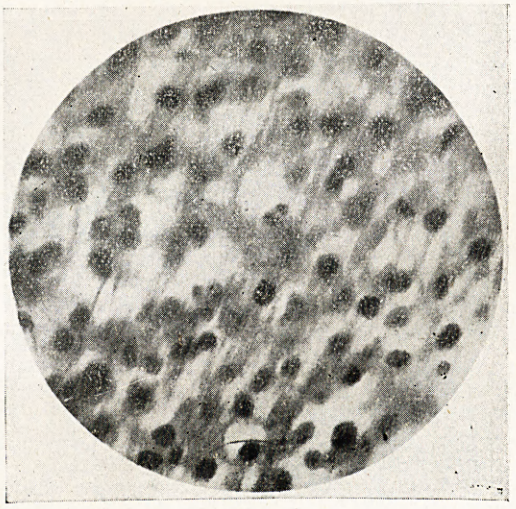

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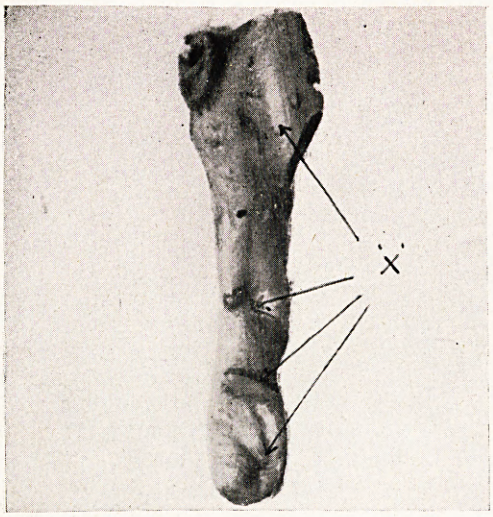

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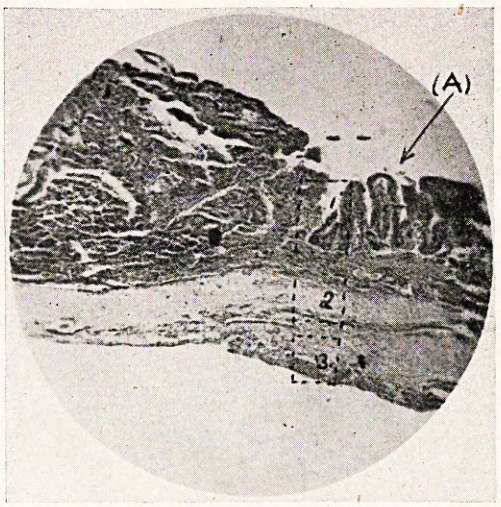

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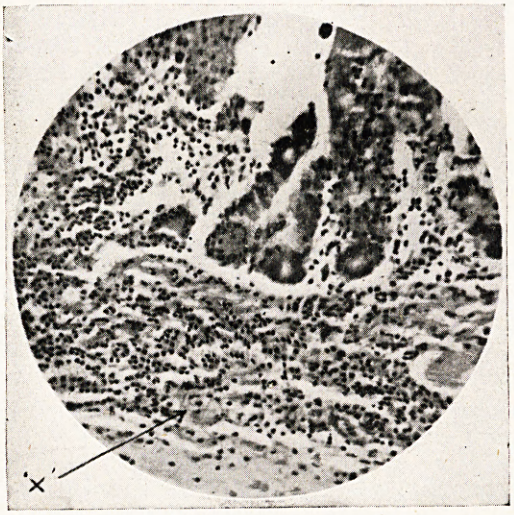

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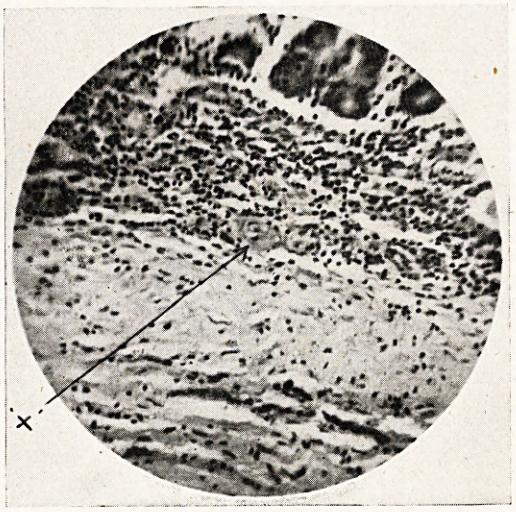

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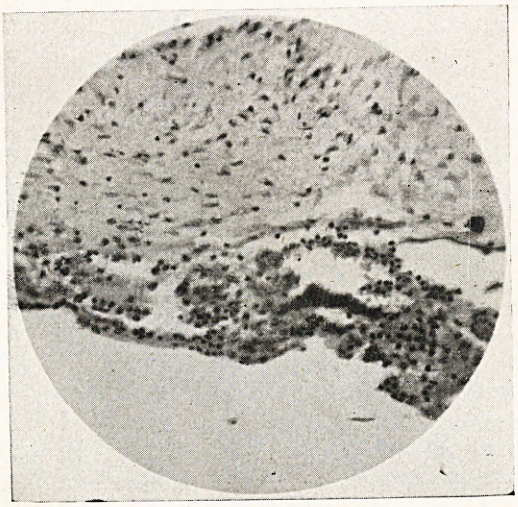

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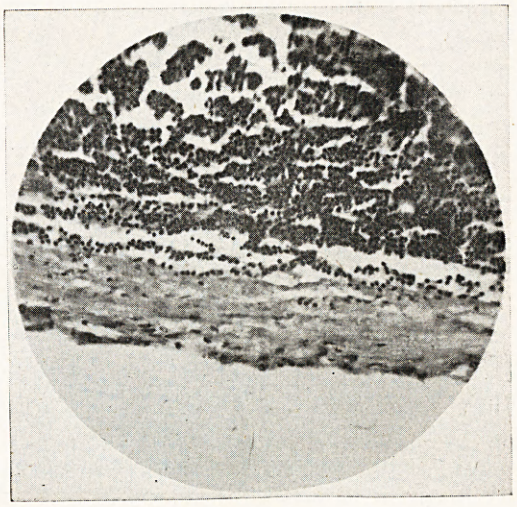

Fig. 23.

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HISTOPATHOLOGICAL CHANGES IN LIVER IN CONGESTIVE HEART FAILURE

(STUDY BY NEEDLE BIOPSY)

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THE usual textbook description of the changes produced in the liver in chronic venous congestion, the so-called nutmeg liver, are based on the post-mortem findings which obviously could not depict an early picture. The purpose of the present investigations was to study the histopathological changes produced in the liver in ward patients showing various grades of congestive heart failure.

Mallory (1911) demonstrated focal hæmorrhagic necrosis in many livers with severe passive engorgement. Lambert and Allison (1916) in their review of 112 cases from literature, in which chronic venous congestion of the liver was most marked, described in detail many variants from the usual histological picture. Some of their cases showed fatty changes rendering the centre of the lobule yellow with a surrounding red ring as a result of hyperæmia. Other cases showed regeneration of liver cells in the periphery of the lobules. A few cases were conspicuous by changes in the reticular and collagenous skeleton. Eppinger (1920) found bile thrombi in the bile ducts of some of his cases. Boland and Willius (1938) described three general groups of histopathological changes in cardiac livers.

Katzin, Waller and Blumgart (1939) found that in 286 cases, in which death was due to heart failure, the incidence of hepatic fibrosis was three times as great as in 1,714 control necropsies. The incidence and severity of fibrosis increased with the duration of right heart failure. Garvin (1943) observed 35 cases of cardiac cirrhosis among 790 autopsied patients in whom heart disease was the chief cause of death; while Koletsky and Branebee (1944) reviewed 4,200 autopsies and found 30 such cases for their study. In both these studies cardiac cirrhosis occurred essentially in patients with rheumatic heart disease. It was less frequent in hypertensive patients and rare in other ætiological forms of heart disease except chronic constrictive pericarditis. Both authors came to the conclusion that repeated episodes of decompensation favour the development of the lesion.

Costero and Moguel (1947) in a paper read before the second Inter-American Congress of Cardiology have described the histological changes in the liver during congestive heart failure passing through the following stages :— (*a*) congestion of the central venules with intense anoxia of the reticular endothelium forming the wall of sinusoidal blood capillaries; (*b*) hyperplasia of the reticular endothelium forming the wall of sinusoidal blood capillaries; (*c*) elaboration of precollagenous fibres by this hyperplastic reticular endothelium; (*d*) intense compression of the trabeculæ through spontaneous retraction of the recently formed fibres with collapse of the intratrabecular bile capillaries and compression atrophy of the liver cells; (*e*) fragmentation of the trabeculæ into isolated cells; (*f*) reabsorption of the isolated atrophic cells.

Needle Biopsy of the Liver

The twelve cases selected for the present study were carefully prepared for the needle biopsy of the liver in view of the profuse bleeding from the site of the puncture in chronic venous congestion reported by Hoffbauer (1947). The bleeding, coagulation and prothrombin times of each patient were determined and Kapilin 5 mg. intramuscular injections were given the previous evening and on the morning of the biopsy as a routine. The danger of the symptoms of acute heart failure supervening after the biopsy was realized during the initial part of the investigations; thereafter it was made a rule not to undertake the biopsy unless the patient was completely digitalized. The details of the preparation of the patient, puncture of the liver and after care have been described by Wahi (1946). Vim Silverman needle was used for liver biopsy.

The details of the histological findings along with very brief case reports are given below :—

Case Reports with Histological Findings of Biopsy Tissue

Case 1.—R. P., 50 years, Hindu female, on admission to hospital complained of cough, duration 5 years; shortness of breath, duration 1 year; and œdema of feet, legs and abdomen, duration 1 month. She was diagnosed 'Chronic bronchitis and emphysema with congestive heart failure'. She gave a history of two previous