Thesis entitled

# ANTEMORTEM THROMBOSIS IN STILLBIRTHS, NEONATES, INFANTS AND CHILDREN, WITH PARTICULAR REFERENCE TO DISSEMINATED FIBRIN THROMBO-EMBOLISM,

submitted by

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## SYNOPSIS

This thesis reports the results of histological investigations into the occurrence, incidence, and distribution by organs of thrombosis in stillborn infants, neonatal deaths and deaths among infants and children. Sixty-eight cases showing antemortem thrombosis are recorded and a further three cases of thrombosis in relation to malignant tumours are illustrated. Particular attention has been paid to stillbirth and neonatal deaths, which tend to exhibit thrombi which are rich in fibrin. This finding is illustrated well, and can be compared with the findings in infants and children showing antemortem thrombi. These latter tend to be mixed thrombi, containing corpuscular elements as well as fibrin. The high incidence of hepatic thrombi particularly in stillborn infants, but also to a lesser degree among early neonatal deaths, (i.e. infants living less than 48 hours), suggests that the clotting process was initiated in the placenta.

These two conclusions, namely (1) that the clotting episode is initiated in the placenta, and (2) that the thrombi are rich in fibrin, lend support to Schneider's hypothesis regarding "obstetric shock" in the mother, which states that the clinical picture of "obstetric shock" can be explained by the

sudden release of thromboplastin of decidual or placental origin (these two tissues being extremely rich in this substance), into the maternal circulation. The results reported in this thesis suggest that placental thromboplastin is also capable of entering the foetal circulation. The reported cases illustrate various aspects of thrombosis and embolism in several organs particularly in the liver, lung, adrenal gland, brain, and spleen and the results of the temporary bleeding state which can ensue. The fact that this can occur without any apparent maternal upset suggests that less thromboplastin is necessary to cause foetal death than maternal death, and this would be expected.

A survey of fibrinogen levels has been carried out in over 400 infants, and the results suggest that one of the essential features of the histological picture illustrated in the cases recorded is that these babies possess a high fibrinogen level before the clotting episode occurs.

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VOLUME I.

# I. INTRODUCTION

"The life of the individual commences with the fertilization of the ovum and progresses without any serious break from that time onwards; the change of environment incidental to expulsion from the uterus is in no way fundamental, scarcely more so than getting out of bed; true it entails some minor adjustments, but these creep in gradually; such as the closing of the ductus arteriosus and the foramen ovale." (Barcroft 1946).

The fundamental cause of many stillbirths and neonatal deaths remains unsolved. It seems very unreasonable that a foetus should die suddenly in utero, or even during delivery without anything to account for its death being found not only at post-mortem but also on microscopical examination later. The same remark applies to many neonatal deaths. While infection can be demonstrated in a large proportion of cases, the clinical impression, which is supported sometimes by the histology of the tissues, is that the infection is really terminal and that for some reason the child's condition was never satisfactory from the time of birth.

It is apparent from the "historical review" in the next section that many people have tackled this problem previously but have failed to find an important link.

My opportunity arose from the local experience of three members of the Pathology Department of the University and Western Infirmary (Johnstone and McCallum 1956; and Anderson and Johnstone 1956). This brought home to me the existence of the condition of hypofibrinogenaemia in pregnancy which had been established as an entity by Schneider (1951) in the 1940s. In this condition, there is a sudden release of thromboplastin of decidual or placental origin into the maternal

circulation, usually associated with abruptio placentae, and this results in widespread intravascular coagulation. This occurs mainly by the time the blood has reached the pulmonary circulation and, if fatal, can be demonstrated as widespread capillary fibrin thrombi. A small quantity may overflow into the systemic circulation to affect other organs. If not immediately fatal, the mother is depleted temporarily of blood clotting factors and she may then suffer from uncontrollable antepartum, intrapartum, or postpartum haemorrhage.

This is a situation which is also applicable to the baby which dies in utero, or which dies during or shortly after birth.

From the academic point of view it is important to know whether or not this thromboplastin is capable of entering the foetal circulation. If a survey of a reasonable number of infant deaths for antemortem intravascular fibrin is negative, then it may be assumed that maternal thromboplastin is incapable of entering the foetal circulation as easily as it may do in regard to the maternal circulation. This fact would be important to know, but not very exciting from the point of view of reducing further the stillbirth or neonatal death rate.

To find one infant, a stillbirth or neonatal death,

showing frank antemortem fibrin thrombosis with a similar pattern to that illustrated in fatal human cases and in experimental examples, would, making allowance for the differences in the maternal and foetal circulations, be sufficient to sustain the thesis that thromboplastin of decidual (maternal) or placental (foetal) origin is capable of entering the foetal circulation and of causing foetal death. This would be a fresh step forward.

Thirty-six cases showing this feature (Cases 1 - 9, 11 - 18, 20 - 23, 25 - 38, and 50) are reported in this thesis. This number allows a great deal more scope with regard to the variations by which such a pathological process may reveal itself clinically and pathologically. It is not considered that all possibilities have yet been unravelled, and further experience is yet required in this field before a complete picture will be available. It is apparent however that this process of disseminated thrombo-embolism is found in about 1 in 11 stillbirth and neonatal deaths, and is responsible entirely or partly for death in about 1 in 20 cases. This finding issues a fresh challenge to the obstetrician, paediatrician and pathologist alike.

# II. HISTORICAL REVIEW

"One is apt to think of life as beginning at birth with the child's first breath: this, of course, is biologically quite erroneous." (Ballantyne 1922).

The problems relating to stillbirth and neonatal death have occupied the minds of obstetricians, paediatricians and pathologists for many years. The obstetrician has been concerned in case treatment employed by him towards the mother may be responsible for the death of the infant, and he is continually trying to improve his technique of antenatal, intrapartum and postpartum care in order to reduce maternal and foetal morbidity and death. The paediatrician has become concerned with the newborn infant for two reasons. Firstly, by doing so, he allows the obstetrician's full attention to be focussed on the mother's postpartum condition; and secondly, it has become recognised that the physiology and pathology of the newborn infant are different from those in adult life, and as such, it becomes the proper domain of the paediatrician who may be required to look after the infant at any future date in childhood. A long time ago, his attitude may have been a rather resigned one since the infant may have been in a very precarious state at birth as a result of obstetrical manoeuvres. However, as the years passed and clinical assessment of these cases became more accurate,

interest livened and the standard of paediatric care improved. In the cases of stillbirth and neonatal death, the pathologist has been expected to examine the bodies and find why the infant died, and it is satisfying to him to be able to demonstrate haemorrhage, or infection, or congenital anomalies. Such cases however, are not frequent and in recent years many cases are explained on the basis of prematurity, foetal asphyxia, or atelectasis: but why the prematurity, why the foetal asphyxia, and why the atelectasis ? Again with the passage of years and with increasing experience, explanations have been advanced, some of which have stood the passage of time. Today, we have almost reached an impasse unless new methods are employed.

In 1891, Spencer reported the findings in 130 autopsies performed on fresh stillborn foetuses. He concentrated on the incidence and distribution of the visceral haemorrhages commonly seen in stillborn infants. This was a very systematic review reporting gross pathological findings with minimal histology. In the course of it he noted four cases of thrombosis. They all involved the superior sagittal sinus. Haemorrhages and haematomas of the organs and tissues were much more common. He suggests three possible factors concerned in the aetiology of these visceral haemorrhages:- (1) thinness and weakness of the vessel walls, (2) alteration of the blood rendering

it prone to escape, and (3) rise of blood pressure as a result of asphyxia. Spencer did not believe that the second possibility was very important, and at the same time pointed out that congenital syphilis did not weaken the vessel walls at this stage in its course. He was concerned primarily with the obstetrical abnormalities predisposing to stillbirth and showing the postmortem features of visceral haemorrhages; he found them to be most commonly associated with breech presentations, premature rupture of the membranes, and artificial dilatation of the parturient canal.

In 1902, Ballantyne's textbook appeared and gave a concise account, with accurate coloured drawings, of foetal pathology. It is interesting to note from it that the process of autolysis following intra-uterine death had been receiving considerable attention in the latter half of the 19th century (pp. 420 - 425). On p. 374 there is an interesting observation on antenatal atheroma in which he cites a case reported by Durante in 1899. From Ballantyne's description of this case, today we would probably call it metastatic calcification of the media of the great vessels. However his opening sentence is worthwhile quoting in full:- "Little is known regarding diseases of the blood vessels in foetal life, save in connection with the changes which they undergo in syphilis." It is

strange that such a remark has not been pursued systematically since then either by Ballantyne himself or by others.

Little in the way of reviews appeared after this for 20 years, although clinical "oddities" were occasionally reported in the literature. Some of these are pertinent to the present thesis, but reference will be made to them later.

Thereafter, Margaret Warwick (1921) reported her findings in 200 infants who were stillborn or who died within one week of birth — thus eliminating to a certain extent the occurrence of postnatal infection. Her examinations were most thorough but histological study was lacking. She was unable to explain the infant's death satisfactorily in 24 cases (12 per cent)at least.

At this time there appears to have been a heightened interest in this country into foetal deaths either antenatally or in the neonatal period. Strachan (1922) recorded from the Welsh National School of Medicine, on behalf of the Medical Research Council, the pathology of foetal maceration based on a study of 24 cases. His gross findings were similar to those quoted by Ballantyne (1902) some of whose information goes back to Lempereur (1867) and Ruge (1877). However, Strachan's contribution is important for three reasons:-

(1) he supplemented his gross findings with a histological description, (2) he stated that "maceration is no index of syphilis and is more likely to be associated with maternal albuminuria", and (3) he urged that the placenta should be studied in all cases of intra-uterine death. In the same year, Holland (1922) issued a report on the causation of foetal death. One of his introductory remarks is worth quoting for it may, with a little author's licence, reflect the situation at that time:- "Neglected by the clinician, the dead foetus has in consequence been neglected by the pathologist." His review of 300 stillborn infants is important from several points of view: (1) Holland attempted to minimise postmortem change by keeping the bodies in a cool chamber until autopsy was carried out, (2) he carried out routine bacteriological examination using both aerobic and anaerobic culture of heart blood, (3) histological examination was carried out routinely except in macerated cases, of which there were 133, (4) of the placental states associated with stillbirth, just over half (10 out of 18) were due to abnormally small placentae (i.e. true placental insufficiency) in relationship to foetal size, (5) he, as did Strachan, stated that syphilis as a cause of foetal death had been given an exaggerated prominence,

and (6) cases No. 28 and 48 in his series are recorded as showing areas of liver necrosis. This report along with Browne's (1922) (see below) are the earliest ones I have found on hepatic necrosis in the stillborn infant. In the following year Palmer (1923 - 24) demonstrated the liver of a stillborn foetus showing venous infarction to the Royal Society of Medicine, and this may have been one of Holland's cases for both worked at the London Hospital at this time. These records are important, for my thesis includes one case which is similar to Palmer's from the pathological point of view and others which are similar to Holland's case No. 48. Lastly, Holland cited 32 cases for which he could give no adequate cause for death but he felt that this was due to inadequate investigation. Also in the same year, Ballantyne (1922) delivered an address to the British Medical Association, his subject being "Antenatal, Intranatal and Neonatal Death". In his paper he was quite dogmatic in his attitude towards macerated foetuses. They must have as thorough an autopsy supported by histological and bacteriological examinations as any other foetus required. At the same meeting Browne (1922) discussed 153 neonatal deaths. Over half were traumatic, while 40 per cent were due to infection. In his classification of the

remaining cases he included the heading "toxaemic" under which he quotes one case of hepatic necrosis in a foetus, with eclampsia in the mother.

In 1927, Christine Thomson gave a very detailed account of the pathology of foetal maceration based on a study of 27 cases. While attention has been paid to the gross and to the histological features, there is little doubt that this was the best histological review to date on this subject.

Following this, Cruickshank (1930) reported to the Medical Research Council on 800 neonatal deaths at the Royal Maternity and Women's Hospital, Rottenrow, Glasgow. He was no doubt encouraged in his work by Professor Robert Muir (as he then was) who was a member of the Council of the M.R.C. at this period. Of these deaths, 540 (67.50 per cent) were due to conditions associated with delivery, 238 (29.75 per cent) were due to some infective condition, and 22 (2.75 per cent) were due to developmental defects and anomalies. Congenital syphilis was established in less than 1 per cent of cases. Many of the nonproven cases appear to have been in retrospect examples of haemolytic disease of the newborn. The occurrence of visceral haemorrhages receives as much attention in this report as in many previous reports, but in addition, Cruickshank recorded thrombosis as an occasional finding. Among his 800 cases,

he noted it once only in the lungs. In connection with the central nervous system, he noted that intracranial bleeding is often associated with toxaemia of pregnancy in the mother. The bleeding is most often intraventricular, but there is sometimes an extension into the brain substance, and in some cases the bleeding arises in or under the meninges. Further, renal vein thrombosis with infarction occurred in 15 cases. Section 10 of Cruickshank's report has a strong bearing on the present thesis, and he discusses in this the occurrence of visceral haemorrhage and thrombosis. Visceral haemorrhage occurred in 10 per cent of cases, the lung being most frequently involved (28 out of 81 cases) and followed in order by the adrenal glands, kidneys and liver. In only 10 cases was the mother in normal health. In 32 cases, the mother gave a history of cardiac or pulmonary disease, and in 20 cases she had toxaemia of pregnancy. To quote the last sentences of this paragraph:- "Reference has been made to the connection between thrombosis and toxaemia. These haemorrhagic lesions appear to be of the same origin, but the mechanism of their production is not understood. There is at present no information available on which a reasonable hypothesis can be based." He next reports that there were 30 cases of thrombosis in his series, the

incidence being:- intracranial sinuses - 18 cases, kidneys - 15 cases, lung - 2 cases, mesentery - 1 case. Eleven of the mothers suffered from toxaemia of pregnancy, while in most of the remainder the infant was considered to be suffering from septicaemia.

This problem of infantile thrombosis had obviously been given a great deal of thought by Cruickshank as the following paragraph shows. It is quoted in full from his report:-

"It would appear that in a certain proportion of cases of toxaemia of pregnancy, and particularly in eclampsia, there is a tendency to the occurrence of thrombosis in the viscera and in the intracranial sinuses such as may be found in the mother in these states. Similar thromboses have been noted in the stillborn infants of eclamptic and toxaemic women, but it is surprising to find the incidence so inconstant. Indeed, the relative infrequency of thrombosis in the infants of eclamptic women suggests the existence of some other factor in the production of these lesions. It is possible that this factor may be sepsis. In the majority of cases of thrombosis occurring in the present series definite septicaemia was found but here again the explanation is not quite obvious, for the proportion of septicaemic cases showing thrombosis is small.

It might be supposed that the incidence of thrombosis would be greater in the small, feeble and emaciated infants than in strong mature ones, but the figures obtained from this series do not bear this out. The explanation of the factors determining the onset of thrombosis in the newborn is, therefore, still incomplete. Further knowledge regarding it is not likely to be obtained except from the careful study of such cases during life."

The above paragraph states lucidly the problem which the present thesis tries to solve.

Other points from Cruickshank's report include:- (1) sections of kidneys showing renal vein thrombosis were stained for fibrin, and occasionally showed very little or none, and as a result he recognised the existence of platelet thrombosis — examples of which are incorporated in the present thesis; (2) he compared neonatal renal vein thrombosis and maternal renal cortical necrosis, in both of which minimal intravascular fibrin is found; (3) pulmonary thrombosis was rare; (4) pulmonary haemorrhage was common and found most frequently when the mother had toxaemia of pregnancy, and it is possible that the two conditions may be related to some extent; and (5) intracranial thrombosis seemed to show a more definite association with marasmus and with birth

asphyxia than with toxaemia and sepsis, although sepsis is sometimes a factor in the aetiology of intracranial thrombosis.

The next major review of the pathology of stillbirth and neonatal death was by MacGregor (1946) in which she recorded the results of 1053 cases — 435 being stillbirths and 618 being cases of neonatal death. Her four main pathological groups consisted of defects of development, asphyxia, intracranial haemorrhage and infective diseases. Intracranial haemorrhage showed an equal incidence among stillborn and live-born children but the incidence of the other groups varied from the stillbirth group to the neonatal group. It is interesting that even with such a painstaking survey, 10 per cent of all stillbirths remained unexplained, while 1 per cent of neonatal deaths remained so.

In spite of all the exhortations cited previously it is disconcerting to note that when Morrison's book on Foetal and Neonatal Pathology was published in 1952, it stated on p. 102 that "autopsies are of very limited value in these infants (antepartum stillbirths). The foetus is usually macerated and little can be learnt from it, and the placenta undergoes changes with cessation of the foetal circulation." The main value of examining such infants at present seems

to be to exclude congenital abnormalities, syphilis and rhesus incompatibility. Morrison goes as far as to suggest that 40 per cent of all stillbirths are not explained by autopsy. On page 326, he states that thrombosis is "much more common than at any other period of life. It often depends on circulatory conditions favouring stasis and may be contributed to by dehydration and haemo-concentration. Thrombosis may occur without demonstrable infection. Often any infection associated with thrombosis is a low-grade reaction and occurs in areas so remote from the affected blood vessels that its significance may be debatable. Nevertheless, it will usually prove useful to regard intravascular thrombosis as a symptom of infection until the opposite is proven."

More recently, Baird, Walker and Thomson (1954) attempted to classify 1008 stillbirth and first week deaths in Aberdeen occurring over the last 15 years. In this series, a clinical classification was devised, and even so, one out of every three deaths was "clinically unexplained", and 60 per cent of them (forming 19.7 per cent of the total series) were associated with prematurity of unknown aetiology, in spite of the Aberdeen infant mortality rates being lower than the national figures.

In 1956, Bound, Butler and Spector reported a pathological survey of 337 consecutive autopsies in stillborn, prematurely live-born, and mature live-born infants. From this survey, these investigators were able to identify a condition which they named the "pulmonary syndrome of the newborn". This occurs particularly among premature infants born by Caesarean section, who formed 10 per cent of neonatal deaths. The syndrome however was found in 27 per cent of all neonatal deaths. The infants were in poor condition at birth with difficulty in establishing respiration in 50 per cent of cases and the rest developed the condition within 12 hours of birth. Blood-stained frothy fluid pours from the mouth and nostrils. About one third developed convulsions, or cerebral irritation without convulsions. Histological examination reveals a combination of resorption collapse with atrial distension, hyaline membrane formation, intra-alveolar haemorrhages, and pulmonary oedema.

From this pilot survey there developed a country-wide survey, known as the Perinatal Mortality Survey sponsored by the National Birthday Trust, and held from March to May inclusive in 1958. The detailed results of this very thorough survey have yet to be reported. This survey involved

obstetricians, midwives and pathologists, with histological reports being issued on dead infants subjected to postmortem.

This brings the survey of stillbirth and neonatal death up to the present time, but there is an important line of investigation concerning "obstetric shock" affecting the mother which requires mention for it would seem to be appropriate to the present thesis. Schneider (1950, 1951) in Detroit started to study this condition of "obstetric shock" in 1946. In the course of these studies he showed that uterine decidua and placental tissue during the first trimester of pregnancy possessed intensely strong thromboplastic activity. If this thromboplastin were released into the maternal circulation widespread fibrin thrombi occurred mainly in the pulmonary circulation but also in some of the systemic organs. This situation led to shock, and possibly death. If death did not result, the mother's blood was so depleted of clotting factors that the blood would not clot for a time and therefore a bleeding tendency ensued. This showed itself usually as widespread uterine bleeding before, during or after labour according to the time of the onset of the episode. Schneider's series of reports have achieved world-wide acceptance for the high standard of experimental

work and observation, for his clinical observations concerning such cases coming under his care, and for the rational methods of treatment which can now be applied to a condition which was formerly not understood. Indeed, other investigators (such as McKay, Merrill, Weiner, Hertig and Reid 1953) are investigating the possibility of the same mechanism being responsible on a less dramatic scale for the clinical and pathological features of toxaemia of pregnancy. In pursuit of the above hypothesis, Johnstone and McCallum (1956) reported a typical case of death from obstetric shock and demonstrated widespread fibrin thrombi in the lung capillaries, in the renal glomerular capillaries and in the adrenal glands and ovaries. A fatal case in an iso-immunised doe rabbit during labour was reported by Anderson and Johnstone (1956).

By common usage the condition is known as "hypofibrinogenaemia of pregnancy", for at the height of the condition the mother's blood shows very reduced amounts of fibrinogen, most of it having been converted to fibrin intravascularly. This term is very inaccurate for not only is fibrinogen depleted, but so are all other blood clotting factors. More recently, Sharp, Howie, Biggs, and Methuen (1958) have investigated this syndrome in four cases from the haematological aspect. They

prefer to use the term "defibrination syndrome of pregnancy". This term is also unsuitable for two reasons:- (1) it lays too much emphasis on the fibrinogen to fibrin reaction, and (2) the condition is one of defibrinogenation rather than one of defibrination. By employing a large battery of tests, these investigators found (a) that there may be a qualitative alteration in the reactivity of fibrinogen to thrombin, (b) that none of the patients showed fibrinolytic activity in their plasma, and (c) that their results supported Schneider's hypothesis.

None of the terms mentioned above describes the condition accurately. Schneider (1951) offered two terms, the first being preferred by him —— fibrin thrombo-embolism, or disseminated intravascular coagulation. The first describes the pathological findings accurately — namely thrombi which are simultaneously emboli and are composed almost entirely of fibrin. In his second term the word "coagulation" implies clots with red and white blood corpuscles incorporated. This is not an accurate description of the features noted. The term preferred by me is one also used by Schneider on another occasion. It is "disseminated fibrin thrombo-embolism of pregnancy", although it is admitted that this too has its deficiencies.

To summarise this review of the past literature, there have been many attempts at classifying and understanding the causes of stillbirth and neonatal death. In 1922 and 1923, Holland, Browne and Palmer recorded separately the occurrence of venous infarction in the liver, and in 1930 Cruickshank recorded various thrombotic states in stillborn foetuses and in neonatal deaths but failed to find an explanation for these. Morrison in 1952 also noted thrombosis in infants and reluctantly accepted that most bear some connection with infection.

In recent years Schneider has elucidated the nature of "obstetric shock", as being due to disseminated fibrin thromboembolism, initiated by the release of thromboplastin into the maternal circulation from the vicinity of the placental site.

Could this thromboplastin enter the foetal circulation ? Or, could the incident which releases thromboplastin into the maternal circulation also cause thromboplastin to become activated in the foetal circulation to cause foetal death from thrombosis ? Is there a connecting link between these two lines of investigation ? This thesis is concerned with Cruickshank's plea (1930):-

"Further knowledge regarding it (thrombosis in the newborn) is not likely to be obtained except from the careful study of such cases during life."

# III. MATERIALS AND METHODS

1. Postmortem Examination. This was carried out in the normal fashion, being modified to suit the varying circumstances of each case. A full description of the procedures involved was given by Baar (1946) and requires no amplification here.

2. Histological Examination. Some of the retrospective material studied is deficient in the number of blocks of tissue taken for examination. Current material had 3 blocks of lung, and one each of heart, thyroid gland, lower oesophagus, liver, pancreas, spleen, kidney, adrenal gland, salivary gland, pituitary and medulla. Skin was often studied and other lesions necessitated additional blocks of tissue.

Tissue from babies are very liable to show "formalin deposit" if ordinary acid formalin fixation is used, and for this reason 10 per cent neutral buffered formol-saline was preferred as the primary fixative. After 24 hours, the blocks were trimmed and were fixed further in formol-corrosive before being processed.

Sections were cut, and stained routinely with Mayer's haemalum and eosin. The method is so routine and well known that further description is unnecessary.

Duplicate sections from every block of tissue were cut and stained for fibrin using Lieb's phosphotungstic acid haematoxylin.

Lieb's P.T.A.H. Stain (1948)

Preparation of Stain. Dissolve 500 mg. of haematoxylin in a little water with the aid of heat. Meanwhile dissolve a little phosphotungstic acid ("AnalaR") in the rest of the 500 cc. of water with the aid of heat and then add this to the haematoxylin solution. Bring the mixture to the boil cautiously and add 400 mg. of red mercuric oxide. Remove the vessel from the flame, and shake it to dissolve the mercuric oxide. Set aside to cool. Add 2 drops of 10 vol. hydrogen peroxide. Wait for several days before using the stain, which can be used repeatedly.

Staining Method. The staining method can be adapted easily for bulk staining of slides by setting up a series of staining dishes similar to those employed for routine H. and E. staining.

1. Sections brought to water through xylol and alcohol baths.
2. Lugol's iodine and hypo in order to remove mercury deposit.
3. 0.5 per cent potassium permanganate for 3-5 minutes.
4. Rinse in water.
5. 5 per cent aqueous oxalic acid solution for 3-5 minutes.

6. Rinse quickly in water.

7. Phosphotungstic Acid Haematoxylin overnight for 12-24 hours.

8. Wash in water.

9. Differentiate sections individually in 95 per cent alcohol.

10. Dehydrate in further bath of 95 per cent alcohol, then absolute alcohol, and clear in xylol.

11. Mount in D.P.X.

Result

| | |
|---|---|
| Nuclei and Mitochondria | - deep blue |
| Fibrin and Muscle | - deep blue |
| Red blood corpuscles | - blue |
| Neuroglia | - blue |
| Collagen and Elastica | - red-brown |

3. Micro-Kjeldahl Method for Fibrinogen Estimation

The method employed is that described by King and Wootton (1956). It is important that the same procedure is used throughout with each specimen, so that the results can be compared. I shall not give a detailed description of the method but I shall add a few remarks to augment the description as given in the above reference. (a) I adhered strictly to the time of 2 hours incubation for maximal clot production. (b) The clot was

extracted by winding on a glass rod, was washed in physiological saline and dried on filter paper three times to rid it of any excess plasma protein. (c) The digestion time of 2 hours was strictly adhered to, and a glass bead was added to the digestion mixture to aid agitation and to minimise explosive bubbling. (d) After the contents of the digestion flask were added to the distillation chamber of the micro-Kjeldahl apparatus, the neck of the digestion flask and the bulb of the flask were rinsed three times with small volumes of glass distilled water, these washings being added to the distillation chamber. (e) The reservoir and glass stopper leading to the distillation chamber were washed three times with small quantities of distilled water before distillation was begun. (f) By using a timing clock, I controlled the time of distillation from the moment a condensate formed at the upper end of the cooling tube to 5 minutes, the lower end of the cooling tube being under 5.0 ml. of boric acid solution in a 50 ml. conical flask at this time, and a further 1 minute was allowed with the conical flask lowered so that the lower end of the cooling tube could be washed clean by further distillate which consisted by this time of steam only. (g) The contents of the conical flask contained ammonia

derived from the digested fibrin clot, and I preferred to use N/100 sulphuric acid for titration rather than N/70 as recommended by King and Wootton (1956). (h) 0.07 ml. of Tashiro's indicator was used.

By paying close attention to these points as well as those detailed by King and Wootton, a standard procedure was employed and sources of errors were minimised.

4. Rapid Fibrinogen Method of Stirland (1956). This method depends on the fact that in neutral solution fibrinogen precipitates at 56°C. while other plasma proteins precipitate at 60°C. I adhered strictly to the original instructions of Stirland. My neutral solution, like Stirland's, was 1 per cent sodium chloride. I used the "AnalaR" preparation, and each Winchester of this stock solution was checked against standard silver nitrate solutions to verify that the concentration was indeed 1 per cent. 0.2 ml. plasma was added to each of two test-tubes containing 3.0 ml. of 1 per cent sodium chloride solution. One was placed in a 56°C. water bath for 15 minutes, using a timing clock to control this, while the contents of the other tube acted as the control. The optical density of each sample was determined against its own control on a "Unicam S.P. 600" spectrophotometer at 650 mμ using 1.0 cm. calibrated glass

cells. Stirland compared his optical density values with that of a standard barium sulphate suspension, but I found this to be unreliable (Boyd and Sommerville 1960) as have Maclagan (1951), Ducci (1947) and Varley (1958). I therefore could not accept the calculations reported in the latter part of Stirland's article, although, as I shall show, the method itself is sufficiently accurate for my purposes, the scatter being 2 per cent, the same as with the micro-Kjeldahl method. It was necessary therefore to start afresh with this method and to produce my own graph, correlating optical density values directly with micro-Kjeldahl values, and omitting the intermediary of standard barium sulphate suspensions.

5. Plasma Paper Strip Electrophoresis. The electrophoresis of plasma is technically not as satisfactory as that of serum for the fibrinogen band tends to overlie, sometimes completely, that of gamma-globulin, and this makes the calculation of the quantity of these substances present rather difficult. Occasionally however, one obtains a strip in which the fibrinogen band is clearly demarcated, and under these circumstances, plasma electrophoresis may be used to check the other two methods described above. This was done on random samples in this series and close correlation was obtained between

all three methods.

When using this method, the total plasma protein was determined by the conventional biuret method, with 0.2 ml. plasma. The final readings were made on an "Eel" colorimeter and a calibration curve prepared with "Armour's" protein standards.

The electrophoresis method employed is as follows. Specimens were run in pairs and each specimen was run twice, so that four strips were run simultaneously. Four strips of Whatman No. 3 MM. filter paper 4.0 cm. wide and 36.0 cm. long were suspended over a glass ridge pole, and their ends draped into electrode baths containing barbitone buffer at pH 8.6. The strips were soaked evenly with buffer, and thereafter 0.02 ml. plasma was applied evenly along a previously drawn straight pencil line 3.0 cm. long lying in the centre of the paper and along the apex of the ridge. The electrodes were connected to a "Shandon" stabilising power unit, which was adjusted to give 110 volts, and 7 amps., once the current was switched on, and the run took 17 hours.

The wet strips were then suspended carefully on glass rods and dried in a hot air oven at 105°C. for 15 minutes. They were stained in 1 per cent bromophenol blue in a saturated

solution of mercuric chloride in absolute alcohol for 5 minutes, and differentiated by washing in running tap water until background staining was removed. The paper strips were blotted gently and dried in the hot air oven. When dry, the strip was immersed in liquid paraffin for 5 minutes in the hot air oven, removed, and placed in a dessicator jar which was evacuated for $\frac{1}{2}$ - 1 hour so that air bubbles over the paper would be removed. In compliance with instructions, the strip was placed carefully between two glass plates and a graph was constructed of the width and density of the separated protein bands with an "Eel" scanner. Thereafter, by using a planimeter, the total area of the graph above the zero line was found and also the proportion of the total occupied by each protein constituent of the plasma. Since the total plasma protein value has been estimated previously it is now possible to calculate the concentration of each fraction of the plasma protein in g. per 100 ml.

6. Umbilical Vein Blood Specimens. At the time of delivery the umbilical vein is distended with blood and this situation usually persists for 2 - 3 minutes after delivery. Blood was obtained by venepuncture at a point roughly 8 inches (20.0 cm.)

from the umbilicus using a dry, sterile syringe and a wide-bore needle. This site was selected because it was near the point where the midwife cut the cord once it had been tied. The person handling the needle and syringe, and also the cord, had to be scrubbed up before performing this minor procedure during which strict asepsis had to be observed. Having collected an adequate sample of blood, 5.0 ml. were placed in a bijou bottle containing dry anticoagulant (either sodium potassium oxalate, or heparin) and mixed thoroughly. By centrifugation, the supernatant plasma was obtained. Mild haemolysis made no difference to the fibrinogen results, but grossly haemolysed samples, which were rare, were discarded.

7. Non-Clotted Heel Stab Blood Samples. The technique of obtaining an adequate sample of blood from the heel is only acquired by practice. No written description will supplant the experience gained by practice. I found that the most important aid was to use sharp, straight Hagedorn needles each with a good cutting edge. It is difficult to appreciate when a needle is becoming blunt. Since I was performing 4 - 6 heel stabs per day every day, I changed to a new needle routinely every alternate day. It is necessary to scrub up before stabbing

each heel in order to reduce the chances of carrying infection to the infants many of whom were premature, and it is necessary to have all equipment at hand before starting. A sheet of tissue paper is placed below the infant's buttocks and legs to reduce the chances of blood soiling the cot or incubator bed linen. The infant's foot is flexed dorsally towards the front of the leg and the whole is grasped with one hand to leave the conical shaped heel protruding. The skin is swabbed generously with spirit and is dried with sterile cotton wool. The Hagedorn needle is gripped firmly at the middle of the shaft in the same fashion as one grips a pen or pencil, but with the palm of the operator's hand facing upwards and with the cutting edge of the needle facing the operator who is standing at one side of the infant. The tip of the needle is placed against the apex of the conical heel and inserted under the plantar skin of the heel and between it and the plantar fascia until the cutting edge has just disappeared. With a sweeping movement the sharp point of the needle is made to describe a short arc (about $30^{\circ}$) while in this subcutaneous position, without enlarging the skin puncture. This arc usually commences <u>just</u> medial to the midline of the sole of the foot and passes laterally. (The needle point is not near the plantar vessels which are deep

to the plantar fascia). Thereafter, the needle is withdrawn and a generous flow of blood results. By gentle massage it should be possible to maintain a steady flow of blood without clots forming. When the sample has been obtained the heel is washed with water to remove the unavoidable crusts of blood, then with spirit, dried, and a small wisp of cotton wool is left over the heel wound which heals rapidly. The tissue paper is removed and destroyed.

To collect the samples of blood I used Dreyer agglutination tubes measuring 3" x $\frac{1}{4}$" (3.75 x 0.6 cm.) because of their generous lip at the top which aids the flow of blood from the wound into the tube. The tubes were coated internally with silicone and dried, and also contained dry heparin (or oxalate mixture) in the same proportions as used for the bijou bottles (Fig. 1). The Dreyer tubes held 2.0 cu. cm. of blood, and thus 0.1 ml. of injection of heparin B.P. was added before use, and allowed to dry. Immediately before use a glass bead was inserted, and during the collection of the specimen the tube was inverted frequently and shaken to aid mixing between the blood and the anticoagulant. Having collected the specimen a label was applied with the infant's name, case sheet number, and date. Such specimens gave more than 0.5 ml. plasma which

was sufficient for either the micro-Kjeldahl or the rapid fibrinogen method. There was nearly always sufficient extra plasma for plasma electrophoresis if required. An occasional case showed such a low packed cell volume that there was sufficient plasma in this small tube for all three tests. Before each specimen was centrifuged it was "fished" with a glass hook to ascertain that no clots were present. Very early in the series, it was appreciated that haemolysis was absent more often with heparin as an anticoagulant and this substance was used constantly thereafter. If, once the plasma had been tested, a very low fibrinogen value had been obtained the packed corpuscles at the foot of the Dreyer tube were re-examined to exclude the possibility of clot formation having occurred. If clots were found at any time, and this occurred rarely, a fresh specimen was obtained. If there were clots, it could be implied that the baby's blood was not wholly devoid of fibrinogen.

# IV. RESULTS

When Lieb's P.T.A.H. is used as a routine stain, and when sections are scanned with the low power objective lens, (2/3 inch, 16 mm.) intravascular fibrin deposits are found in the minority of postmortems. In this series the incidence is 222 in 755 cases (29.4 per cent). Closer study of these deposits shows that some are obviously antemortem in variety, while others are probably agonal (i.e. still laid down before death, but formed immediately before death), and yet others are postmortem fibrin deposits.

It is as well to attempt a written description of these three varieties, although their features will become more apparent during the course of the illustrations relating to individual cases.

(1) Antemortem Thrombus. The fibrin strands tend to be long, tend to lie along the direction of blood flow, tend to lie parallel to one another if multiple and to be packed together, tend to stain deeply, and tend to show a saddle embolus effect at selected points. All these features suggest that the fibrin has been laid down in vessels through which blood is passing at high velocity. Further proof of their antemortem formation is revealed by ischaemic changes in organs, tissues and cells in the vicinity of such thrombi.

(2) Agonal Thrombus. In this case the majority of fibrin strands tend to lie along the course of a blood vessel but a significant number of strands lie obliquely or transversely in the vessel lumen. The strands are less tightly packed; they may stain deeply or variably, and they may show a saddle embolus effect at appropriate points. These features suggest that they have formed when the blood flow has become sluggish. It should be appreciated however that when thrombi are formed in a child with heart failure or with reduced rate of blood flow for any reason — e.g. certain forms of congenital heart disease or shock — frankly antemortem thrombi may under these circumstances assume the features of agonal thrombi.

(3) Postmortem Thrombus. The fibrin strands in this case are delicate, arranged haphazardly through the thrombus, appear to arise from "knots" of fibrin (probably platelets), and the strands pass centrifugally from one focus to link with other foci of similar size. A few of the major strands may show a tendency to lie along the course of a vessel and this may suggest that the thrombus was really agonal in character. Even after death however a certain amount of movement of blood or of its constituents must take place — e.g. to produce the features of hypostasis — and such

currents may give to postmortem thrombi some of the features of an agonal thrombus. Other postmortem thrombi assume a spiral shape. I interpret this finding as being due to a thrombus forming in a medium sized vessel and, as a result of manipulation of the body later, the thrombus becomes dislodged and slips backwards in the case of an artery or forwards in the case of a vein to lie in a vessel of larger diameter, in which it assumes a tortuous or spiral form.

Study of the antemortem thrombi found in this series of cases shows that they may be of several varieties — pure fibrin, mainly fibrin with a minor incorporation of red or white corpuscles or of platelets, frankly mixed thrombi (not apparently infected), and obviously infected mixed thrombi. It is a point of importance that the first two varieties are found mainly in stillborn infants and in early neonatal deaths, while the last two varieties tend to be found in late neonatal deaths and in infants surviving the neonatal period.

This thesis is based on a systematic histological search for thrombosis in 755 infants who were stillborn (331 cases), who died in the neonatal period (345 cases), or who died in infancy and childhood (79 cases), and came to postmortem examination. Thrombi were found in 222 of these (29.4 per cent)

and were considered to be antemortem in variety in 71 cases (9.4 per cent). The histological findings are supported in two of these cases and in thirteen others by antemortem fibrinogen values, as well as by a survey of fibrinogen values in over 400 infants who did not die.

The following abbreviations are used for the various hospitals:-

R.M.W.H. - Royal Maternity and Women's Hospital, Glasgow.

R.H.S.C. - Royal Hospital for Sick Children, Glasgow.

S.R.I. - Royal Infirmary, Stirling.

Redlands - Redlands Hospital for Women, Glasgow.

## CASE REPORTS

### A. STILLBIRTHS

Among 331 stillbirths there are 10 cases which show significant intravascular fibrin thrombus and fibrin embolism. In six cases, (numbers 1, 2, 3, 4, 7 and 8) the thrombi are believed to have been wholly or partly responsible for death. Another 47 cases show agonal thrombus with or without postmortem thrombus and these are not considered further here. The ten 'positive' cases will be reported in complete detail and in order of increasing maturity of the foetus as determined by the date of the last menstrual period.

Case 1. (B 2938/48. Baby McA. R.M.W.H.)

The mother, para-1, 22 years, was admitted on 29.8.48 in premature labour. Her pregnancy had lasted 31 weeks and her general condition was good. She gave a history of having felt foetal movement from the 20th week, but had felt none during the last two weeks. She was delivered of a premature macerated stillborn female foetus weighing 1 lb. 6 oz. (624 g.). The placenta was infarcted and showed retroplacental clot as a result of a concealed accidental haemorrhage. The puerperium was satisfactory.

Postmortem Examination (R.M.W.H. 160/48). This showed the usual features of a very macerated infant which had been dead *in utero* for some considerable time. The liver was normal in size with a smooth capsule and did not appear to be syphilitic.

Histological Examination. Only the liver was examined. This shows the features of autolysis. Routine H. and E. stained sections reveal no further information, but sections stained by Lieb's phosphotungstic acid haematoxylin (P.T.A.H.) reveal a large amount of intrasinusoidal pure fibrin deposition (Figs. 2 and 3). The deposits are heaviest in the midzones of nearly all lobules, and by their morphological features, namely the streaming appearance, tendency to link with one another, the saddle embolus effect where the deposits impinge against the spur of a cord of liver cells and by their depth of staining, it can be deduced that these deposits were laid down while the blood was still flowing through the sinusoids, and they are thus justifiably called antemortem fibrin thrombi or emboli. They show no evidence of being infective in origin.

Comment. Because other tissues are not available for histological study, no firm conclusion can be applied to this one finding. Three suggestions are possible however, 1) that this widespread

hepatic intrasinusoidal fibrin deposition might have led to embarrassment of the foetal circulation by impeding the flow through the liver from the umbilical vein to the inferior vena cava, 2) that these fibrin deposits may have resulted in hepatic insufficiency not only by causing ischaemia of the cells of the mid- and central zones of the liver lobules but also by increasing the circulatory by-pass of the liver via the ductus venosus if the mechanical blockage was serious, and 3) this foetus shows no fibrinolytic activity. If fibrinolytic activity had been present, these deposits would have disappeared before birth, because fibrinolysins function best at 37°C., and should therefore function in a foetus in utero, since it is known that they can function after death (Mole 1948). Had the enzymes been present, their action would normally be expected to have completed the digestion of any fibrin deposited intravascularly well within the two weeks interval between foetal death in utero and delivery.

Case 2. (C 3208/48. Baby D. Twin II. R.M.W.H.)

The mother, 30 years, para-5, was admitted with a twin pregnancy and with the signs of moderate pre-eclamptic toxaemia. The foetal heart sounds were heard with certainty two days later. One week after admission, on 26.9.48, the patient went into

premature labour. She was then in the 32nd week of her pregnancy. After 12½ hours she delivered herself spontaneously of a live mature female infant weighing 6 lb. 3 oz. (2,810 g.). One half hour later, a leg of the second infant was brought down and the child was born as a manual breech delivery. The child, a premature female infant weighing 3 lb. 7 oz. (1,560 g.), could not be resuscitated and was stillborn. The placenta was removed manually, appeared to be uniovular, and showed no abnormality. The mother developed fever in the puerperium which responded satisfactorily to penicillin, and she dismissed herself irregularly on 4.10.48.

Postmortem Examination of Twin II. (R.M.W.H. 187/48)

The main cause of death was a tear of the falx cerebri, with extensive subdural haemorrhage there and spreading over both cerebral hemispheres. The body showed marked generalised cyanosis with gross congestion of all organs and some sub-pericardial haemorrhages along the atrio-ventricular groove. The lungs were atelectatic with a narrow margin of aeration along their anterior borders. There was a small subcapsular haematoma over the right lobe of the liver. The left lobe was pale.

Histological Examination. This confirms the severe venous congestion of the liver, spleen, kidney and ovary. The lungs show more expansion than was to be expected (Fig. 4). There is severe capillary congestion and clumps of amniotic squames in some of the partly expanded alveoli. There is no evidence of intra-uterine or intrapartum pneumonia, or of infection elsewhere.

Lieb's P.T.A.H. shows intravascular pure fibrin thrombi only in the liver (Fig. 5). The deposits are located in the midzones of the lobules and are moderately numerous. The block of tissue was selected from the left lobe of liver and had thus no direct connection with the small subcapsular haematoma of the right lobe. (Generally this latter lesion seldom reveals any significant quantity of fibrin throughout its substance and often it is quite negative.) The fibrin strands in the sinusoids tend to lie parallel to the walls of the sinusoids (Fig. 6), show a streaming effect, and a tendency to linkage between deposits (Fig. 7) i.e. all the characteristics of having been formed antemortem while the blood was yet flowing through the sinusoids. While the thrombi are antemortem in type, death of the foetus could not have been delayed much after the formation of the thrombi for they have not caused any anoxic

effects on the centrilobular cells such as fatty change, or cytolytic necrosis, nor do the unaffected sinusoids show evidence of compensatory dilatation.

Comment. It is not claimed that the hepatic sinusoidal fibrin deposits were directly responsible for this infant's death, which was obviously due to a tear of the falx cerebri with subdural haemorrhage. It may be however that there is an indirect connection. As the hepatic sinusoidal fibrin deposits formed, the circulating blood was temporarily depleted of blood clotting factors. A temporary bleeding tendency resulted. The tear of the falx is an inevitable risk of all breech deliveries where the head has inadequate time to mould, but it may be that this temporary bleeding tendency resulted in a larger subdural haemorrhage than would otherwise have occurred. That this bleeding tendency did exist is supported by the presence of a small subcapsular haematoma of liver which was precipitated probably by the manipulative procedures of the obstetrician. It is unlikely that these were forceful to any serious extent for the birth passages had recently accommodated a 6 lb. (2.8 kg.) baby with ease, while this present infant was only $3\frac{1}{2}$ lb. (1.56 kg.), and further there is no mention in the operation notes of any difficulty having been encountered. Lastly, it is unlikely

that the bleeding tendency was the result of haemorrhagic disease of the newborn due primarily to hypoprothrombinaemia, for under these conditions no clots would have formed at all and thus none would have been found in the hepatic sinusoids. If hypoprothrombinaemia existed, it did so after the formation of the hepatic sinusoidal thrombi, as part of a generalised depletion of blood clotting factors and was therefore secondary.

Case 3. (Redlands, Baby McK.)

The mother, para 0+1, 39 years, had attended the antenatal clinic regularly and her clinical state was good. At her visit on 25.2.58 the foetal heart was not heard. X-ray confirmed death of the foetus, and the patient was admitted on 20.3.58 in the 33rd week of her pregnancy for induction of labour. After a $5\frac{1}{2}$ hour labour on 21.3.58, the patient was delivered of a grossly macerated stillborn female infant weighing 2 lb. (920 g.). The placenta and membranes showed no abnormality. The puerperium was satisfactory and the patient was discharged home on 30.3.58.

Postmortem Examination (R.M.W.H. 42/58). The body was that of a badly macerated female infant weighing 2 lb. (920 g.) and with a crown-heel measurement of 14 inches (35.0 cm.). Internal examination showed the usual features of severe maceration —

sero-sanguineous fluid in all the body cavities and pink, soft, organs from which most of the fine detail had disappeared. The liver, which weighed 32 grams, showed a very unusual appearance, consisting of serous deposits of fibrin over certain areas which were raised above the general level of both lobes. The former were firm, showed a tendency to confluence, were of pale yellow colour and on section they were irregularly wedge shaped, while the latter were soft and on section revealed the normal tendency of severely macerated liver to become diffluent. The lesions resembled hepatic infarcts (Fig. 8).

Histological examination of the lungs, heart, liver, kidneys, adrenal gland, brain, skin and umbilicus show the usual features of severe autolysis. All tissues are eosinophilic and nuclear detail has disappeared completely from the lungs, adrenals and brain. Scanty nuclear remnants persist in the myocardium, liver and skin. Persisting nuclei, almost of normal morphology, are present in the subcapsular foetal glomeruli of the kidney. Tissues can be identified best by the persisting collagenous and reticular stromal pattern. Other sections stained by Lieb's P.T.A.H. show intravascular pure fibrin thrombi in only one organ — the liver. Here, a most striking histological picture is revealed. The areas of suspected infarction

turn out to be so by the presence of widespread intrasinusoidal fibrin deposition, which has occurred some time before the foetus died and was probably responsible for its death. As expected from the gross appearances, there are areas in the liver devoid of fibrin deposition (Fig. 9), but these are not many. In the affected areas the fibrin is deposited mainly in the periportal or peripheral zones of the lobules (Fig. 10), although it extends in lesser degree into the mid- and central zones in most affected lobules. Most of the portal tracts are normal and free from thrombus in the branches of the portal vein. One field however (Fig. 11) shows laminated thrombus in a small radicle of the portal vein, while in another field (Fig. 12) there is an appearance resembling very closely that of cavernous transformation of the portal vein. This would suggest, if the appearance has been interpreted correctly, that an earlier episode of more localised portal vein thrombosis had taken place, and that this had become organised and recanalised. Under such circumstances one might expect to find a segment of liver atrophy with scarring, but this is not necessarily a sequel to localised portal vein thrombosis, and cannot be found in this present case. A striking appearance is noted however in some subhepatic veins (Figs. 13 and 14) and consists of laminated thrombus laid down on the intima of these

vessels. It is apparent that this thrombus has been present for some time because retraction has occurred with re-establishment of the vessel lumen. This appearance is also seen to a lesser degree in the central vein of some lobules (Fig. 15) and in the sinuosids themselves (Fig. 16). The placenta (Fig. 17) shows histological evidence confirming that the vessels have not been functioning for some considerable time.

Comment. This infant's death in utero was not accompanied by any symptomatic upset in the mother who was an elderly primigravida. Postmortem examination of such macerated foetuses is usually very unsatisfactory on account of the degree of autolysis. This particular case was very rewarding and the following observations appear to be justifiable: 1) that the degree and extent of the liver necrosis was so great that the foetus died from hepatic failure, 2) that several episodes of intra-hepatic fibrin deposition appear to have been probable, the first being very local in the left lobe, being organised with localised cavernous transformation of the portal vein and the ensuing one being more widespread and more serious, 3) that the thrombi are not infective in nature, for the umbilicus is histologically normal, there is no evidence of polymorphs or of organisms in any of the thrombi, and there was no maternal

symptomatology to suggest the presence of intra-partum infection, 4) that although some thrombi are of longer duration as shown by their lamination and their retraction to allow the lumen of these vessels to become reformed, there is no histological evidence of organisation of these thrombi by ingrowth of new capillaries and fibroblasts; this may be corroborative evidence that the fibrin depositions are sterile, 5) later cases in the neonatal series will show that such a degree of organisation is seen first two weeks after its occurrence: overgrowth by endothelium is a vital reaction and is seen first about 3 weeks after the thrombus forms: its absence here is due to foetal death; these features coincide with the length of foetal death in utero and thus retraction of thrombus may be entirely a physical process requiring no vital activity on the part of the infant, and 6) this foetus has lacked fibrinolysins, for if these enzymes had been present the fibrin would have been digested within the four weeks during which the foetus was dead in utero.

Case 4. (C 4191/48. Baby M. R.M.W.H.)

The mother, 27 years, para-4, was admitted on 15.12.48 following vaginal bleeding on the 9th and 10th of December.

Her pregnancy had lasted 33 weeks at that time. On admission the foetal heart sounds were audible and the bleeding was found to be due to a marginal placenta praevia. On 17.12.48 labour was induced by artificial rupture of the membranes at 1.10 p.m. Labour pains commenced at 2.00 p.m. and continued overnight. The foetal heart was heard on 18.12.48 but disappeared at some point in the course of the morning. At 1.55 p.m. a premature male stillborn infant was delivered, weighing 4 lb. 5 oz. (1,956 g.). The placenta and membranes were intact. The puerperium was uneventful and the mother was dismissed on 29.12.48.

Postmortem Examination (R.M.W.H. 244/48). The body was that of a premature very cyanosed male infant. Internally the organs were fresh, and showed numerous petechial asphyxial haemorrhages over both pleural surfaces, the lungs, thymus, and along the atrio-ventricular groove of the heart. The liver, spleen, kidneys and adrenal glands showed marked congestion. The brain showed no gross abnormality.

Histological Examination. There is no evidence of autolysis and this finding confirms that foetal death occurred not long before delivery. The lungs are atelectatic and show numerous

subpleural and interstitial perivascular haemorrhages. The thymus shows interstitial haemorrhages. The liver and spleen show moderate acute congestion.

Staining these tissues for fibrin shows it intravascularly in the sinusoids of the spleen.

Figure 18 shows the widespread intravascular fibrin deposition in the sinusoids of the spleen. The Malpighian corpuscles are apparent by the absence of fibrin in these structures. The fibrin deposits extend also into some of the smaller tributaries of the splenic vein. The streaming effect of these deposits as well as those in Figure 19 is convincing proof that the deposits were laid down while there was yet a rapid rate of blood flow.

No intravascular fibrin was found in the lungs or in the thymus. Scanty antemortem thrombi are present in a few central veins of the liver (Fig. 20).

Comment. Assessment of these findings leads to the following suggestions: the splenic deposits of intrasinusoidal and intravascular fibrin gave rise to the first unusual episode during the infant's birth. This must have resulted in a marked reduction of blood flow through the splenic and portal veins and thence through the left lobe of the liver. While the

sinusoidal flow through the liver was in this sluggish state, a second, less severe episode of intravascular clotting occurred. This resulted in the hepatic thrombi. It is not known what proportion of the total peripheral circulation of the foetus is occupied by the vascular bed of the spleen, or whether this widespread splenic thrombosis would have resulted in circulatory embarrassment, and it is not known if intravascular thrombosis occurred in any other organ not examined histologically, but it can be assumed from the widespread haemorrhages found at postmortem that a terminal asphyxial state resulted, and because the blood was depleted by this time of all its clotting factors, the asphyxial haemorrhages were more numerous and larger than are usually found, but were present in such a degree that a pathologist would have stated with reasonable certainty that the infant had suffered from "severe asphyxia".

Case 5. (C 2885/58. Baby S. R.M.W.H.)

The mother, age 30 years, para 2+1, was admitted on 1.10.58 in premature labour of 12 hours duration, the membranes being intact. Her pregnancy had lasted for 34 weeks. Examination revealed hydramnios, and the child was presenting as a breech. The foetal heart was heard. At 12.15 a.m. on 2.10.58 the membranes were ruptured artificially. At 7.40 a.m. the foetal

heart was still audible and at 7.45 a.m. an assisted breech delivery was performed. The child was stillborn, premature, female, and weighed 5 lb. 2 oz. (2,326 g.). It showed hydrocephalus, an unusual shape of chest, rectal prolapse and superficial necrosis of the vulva. The placenta and membranes were normal. The puerperium was satisfactory and the mother was dismissed on 3.10.58 under the care of her practitioner.

Postmortem Examination (R.M.W.H. 186/58). The organs were fresh and the unusual shape of the chest was due to splaying of the lower ribs for which no cause could be found. There was generalised oedema and 20.0 ml. of straw-coloured ascitic fluid. No other abnormality was present in the thorax or abdomen. Examination of the head showed wide sutures, a bulging anterior fontanelle and dissection showed these to be associated with severe external hydrocephalus. The brain was small in this large cavity, and rested on the base of the skull. The convolutions were poorly formed, were flat, and there was fusion of both cerebral hemispheres. Dissection of this cerebral sphere showed a single ventricle. No cause was found for these abnormal findings.

Histological Examination. The lungs are atelectatic. No abnormality is present in the trachea, thyroid gland, heart, liver, pancreas, spleen, kidneys or adrenal glands.

Lieb's P.T.A.H. shows intravascular pure fibrin thrombi to be present only in the liver, and in only small amount. The deposits are located mainly in the mid- and central zones (Figs. 21 and 22). The sinusoids in relationship to them appear collapsed while the unaffected sinusoids show a compensatory dilatation. These features suggest a vital reaction of the liver to the presence of these fibrin deposits although they are scanty. They have been present for only a short time for there is very little evidence of necrosis of liver cells. The features however are sufficient to state that the thrombi are antemortem.

Comment. It is apparent that the hazards of the delivery especially when accompanied by a congenital abnormality of the central nervous system and hydrocephalus, were responsible for this child's death. At the same time however, before its death there has been a mild episode of pure fibrin thrombosis confined to the hepatic circulation as far as can be determined. It is not considered that this episode played any serious part in causing this child's death.

Case 6. (B 1763/58. Baby A. R.M.W.H.)

The mother, 32 years, para-2, presented for the first time at the antenatal clinic when 26 weeks pregnant. Two months later the uterus was unchanged in size and X-ray examination revealed an anencephalic foetus. On 20.6.58, when 35 weeks pregnant, she was admitted at 11.45 p.m. in premature labour and draining liquor. It is doubtful if the foetal heart was heard at this time, and six hours later a stillborn, male, anencephalic foetus weighing 2 lb. 10 oz. (1,191 g.) was delivered. The placenta was small but otherwise normal. The puerperium was satisfactory and the mother was dismissed on 27.6.58.

Postmortem Examination (R.M.W.H. 124/58). The body was fresh and showed the usual features of anencephaly unassociated with spina bifida. Internally, the adrenal glands were small but not as small as expected. The right testis was descended, and the left one lay in the false pelvis. Dissection of the congested haemorrhagic mass of pia-arachnoid and cerebral tissue revealed a congested, haemorrhagic pituitary gland seated in a shallow fossa. The lungs were atelectatic.

Histological Examination. The lungs are atelectatic and immature. No abnormality is found in the heart, liver, pancreas, kidney, or pituitary gland other than congestion in various degrees.

The adrenal glands show marked medullary congestion, but their relatively large size is due to the presence of an involuting foetal zone which is still of some depth compared with that of the definitive or adult cortex.

Sections stained for fibrin show a solitary saddle embolus of almost pure fibrin in a portal venule in the liver (Fig. 23). No other tissue shows intravascular fibrin. The tendency for the strands to be arranged parallel to the direction of blood flow, the saddle effect, and the adhesion of numerous platelets to a mainly fibrin clot, all suggest that this lesion occurred before death while the blood flow had some reasonable force behind it.

Comment. As with Case 5 above, it is not claimed that the lesion described played any part in causing death of the foetus. Indeed, anencephaly is incompatible with sustained life of any significant duration. However, this hepatic lesion is described as evidence of almost pure fibrin thrombosis which has occurred, admittedly to a minimal degree, during the life of the foetus, probably appearing at some time early in labour.

Case 7. (B 683/58. Baby W. R.M.W.H.)

The mother, age 18 years, was an unmarried mentally defective primigravida. Very little history could be obtained.

She was admitted on 18.3.58 with moderate pre-eclamptic toxaemia at about 36 weeks gestation, and the foetal heart was heard. Labour pains commenced at 1.45 p.m. on 21.3.58 and the membranes ruptured at 3.00 p.m. The mother had an intra-partum eclamptic fit and the child was born 20 minutes later as a spontaneous breech delivery. It was a stillborn, premature, female infant weighing 4 lb. 3 oz. (1,899 g.). The placenta and membranes were expelled normally. The puerperium was satisfactory and the mother was dismissed on 9.4.58.

Postmortem Examination (R.M.W.H. 44/58). The body showed no signs of maceration. Internally, the lungs were atelectatic and showed scanty subpleural petechial haemorrhages. Similar haemorrhages were present over the pericardium, and the right side of the heart was dilated. All the other organs showed congestion. The brain weighed 280 grams and showed marked congestion.

Histological Examination. The lungs show well expanded alveoli with very occasional amniotic squamous cells (Fig. 24). There is capillary congestion with scattered interstitial haemorrhages. The heart, oesophagus, liver, pancreas, spleen, duodenum, ovaries, central nervous system and pituitary gland show congestion. The

umbilicus and placenta show no abnormality. One adrenal gland shows foci of ballooned vacuolated cells in the lower layers of the cortex (Fig. 25). The degree of vacuolation is greater than normal. These areas show a tendency to confluence.

Sections stained for fibrin show it in the adrenal gland only. Here, intrasinusoidal fibrin is present in large amount, and is well stained. Figure 26 shows that small foci of cytolytic necrosis of the definitive or adult cortex are related to the areas of intravascular thrombosis. These thrombi are obviously antemortem in origin because the fibrin strands lie parallel to the lumen, and because they show signs of being teased out in other areas (Fig. 27). It is unfortunate that, from the point of view of demonstration, a finer, more delicate fibrin deposition is present in many areas to confuse the picture, and I interpret this variety of thrombosis as being formed after death when blood flow has stopped. It is difficult from histology alone to decide whether vacuolation preceded the thrombotic phenomenon, or whether thrombosis preceded the vacuolation changes in the cortical cells. It is possible to select fields in favour of both suggestions. An involuting foetal zone is present in the normal situation. It is also unfortunate that only one adrenal gland was examined histologically.

Comment. As is customary with stillbirth deaths, several events occur within short succession of one another, and it is difficult to assess the importance of each factor and its position in the train of events resulting in feotal death. My interpretation of the findings in this case is as follows:- As a result of the mother's moderate pre-eclamptic state, the infant in utero exists in more anoxic surroundings than normally. This is due to anaemia, oedema and other factors which are not clearly determined. During the intrapartum eclamptic fit the mother was temporarily very cyanotic and the anoxic state of the infant was made worse. This may have precipitated the premature respiratory efforts of the infant. Certainly, some episode, if not the fit, triggered off the respiratory efforts and at this time, the child must have been alive in order to make this effort. Coincident with this, or very shortly thereafter, the circulation converted from the foetal to the adult form, with the one exception that, since the chest was confined within the birth passages, respiratory efforts were restricted even although they were successful in causing air to enter the alveoli. The restriction prevented that blood which entered the right ventricle from passing entirely into the pulmonary circulation and the circulation remained foetal to the

extent that some of this blood continued to pass through the ductus arteriosus as a right-to-left flow. At this time, a thrombotic episode occurred and the blood involved, which was travelling from the placental site, lodged in the adrenal gland just as clotting was taking place, to produce the appearances already described. The final act is also concerned with the expansion of the lungs, which, by causing depression of the diaphragm, led to increased girth of the abdomen with pressure on the umbilical cord which lay between it and the wall of the birth passages. Thus the asphyxial state was further aggravated, and death must have followed shortly afterwards.

It is to be noted that adrenal failure has not been mentioned as a possible cause of death. The reasons are as follows: (1) it is uncertain that the other adrenal gland showed the same picture; (2) while the pure fibrin thrombi have caused foci of necrosis in some areas of the cortex of the adrenal gland examined, it is apparent that <u>at the time of foetal death</u>, most of the cortex of this gland is still viable; (3) at the same time, maternal cortical hormones are no doubt present in sufficient quantity to satisfy the foetal requirements. Thus the foetus has died before adrenal failure

had time to become manifest.

Case 8. (A 2635/48. Baby P. Twin I. R.M.W.H.)

The mother, 30 years, para-2, was blood group O rhesus negative, and had been attending the antenatal clinic regularly since 12.4.48. Later, the presence of a twin pregnancy was confirmed, and she was admitted to hospital on 2.8.48 with the symptoms and signs of moderate pre-eclamptic toxaemia.

Her condition failed to improve during the next month and on 4.9.48, when 36 weeks pregnant, labour was induced by artificial rupture of the membranes. The foetal heart sounds were present during that day and were recorded at 6.00 a.m. on 5.9.48. Because little progress had been made, the first infant was delivered at 2.50 p.m. by low forceps. The cord was pulseless and the infant was a stillborn, mature, female weighing 5 lb. 10 oz. (2,552 g.). The second twin was delivered easily by breech extraction with high forceps applied to the after-coming head. It also was a stillborn, female infant, weighing 4 lb. 15 oz. (2,246 g.). The placenta was uniovular and the puerperium was uneventful. The mother was allowed home on 14.9.48.

Postmortem Examination of Twin I (R.M.W.H. 169/48). The body was that of a very cyanosed mature female infant. Internal

examination showed severe congestion of all organs with numerous severe asphyxial haemorrhages over the pleural and pericardial surfaces and affecting the thoracic organs. The lungs were atelectatic. The peritoneum showed a few scattered haemorrhages. The liver was very congested and showed a subcapsular haematoma on its inferior surface. Apart from congestion the brain showed no gross abnormality.

Histological Examination. The lungs show atelectasis with severe congestion in most areas and with numerous interstitial and subpleural haemorrhages. Some alveoli show moderate expansion and contain amniotic squames (Fig. 28). The liver, spleen, kidney, adrenal gland, ovary and uterus show severe acute congestion.

Lieb's P.T.A.H. show pure fibrin thrombi in the liver only. These deposits were scattered diffusely throughout the organ (Fig. 29). At first glance, the thrombi resemble agonal thrombi, but there are numerous areas where linking of thrombi can be seen (Fig. 30), and in such fields the thrombi no longer occupy an axial position in the sinusoids but are sited in the peripheral stream. This is identical with the first stage of organisation of thrombi, and there is also dilatation of unaffected sinusoids with collapse of affected ones. These features suggest that the thrombi formed about two weeks

before death.

Postmortem Examination and Histology of Twin II. Twin II showed gross features similar to those of Twin I. Histology also showed the same features, but the organs were entirely negative for fibrin thrombi.

Comment. The location of these fibrin thrombi against the endothelium of the hepatic sinusoids suggests that they are of some duration. In the later cases of neonates, it is possible to suggest that this phenomenon occurs about two weeks after the thrombi have formed. This would suggest that they were formed during the mother's stay in hospital while suffering from pre-eclamptic toxaemia, although the history gives no indication of any particular episode which might have brought this about. During birth, the baby made premature respiratory efforts, as shown by the amniotic squames in the alveoli, and caused filling out of the chest. While still within the birth passages, the effect of this would be to diminish the venous return to the heart, and this would lead rapidly to asphyxia with ensuing heart failure. The intense venous congestion of the liver is not due, in my opinion, as much to heart failure as to inability of the venous return to reach the heart because of the partial expansion of the lungs in a restricted space.

The hepatic thrombi must represent a considerable proportion of the blood fibrinogen but, since this episode is thought to have occurred about two weeks ago, any temporary bleeding tendency will be fully corrected at the time of birth.

Case 9. (Baby G. Redlands)

The mother, age 25 years, primigravida, had been well throughout pregnancy and went into labour at 38 weeks by her dates. The first stage of labour lasted 20 hours, and the second stage 45 minutes, at the end of which a mature, stillborn, female infant weighing 6 lb. (2,722 g.) was delivered spontaneously. The foetal heart sounds had not been heard for 15 minutes before delivery, and the umbilical cord was tightly round the infant's neck. Attempts at resuscitation were in vain.

Postmortem Examination (R.M.W.H. 39/58). The infant was mature and showed marks caused by the umbilical cord being wound tightly round its neck. Dissection revealed atelectatic lungs which were congested and had subpleural haemorrhages. None of the other organs in the thorax, abdomen or head showed any gross abnormality. The placenta weighed 400 grams and measured 7 x 5 inches (17.5 x 12.5 cm.). Apart from an excess of subchorionic fibrin deposition there was no abnormality.

Histological Examination. The lungs show a poor attempt at expansion, and the partly expanded alveoli contain scanty amniotic squames. The liver shows marked diffuse fatty change, equally severe in both lobes. No abnormality is present in the heart, oesophagus, pancreas, spleen, kidney, adrenal gland, ovaries, uterus, umbilicus, thyroid gland, submaxillary gland, central nervous system or pituitary gland. There is neither severe congestion nor severe ischaemia. Staining other sections of these tissues for fibrin shows none to be present in any of these organs. Study of a section of placenta however shows with H. and E. stains, and to better advantage with Lieb's P.T.A.H., that the subchorionic depositions are really haemorrhages of some standing (Fig. 31) because the enmeshed fibrin appears to be laid down in several layers and in some areas the trapped red blood corpuscles show evidence of lysis. In addition, two branches of the umbilical arteries show organising thrombus in their lumina (Fig. 32). These thrombi are being organised by retraction of the clot to one side of the vessel wall and overgrowth of the clot surface by vessel endothelium (Fig. 33). There is no capillary ingrowth or fibroblastic proliferation.

Comment. It is clear that this infant's death was the result

of the cord being wound round the infant's neck. While this must have arisen before labour started, and before the head became engaged, the cord did not become tight until the rather rapid second stage of labour, and I would suggest that it became so quite suddenly. If it had done so gradually, the umbilical vein would have been compressed before the umbilical arteries, since the vein possesses a thinner wall, and a very pale ischaemic child would have resulted. Since the child was neither ischaemic nor extremely congested, it is suggested that the circulation through the cord was interrupted suddenly and completely. This act caused foetal asphyxia which resulted in a poor premature respiratory effort. While this failed to cause significant alveolar expansion it appears to have been successful in diverting the main pulmonary artery flow into the pulmonary capillary bed to cause congestion of the lungs.

The fibrin thrombi in the two branches of the umbilical artery are however of much longer duration than even the duration of labour. The maternal history fails to give any guide in this respect. The cause of the rather diffuse sub-chorionic haemorrhage, which is of some duration, is also undetermined. Could these two findings be related to one another ? This, however, is another example of pure fibrin thrombosis in a

foetal organ (the placenta) occurring in an apparently uneventful pregnancy, and having no direct connection with the mechanics of labour. Case 3 above is an extreme example of this. With regard to the present case, it may be stated with reasonable certainty that this infant did not possess any local or circulating fibrinolysins, and lastly that these thrombi show no evidence of being infective in origin. I consider that the lack of capillary and fibroblastic response on the part of the vessel intima may be further evidence in support of their aseptic state.

Case 10. ( C 1487/58. Baby K. R.M.W.H.)

The mother, age 29 years, para-2, first attended the antenatal clinic when 38 weeks pregnant. Her general condition was good. She was admitted a fortnight later, at 6.30 a.m. on 26.5.58 in labour. The membranes ruptured on admission. It was reported at 10.40 a.m. that the foetal heart sounds became slow with each uterine contraction. At 11.10 a.m. no foetal heart could be heard. The baby was born at term as an assisted breech delivery, the head being delivered at 11.30 a.m. The child was a mature, male, stillborn infant weighing 7 lb. 14 oz. (3,572 g.). The placenta and membranes were normal. The

The puerperium was satisfactory, and the mother was dismissed on 1.6.58.

Postmortem Examination (R.M.W.H. 109/58). The infant showed some cyanosis of the lips. Internally, the lungs were atelectatic, the heart showed dilatation of the right side, and the other organs showed severe congestion.

Histological Examination. This shows moderate alveolar expansion in the lungs but most contain numerous amniotic squames. The heart, liver, pancreas, kidney, adrenal gland, brain, pituitary and skin show varying degrees of venous congestion.

Sections stained with Lieb's P.T.A.H. show thrombi composed almost entirely of fibrin in the skin only (Fig. 34). Here fibrin is seen in a vessel at the level of the sweat glands and causing some distension of it locally. Fibrin thrombosis is not present in any other organ.

Comment. This case is recorded because it shows another type of antemortem fibrin thrombus in a stillborn infant. It is my opinion however that this example is due to the necessary manipulative procedures used by the obstetrician to aid the delivery of this rather large infant which presented as a breech. This section of skin was taken from the front of the sternum. No sign of

bruising was seen there at postmortem, nor is there evidence of it histologically. It is extremely unlikely that obstetrical manipulations could have produced this lesion after death. This thrombus is the result of physical trauma, and does not belong to the category of fibrin thrombo-embolism described above.

## B. NEONATES DYING WITHIN 48 HOURS OF BIRTH

Two hundred and twenty six infants dying within 48 hours of birth have been examined. Of these, 58 showed intravascular thrombi of various kinds, and in 9 cases these were considered to have been formed some considerable time before death. In seven of the nine cases (numbers 11, 12, 13, 14, 15, 16 and 18), death has been due wholly or partly to the occurrence of fibrin thrombi. The remaining 46 cases showed thrombi which I consider to have been formed agonally or after death, or both. The nine "positive" cases will be reported in detail in order of increasing survival after birth.

### Case 11. (S.R.I. 5/128. Baby P. Twin I. Less than 12 hours)

The mother was admitted on 11.7.55, when 26 weeks pregnant, draining blood-stained liquor. By X-ray examination, the presence of twins was confirmed, and while in hospital the mother showed signs of mild pre-eclamptic toxaemia. Labour commenced on 27.7.55 and live, male twins were born. The placenta and membranes followed shortly afterwards and were those of a uniovular twin pregnancy. The first twin died at 9.30 p.m. on the day of the birth when less than 12 hours old and the second twin, which was larger and which was delivered by low forceps over the perineum, died at 2.30 a.m. on 28.7.58.

The puerperium was satisfactory.

Postmortem Examination of Twin I (S.R.I. 5/128). The body was that of a premature male infant weighing 1 lb. 11 oz. (753 g.). Internally there was a blood-stained right pleural effusion. Both lungs floated in water, but there were patchy areas of atelectasis. No other abnormality was found in the thorax, abdomen or head.

Histological Examination. Only the lungs were examined histologically and four blocks of tissue were taken. All lobes show patchy aeration with mild oedema of the expanded atria and alveoli, without any evidence of infection (Fig. 35). In other sections stained by Lieb's P.T.A.H., widespread intravascular thrombosis is found in three of the four blocks of tissue. The thrombi were laid down before death, because the strands of fibrin lie parallel to the vessel walls, are stained deeply, and show signs of becoming teased out in some areas. They are pure fibrin thrombi, and are located in the pulmonary arterioles (Fig. 36), in lung capillaries to the extent that the capillary beds of whole lung segments become functionless (Fig. 37) and also in the pulmonary venules (Fig. 38). The affected lung parenchyma is showing signs of ischaemia, such as loss of cohesion between cells, shedding of cells into the alveoli, loss of nuclear detail, and a

tendency to uniformity of staining, although no area of frank necrosis or infection is present. An assessment of these sections suggests that fully three-quarters of the vascular bed of each affected lobe is blocked by such thrombi.

Postmortem Examination of Twin II. At postmortem, this infant also showed prematurity and atelectasis. No fibrin thrombi are present in its lungs on histological examination.

Comment. Case 11 has been published (Boyd, 1958, Case 2). Although no other organs were studied histologically, it would seem that this widespread pulmonary thrombosis is sufficient to account for death in this case. It is important to note that the thrombi are fibrin thrombi with no admixture of red blood corpuscles, that they occupy the axial portion of the vessel lumen, that the fibrin strands stain deeply and lie parallel to one another, that they are teased out along the course of the vessels, and that they show no evidence of being infective in nature. The infant survived this episode for a sufficient time for ischaemic changes to appear in the lung parenchyma without there being frank infarction. It cannot be determined accurately at this late stage how long the child lived, but it is certain that it lived no more than 12 hours at the maximum. Further, since the process initiating the

thrombosis is affecting moving blood within the vascular system, and since there is a certain latitude in the normal clotting time, it is to be expected that the thrombi are to be found in arteries, capillaries and veins. Such a finding virtually proves that these thrombi were not formed elsewhere to be transferred later as emboli to the lungs, but were formed in situ as the blood was still flowing. Under these circumstances the episode which started the clotting mechanism must be located proximal to the lungs, and it is my belief, to be supported later by other data, that it was located at the placental site. If this belief is correct, then the thrombotic episode occurred after the child had breathed but before the cord was ligated, and that the pre-determining conditions were located at that part of the placenta supplying only this infant, because the second twin failed to show a similar picture.

Another speculation which is supported by the results of section F may be admissible. If this infant's fibrinogen level were normal (200 mg. per 100 ml.), and if this baby's circulating blood volume is estimated generously as 300 ml. including that in the placental circulation, and if all the infant's fibrinogen were converted to fibrin and lodged in the lung vessels, then 600 mg. of fibrin would be present. While it is obviously

impossible to estimate how much fibrin is actually present from histological preparations it is my opinion that a lot more fibrin than 600 mg. was present intravascularly in these lungs, and therefore a necessary condition for a histological picture such as this one is a pre-existing abnormally high blood fibrinogen level. Lastly, it is apparent that all the fibrinogen possessed by this infant was not utilised in this massive thrombotic episode, because there has been an excess available to produce a delicate coagulum in the alveolar exudate as Figs. 36 and 37 show. Thus, this infant's blood fibrinogen level must have been very high indeed before the thrombotic episode, after which it was left relatively depleted of this substance.

Case 12. (S.R.I. 3/13. Baby T. Less than 12 hours.)

The mother was para-2, with blood group O rhesus negative, and at term her antibody titre, which had been low, rose to 1/128. The baby was a full term male infant who was grey and limp. After delivery the mother had a mild post-partum haemorrhage. The cord blood haemoglobin was 5.3 g. per 100 ml. (36 per cent), the cord serum contained 4.5 mg. per 100 ml. of bilirubin which was all "indirect" in variety. Blood films showed numerous erythroblasts and other nucleated red blood corpuscles. A replacement transfusion was performed during which the condition of the infant improved,

but the child collapsed suddenly, coughed up blood-stained mucus, and died just at the end of the transfusion when it was less than 12 hours old.

Postmortem Examination (S.R.I. 3/13). The features of erythroblastosis foetalis with heart failure were present. The lungs were almost fully expanded and the right side of the heart was dilated but there was no cardiac enlargement. The spleen was moderately large. The brain showed no abnormality.

Histological Examination. The lungs are almost completely expanded. The liver shows numerous foci of erythropoiesis throughout its substance and they tend to obscure the normal liver structure. Numerous erythropoietic foci are present also in the spleen and pancreas. No abnormality of the lungs, myocardium, kidneys, thyroid and thymus glands are noted, and the cerebrum, cerebellum and brain stem appear normal.

Lieb's P.T.A.H. shows fibrin thrombi in several of the pulmonary arteries (Figs. 39 and 40). These are rather dense thrombi and the fibrin strands are not easily demonstrated by photography for the thrombi are heavily coated with platelets (Fig. 41). In the liver scanty thrombi are present, one variety (Fig. 42) being composed of delicate, loosely packed strands arranged parallel to the vessel. These thrombi I interpret

as being agonal. The other variety consists solely of platelets (Fig. 43). In my experience, platelet thrombi are very rare in stillborn and neonatal infants. I have records of 7 such cases from 755 postmortems and it is my opinion that the finding of these thrombi is important although I am not yet certain of their significance. (see also Case 15). Other platelet thrombi, some being superimposed apparently on pre-existing small fibrin thrombi are present in small numbers in the myocardium, thyroid gland, thymus and pancreas (Fig. 44). They are also scattered haphazardly throughout the cerebral cortex, white matter and cerebellum. They appear to be most dense however in the brain stem, under the floor of the fourth ventricle near the vagal and glossopharyngeal nuclei (Fig. 45). No secondary effects have resulted, such as neuronal degeneration, cerebral softenings, or glial reaction. No thrombi can be found in either kidney or in the spleen.

Comment. This case has been published (Boyd, 1958, Case 1). This is an example where fibrin thrombi are few in each organ and where more organs show their presence. The fibrin thrombi are seated in the lungs mainly, although it is suspected that several of the cerebral thrombi are also fibrinous in nature by virtue of the parallel rows which the platelets tend to assume, although it is difficult to demonstrate this by photography.

Fresh blood was used for the exchange transfusion in this case, and it is possible that the platelet content of this was not greatly depleted, so that on transfusion, the injected platelets adhered to the scattered fibrin thrombi which were already present. It is tempting to suggest that the thrombi already present were made larger thereby, and possibly caused a significant, irreversible ischaemia of the vital medullary centres, with death resulting. It is only in this site that thrombi are reasonably numerous. The postmortem findings however are more in favour of cardiac overloading. Although the liver shows scanty thrombi, which are mainly of agonal form and are located in the central and sub-hepatic veins, as opposed to the sinusoids, which are empty, the occurrence of most thrombi in the pulmonary vessels and those of the systemic organs suggests that the thrombotic episode, mild though it has been, occurred after respiration had been established and before the cord was tied.

Case 13. (B 633/58. Baby B. 12 hours. R.M.W.H.)

The mother, age 46 years, and para-13, was admitted at 4.30 a.m. on 14.3.58, not being in labour, with a history of having had vaginal bleeding since 2.30 a.m. Clots of blood were passed. Her general condition was good, the foetal heart was audible, and the membranes ruptured spontaneously at midnight

on 15.3.58. She did not go into labour until mid-day on 22.3.58, when she was 36 weeks pregnant, and 40 minutes later she gave birth by spontaneous vertex delivery, to a live, premature, male infant weighing 4 lb. 11 oz. (1,928 g.) who was cyanotic and limp at birth. He responded slowly to resuscitation and to oxygen, and was admitted to the sick nursery. The placenta showed a large, old infarct. The mother developed puerperal pyrexia which responded to crystalline penicillin, and she was dismissed on 4.4.58.

The cord blood fibrinogen value by the micro-Kjeldahl method was 458 mg. per 100 ml. and this is twice the normal value.

In the sick nursery, the baby was given $\frac{1}{4}$ cc. of nikethamide ("coramine") intramuscularly and 1 mg. of nalorphine ("lethidrone") with some benefit. Breathing became established, and at 4.30 p.m. intramuscular oxytetracycline ("terramycin") was started in doses of 25 mg. twice daily. In the evening the child had several cyanotic attacks while lung aeration was good, and at 11.00 p.m. 1 mg. of Vitamin K was given intramuscularly following the appearance of haematuria. The child died on 23.3.58 at 12.35 a.m. having lived for 12 hours.

Postmortem Examination (R.M.W.H. 47/58). The body showed mild generalised cyanosis, weighed 4 lb. 8 oz. (2,050 g.) and measured

$15\frac{1}{2}$ inches (42.5 cm.) from crown to heel. Internally, the lungs were uniformly dark, firm and atelectatic apart from the right middle lobe which showed some aeration. The heart was normal. The liver (109 g.) was congested, and both kidneys showed severe congestion. Both adrenal glands showed medullary haemorrhages which did not distort the shape of the organs. The brain weighed 275 g., showed marked congestion, and dissection showed that both lateral ventricles were filled with blood.

Histological Examination. There is poor alveolar expansion and marked congestion of the lungs, liver, spleen, kidney, adrenal glands, testis and brain. There is no evidence of respiratory infection. Scanty erythropoietic foci are present in the liver, pancreas and spleen. There is a focal haemorrhage at one pole only of a suprarenal gland. The brain shows numerous perivascular haemorrhages, subependymal haemorrhages and Virchow's "encephalitis" which is evidence of immaturity. The umbilicus is healthy, and the portion of placenta examined shows no abnormality.

Sections stained by Lieb's P.T.A.H. show antemortem intra-sinusoidal pure fibrin thrombi in one adrenal gland, and in the liver. No fibrin is present intravascularly in any other organ. In the adrenal gland the fibrin is situated in the region of the "focal haemorrhage" described above, which is more correctly

labelled a red infarction (Fig. 46). The fibrin strands are long, deeply stained and the major ones lie in the axial stream parallel to the sinusoid walls. Where the fibrin is dense the sinusoids are collapsed, and in neighbouring areas there is attempted compensatory dilatation of other sinusoids even although they too may contain fibrin deposits (Fig. 47). In yet other areas the fibrin is obviously of longer duration; it no longer occupies the centre of the sinusoid but is lying on the endothelial lining ready to be removed from the circulation (Fig. 48). The deposits pass through the cortex and medulla and are involving the medullary vein of the gland (Fig. 49). Since these widespread deposits of fibrin have been present for some time necrosis of cells in all parts of the affected pole of the gland is apparent, while an unaffected pole of the same gland (Fig. 50) acts as a control. This necrosis which has affected almost an entire pole of the gland contributes also to the sinusoidal distension. It is apparent also at higher magnifications (Fig. 51) that the original antemortem fibrin thrombi are partly obscured by superadded fibrin laid down on top of these "primary" thrombi.

The liver (Fig. 52) shows widespread intrasinusoidal thrombi scattered evenly throughout the whole organ.

Individually the thrombi are short, and many resemble agonal thrombi. On the other hand it is apparent that cellular detail is poor and it is possible that this early cytolytic necrosis could be due in part to anoxia as a result of the presence of numerous small thrombi, and further, the pre-existing severe degree of congestion could have reduced the rate of flow and therefore prevented these thrombi from acquiring the normal antemortem morphology. For these reasons, I prefer to consider these thrombi as antemortem in origin.

Comment. The demonstration of such serious fibrin deposits in the one adrenal gland together with the widespread thrombosis in the liver puts a new interpretation on the postmortem findings in this infant.

The focal necrosis of the adrenal gland is certainly not just 12 hours old. The advanced state of necrosis, and the advanced state of "organisation" of many of the intrasinusoidal fibrin deposits are more likely to be of 10 - 14 days duration, which carries us back to a point prior to when the patient was admitted with bleeding. As the placenta showed later, the maternal haemorrhage probably arose from partial premature separation and was accompanied by infarction of that area. A thrombotic episode was initiated in some of the placental

blood destined for the adrenal gland a day or two prior to the maternal episode, and coagulation occurred as the blood passed through the gland. Once thrombosis occurred there, as the condition was not immediately fatal, further blood was carried into the area and further layers of thrombus were laid down. At this stage we have an infant who is premature, whose environment has suddenly become more anoxic because of the loss of function of a large area of placenta, and who has lost the function of a portion (estimated at a quarter) of its adrenal tissue. This state of anoxia may have caused heart failure while the foetus was still in utero for the degree of engorgement of the organs was very marked indeed. Therefore, during labour which fortunately only lasted 40 minutes, further anoxia would be experienced, and at the same time the placenta, which is precariously attached to the uterus, became detached further, and this coincides with a further thrombotic episode arising in the placental region. Since at this time the blood flow is sluggish, clotting occurs throughout the vascular bed of the liver, and after it, the infant is left temporarily depleted of blood clotting factors. This reveals itself eleven hours after birth on top of the chronic venous congestion by an episode of haematuria, and later at postmortem by bilateral

intraventricular haemorrhages and severe interstitial haemorrhages in many organs. This would suggest that the multiple small thrombi, such as are illustrated in Fig. 52, distributed evenly throughout a 109 g. congested liver are nearly equivalent to the 458 mg. per 100 ml. of fibrinogen, the level found in the cord blood. Section F lends support to this suggestion.

Case 14. ( A 2753/49. Baby L. 13½ hours. R.M.W.H.)

The mother, age 28 years, para-5, first attended the antenatal clinic when five months pregnant. Her general condition was good throughout. She was admitted at 10.35 p.m. on 8.8.49 with a mixed accidental haemorrhage of 2 hours duration. She was moderately shocked, and the foetal heart sounds were heard. At 7.40 p.m. on 9.8.49 the membranes were ruptured artificially and blood-stained liquor obtained. At 4.15 a.m. on 10.8.49, she was delivered of a live, premature, female infant weighing 5 lb. 4 oz. (2,381 g.). It was admitted to the sick nursery. There was an 8 oz. (240 ml.) retroplacental haematoma. The puerperium was satisfactory and the mother was dismissed on 16.8.49.

The infant's breathing was laboured at first but it responded to oxygen, and 1 cc. of lobeline. Its colour was good. Eleven hours later, its respirations became sighing in

character, and it died at 5.45 p.m. after a nasal haemorrhage, having lived for 13½ hours.

Postmortem Examination (R.M.W.H. 155/49). The body was that of a pale, premature, female infant showing some cyanosis of the ears and of the limbs. Internally there was bilateral apoplexy of the adrenal glands. The lungs were solid with numerous confluent haemorrhages which caused an increase in consistency, and there were many subpleural petechiae. The heart showed epicardial haemorrhages, and the liver showed irregular congestion. The kidneys were pale. The brain was congested.

Histological Examination. The partly expanded alveoli of the lungs are stuffed with blood and there is also widespread interstitial haemorrhage. There is no evidence of infection. The liver shows moderate congestion. One kidney is normal. There is obvious focal haemorrhage in one adrenal gland (Fig. 53).

Sections stained for fibrin show laminated antemortem thrombosis of the adrenal vein (Fig. 54) which is distended, and the contained thrombus shows the typical blunt head of an antemortem thrombus. There is no histological evidence that this thrombus is infected. There are two focal cortical haemorrhages which seem to be red infarcts, for there is widespread intra-sinusoidal pure

fibrin deposition in relation to each (Figs. 55 and 56) and this is also found to a less severe degree at several other points in the cortex (Fig. 57). Most of the fibrin strands are compact, situated centrally in the lumen, with strands being parallel to one another and with an appearance in places of being teased out. There is only one field (Fig. 58) which shows the fibrin deposits lining the endothelial surface. No fibrin thrombus is present in any other organ.

Comment. This infant survived in utero for 32 hours after the onset of the mixed accidental haemorrhage, and had an extra-uterine existence of 13 hours. It therefore survived for a total of nearly 2 days after the accidental haemorrhage. While the one histological field illustrated in Fig. 58 might suggest that the fibrin deposits are of longer duration than 2 days (see 'Comment' of Case 13 above), I consider that this could be due to chance, most of the fibrin deposits, including the adrenal vein thrombus, being recent and they are compatible with a duration of about 2 days. This has also been sufficient time for necrosis of the cells of the adrenal gland to become complete in two of these areas with resulting red infarctions (called "haemorrhages" on gross examination). It would appear that the anoxia resulting from retroplacental haemorrhage caused heart failure, and it would appear also that the intrasinusoidal fibrin depositions

in the adrenal gland (probably in both glands although only one was examined histologically) removed sufficient clotting factors from the blood to produce a bleeding tendency as shown by the widespread intrapulmonary haemorrhage.

Case 15. (B 770/58. Baby O. 21 hours. R.M.W.H.)

The mother, 31 years, para-4, first attended the antenatal clinic when 34 weeks pregnant. Her blood pressure was 150/90 mm. of mercury. She also suffered from chronic bronchitis. She was admitted in labour at 10.10 a.m. on 26.3.58 when 38 weeks pregnant. The membranes ruptured spontaneously half an hour later, and at 12.25 a.m. on 27.3.58, by spontaneous vertex delivery she gave birth to a live, mature, female infant weighing 5 lb. 10 oz. (2,552 g.). Its colour was good and it was admitted to the unit nursery. On 28.3.58, during the puerperium, the mother developed fever due to an exacerbation of her chronic bronchitis, and showed early heart failure. She was transferred to Robroyston Hospital, and responded well to treatment. She was discharged to her home on 27.4.58.

Three hours after birth, the infant was transferred to the sick nursery because she had become cyanotic with grunting respirations. On examination, air entry was good and occasional fine rales were audible. She was placed in a humid incubator

with 100 per cent oxygen supplied. At 11 a.m. colour had improved and remained normal, and 25 mg. of oxytetracycline ("terramycin") intramuscularly was started, to be given twice daily. At 1 p.m. a systolic murmur was audible, the child's condition deteriorated and she died at 10 p.m. having lived for 21 hours.

Postmortem Examination (R.M.W.H. 52/58). The body was that of a well developed female infant showing mild jaundice and no cyanosis. Internally, the lungs were well aerated. The heart was enlarged due to dilatation of the right auricle and ventricle. Dissection showed two firm fibrinous vegetations on the posterior cusp of the tricuspid valve, one being illustrated in Fig. 59. There was no evidence of fibro-elastosis. The pulmonary artery and aorta were normal and the ductus, which was free from thrombosis, showed signs of closing. No abnormality was noted in any other organ.

Histological Examination. The lungs show well marked atrial expansion, poor alveolar expansion, and moderate hyaline membrane formation (Fig. 60), which is mostly poor in fibrin content. The explanation for this may be apparent shortly. Study of the other organs show intravascular fibrin in many, and this was the main feature to be noted in the H. and E. sections.

Lieb's P.T.A.H. stain on the section of placenta shows delicate, scanty intravascular fibrin deposits (Fig. 61) which

I interpret as being "agonal" in variety and formed when the circulation within these vessels was sluggish. The vessels at the umbilicus (Fig. 62) are essentially negative, and scanty delicate strands seen in this situation can be explained easily by trauma to the vessel walls when ligating the cord. Section of the liver shows laminated mixed thrombus in the portal vein of the left lobe (Fig. 63) with widespread propagated pure fibrin thrombus in the smaller radicles of the vein throughout this lobe (Fig. 64) and with small seedlings into the central and subhepatic veins, while the branches of the right portal vein in the right physiological lobe are entirely free from thrombus (Fig. 65).

The other tricuspid valve vegetation is composed mainly of a homogeneous agglomeration of platelets (Fig. 66), but the ability of the vegetation to reach such a size has been due to a basic network of fibrin strands. It is noticeable that the base of the vegetation (Fig. 67) is composed of fibrin, and there are no detectable clumps of cellular elements such as polymorphs, nor are there clumps of bacteria, and the valve stroma shows no reaction as yet to this mass. All these features suggest that the mass is not infective in origin. Further examination of the same section shows similar thrombus in a small myocardial vessel (Fig. 68).

While the lungs show hyaline membrane formation as has been illustrated, sections of all five lobes shows fibrin thrombi in the pulmonary arterioles (Fig. 69). Most of the intravascular lesions in the lungs (Fig. 70) however show characteristics resembling those of the vegetation of the tricuspid valve and are thus probably embolic in nature from this valve site. There is also evidence (Fig. 71) that some of the lesions have existed for some time, because they have become adherent to the vessel endothelium, the first step in organisation of the lesion. In the systemic organs, although oesophagus, pancreas, spleen, intestine, kidney, adrenal gland, ovary, skin, parotid gland, pituitary and brain have been studied, antemortem thrombi are found only in the kidney. Here a very striking picture is found (Figs. 72 and 73), the fibrin thrombi being located only in the capillaries and venules of the medullary pyramids. There is no evidence of medullary necrosis.

Comment. While there is no history of any maternal catastrophe to have initiated an intravascular thrombotic episode in this infant, the distribution of the lesions is very strongly in favour of the view that the thrombotic process started in blood as it passed through the placenta and culminated as some of the blood passed through the left lobe of the liver, while some was

deposited on the posterior cusp of the tricuspid valve as the circulation would be sluggish by this time, a little became deposited in the lungs and the remainder in the medullary pyramids of the kidney. The small amount deposited on the heart valve built up quickly and fragments became detached (probably when the child had been born for 3 hours) to form pulmonary emboli. As these increased in number, circulatory and respiratory embarrassment resulted which terminated in death. None of the thrombi shows evidence of being infective in origin. The left lobe of liver shows no evidence of necrosis because (a) all the portal vein radicles are not involved, (b) the sinusoids are almost entirely free from thrombus, and (c) the hepatic arterial circulation is unaffected.

In order to produce such numerous fibrin thrombi, this baby's blood fibrinogen level must have been very high initially and all of it has not been utilised in producing the intravascular thrombi because the hyaline membrane formations illustrated (Fig. 60) show a few which are rich in fibrin while the majority are not. It is my experience from using Lieb's P.T.A.H. as a routine stain, that about one third of cases with hyaline membrane shows fibrin to be present within them, and nearly all of the remaining two thirds show no fibrin,

while a few cases show a mixed picture as this case does.

The mixed fibrin-platelet thrombi shown in Figs. 70 and 71 resemble closely the thrombi which I considered to be of the same nature in Case 12 above (Figs. 41 and 43).

Case 16. (C 4693/52. Baby McC. 25 hours. R.M.W.H.)

The mother, age 38 years, para-3, had attended the antenatal clinic since she was 24 weeks pregnant. She was admitted on 3.12.52 at 12.30 a.m. when 39 weeks pregnant, giving a history that the membranes had ruptured two nights previously and that she had been draining liquor since then. Labour pains had started on the previous evening. The foetal heart was heard, and at 2.50 a.m. by spontaneous vertex delivery she gave birth to a live, mature, female infant weighing 9 lb. 1 oz. (4,111 g.). At delivery, a true knot was present in the cord, and a brisk, moderate post-partum haemorrhage followed expulsion of the placenta. On 2.12.52, the mother developed a fever of 104°F., and a high vaginal swab grew haemolytic streptococci. She was transferred to Robroyston Hospital.

The baby cried at birth and was admitted to the unit nursery, but 6 hours later had to be transferred to the sick nursery because it showed cyanosis. At 10 p.m. the child

showed gross cyanosis and was in a state of peripheral circulatory failure. She died at 3.30 a.m. on 4.12.52, having lived for 25 hours.

Postmortem Examination (R.M.W.H. 268/52). The body showed marked cyanosis. The air passages contained blood-stained mucus, and the lungs were haemorrhagic and oedematous as a result of developing pneumonia. There were blood-stained serous effusions in both pleural cavities. The liver showed diffuse fatty change and scanty subcapsular haemorrhages. The spleen showed haemorrhages in its pulp. Each adrenal gland was twice the normal size and on section both showed much central softening. Both kidneys were pale, and showed subcapsular haemorrhages. There was congestion of the meninges.

Histological Examination. An established confluent haemorrhagic pneumonia (Fig. 74) is present. The perivascular lymphatics are distended with cells, polymorphs being predominant. In these channels there are also numerous gram-positive cocci arranged in chains which also show well in the P.T.A.H. stained section (Fig. 75). The liver shows diffuse fatty change and organisms can also be identified. The umbilicus (Fig. 76) is healthy. One adrenal gland shows severe medullary congestion with necrosis and central softening.

Sections stained by P.T.A.H. show a minimal amount of fibrin in the vessels at the umbilicus, and antemortem thrombus in a small portion of the adrenal gland (Fig. 77). Higher magnification shows this to bear superadded more delicate agonal thrombus (Fig. 78). There is no cytolytic necrosis in this area. Agonal thrombus is present in a congested subependymal vessel in the floor of one lateral ventricle (Fig. 79).

Comment. This infant has died from an overwhelming pneumonia and septicaemia, for organisms can be found in all blocks of tissue taken for histology. The organism has the features of a streptococcus and it would be reasonable to assume that the infant acquired the haemolytic streptococcus which also caused puerperal pyrexia in the mother, and that the infant acquired its infection via the respiratory tract. One well recognised effect of infection by this organism is the severe, almost purulent lymphangitis, well shown in the lungs in this case. Next there is the action of streptococcal fibrinolysin *in vivo* to be considered. The only antemortem intravascular fibrin which I have been able to demonstrate in this case has been that shown in Fig. 77, in a small corner of one adrenal gland. On the other hand, haemorrhagic phenomena have been severe in

this infant. Was its normal blood fibrinogen level very low ? Or, have antemortem fibrin thrombi been digested before death by the action of streptococcal fibrinolysin so that these thrombi are no longer detectable microscopically ? These questions can never be answered. It is noted that the mother had a brisk post-partum haemorrhage accompanying the expulsion of the placenta, no doubt at a time when she herself was incubating a uterine infection. This incident could have initiated a thrombotic episode in the foetal blood passing through the placental circulation, the thrombi lodging in the foetal pulmonary circulation, producing haemorrhagic infarcted areas similar to those illustrated in Case 11 above, and this situation would have allowed any inhaled organism a good opportunity for establishing itself and for proliferating. Since the organism produces fibrinolysin the clots so formed intravascularly are digested later and no trace left. This series of events is pure speculation, but I consider that in theory such a train of events is possible and therefore worthy of mention while discussing the present case.

Case 17. (R.H.S.C. 3108/59. Baby McG. 31 hours.)

The baby was a full term, male infant weighing 6 lb. 8 oz.

(2,949 g.) born by spontaneous delivery at 6.00 p.m. on 3.4.59 after a normal pregnancy. He was found to have a moderately large exomphalos with an intact covering, and was transferred to the Royal Hospital for Sick Children. Five mg. of Vitamin K intramuscularly were given and also injection of chloramphenicol 125 mg. stat., to be followed by 125 mg. b.d.. An operative repair of the condition was performed by sliding the lateral abdominal skin in front of the sac and suturing the two flaps together. No attempt was made to oppose the muscle layers and the whole procedure was completed without entering the peritoneal cavity. At 2.00 p.m. on 4.4.59, feeding was started, but the baby was not keen and it vomited nearly all its feed. At midnight it became very cyanotic with laboured respirations and the child died 55 minutes later.

Postmortem Examination (R.H.S.C. 9669). There was a healthy 5 inches (12.5 cm.) midline linear surgical incision with sutures in place. The abdomen was still protuberant and was very tense. In the thoracic cavity the lungs were well aerated, and the heart was enlarged due to dilatation of all chambers, but particularly those on the right side. The ductus arteriosus was widely patent, its diameter being equal to that of the aorta at this level. Abdominal examination showed the whole small intestine and seven

eighths of the liver within the exomphalos sac. There was no other abnormality here, and examination of the head showed only mild bruising of the falx cerebri.

Histological Examination. No abnormality is noted. The lungs are well aerated and show no evidence of infection.

Fibrin thrombi are revealed by Lieb's P.T.A.H. in an adrenal gland, the thyroid gland, and in the pituitary. None is present in the lungs, heart, liver, pancreas, spleen, kidney, oesophagus and trachea. In the adrenal gland, scanty antemortem deposits are present (Fig. 80) at two points. The thrombi stain densely, are long, and the strands are tightly packed together and lie parallel to the direction of blood flow.

In the thyroid gland, one focus (Figs. 81 and 82) of obvious antemortem capillary thrombosis is present, but throughout the gland there is a more delicate intravascular fibrin deposition such as is illustrated in Fig. 83. It is difficult to be certain what this finding represents but it is my opinion that this is a variety of agonal thrombosis.

The pituitary gland shows several, short, blunt fibrin thrombi (Fig. 84) throughout the gland. I interpret these as being formed agonally.

Comment. It was considered that this case suffered from such a great increase of intra-abdominal pressure as a result of the

repair that the diaphragm was displaced upwards and cardiac embarrassment resulted with ensuing heart failure and death. At the time of necropsy, this seemed to be an adequate explanation, with the non-constricted ductus arteriosus contributing perhaps to the embarrassment of the right ventricle. It is a coincidence that the fibrin thrombi are found only in endocrine glands in this case. Those demonstrated in the adrenal and thyroid glands are definitely antemortem in type but they are not sufficiently widespread in either gland to have caused any endocrine imbalance. Those in the pituitary gland have none of the features of frankly antemortem thrombi and are considered to have appeared agonally. The antemortem thrombi in the adrenal and thyroid glands are believed to be related to a minor thrombotic episode arising at birth, and the agonal thrombi illustrated in the thyroid and pituitary glands may also be so connected in some indirect way.

Case 18. (B 78/56. Baby G. 32 hours. R.M.W.H.)

The mother, 31 years, para-3, was admitted at 2.40 a.m. on 6.1.56, being 40+ weeks pregnant with delayed labour which had started at 6.0 a.m. on 5.1.56. Examination under anaesthesia at 1.00 p.m. revealed disproportion and at 2.30 p.m. a lower uterine segment Caesarean section was performed. A live, male, mature infant weighing 10 lb. 5 oz. (4,678 g.) was born at 2.45 p.m.,

and was admitted to the sick nursery. The post-operative period and puerperium were satisfactory, the mother being dismissed home on 20.1.56.

On admission to the sick nursery, the baby was pale, and appeared to be suffering from the effects of morphia administered to the mother, and thus 0.5 cc. nalorphine ("lethidrone") was given. Later that day and during the next day it had cyanotic attacks, and its legs and arms showed mild spasticity. Later, a distinct cerebral cry developed, and the child showed persistent cyanosis before death at 10.50 p.m. on 7.1.56.

Postmortem Examination (R.M.W.H. 9/56). The body showed severe cyanosis. Internally, the lungs were very congested and haemorrhagic, the liver and spleen were enlarged and congested, as were the adrenal glands and kidneys. The brain showed multiple confluent haemorrhages in the left frontal lobe with widespread early cerebral softening, and there were multiple smaller petechial haemorrhages elsewhere throughout the brain.

Histological Examination. The lungs show reasonable alveolar expansion but there is widespread alveolar and interstitial pulmonary haemorrhage. The liver, spleen, kidney and adrenal gland show congestion. Of five blocks of cerebral hemisphere, two are from the left frontal lobe and show confluent punctate haemorrhages intermingled with an area of early softening.

Sections stained with P.T.A.H. show fibrin thrombi in the brain and adrenal gland only. In the brain, it is important to note that the haemorrhages themselves (Fig. 85) are devoid of stainable fibrin although one expects blood to clot once it lies extravascularly in the tissues. Intravascular fibrin is only found in vessels in the area of haemorrhage (Fig. 86). Occasionally, (Fig. 87) wisps of fibrin are noted in areas of haemorrhage with appearances which suggest that they lay intravascularly at one time, but following the destruction of the capillary walls they now lie free in a haemorrhagic area. The appearances do not suggest that they formed when the haemorrhage formed because they are too compact and the fibrin strands tend to lie parallel to one another. No fibrin is present elsewhere in the brain.

In the adrenal gland, scanty loosely formed fibrin deposits are present deep in the "foetal zone" of the adrenal cortex (Fig. 88), and I consider these to have formed agonally.

Comment. This baby died from a combination of cerebral and pulmonary haemorrhage. This could be due to a degree of intrauterine asphyxia as a result of the prolonged labour. The site of the cerebral haemorrhage is very unusual in the absence of serious trauma, such as that accompanying a fracture of the skull. The findings which I have illustrated suggest that there has been

widespread pure fibrin thrombosis of the deep branches of the left anterior cerebral artery, with a resulting recent red cerebral infarction. It is suggested that the thrombotic process was initiated in some of the placental blood probably at the time of operation. It would appear that a bleeding tendency followed this which would explain the widespread intrapulmonary haemorrhage. During the next 30 hours or so a partial replenishment of the blood fibrinogen occurred, some of which revealed itself by forming small agonal thrombi in the adrenal gland. It is not known why this gland should be selected rather than any other organ. For this reason, it is tentatively suggested that even the site, distribution, and quantity of agonal thrombosis may be found to have some significance in the future although I can offer no explanation at the present time.

Case 19. (No. 934/57. Baby C. Twin II. 46 hours. Ross Hospital)

The mother was para-4, and was admitted on 8.11.57 because of persisting vomiting, and she went into premature labour on 11.11.57 at 34 weeks gestation. She was known to have a twin pregnancy, and it was also known that she was rhesus negative, but had not shown antibodies in her blood to date.

The first twin was born by spontaneous vertex delivery at 12.15 p.m. after 5 hours labour and was alive. At 12.30 p.m. there was fairly brisk bleeding and the second twin was born at 12.40 p.m. as a breech extraction after internal podalic version. The placenta was expressed immediately afterwards and was binovular. The puerperium was satisfactory, the mother being dismissed home on 23.11.57. This second infant was premature, female, alive, and weighed 4 lb. 7 oz. (2,013 g.). It responded well to resuscitation at first, but later her respirations became irregular. The infant collapsed on 13.11.57 having lived for 46 hours. The first twin remained alive and made good progress.

Postmortem Examination (R.M.W.H. 238/57). The body was that of a premature female infant showing faint jaundice. Internally, there was a right spontaneous pneumothorax under moderate tension and causing displacement of the heart to the left. While the right lung was collapsed towards the mediastinum, it showed that the upper and middle lobes had been aerated, and the latter showed bullae of interstitial emphysema along its lower border. The left lung appeared to show primary atelectasis. No abnormality was detected in the abdominal cavity or in the head.

Histological Examination. Interstitial emphysema of the right middle lobe, and atelectasis with patchy atrial expansion only

of the left lung are present. Mild congestion is present in the other organs.

Sections stained for fibrin show it to be present in antemortem form in some of the portal veins of the liver. The features seen (Fig. 89) are more those of adherent red thrombus on account of the admixture of red blood corpuscles. The second example (Fig. 90) suggests strongly that the thrombosis is infective in origin because a focus of early suppuration is present in the lumen. No gram-positive organisms can be identified. These features have been found even although the umbilicus and the portion of umbilical vein within the falciform ligament appeared healthy at postmortem.

Fibrin thrombosis is found in the kidney also, and here the lesion is typically postmortem in variety (Fig. 91) and situated in a renal arteriole. The trachea, lungs, heart, pancreas, adrenal, brain stem, parotid gland and skin are negative for fibrin.

Comment. It is apparent that the spontaneous pneumothorax was probably responsible for death in this case by causing cardiac and respiratory embarrassment. It is also clear that sub-clinical, and sub-pathological, umbilical sepsis was present which was detected only on histology of the liver. Since gram-positive

organisms cannot be identified in tissue sections of the infected vessels, it is possible that the organisms involved are coliform bacilli which are gram-negative. Death has not resulted from thrombosis directly or indirectly in this case, and it seems likely that the thrombosis is the result of low grade infection, and thus this case belongs more to the group of infective thrombi which are considered later (see Groups C. III and D. III).

## C. NEONATES DYING MORE THAN 48 HOURS AFTER BIRTH

Of 119 infants in this group, 63 showed thrombi affecting different organs, in various degrees. Thirty-three of these cases were considered to have thrombi formed before death, and they will be considered under the following headings:-

| | | No. of Cases |
|---|---|---|
| I. | Aseptic Fibrin Thrombi of the Variety Described under Groups A and B above. | 5 |
| II. | Aseptic Fibrin Thrombi, but patient now showing evidence of infection either at the same site as the thrombi or at other sites. | 14 |
| III. | Thrombi Arising as a Result of Infection. | 10 |
| IV. | Thrombi Associated with Congenital Lesions. | 2 |
| V. | Thrombi Associated with Surgical Conditions. | 2 |
| | Total | 33 |

The thrombi are considered to be wholly or partly responsible for death in 19 of the 33 cases. These cases are numbers 20 - 24, 26 - 35, 45 - 46, and 50 - 51 inclusive. The remaining 30 cases show thrombi which have been classified as agonal or postmortem in type.

Group I. Aseptic Fibrin Thrombi

Case 20. (C 454/58. Baby U. 51 hours. R.M.W.H.)

Mother 29 years, para-3, admitted at 37 weeks with antepartum haemorrhage due to placenta praevia. Lower uterine segment Caesarean section. Mature, female infant, weighing 6¼ lb. (2,835 g.). Sent to unit nursery first, but was transferred to sick nursery 1½ hours later because colour poor, whimpery and slightly cyanotic. Repeated cyanotic attacks. Oxytetracycline ("terramycin") 25 mg. b.d. intramuscularly. Sternal recession. X-ray of chest — very poor expansion. Died at 51 hours. Postmortem Examination (R.M.W.H. 27/58). Moderate cyanosis, mild jaundice, atelectasis of both lungs apart from anterior borders, dilatation of right side of heart, congestion of brain. Histological Examination. Atelectasis, pulmonary haemorrhages, moderately widespread hyaline membrane formation (Fig. 92) which contains no fibrin, perivascular cerebral haemorrhages. No infection present. There are pure fibrin thrombi in the liver, adrenal gland and brain. All other organs including the umbilicus contain none. In the liver, the thrombi are present in the mid- and central zones of the lobules (Fig. 93). They are accompanied by some fatty change. A certain degree of venous congestion has prevented the thrombi from assuming a typically antemortem appearance,

but some fields are convincing (Fig. 94). In one corner of one adrenal gland, fibrin thrombi are present in the sinusoids of the cortex. The thrombi are located in the foetal zone (Fig. 95). In the brain, scanty loosely-formed fibrin deposits are present in the subcortical white matter at one point. It is apparent that the vessel walls have ruptured recently so that the fibrin strands are breaking through to lie partly in the tissues (Fig. 96). The appearance would suggest that the fibrin was laid down before death and that the strands became disorientated as haemorrhage occurred. The pituitary shows one antemortem mixed fibrin-platelet thrombus (Fig. 97).

Comment. This is a typical example of a baby being born by Caesarean section and dying with atelectasis and hyaline membrane formation. As explained earlier (Case 15, Fig. 60) I have sometimes found hyaline membrane to be rich in fibrin, but this is another example where the membrane is deficient in fibrin. The explanation could be that most, if not all, the circulating fibrinogen was converted to fibrin in the liver, adrenal gland and brain. The blood would be left depleted of clotting factors temporarily, thus none would be available for the hyaline membrane. At the same time a haemorrhagic tendency would result. This has been described in the lungs and brain of this case, and would be accentuated in an asphyxiated baby.

Case 21. (B 4218/50. Baby C. 74 hours. R.M.W.H.)

Mother, 28 years, para-3, mitral stenosis. Admitted on 22.12.50 at 36 weeks maturity in premature labour. Premature, male infant born by spontaneous vertex delivery, and weighed 4 lb. 9 oz. (2,069 g.). Puerperium satisfactory. Child's condition good for 2 days, and then became whimpery, cyanotic, feeble, and with boggy anterior fontanelle. Lumbar puncture showed a blood-stained C.S.F. under pressure. Died at 74 hours.

Postmortem Examination (R.M.W.H. 298/50). Premature, left lung expanded, right lung collapsed, both showed haemorrhagic firm areas, dilatation of right side of heart, liver mottled, meninges intact, convolutions flattened, congested cerebral vessels and small subarachnoid haemorrhage around base of brain.

Histological Examination. Alveoli well expanded, pulmonary haemorrhages with secondary collapse; some fatty change in the liver. No infection.

Sections stained for fibrin show pure fibrin thrombi in the liver, spleen and adrenal gland. In the liver (Fig. 98) the deposits are situated in the mid- and central zones of the lobules, and again the antemortem nature of the thrombi is apparent by the saddle effect, the linkages which are present

(Fig. 99) and by the resulting fatty change. In the spleen, patchy sinusoidal thrombosis is present (Fig. 100). These thrombi are located in the red pulp close to the Malpighian corpuscles. The adrenal gland shows widespread loosely-formed thrombi in the sinusoids of the depths of the cortex (Fig. 101). I consider that most of these have been formed agonally, although possibly superimposed on pre-existing antemortem fibrin thrombi.

Comment. This example of disseminated fibrin thrombi has primarily affected the hepatic circulation, and that affecting the spleen is of secondary importance but has occurred before death because there is collapse of the affected sinusoids and compensatory dilatation of the remainder. The thrombi in the adrenal gland are thought to be mainly agonal, but smaller antemortem thrombi may have acted as nuclei for the agonal thrombi. If not, why do the agonal thrombi select the adrenal gland while sections of the lungs, kidneys, brain and pituitary are free ?

Case 22. ( S.R.I. 6/98. Baby N. 4 days.)

Mother primigravida. Normal pregnancy. Labour 12 hours. Foetal distress immediately before spontaneous vertex delivery on 15.5.56. Baby limp and cyanotic at birth. Placenta and puerperium normal. Birth weight of infant $5\frac{1}{2}$ lb. (2,495 g.). Oxygen,

lobeline, and "alevaire" (a proprietary preparation taken as an aerosol in order to thin any mucus blocking the air passages) were given. Respirations shallow and gasping till death. Cry feeble. Colour poor. Tracheal secretions blood-stained and cyanosis was gross immediately before death on 19.5.56.

Postmortem Examination (S.R.I. 6/98). Lungs well expanded but wedges of pulmonary haemorrhage present which were confluent in the lower lobes. Heart normal. Abdomen and head showed congestion only.

Histological Examination. The lungs are well expanded, show no evidence of infection but there are numerous haemorrhages. The affected segments stain poorly with nuclear stains, resemble infarcts and even at low magnification, with P.T.A.H. and trichrome stains, widespread pure fibrin thrombosis of capillaries and larger vessels is noticeable (Fig. 102). Extensive involvement of large and medium sized vessels is apparent (Fig. 103). Figures 104 and 105 show capillary involvement, and illustrate the severe confluent state of the condition. The alveolar exudate consists of red blood corpuscles in some areas, and in others consists of a coagulum of protein-rich fluid with a delicate network of fibrin. No other organs were examined histologically.

Comment. There is little doubt that these deposits were

responsible for foetal distress immediately before delivery, and at least four important observations can be made:- (1) it is remarkable that the infant was able to survive for 4 days with lungs in such a state; (2) it is remarkable that such lungs failed to become infected during that period; (3) the infant's blood fibrinogen level must have been very high initially; and (4) this infant lacked fibrinolysin, for the fibrin had lain for 4 days intravascularly before death, and postmortem examination was not carried out until 21.5.56, two days after the infant had died, the body having lain meanwhile in a cool but non-refrigerated mortuary. In spite of all this, the picture described above is to be found.

Case 23. (C 2155/58. Baby C. 4 days. R.M.W.H.)

Mother 37 years, para 7+1, rhesus negative without antibodies, admitted when 36 weeks pregnant with mild pre-eclamptic toxaemia. Membranes ruptured artificially. Labour 10 hours. Spontaneous vertex delivery of mature, female infant weighing 6 lb. 7 oz. (2,920 g.). The cord was once round its neck at birth. Admitted to sick nursery. Placenta showed small infarcts. Puerperium normal. Infant pale and limp at birth. No evidence of haemolytic disease of newborn in cord blood. Well enough next day to go to unit nursery. Readmitted

to sick nursery two days later, because refused feeds and vomited. Oxytetracycline ("terramycin") 25 mg. intramuscularly b.d. Collapsed suddenly and died at 4 days.

The cord blood was not available for fibrinogen estimations, but the heel blood at 12 hours of life gave a value of 245 mg. per 100 ml.

Postmortem Examination (R.M.W.H. 157/58). Pale, mild icterus, thorax normal, 5.0 ml. blood in peritoneum; massive bilateral suprarenal haemorrhages, right totally destroyed, and blood surrounded kidney, left two-thirds unaffected, total blood loss about 50.0 ml. (Fig. 106). No other abnormality.

Histological Examination. Lungs well expanded, no infection, focal necrosis of left adrenal cortex in relation to haemorrhage and total destruction of the right one.

Sections stained for fibrin show antemortem thrombi in both adrenal glands, and postmortem thrombi in the pancreas (Fig. 107). The remnants of the capsule of the right adrenal gland show no viable cortical cells. The sinusoidal architecture of the gland is apparent however, because of the widespread pure fibrin thrombi within them (Fig. 108 and 109). In the left adrenal gland the necrosis has been more focal, but the same pure fibrin thrombosis is seen (Fig. 110). Since this section

is not through the frankly necrotic sector, but at the margin of it, the ghost outlines of necrotic cells remain visible while the zona glomerulosa is intact. The quantity of intrasinusoidal fibrin in these two organs presents a marked contrast to the amount in the haemorrhage surrounding the gland (Fig. 111).

Comment. This case is not so much an example of a secondary haemorrhagic state resulting from depletion of blood clotting factors since fine fibrin strands are present in the haemorrhages to indicate that the blood can still clot although bleeding has taken place, as an example of severe bilateral adrenal gland infarction (total in the case of the right, and partial in the case of the left) due to heavy pure fibrin thrombi formation within them. The infarcts took two days to become colliquative, and thereafter the blood loss was possibly due to severe venous oozing from the central vein of the right adrenal gland, and to less severe oozing from the venous end of gaping sinusoids of the left adrenal gland, although the possibility of arteriolar bleeding cannot be excluded completely. It is unfortunate that the cord blood specimen was not available for the estimation of fibrinogen. It is noted that the placenta showed small infarcts and these infarcts may be related to the same thrombotic episode which resulted in the adrenal gland infarcts.

Case 24. (R.H.S.C. 12456/58. Baby W. 10 days.)

Mother primigravida, moderate pre-eclamptic toxaemia. Infant born by spontaneous vertex delivery at 41 weeks gestation on 8.12.58. Birth weight 11 lb. (4,990 g.). Puerperal pyrexia. Mother isolated. Baby restless. Given chloral. Fontanelle tense, umbilicus sticky. Transferred to Royal Hospital for Sick Children. Swab from umbilicus grew coliform organisms on culture. Lumbar puncture —— C.S.F. blood stained. Died at 10 days.

Postmortem Examination (R.H.S.C. 9620). Vein of Galen torn with much subdural bleeding around base of brain, yet vein still appeared turgid rather than collapsed. No abnormality in thorax or abdomen.

Histological Examination. The only abnormality was found in the central nervous system, and this consisted of laminated thrombus in a sub-ependymal vein of the third ventricle in the substance of the thalamus. This vein is a major tributary of the vein of Galen, and the features are well shown in the section stained by P.T.A.H. (Figs. 112 and 113) which show that the lesion is a mixed thrombus composed of red blood corpuscles as well as fibrin.

Comment. This is an example of retrograde venous thrombosis as a result of birth trauma causing a tear of the vein of Galen. Therefore, as in Case 10 above, this is an example of localised

traumatic thrombosis, and is not the result of disseminated fibrin thrombo-embolism where the thrombotic episode is thought to have occurred in relation to the placental circulation. It is also worthwhile noting that there is no sign of this 10-day old thrombus undergoing organisation, which is evidence in favour of its aseptic state.

Group II. Patients with Aseptic Fibrin Thrombi and with Secondary Infection

Case 25. (R.H.S.C. 12,431/58. Baby T. 2 days)

Delivered at home. Fifth child of healthy parents. Thirty-nine weeks gestation. Birth weight 4½ lb. (2,041 g.). Admitted on second day because of prematurity and hypothermia, had cyanotic attacks same day, started on intramuscular tetracycline 25 mg. four times daily, but died.

Postmortem Examination (R.H.S.C. 9618). Consolidation of both lower lobes. Culture: no growth but on smear numerous gram-positive diplococci showing lanceolate form and capsule formation.

Histological Examination. Lungs immature, atrial expansion only, early suppurative bronchopneumonia (Fig. 114). Other organs appear normal but staining by P.T.A.H. shows widespread pure fibrin thrombi in the one adrenal gland taken (Figs. 115 and 116).

Case 26. (R.H.S.C. 11,987/58. Baby T. 3½ days.)

Born at home but catheter would not pass down oesophagus to aspirate stomach. Admitted at 3 days in peripheral circulatory failure and died shortly afterwards.

Postmortem Examination (R.H.S.C. 9611). Common variety of oesophageal atresia with tracheal fistula, right lung composed of one lobe only, true dextrocardia, complete horse-shoe kidney, and bilateral pneumonia. Bacteriology: Lung — staphylococcus aureus resistent to penicillin.

Histological Examination. Bilateral suppurative pneumonia, fatty change in the liver. Sections stained by P.T.A.H. show widespread antemortem pure fibrin thrombi in the liver (Fig. 117) which seem to be responsible for fatty change at the periphery of the lobules and centrilobular necrosis. The spleen also shows sinusoidal thrombi of some duration as a result of which there is compensatory sinusoidal distension (Fig. 118). No other organ shows similar thrombi.

Case 27. (S.R.I. 5/66. Baby S. 4 days.)

Child born two weeks premature at home, before the arrival of the midwife, after a normal pregnancy. Mother para-4. Birth weight 4½ lb. (2,041 g.). Admitted, cold, pale, lethargic, feeble cry. Chlortetracycline ("aureomycin") 25 mg. 4 hourly. Improvement.

Intermittent epistaxis and melaena. Died.

Postmortem Examination (S.R.I. 5/66). Premature, marked cyanosis, lungs aerated, but multiple punctate abscesses. Liver acutely congested.

Histological Examination. The lung shows confluent pneumonia with areas of suppuration. Sections of the organs stained by P.T.A.H. show pure fibrin thrombi only in the lungs (Fig. 119). Here, there is to be seen the pattern noted in some of the previous cases. The thrombi are located in the alveolar capillaries (Fig. 120), in the larger vessels (Fig. 121), and in a few arteries, and veins also, where the thrombi may be seen against the endothelial aspect rather than occupying the centre of the channel (Figs. 122 and 123). All these figures show the widespread pneumonic process as a result of which fibrin is also present in the alveolar exudate in many places and in the lymphatic channels.

Case 28. (R.H.S.C. 3399/59. Baby L. 6 days.)

First child of healthy parents, born at home, full term, spontaneous delivery. Birth weight $8\frac{1}{2}$ lb. (3,856 g.). Two days later, the child was noticed to be pale and had grunting respirations. She was given half a million units of penicillin and $\frac{1}{2}$ g. streptomycin, and admitted on the following day. Intramuscular tetracycline 25 mg. 4 hourly was started and X-ray of the chest showed pneumonia.

Two days later digoxin ("lanoxin") 0.02 mg. four times daily orally was commenced. The child collapsed suddenly and died, aged 6 days.

Postmortem Examination (R.H.S.C. 9675). Atrophic dry umbilical stump, pus in air passages, haemorrhagic consolidation of lower lobe of right lung with diaphragmatic pleurisy, haemorrhagic areas in left lung, dilatation of right side of heart, severe bilateral intraventricular haemorrhages with involvement of third ventricle and rupture posteriorly to produce subarachnoid and subdural haemorrhages. Bacteriology of lung — coliform bacilli were grown.

Histological Examination. In right lower lobe, confluent bronchopneumonia with fibrinous pleurisy and early suppuration, wedge-shaped haemorrhages with incipient infarction in the left lung, small exocrine adenoma in the pancreas (Fig. 124), and subarachnoid haemorrhage over the brain.

Sections stained for fibrin show one small field in the consolidated right lower lobe which is, as yet, relatively unaffected by infection, and here capillary and venous pure fibrin thrombi are to be seen (Fig. 125) with the same features as described in earlier cases. I consider this to be evidence in favour of antemortem pulmonary thrombosis in the infected lobe and these are now mostly destroyed by the infection. This section

also shows haematoxyphil cocci in clusters which are gram-positive to suggest that the case is suffering from a staphylococcal pneumonia. The haemorrhagic areas in the opposite lung are neither infected nor the seat of thrombosis. The only other organ to show thrombi is the pituitary (Fig. 126), and here, the lesions are considered to be agonal.

Case 29. (C 256/58. Baby C. Twin I. 6 days. R.M.W.H.)

Mother 30 years, para-1, admitted in premature labour with twin pregnancy at 31 weeks gestation. First twin, female, born as an assisted breech delivery weighing 3 lb. 11 oz. (1,673 g.). Second twin, female, spontaneous vertex delivery, 3 lb. 15 oz. (1,786 g.). Placenta binovular, with infarcts in both portions. Puerperium satisfactory. Twin II survived. Twin I active and crying at birth. Placed in humid incubator with 40 per cent oxygen. Mildly oedematous for 2 days, followed by mild jaundice for 2 days. Then irritable, with rolling eyes. Chloral hydrate grain one followed by grain $\frac{1}{2}$ three hourly, and chlortetracycline ("aureomycin") 15 mg. 3 hourly. Colour improved but bizarre limb movements and facial grimacing persisted; peripheral failure appeared and death on sixth day.

Postmortem Examination (R.M.W.H. 19/58). Mild jaundice, multiple pulmonary haemorrhages becoming confluent in lower

lobe, distension of small intestine, pyogenic meningitis of left middle cranial fossa, posterior fossa and left parietal and occipital lobes. In addition, the brain showed confluent petechial haemorrhages in a wedge-shaped area of which the base was over the right motor area and the apex was close to the lateral ventricle. A haemorrhagic softening 2.0 cm. in diameter was present in the left parieto-occipital lobe. Middle ears clean. Bacteriology of meningeal pus — numerous gram-negative bacilli in smear. No growth on culture. Histological Examination. Lungs haemorrhagic but not infected, no umbilical vein sepsis, recent pyogenic meningitis and recent cerebral softenings.

Sections stained for fibrin show numerous fibrin thrombi in the vessels of the softened areas (Fig. 127). It is clear that the strands have lain longitudinally within the vessel, and are thus antemortem in origin (Fig. 128). It appears that the haemorrhagic softenings are the result of widespread fibrin thrombo-embolism of the vessels in the affected areas occurring about the time of labour. No antemortem thrombus is found in any other organ, but postmortem mixed thrombus is present in the lungs (Fig. 129). Although the other organs fail to show any evidence of blood-borne infection, this must have occurred in order to account for the meningitis. The cerebral softening shows no evidence of infection.

Case 30. (C 3502/50. Baby McC. 11 days. R.M.W.H.)

Mother 36 years, para-10, admitted at 37 weeks in premature labour. Breech delivery. Birth weight 2 lb. 6 oz. (1,077 g.). Placenta showed numerous large white infarcts. Puerperium normal. Infant's colour poor. Given lobeline, Vitamin K, adrenal cortical extract ("eucortone") $\frac{1}{2}$ cc. 4 hourly, and penicillin 100,000 units t.i.d. Oedematous. Eight days later, colour still poor, oedema gone, given chlortetracycline ("aureomycin") 15 mg. 4 hourly. Died at 11 days.

Postmortem Examination (R.M.W.H. 250/50). Marasmus, moderate jaundice, muco-pus in air passages, patchy bilateral bronchopneumonia in lower lobes, dilatation of right side of heart, olive green liver, extrahepatic bile ducts normal, congestion of suprarenal glands, kidneys and brain.

Histological Examination. Bilateral bronchopneumonia, fatty change in liver, normal intrahepatic bile ducts but numerous bile thrombi in the canaliculi.

Sections stained for fibrin show numerous antemortem fibrin thrombi in the pituitary gland only (Fig. 130). Many of these are bulky, laminated and causing distension of the sinusoids in which they are lodged. The appearances, seen better at a higher magnification (Fig. 131) are not accompanied by micro-infarcts. It is my opinion that this is due partly to the vascular system

in the pituitary being sinusoidal and partly to the multiple thrombi being solitary and isolated. Infarction results only when linkages take place so that alternative routes of blood flow become blocked. The appearances of these thrombi are consistent with an origin at birth.

Case 31. (B 3342/50. Baby C. 12 days. R.M.W.H.)

Mother 28 years, para-5, admitted for 5 days during 14th week of pregnancy with vaginal bleeding. Admitted at 29 weeks gestation with mixed accidental haemorrhage. Labour started 2 days later and a premature infant was born. Birth weight 2 lb. 9 oz. (1,162 g.). Puerperium satisfactory. Infant cried lustily, colour fair, given Vitamin K, heat and oxygen. In 12 hours had become very cyanotic. Adrenal cortical extract ("eucortone") given. Three doses given next day. Sulphamerazine ("cremamerazine") started. Condition remained unchanged for 5 days. On 10th day, some deterioration. Sulphamerazine ("cremamerazine") stopped, chlortetracycline ("aureomycin") 15 mg. 4 hourly started. Grey cyanosis during next two days with death on the 12th day.

Postmortem Examination (R.M.W.H. 237/50). Very premature, rather dehydrated, lungs bulky and consolidated, pus in smaller bronchi, right side of heart dilated, great veins congested, fatty change in liver, congestion of cerebral veins with postmortem thrombus in superior sagittal sinus, haemorrhage in anterior horn of

left lateral ventricle.

Histological Examination. Very immature lungs with development to atrial level only, no true alveoli, diffuse pneumonia which is resolving; of three blocks of brain, one shows a microscopic cerebral softening close to a vessel with antemortem pure fibrin thrombus. The softening is of recent origin and shows compound granular corpuscles and a glial response.

A section stained for fibrin shows the above feature in a striking fashion (Fig. 132). Closer examination (Fig. 133) shows a distinct layer of endothelium across the surface of this thrombus. Comparing this finding with the thrombi of case 30 (i.e. of comparable age) suggests that this finding is precocious at 12 days. Serial sections show that the thrombus is totally occluding the right hand fork of a bifurcation and that the layer of endothelium is that of the spur at the bifurcation rather than endothelium overgrowth as a result of organisation (Fig. 133). No thrombus is present in the lungs, liver, kidney or adrenal gland. Although the infant is infected, dying from pneumonia, neither the fibrin thrombus nor the infarct is infected.

Case 32. (R.H.S.C. 3532/59. Baby S. 13 days.)

Fifth pregnancy, third living child of healthy parents. Born at Royal Maternity and Women's Hospital, Rottenrow, as

spontaneous vertex delivery at 42 weeks after a normal pregnancy. Birth weight 6 lb. (2,722 g.). Placenta and puerperium normal. Baby had mild jaundice at sixth day when dismissed home. Remained well until tenth day when she vomited all feeds and had five, soft, pale green motions. Admitted to Royal Hospital for Sick Children. Rectal swabs negative for salmonellae, shigellae or specific B. coli types. Given intramuscular tetracycline 12.5 mg. 6 hourly. Became more ill. Fontanelle tense. Antibiotic changed to novobiocin 25 mg. and erythromycin 25 mg., each given 6 hourly. X-ray chest — fluid in left pleural cavity. Paracentesis — blood-stained purulent fluid yielding coagulase positive staphylococcus aureus (phage 80). Died on 13th day.

Postmortem Examination (R.H.S.C. 9676). Air passages injected, bilateral fibrinous pleurisy, haemorrhagic consolidation with suppuration in right middle and both lower lobes, thrombosis of the superior sagittal and transverse sinuses with biparietal subdural haematoma (Fig. 134), bilateral intraventricular haemorrhages (3rd and 4th ventricles free), middle ears clean, abdomen normal. Bacteriology of lung: abundant staphylococcus aureus (phage type 80) sensitive to chloramphenicol ("chloromycetin"), novobiocin, moderately sensitive to streptomycin,

slightly sensitive to erythromycin, resistant to penicillin and chlortetracycline ("aureomycin").

Histological Examination. There is a suppurative pneumonia showing numerous colonies of gram-positive and haematoxyphil cocci. In other areas there are severe pulmonary haemorrhages. Sections stained for fibrin show pure fibrin thrombi in the lung capillaries and other vessels (Figs. 135 and 136), both in the haemorrhagic and infected areas. Thrombi are also found in the renal venules (Fig. 137) and are obviously well organised with reconstitution of the vessel lumen. The appearance of these thrombi suggests that they are at least a fortnight old (i.e. arose before birth) because the thrombi are well incorporated into the intima of the vessel wall and are covered by endothelium. There is however also some propagated thrombus present (Fig. 138) which shows lamination and lies in a larger tributary of the main renal vein. No infarction has resulted from this lesion which shows no evidence of being infected. The sagittal sinus thrombus is obviously antemortem in its origin because of the related subdural haemorrhage and the presence of a bulging fontanelle before death. It is unfortunate that this area was not studied histologically at several levels in an attempt to determine whether or not thrombosis was initiated at birth or with the

onset of respiratory infection. Thrombi are not present in any other organ.

Case 33. (R.H.S.C. 2523/59. Baby R. Twin II. 15 days.)

This child was second of twins, born at term after a normal pregnancy by spontaneous delivery at the Royal Maternity and Women's Hospital, Rottenrow, Glasgow. Birth weight 5 lb. (2,268 g.). Discharged home well on 10.3.59, age 7 days. Three days later, child went off its feeds, but no vomiting or diarrhoea until 17.3.59 when admitted to Royal Hospital for Sick Children. Thin, dehydrated, rectal swab - no pathogens. Given neomycin ("kaomycin") drams one, 4 hourly. Next day, pyrexia, tetracycline 25 mg. intramuscularly 6 hourly. Oxygen therapy. Sudden collapse at 6.00 a.m. and died at 9.30 a.m. on 18.3.59, age 15 days.

Postmortem Examination (R.H.S.C. 9662). Small, 2,041 grams, patchy pneumonia, dilatation of right side of heart, both suprarenal glands normal in size but capsules tense and on section there is "old haemorrhage" with a rather brown tinge occupying the inner zone of each gland; rest of abdomen and head normal.

Histological Examination. Early bronchopneumonia. Both adrenal glands show identical features, namely those of old medullary

haemorrhage. No haemosiderin is present. A possible explanation for this will be apparent shortly.

Staining sections of lungs, heart, liver, pancreas, kidney, both adrenal glands, brain and thyroid gland for fibrin shows it only in the adrenal glands, and it is present to an equal extent in each. The sinusoidal fibrin is located essentially in the region of the "foetal" cortex (Figs. 139 and 140). Some areas show sectors of the adrenal gland packed with fibrin while intervening unaffected areas show compensatory dilatation of the sinusoids (Fig. 141). In many areas the age of these fibrin deposits can be gauged by the fact that they no longer occupy the axial stream but are located peripherally (Fig. 142). While the greater bulk of the fibrin is located in the foetal zone, the adult or definitive cortex has not escaped (Fig. 143), and further, in spite of this almost total blockage of both adrenal gland circulations, there has been very little cellular necrosis or infarction. Due allowance must be made for the normal involution of the "foetal" zone after birth which is accompanied by cytolytic necrosis. That the infant's fibrinogen was not all utilised in producing the adrenal thrombi, or that it has been capable of manufacturing more fibrinogen is shown by the coarse alveolar networks of fibrin in the pneumonic

areas. It seems likely that this infant's death resulted mainly from adrenal failure, whether medullary as a result of ischaemia, or cortical because hormones could not escape easily into the circulation, or both, cannot be determined accurately. At 15 days, with fibrin now lying against the endothelium, it seems reasonable that a circulation of a kind has been re-established through both glands. Any haemoglobin breakdown products could thus be removed before death results, but it is admitted that they are rarely removed as completely as in this present case. It is very difficult to explain why infarction has not resulted, with ensuing haemorrhage (see Case 23).

Case 34. (R.H.S.C. 3775/59. Baby D. 16 days.)

Born postmature by spontaneous delivery after a normal pregnancy at Royal Maternity and Women's Hospital, Rottenrow at 43 weeks. Birth weight 8 lb. 5 oz. (3,771 g.). Jaundice appeared at 24 hours, but faded at third day. Sent home well on sixth day. Four days later had six loose green stools and on next day refused all feeds. Admitted to Royal Hospital for Sick Children. Watery yellow motions and vomiting. No pathogens isolated. Intramuscular oxytetracycline ("terramycin") 25 mg. 8 hourly. N.P.N. 85 mg. per 100 ml.. Intravenous saline. Died five days later at 16 days.

Postmortem Examination (R.H.S.C. 9678). Dehydrated. Thyroid gland absent. Bilateral confluent pneumonia. Mucosal ulceration of small and large intestines. Kidneys normal. Head normal. Bacteriology of small and large intestines: no pathogens isolated. Histological Examination. Extensive pneumonia, extensive enterocolitis with ulceration, and associated with gram-positive cocci in the ulcerated areas. No thyroid gland tissue can be found.

Sections stained with P.T.A.H. show pure fibrin thrombi in the bowel only, and here it is found only in relation to the ulcerated areas. Afferent arterioles of the lower oesophagus show laminated fibrin thrombus (Fig. 144) while there are arterial and capillary pure fibrin thrombi in a superficial gastric erosion (Fig. 145). In the intestine the fibrin thrombi are antemortem, laminated and in the arterioles, capillaries and venules of the submucosa (Fig. 146). The age of the fibrin thrombi illustrated seems to be compatible with an origin at birth. The thrombi show retraction from the centre of the lumen and are seated over the endothelial surface, a necessary preliminary step to their incorporation into the intima. It seems sufficient to explain the alimentary symptoms on the basis of these vascular lesions alone, although it is possible that secondary invasion

of the devitalised areas by gram-positive cocci occurred later, and it is important to note that symptoms did not appear until the tenth day of life. Since it is believed that the thrombotic episode arises in the placenta, it would seem that the blood involved in this process became split into at least two portions, one entering the coeliac artery and left gastric artery to produce the lesions found in the lower oesophagus (within 5.0 cm. of the squamo-mucosal junction) and in the stomach; the other portion entered the superior mesenteric artery and produced the lesions noted in the small intestine and ascending colon. While scanty smaller lesions were present in the descending and sigmoid colons the opportunity was not taken to study these by histology for a vascular episode of this nature had not been considered at the time of postmortem and therefore it cannot be certain that these lesions are of the same nature. There is no evidence that the thrombi themselves are infective in origin. The occurrence of pure fibrin thrombi in arteries, capillaries and veins is in keeping with the lesions illustrated in the lungs in previous cases. The presence of pneumonia could be due to inhalation of infected material regurgitated from the alimentary tract, or could be due to previous thrombo-embolic lung infarctions although no evidence of this exists now if this was the case,

because the infection is so extensive throughout both lungs. The absence of a thyroid gland no doubt helped in producing a fatal termination.

If the alimentary thrombi illustrated were the result of alimentary infection, whose clinical duration was six days, it is unlikely that the thrombi would be in such an advanced state of retraction.

Case 35. (B 1146/50. Baby M. 19 days. R.M.W.H.)

Mother 40 years, para-3, admitted in labour at 42 weeks gestation. Had revealed accidental haemorrhage three weeks earlier. Labour lasted 16 hours. Spontaneous vertex delivery of mature, male infant weighing 7 lb. (3,175 g.). Placenta and puerperium normal, child admitted to sick nursery when 8 days old. Began to pass frequent foul smelling stools with fat globules. No vomiting. Jaundice appeared and deepened. Weight fell. No pathogens isolated. Condition deteriorated in spite of treatment. Died at 19 days.

Postmortem Examination (R.M.W.H. 103/50). Very emaciated. Deep jaundice. Marked abdominal distension. Rectal prolapse. Intestines greatly ballooned. Milk curds in air passages. No pneumonia or lung collapse. Right side of heart dilated, liver olive green, extrahepatic bile ducts normal, 1.5 cm. haemorrhage

in cortex of left suprarenal gland, right one showed medullary congestion, brain congested and showed focus of petechial haemorrhages in left lentiform nucleus.

Histological Examination. Intrahepatic biliary duct atresia with bile thrombi in canaliculi, pancreas normal, left suprarenal haemorrhage, multiple perivascular haemorrhages in region of left lentiform nucleus with localised oedema but evidence of necrosis is confined to the immediate vicinity of each haemorrhage.

Staining other sections for fibrin shows some to be present in the left adrenal haematoma which has remained encapsulated (Fig. 147). Unfortunately the block of tissue taken contains no surviving adrenal tissue other than a few distorted cells of the zona glomerulosa (Fig. 148). Even here, it is possible to suspect the remains of sinusoidal fibrin thrombi. The spleen, while apparently normal with the conventional haemalum and eosin stains, shows with P.T.A.H. widespread venous sinusoid thrombosis extending to the hilum (Fig. 149). This thrombus shows a mixed picture which I interpret as follows. The base of the thrombus in the bottom right hand corner is composed mainly of fibrin with an admixture of platelets. It is aseptic and has shown signs of retraction to this position - i.e. compatible with having been laid down at birth. The remaining 9/10 of

thrombus however is infective in origin, is mixed and laminated, and contains numerous polymorphs between the laminae. In the smaller septal sinusoids, the same picture can be seen (Fig. 150). In all cases, evidence of an aseptic portion can be found, evidence of retraction is present with re-establishment of flow through the newly formed restricted lumen, and further formation of thrombus which is laminated and infected is present at each site. Sinusoid fibrin is not evident in the sections, but may have been present earlier, for the red pulp shows collapse of its sinusoids in some areas with compensatory dilatation in others. The disappearance of the fibrin from the sinusoids could coincide with the onset of retraction of the first fibrin deposit in the larger vessels. The presence of retraction is compatible with these thrombi having formed about the time of birth. In the brain, mixed thrombi are found only in the area of the left lentiform nucleus. Here thrombi are present in relation to many of the perivascular haemorrhages. Although the vessel wall may be destroyed, the fibrin strands lie parallel to one another to suggest that they lay originally in a blood vessel. Only one or two of these thrombi show an aseptic nucleus with infective thrombus shell similar to that in the spleen. Most of the thrombi, however seem to be entirely infective in variety being rich in polymorphs (Fig. 151). The

cerebral lesion therefore probably occurred at some considerable time after birth. This agrees with the absence of marked necrosis as yet.

Case 36. (R.H.S.C. 11,510/58. Baby D. 22 days.)

Second child of healthy parents. Born at home. Mother's blood group O rhesus negative. Infant admitted at 2 days with congenital absence of both rectus abdominis muscles. Baby's blood - Hb. 16.5 g. per 100 ml., R.B.C. 5.6 mill./cu.mm., reticulocytes less than 1 per cent, erythroblasts nil, blood group O rhesus positive, Coombs' test positive. Jaundice next day. Serum bilirubin 22.5 mg. per 100 ml., all indirect. Exchange transfusion performed. Given 50 mg. chloramphenicol ("chloromycetin") 8 hourly. Not thriving and 2 weeks after admission, pus found in urine with staphylococcus aureus on culture. N.P.N. 85.5 mg. per 100 ml.. I.V.P. - right hydronephrosis; left kidney not functioning. Left submandibular abscess appeared and incised. Blood urea - 186 mg. per 100 ml.. Died at 22 days. Postmortem Examination (R.H.S.C. 9612). Submandibular abscess clean and healing; protuberant abdomen due to absence of rectus abdominis muscles, multiple lung abscesses, enlarged siderotic liver and spleen, kidneys pale, diffusely infected and urinary tract infected, both testes lying over sacro-iliac joints, pia-

arachnoid mater opaque over left Sylvian fissure, brain appears normal, no suggestion of kernicterus. Bacteriology of pus from renal pelvis: two types of B. coli; B. proteus, and S. aureus (phage type 80) sensitive to chloramphenicol, moderately sensitive to achromycin, resistant to penicillin and streptomycin. Histological Examination. Bilateral suppurative bronchopneumonia, acute pyelonephritis with cystitis, sub-cortical encephalomalacia confined to the region of the left Sylvian fissure (Fig. 152), no kernicterus.

Staining for fibrin shows remnants of pure fibrin capillary thrombi in the lungs, some in infarcted but non-infected areas but obviously being destroyed with the progress of infection (Fig. 153). The other organ to show antemortem fibrin thrombi is the spleen. The thrombi are located in the red pulp, and have caused collapse of the affected sinusoids while the unaffected sinusoids show compensatory dilatation (Fig. 154). No thrombi are present in any other organ, and in particular thrombosis cannot be utilised as an explanation for the localised sub-cortical softenings. The vessels pervading the affected area are quite patent (compare with Cases 18, 20, 29 and 31).

Case 37. (R.H.S.C. 6569/59. Baby G. 24 days.)

First child of healthy parents born spontaneously after

induction of labour at 42 weeks. Birth weight $5\frac{1}{2}$ lb (2,495 g.). Progress satisfactory until age of 2 weeks when refused feeds and had loose stools. Admitted to Royal Hospital for Sick Children. Dehydrated. Rectal swab grew on culture Shigella sonnei sensitive to chloramphenicol, streptomycin, neomycin, and resistant to achromycin. Treated with intravenous saline, and 125 mg. chloromycetin succinate intramuscularly, 6 hourly. Four days later, the child became cyanotic and oxygen was administered. On 2.7.59, child well, chemotherapy stopped. On 4.7.59 profound collapse, rales over both lungs, 100 mg. erythromycin intramuscularly but child died.

Postmortem Examination (R.H.S.C. 9704). Reasonably hydrated, gastric contents in air passages, consolidation of all lobes of lungs, except right middle lobe, with multiple abscesses, pleural surfaces dull. Heart, abdomen and head showed no abnormality.

Histological Examination. Confluent bilateral suppurative bronchopneumonia with scattered pulmonary artery thrombosis. No abnormality in any other organ.

Sections stained for fibrin show pure fibrin thrombi in some pulmonary arteries in different lobes (Fig. 155). These thrombi are of some duration, show signs of retraction with re-establishment of the vessel lumen, and with endothelial proliferation to line the new channels. Capillary fibrin thrombosis is also found

in the lungs in a few areas which are not yet destroyed by infection (Fig. 156). Thrombi are found in the splenic sinusoids (Fig. 157), and are confined to the red pulp. These are of some duration for compensatory dilatation of the unaffected sinusoids is present, and there is also evidence of retraction of the thrombi to one side of the sinusoids with re-establishment of their lumina (Fig. 158). This dates the splenic thrombi with those in the pulmonary arteries and both sets are compatible with having been formed three weeks earlier, i.e. at birth. It is noted that there is no evidence of splenic infarction, the thrombi are composed entirely of fibrin and no thrombus shows evidence of infection although there is widespread respiratory infection.

Case 38. (R.H.S.C. 3821/59. Baby G. 28 days.)

First child of healthy parents. Full term. Spontaneous delivery at Ross Hospital, Paisley. Birth weight 6 lb. 15 oz. (3,147 g.). Mild "physiological" jaundice. Dismissed well. Five days later found to have bilateral breast abscesses. Admitted to Royal Hospital for Sick Children at 14 days. Novobiocin 25 mg. 6 hourly. X-ray chest - accentuated lung markings, suggestive of infection. Later X-ray showed fluid in right pleural cavity. After one week, clinically improved but

radiologically worse. Then deteriorated. Antibiotic changed to chloramphenicol ("chloromycetin") 100 mg. 6 hourly intramuscularly. Increasing cyanosis and dyspnoea with death at 28 days.

Postmortem Examination (R.H.S.C. 9686). Well developed, right empyema, chronic lung abscesses in right lung, left lung normal, liver showed fatty change, spleen dark, firm and with prominent Malpighian corpuscles, small metastatic abscess in left frontal lobe. Bacteriology: pus from abscess of right middle lobe - abundant staphylococcus aureus (phage type 80) sensitive to achromycin, chloramphenicol, streptomycin, not sensitive to penicillin, slightly sensitive to erythromycin and novobiocin.

Histological Examination. Chronic lung abscesses and pyogenic bronchopneumonia, cerebral abscess.

P.T.A.H. staining reveals intravascular thrombi in the lung, liver and spleen. In the spleen there are confluent areas of fibrin deposition (Fig. 159). Some of these deposits would seem to date from birth (Fig. 160), for they have now retracted towards the endothelial surface to allow blood flow to return within the vessel. These also tend to be pure fibrin thrombi and are consistent with having been formed as a result of a thrombo-embolic episode at birth. The great majority of the

thrombi however are much more recent in their formation and resemble those in Figure 161, and these are mixed thrombi with a predominance of white blood corpuscles. They lie in the centre of the vessel lumen. For these reasons I consider that they are largely contemporaneous with the development of the lung infection episode at birth. When allowance is made for fibrin in the alveolar exudate, it is still possible to identify intravascular thrombi in the lung (Fig. 162). This fibrin forms part of mixed thrombi and is arranged always at the margin of an abscess and is patchy round its circumference. It does not assume the form demonstrated in the cases of aseptic thrombosis, although it seems likely that most of the thrombi are themselves sterile. In the liver the thrombi are situated in the mid-zones of the lobules and show the features of antemortem mixed thrombi which may have no connection with a thrombotic episode at birth. Agonal thrombi are present in the kidney and postmortem thrombi in the thyroid gland. None is present elsewhere.

Comment. In this series there is evidence of antemortem aseptic fibrin thrombo-embolism in varying degree. Some cases (e.g. numbers 27, 28, 32, 33, 34 and 35) would have died as a result of this lesion alone, or as in cases 28, 32 and 35, from the secondary haemorrhagic phenomena resulting from the formation of the

thrombi, without having had acquired an infection which was respiratory in five cases (numbers 27, 28, 32, 33 and 34) and septicaemic in one case (number 35). Further, Case 27 was mildly premature and Case 35 had intrahepatic bile duct atresia, facts which must be considered when the question of survival is raised.

Three cases (numbers 29, 30 and 31) are considered to have been so premature that survival was precarious from the start. It is interesting to note that the thrombi are localised to the central nervous system in two (numbers 29 and 31) and to the pituitary gland in one (number 30). It is believed that the cerebral lesions in Cases 29 and 31 constituted a real hazard to survival, and therefore assume second place to prematurity. Whether or not Case 30 would have shown evidence of pituitary insufficiency had he not succumbed to respiratory infection is debatable. It is the only case I have with such extensive pituitary lesions, and while it is apparent that the baby did not suffer from pituitary insufficiency at the time of death, I suggest that it would have exhibited this feature had it survived. Case 29 died from meningitis of undetermined aetiology, and this may have been a manifestation of a bacteraemia arising from an undetermined source.

Case 26 died primarily from oesophageal atresia. Although she revealed several other congenital defects at postmortem, only

the atresia was incompatible with life. Infants with this condition acquire an infection of the respiratory tract very readily as a result of food-stuff being inhaled. Thus, although this baby showed widespread hepatic and splenic sinusoidal thrombi, which added another hazard to survival, it is felt in this case that the fibrin thrombi are third in importance with regard to the factors causing death.

In four cases (numbers 25, 36, 37 and 38), while fibrin thrombo-emboli are present, it is doubted if they were present in sufficient quantity to have caused death by themselves. In Case 25, the lesions were in the adrenal gland but the child was mildly premature and died from pneumonia. The adrenal lesions barely had time to play any significant part in causing death. Case 37, I consider, was well on the way to surviving the initial thrombo-embolic lesion but unfortunately acquired dysentery with superadded pneumonia. The same applies to Case 38 where scanty thrombi are detected in the spleen, which are the result of an episode during birth, but are obscured by massive secondary thrombosis, the result of an incidentally acquired respiratory infection. Case 36 causes me great difficulty in assessing the relative importance of the various factors. There is no doubt in this case however, as has been shown in other cases, that

pulmonary capillary fibrin thrombosis, causing micro-infarcts, predisposes to pulmonary infection, as occurred in this case.

Group III. Thrombi Arising as a Result of Infection

The twelve neonatal infants in this group are considered in three sub-groups, according to the probable route of entry of the infection, - the respiratory tract, alimentary tract, or via the umbilicus. In each of these sub-groups the youngest infant will be considered first with progression towards the eldest.

Group III A. Respiratory Infections

Case 39. (P.M. 136/58. Baby G. 3 days. Redlands.)

Mother had no antenatal care. Born face-to-pubis. Large encephalocoele present. Placenta and puerperium normal. Cried on resuscitation, but colour poor at intervals with shallow breathing. Died on 4.7.58 aged 3 days.

Postmortem Examination. Mature male. Microcephaly with defects in occiput and in the arches of atlas and axis; encephalocoele sac contained entire brain with dura and pia-arachnoid maters; lungs showed patchy pulmonary haemorrhages; congestion of abdominal organs.

Histological Examination. Areas of collapse in lungs with areas of compensatory emphysema, patchy bronchopneumonia.

Sections stained by P.T.A.H. show thrombi rich in fibrin

in the spleen only. These thrombi are antemortem for there is compensatory dilatation of non-affected sinusoids and the fibrin strands run parallel to one another along the course of the channels. However, there is a certain raggedness about them (Fig. 163), and they are mixed in that red blood corpuscles are incorporated which makes me suspect that they formed once the respiratory infection became established and not until then. My interpretation of this case me be incorrect in the light of further experience.

Case 40. (B 4074/57. Baby McK. 6 days. R.M.W.H.)

Mother 22 years, para-1, admitted in premature labour at 30 weeks gestation. The infant's presentation was face-to-pubis, and because of delay in the second stage, delivery was effected by mid-cavity forceps. Birth weight 3 lb. 7 oz. (1,559 g.). Placenta and puerperium normal. Infant admitted to sick nursery at birth because he showed signs of asphyxia. He showed sclerema later, and oxytetracycline ("terramycin") was started. Marked jaundice appeared with serum bilirubin value of 20.7 mg. per 100 ml. serum. All bilirubin was indirect in variety. Repeated cyanotic attacks followed, and death occurred on sixth day.

Postmortem Examination (R.M.W.H. 257/57). Moderate jaundice,

scanty pulmonary haemorrhage, gallbladder and bile ducts normal. Liver jaundiced; extensive tentorial tear with subdural and subarachnoid haemorrhages. Haemorrhage of surface of cerebellum, and clot in left lateral ventricle. Bacteriology of lung: staphylococcus aureus (phage type 80).

Histological Examination. Patchy bronchopneumonia is the main finding.

Sections stained for fibrin show antemortem mixed thrombi in the lungs only. They are found in relationship to the suppurating areas (Fig. 164). I consider these thrombi to have been formed as a result of the lung infection because they are centred on the infected areas only, and not to be the cause of infection developing, as has been illustrated in earlier cases. The character of these thrombi is quite different from the previous cases (Fig. 165). The fibrin network is loose; although the major strands may be in the line of the blood stream, there are many interweaving strands, and in many, red blood corpuscles are trapped. Therefore, while the thrombi are antemortem without any evidence of being themselves infected, they have developed in relationship to infection and not to a thrombo-embolic episode at the time of delivery. The same case shows postmortem thrombi in the pancreas, intestine, brain stem and skin. No thrombus is found in heart, liver, kidney, adrenal gland or

salivary gland.

Case 41. (R.H.S.C. 4165/59. Baby M. 15 days.)

Second child of healthy parents. Born after a normal pregnancy at Royal Maternity and Women's Hospital, Rottenrow. Birth weight 5 lb. 6 oz. (2,438 g.). Spontaneous vertex delivery. Discharged well at 7 days. Four days later started to vomit all feeds and had frequent green motions rich in mucus. Admitted on following day to Royal Hospital for Sick Children. Dehydrated. Rectal swab - no pathogens isolated. Intramuscular tetracycline 12.5 mg. 6 hourly. Became very lethargic with apnoeic spells. Died on 15th day.

Postmortem Examination (R.H.S.C. 9684). Small; abdominal distension, bilateral confluent pneumonia with multiple abscesses, intestines ballooned, medullary congestion of kidneys, no abnormality in head.

Bacteriology of small and large intestines: abundant lactose fermenting organisms, no specific B. coli type isolated; of lungs: coliforms, B. proteus, beta-haemolytic streptococci (Lancefield group C).

Histological Examination. Confluent bronchopneumonia with early abscess formation, septic pulmonary lymphangitis, and septic thrombus in a pulmonary vein; septic thrombosis of the renal vein without renal infarction.

Sections stained for fibrin show septic thrombi in the pulmonary veins (Fig. 166) and in the renal veins (Figs. 167 and 168). These are obviously antemortem and show no apparent connection with birth, but they show much in favour of their being connected with infection, namely the aggregations of polymorphs into clumps. One field of the section of spleen shows thrombi in the sinusoids which, because they show no streaming characteristics, I consider to be formed postmortem (Fig. 169).

Case 42. (C 3905/50. Baby McL. 20 days. R.M.W.H.)

Mother 22 years, para-2. Premature labour at 38 weeks gestation. Spontaneous vertex delivery. Cord twice round neck loosely. Birth weight 3 lb. 6 oz. (1,531 g.). Feeble, responded slowly to resuscitation. Placenta and puerperium normal. Admitted to sick nursery. Lobeline, Vitamin K, heat and oxygen given. Later 0.5 cc. adrenal cortical extract ("eucortone") 4 hourly and penicillin 20,000 units 4 hourly started. Much improved during next five days. Then became irritable, grey, and chlortetracycline ("aureomycin") 25 mg. 4 hourly started. Some improvement during next seven days. Collapsed suddenly and died on 20th day.

Postmortem Examination (R.M.W.H. 287/50). Premature, widespread consolidation in all lobes of lungs, dilatation of right side of heart, abdominal organs and brain congested except liver which showed fatty change.

Histological Examination. Confluent bronchopneumonia. Liver shows moderate fatty change with tendency to mid-zonal necrosis.

Staining for fibrin by P.T.A.H. shows thrombi in the liver, and none in the lungs, oesophagus, spleen, kidney, adrenal gland, ovary, uterus and tubes, or brain. In the liver, the tendency to mid-zonal necrosis is noted and scattered sinusoidal fibrin thrombi are present (Fig. 170). These thrombi show all the features of being antemortem in nature, i.e. streaming effect, tendency to linkage, strands running parallel to the luminal axis but had these thrombi been formed at birth they would, if Group II above is any guide, now have vacated their central position and be found lying against the walls of the sinusoids, and any hepatic necrosis would be well developed. Further, the thrombi although rich in fibrin show a tendency to being "mixed" by the incorporation of occasional cells (Fig. 171). For these reasons, I consider the thrombi to be related in some way to the overwhelming respiratory infection.

Case 43. (R.H.S.C. 4821/59. Baby M. 28 days.)

This child's history is similar to that of Case 37, having been born at the Ross Hospital, Paisley, showing "physiological" jaundice, dismissed home well, admitted to the Royal Hospital for Sick Children later, with pneumonia and empyema, and dying at 28 days.

Postmortem Examination (R.H.S.C. 9689). Right lung riddled with abscesses, right empyema with broncho-pleural fistula, normal left lung, brain normal. Bacteriology: pus from right lung: moderate growth of staphylococcus aureus (phage type 29/52/79) sensitive to achromycin, chloramphenicol, not sensitive to penicillin, moderately sensitive to streptomycin.
Histological Examination. Multiple chronic lung abscesses, early metastatic spread to the kidney, cytomegaly of the zona reticularis of the adrenal gland.

P.T.A.H. stains show antemortem mixed and septic thrombi in the lung vessels in relation to the abscess cavities (Figs. 172 and 173). Scanty recent antemortem mixed thrombi are also present in the cortex of the adrenal gland (Fig. 174).
Comment. All five cases have died as a result of respiratory infections and their sequelae. There is no evidence in any that the infection became established in the lungs as a result of micro-infarcts due to thrombo-embolic phenomena during birth. Three of the cases showed patchy thrombi in the lungs in relation to the foci of infection. Antemortem thrombosis was also found in the liver, spleen, kidney and suprarenal gland in one case each. It is a well known fact that neonatal infections may cause renal vein thrombosis or sagittal sinus thrombosis, but it is not so

well known that thrombosis may affect the spleen or the liver under these conditions. It is difficult to understand the mechanism of these secondary venous thrombotic phenomena. If it were simply a matter of dehydration with haemo-concentration and increased viscosity, thrombosis should occur universally throughout the body rather than select the spleen, liver or brain or a paired organ such as the kidney.

Group III B. Alimentary Infections

Case 44. (R.H.S.C. 11,892/58. Baby M. 6 days.)

Born at Royal Maternity and Women's Hospital. Birth weight 5 lb. 10 oz. (2,552 g.). Mongol. Two days later, haematemesis. Vitamin K. given. 55 cc. fluid aspirated from stomach. X-ray - duodenal atresia. Transferred to Royal Hospital for Sick Children. Pre-operative intravenous therapy given but never fit for operation. Died at 6 days.

Postmortem Examination (R.H.S.C. 9610). Mongol, moderately jaundiced, thorax normal, atresia of duodenum beyond ampulla of Vater, proximal end greatly ballooned, stercoral ulceration of mucosa, regurgitation of duodenal contents into common bile duct which was ballooned, early peritonitis due to perforation, distal bowel collapsed.

Histological Examination. Early bronchopneumonia, oesophageal and duodenal mucosal ulceration, gram-positive cocci in clusters invading the tissue of these necrotic zones and polymorph cellular reaction present. Ascending infection in pancreatic and common bile ducts, fatty change in liver, scanty bile thrombi, infection of larger bile ducts.

P.T.A.H. shows antemortem capillary fibrin thrombosis in the submucosa of the duodenum which forms the base of the stercoral ulcers (Fig. 175). Postmortem thrombi are present in the salivary and thyroid gland, lungs, brain and spleen only.

Case 45. (R.H.S.C. 1267/59. Baby W. 12 days.)

Born at term after a normal pregnancy in Royal Maternity and Women's Hospital. Birth weight 8 lb. 1 oz. (3,657 g.). Well for 7 days. Dismissed home well. Next day, vomiting with five loose green offensive stools. Admitted to Royal Hospital for Sick Children. Cyanosis, dehydration. Rectal swab - no pathogens isolated. Intravenous saline and oxytetracycline 20 mg. 8 hourly administered. Blood urea rose to 289 mg. per 100 ml. Died on 12th day.

Postmortem Examination (R.H.S.C. 9649). Small intestine injected, serosa dull, kidneys rather small but otherwise normal.

Bacteriology of small and large intestines: no pathogens isolated.

Histological Examination. Thrombosis of renal veins. Lieb's P.T.A.H. confirms that the only antemortem mixed thrombi are in the renal veins causing great ballooning of these veins and of the arcuate veins (Fig. 176). The thrombi are laminated (Fig. 177) with clusters of polymorphs in places (Fig. 178) suggesting that they have an infective basis. Lamination suggests that the thrombi have been present for some time but there is no evidence of renal infarction. There is no thrombosis in the intestinal tract.

Case 46. (R.H.S.C. 12,553/58. Baby McD. 13 days.)

Born at home. Full term. Birth weight 7 lb. 12 oz. (3,515 g.). On fourth day became drowsy, refused feeds. Admitted to Royal Hospital for Sick Children on 12th day when diarrhoea and vomiting appeared. Dehydrated, right kidney palpable, oliguria. Given intravenous fluids with hydrocortisone, and oral tetracycline 25 mg. 6 hourly, but died on the following day.

Postmortem Examination (R.H.S.C. 9623). No abnormality in thorax, intestines appear normal, left kidney hypoplastic measuring 1.8 x 1.5 cm., and shows multiple cysts, right kidney hyperplastic, plum coloured with renal vein thrombosis, inferior vena cava normal, no abnormality in head. Bacteriology of ileum and colon: no pathogens isolated.

Histological Examination. Pulmonary oedema and congestion, no pneumonia, right renal vein thrombosis, left kidney probably non-functioning.

Sections stained by P.T.A.H. show antemortem thrombosis only in the right kidney. The left kidney is not affected (Fig. 179) nor is the intestine. The right kidney shows extensive renal vein thrombosis (Fig. 180) with haemorrhagic infarction of the medullary pyramids. Most of the thrombus is recent and "mixed" (Fig. 181) but in one or two fields older thrombus is present (Fig. 182). Here the thrombus is laminated or is showing signs of retraction towards the side of the lumen, and the entrapped polymorphs suggest that this older thrombus is infected while the recent thrombus is not obviously infected. The recent thrombus extends into the capillaries surrounding the tubules, but does not affect the glomeruli or arteries, and here it tends to be almost pure fibrin thrombus for some unknown reason.

Case 47. (R.H.S.C. 4,688/59. Baby S. 28 days.)

Seventh child of healthy parents. Born at home. Cord three times round neck. Birth weight 6 lb. 2 oz. (2,892 g.). When 27 days old, started to vomit, without diarrhoea at first. Admitted to Royal Hospital for Sick Children. Ill. Dehydrated. Rectal swab - no pathogens isolated. Saline given, and intra-

muscular oxytetracycline ("terramycin") 25 mg. 6 hourly. Deteriorated. Adrenal cortical extract. Nikethamide ("coramine"). No effect. Died next day.

Postmortem Examination (R.H.S.C. 9691). Large volume inhaled gastric contents. Intestines ballooned, injected, inflamed. No other abnormality. Bacteriology of small and large intestines: B. coli (type O 55).

Histological Examination. Early inhalational pneumonia, oedema and chronic inflammatory response in the small intestine associated with invasion of the intestinal mucosa with gram-positive cocci arranged in clusters.

Sections stained for fibrin show antemortem thrombi in the intestine only. The thrombi are in capillaries at the tips of villi in the small intestine which have been denuded of columnar epithelium (Fig. 183).

Comment. These infants presented clinically with the symptoms of alimentary infection. Histology shows antemortem alimentary thrombi in two (Cases 44 and 47) and renal vein thrombosis in two cases (Cases 45 and 46). It may be simpler to discuss them in order from Case 47 to Case 43. Case 47 had a proven B. coli type O 55 infection and showed intestinal capillary thrombi consistent in appearance with a two days' history. It may be however that the gram-positive

cocci identified in the mucosa on tissue section are responsible for the presence of antemortem capillary thrombi. Case 46 developed anorexia at the 4th day, and diarrhoea with vomiting did not appear until terminally. It would seem that this child acquired a blood-borne infection about the time of birth. This infection settled in the healthy kidney and at 13 days the thrombi are showing signs of retraction. They were responsible however for causing propagated and retrograde thrombosis throughout the whole renal vascular system, the secondary thrombosis being fortuitously non-infected, and resulting in total infarction. Although the infant appeared to have an alimentary infection clinically, it is possible that the terminal diarrhoea and vomiting could be manifestations of renal failure. Case 45 is difficult to assess. It is possible for these infected thrombi in the renal veins to have arisen from a thrombo-embolic episode in connection with birth, the difference from the other cases being that the thrombi are infected. There is no history relating to Cases 45 or 46 to substantiate puerperal infection in the mother, or neonatal infection in the infant at birth and indeed there is evidence against this. Infection must have established itself therefore very early in the neonatal period to have produced infective thrombi which could simulate with

regard to age an aseptic thrombo-embolic episode occurring at birth. What is the evidence that these thrombi are infective ? Two slender pieces of evidence exist:- (1) both infants had bouts of diarrhoea and vomiting resembling gastro-enteritis but from which no pathogen was isolated, and (2) clusters of polymorphs entangled among the fibrin strands. It may be therefore that while I have chosen to include these two cases in Group III B, they should be classified in Group I above. A point in favour of this is the lack of granulation tissue reaction in an attempt to organise these thrombi in a fashion similar to other known cases of septic thrombosis (e.g. Cases 43 and 48). Case 44 had duodenal atresia, a sufficient cause for death if left untreated, but the presence of mucosal capillary thromboses in association with invasion of the tissues by gram-positive cocci in clusters and a cellular response by the host resembles so much those illustrated in Case 47 and cases of proven gastro-enteritis in Group D infants (see below), that one reason for this infant's condition deteriorating much more rapidly than usual could be the presence of an unsuspected enteric infection, probably by staphylococci, whose progression was hindered by the atretic duodenum so that infection was

deviated into the common bile duct and pancreatic duct.

Group III D. Umbilical Infection

Case 48. (R.H.S.C. 6,471/59. Baby R. 17 days.)

First child of healthy parents. Full term. Spontaneous delivery. Admitted to Royal Hospital for Sick Children at 17 days and died on the same day. During the previous three days an umbilical infection had been noted and the child refused to feed. Abdomen distended, umbilicus everted, very toxic, gasping respirations. Died.

Postmortem Examination (R.H.S.C. 9701). Sero-sanguineous exudate in base of ulcerated area over umbilicus, purulent peritonitis, purulent phlebitis of the vein in the falciform ligament, in the main portal vein and its intra-hepatic branches, and in the splenic vein. Bacteriology of peritoneal pus: abundant growth of beta-haemolytic streptococci sensitive to penicillin, achromycin, chloramphenicol, bacitricin and slightly sensitive to streptomycin: soluble haemolysin positive. Histological Examination: Extensive suppurative phlebitis of the falciform ligament portion of the umbilical vein, the portal vein branches within the liver and the splenic vein. No pulmonary infection.

Sections stained for fibrin show antemortem thrombi in the infected veins only and is undergoing organisation which has been proceeding for some time. The fibrin is laminated in some vessels (Fig. 184) but in most of them it assumes an irregular craggy deposit against the intimal surface and is being organised by recanalisation and fibrosis with an ingrowth of new capillaries and fibroblasts (Fig. 185).

Comment. This case is a very typical example of neonatal umbilical infection by the organism causing puerperal sepsis - the beta-haemolytic streptococcus. Fortunately, although a typical example, such fatal cases are rarely encountered nowadays. It serves as a very adequate example however of the method of organisation of septic thrombi, and illustrates well the mechanisms involved and how they differ from those involved in removing aseptic fibrin thrombi which this series of cases illustrates well. It could be argued however, that the method of organisation and removal of thrombi may be different for different organisms causing thrombosis. Figure 172 shows the same appearances when the staphylococcus aureus is responsible. It is my experience with regard to deaths in adults that septic thrombosis becomes organised in this fashion regardless of the organism, provided it belongs to the pyogenic group. It is with this in view that

one of the conclusions which this series suggests is that aseptic thrombi are not "irritant" in the way that septic thrombi appear to be.

Group IV. Thrombi Associated with Congenital Lesions.

Case 49. (R.H.S.C. 5,712/59. Baby A. 3 days.)

Admitted to Royal Hospital for Sick Children, at 3 hours with ectopia vesicae, nonfusion of lower abdominal wall and perineum, and spina bifida. Died at 3 days.

Postmortem Examination (R.H.S.C. 9696). Mongoloid facies, ectopia vesicae, persistent proctodoeum, pedunculated sacral myelomeningocoele, two uteri each with a cervix, tube and ovary. Arnold-Chiari malformation, nonfusion of symphysis pubis, deficient coccyx.

Histological Examination. No infection, ectopia vesicae covered partly by transitional epithelium and partly by columnar epithelium.

Sections stained for fibrin show antemortem mixed thrombi in the wall of the ectopic bladder only. Even although the myelomeningoeoele is infected there is no thrombosis in the vicinity. In the bladder wall the thrombi are widespread throughout the mucosal capillaries, submucosa, and muscularis (Fig. 186). In some areas the mucosa is ulcerated but there is no evidence of infection and the thrombi are not centred on these

any more than in the areas where the mucosa is intact.

I consider this to be another example of traumatic thrombosis, on this occasion in relation to a congenital defect.

Case 50. (R.H.S.C. 10,120/58. Baby R. 5 days.)

Born on 5.10.58, full term, spontaneous delivery. Birth weight 6 lb. 10 oz. (3,006 g.). Family history of tuberculosis. At 3 days, jaundice appeared and later in the day he had a cyanotic attack. Transferred to Royal Hospital for Sick Children, Glasgow. Liver enlarged. Serum bilirubin 21 mg. per 100 ml. Next day, had two convulsions, liver and spleen much enlarged, cyanosis, bradycardia. Died at 5 days.

Postmortem Examination (R.H.S.C. 9585). Livid, numerous subpleural haemorrhages. Heart small, right side dilated with marked right ventricular hypertrophy, left auricle small, left ventricle hypoplastic with greatly thickened endocardium, aortic diameter is one third of pulmonary artery diameter, ductus arteriosus widely patent, other organs markedly congested.

Histological Examination. Partial atelectasis, marked fibroelastosis of left ventricular endocardium (Fig. 187). Venous congestion of all organs, and fatty change in the liver.

Sections stained for fibrin show this to be present in

the form of antemortem pure fibrin thrombi only in the liver and an appearance is seen which is longer than the infant's life of five days. The thrombi are in the sinusoids and are located in the mid- and central zones of many lobules (Fig. 188). It is apparent however that these thrombi are not in the centre of the sinusoids but are lining endothelial surfaces. As illustrated in earlier cases, this change does not occur until the thrombi have been present for about two weeks. It would appear therefore that these thrombi were the result of a thrombo-embolic episode experienced by the foetus while in utero. That the liver suffered suggests that the site of commencement of thrombosis was in the placenta. This phenomenon may be important also when the aetiology of fibro-elastosis is considered. No stainable fibrin can be found in the endocardium of this case.

Group V. Thrombi Associated with Surgical Conditions

Case 51. (R.H.S.C. 10,379/58. Baby S. 8 days.)

Admitted to Royal Hospital for Sick Children, Glasgow at 2 days. Full term. Forceps delivery for deep transverse arrest. Birth weight 7 lb. 11 oz. (3,487 g.). Next day developed abdominal distension and intestinal obstruction. Laparotomy - volvulus of small intestine on narrow mesenteric pedicle.

Untwisted. Failed to improve post-operatively and died at 8 days.

Postmortem Examination (R.H.S.C. 9590). Clean, healing, linear surgical wound across epigastrium, early pulmonary infection, fibrinous peritonitis with gas, gangrene of middle third of small intestine, narrow mesenteric pedicle, secondary internal hernia with obstruction, widespread superior mesenteric vein thrombosis not involving portal or splenic veins. Bacteriology of peritoneal tissue: staphylococcus aureus (phage type 29) sensitive to chloramphenicol and achromycin, resistant to penicillin and streptomycin.

Histological Examination. Early respiratory infection, widespread non-infective antemortem thrombosis of the superior mesenteric veins.

Sections stained for fibrin by P.T.A.H. confirm the thrombi in the superior mesenteric vein (Fig. 189) and its tributaries, for instance the right colic vein.

There is little doubt that this venous thrombosis resulted from the severe torsion of the mesentery, and led to gangrene of the bowel with peritonitis.

Case 52. (R.H.S.C. 3,991/59. Baby H. 9 days.)

Born at home. Birth weight 7 lb. (3,175 g.). No forearms or hands. Stumps of arms only. Forceful vomiting started.

Admitted to Royal Hospital for Sick Children, Glasgow at one and a half days. X-ray suggested duodenal atresia. Laparotomy - annular pancreas. Ring divided. Duodeno-duodenostomy to by-pass the stricture. Gastrostomy performed. Three days later, after making satisfactory progress, the child's condition deteriorated and he died at 9 days.

Postmortem Examination (R.H.S.C. 9685). Clean, healing, transverse, linear surgical wound, possible antemortem perforation of subhepatic caecum with faeces in peritoneum to which there is no reaction. Thrombosis of left renal vein.

Histological Examination. No pulmonary infection. Thrombosis of left renal vein. Congestion of interlobular veins and of glomeruli.

Sections stained for fibrin show antemortem thrombosis only in the left renal vein where there is antemortem mixed, laminated, non-infective thrombosis with involvement of the arcuate veins (Fig. 190) but the interlobular veins, and renal parenchyma are undamaged.

I consider that operation in the region of the pancreas and duodenum resulted in pressure or trauma to the main left renal vein specially vulnerable on account of its length, and this led to thrombosis. It is unfortunate that the left testicular

vein and left adrenal veins were not studied specifically.

D. INFANTS AND CHILDREN

Seventy-nine infants surviving beyond the neonatal period, and older children have been studied. Forty-four revealed thrombi of various types, and sixteen of these are considered to be antemortem in nature. Employing the same classification as that used under Group C above, these sixteen cases can be classified as follows:-

| | | No. of Cases |
|---|---|---|
| Group I. | Aseptic Thrombi | 0 |
| Group II. | Aseptic Thrombi with Secondary Infection | 0 |
| Group III. | Thrombi Arising as a Result of Infection | 9 |
| Group IV. | Thrombi Associated with Congenital Lesions | 5 |
| Group V. | Thrombi Associated with Surgical Conditions | 1 |
| Group VI. | Allergic Lesions | 1 |
| | Total | 16 |

In no case were the thrombi wholly responsible for death, and in 8 cases they were partly responsible for death. These cases are numbers 53, 54, 59, 63, 64, 65, 66, and 68. The remaining 28 cases show thrombi which are considered to be agonal or postmortem in type.

Group D. III. Thrombi Associated with Infection

Case 53. (R.H.S.C. 9955/58. Loraine D. 5 weeks.)

Third child of healthy parents. Heavy cold with fever on 1.10.58. Admitted on 4.10.58. Very ill. Dehydrated, fever, cyanosis, treated with saline, hydrocortisone and tetracycline. Died on 5.10.58.

Postmortem Examination (R.H.S.C. 9582). Bilateral bronchopneumonia, bilateral renal vein thrombosis with retrograde thrombosis of left adrenal vein. Bacteriology of lung:- scanty staphylococcus albus only.

Histological Examination. Bilateral bronchopneumonia with extensive suppuration, bilateral vein thrombosis.

Sections stained by P.T.A.H. show more information than is revealed by H. and E. staining. Organising renal arteriolar fibrin thrombi can be detected in some areas (Fig. 191), and they are accompanied by widespread renal glomerular capillary fibrin thrombi (Fig. 192). These are features more in keeping with renal cortical necrosis rather than with renal vein thrombosis although the latter condition is also present. The venous thrombosis shows two features. In the interlobular straight veins there is a tendency to early lamination (Fig. 193), while in the more major vessels the thrombi are mixed, are more recent, and occlude the whole vessel (Fig. 194). In the left adrenal gland where one expects to find only retrograde

thrombosis, there are also thrombi of some duration (Fig. 195a) in the sinusoids of the zona reticularis, as well as thrombi which are recent (Fig. 195b). Finally, there is a focus in one lung showing recent pulmonary embolism probably arising from the renal vein thrombosis (Fig. 196).

Comment. The main renal vein thrombi in this case are recent on the whole, while those in the interlobular veins are older (just on two weeks if the previous cases are any guide), and these seem to have arisen as a result of widespread glomerular thrombosis, which, in turn, has arisen as a result of renal artery thrombosis which is not less than two weeks old, and unlikely to be over three weeks old because the thrombi are not yet incorporated into the intima by overgrowth of endothelium. At the same time as this arteriolar thrombosis occurred a similar episode affected part of the adrenal gland. It is not possible to date these thrombi with the child's birth and the only history obtainable is a blister on the child's buttock when 2 weeks old from a hot water bottle. The family practitioner was called in to attend to it. Is there any connection ? One point is certain, and it is that the renal vein thrombosis did not result from the respiratory infection, but possibly the terminal respiratory infection resulted from pulmonary ischaemia as a result of pulmonary artery embolism from the renal vein thrombosis which is a consequence of renal artery thrombosis

which is the result of —— ? a minor burn. (See Medical Research Council Special Report Series No. 249 (1945) - Studies on Burns and Scalds, pp. 192 - 202).

Case 54. (R.H.S.C. 5453/59. Catherine McT. 2 months.)

Admitted with history of vomiting for one day, and with passing fresh blood per rectum. Operation - ileo-colic intussusception found, reduced, bowel viable. Intravenous fluid, chloramphenicol 125 mg. b.d. Post-operative ileus. Erythromycin 50 mg. intramuscularly 6 hourly. Death three days later.

Postmortem Examination (R.H.S.C. 9695). Clean, healing, linear surgical incision, inhaled gastric contents, left pneumothorax not under tension, no respiratory infection, diffuse adhesive peritonitis, ballooned small intestine with dark haemorrhagic areas associated with patchy venous thrombosis at mesenteric attachments not only of portion involved in the volvulus but also of uninvolved portions, induration and oedema of apex of reduced intussusception with viable bowel, patchy mucosal sloughs along whole length of small and large intestine.

Histological Examination. Mucosal necrosis with superficial ulceration in many other areas of small intestine as well as in the region of intussusception; clusters of gram-positive cocci found, some being intracellular, in ulcerated areas only.

Sections stained by P.T.A.H. show mixed thrombi in the intestinal sloughs and superficial gastric erosions (Fig. 197). In the region of the intussusception similar mucosal sloughs are detectable, but are more numerous and severe (Fig. 198). It is interesting that the germinal follicles of the Peyer's patches are spared, and that the fibrin thrombi are laminated against the endothelial surface of the vessels. This is all the more remarkable when it is also noted that the same features are present in the spleen (Fig. 199) and in the jejunum.

Comment. The extent of these thrombi along the alimentary tract, and their occurrence in the spleen, is peculiar in view of the nature of this child's illness - an intussusception with sudden onset and with rapid proficient treatment, in spite of which the child failed to recover. The nature of the thrombi however suggests that they have been present for 2 - 3 weeks, and when compared with cases 34, 44 and 47 above they suggest that the child suffered from an enteric infection of undetermined nature, and this may have precipitated the intussusception. It seems that the staphylococcus may be implicated. The history is unfortunately uninformative on this point. The presence of splenic thrombi may be evidence of a bacteraemia.

Case 55. (R.H.S.C. 8227/58. Helen J. 3 months.)

At 5 - 6 weeks of age, admitted to Belvidere Hospital, Glasgow with gastro-enteritis. More recently, vaccination abscess of arm treated at Royal Hospital for Sick Children, Glasgow. Dismissed on 6.10.58. Re-admitted on 9.10.58 with history of loose green motions and refusal to take feeds for two days. Rectal swab grew B. coli O 128 on culture. Infant died on the same day.

Postmortem Examination (R.H.S.C. 9584). Healing vaccination mark on right arm, ballooned small intestine with six agonal intussusceptions, fatty streaking of aorta.

Histological Examination. Congestion of bowel mucosa but no ulceration.

Sections stained by P.T.A.H. show no thrombi in the bowel. The fatty streaking of the aorta turns out to be granulomata deposited on the endothelium and composed of mononuclear cells, early small giant cells and strands of fibrin (Fig. 200). A layer of new endothelium almost completely covers the lesions.

Comment. It is difficult to know to which of the three infections these aortic granulomata ("fatty streaks") are related. Firstly, it takes a week or two for giant cells to form as a rule, and secondly it also takes three weeks before endothelial thrombi are

incorporated into the intima of a vessel. It would seem therefore that these aortic deposits are concerned more with the abscess of the vaccination site than with either attack of gastro-enteritis. Is it indicative therefore of a bacteraemia at that time ? No gram-positive organisms can be identified in these lesions.

Case 56. (R.H.S.C. 935/59. Georgina H. 15 weeks.)

Admitted on 29.1.59 with heavy, laboured breathing, refusal to feed, pallor, pyrexia. On admission, fontanelle depressed, very ill, one loose green stool. Rectal swab - no pathogens isolated. Intramuscular hydrocortisone and tetracycline. Sudden collapse and died at 1.10 am. on 30.1.59.

Postmortem Examination (R.H.S.C. 9639). Lungs showed basal congestive changes only, scanty petechial haemorrhages along atrio-ventricular groove, bowel showed no abnormality, head normal.

Bacteriology (1) of ileum and colon - no pathogens isolated; (2) of lung - mixed growth of coliforms, enterococci, and beta-haemolytic streptococci sensitive to penicillin.

Histological Examination. Patchy pneumonia, toxic myocarditis (Fig. 201), ileum and spleen show follicular reaction (Figs. 202 and 203) considered to be a reaction to subclinical measles. A measles epidemic was widespread throughout the city at this time.

Sections stained by P.T.A.H. show widespread mixed thrombi

in the spleen with collapse of the affected sinusoids and dilatation of unaffected ones (Fig. 204).

Comment. This child had an illness of two days duration according to the history. She has been incubating measles, and pneumonia has developed in which beta-haemolytic streptococci played a part. These organisms have caused toxic myocarditis with sudden collapse. It would appear that one of these infecting agents was responsible for the recent splenic thrombosis.

Case 57. (R.H.S.C. 4121/59. Sandra L. 16 weeks.)

Admitted at 8 weeks with the history of failure to thrive since birth. Found to have fibrocystic disease of the pancreas with chronic respiratory infection which never cleared up. Gradually deteriorated and died on 11.6.59.

Postmortem Examination (R.H.S.C. 9697). Wasted; pus in major air passages, areas of chronic suppuration in both lungs with early bronchiectasis in both lower lobes. Bacteriology of lung - abundant B. pyocyaneus with scanty staphylococcus aureus sensitive to chloramphenicol and streptomycin, resistant to penicillin and achromycin.

Histological Examination. Chronic suppurative bronchopneumonia with abscesses, fibrocystic disease of pancreas.

Sections stained for fibrin show mixed thrombi in the lung vessels in the walls of the chronic abscesses (Fig. 205).

Comment. Death with fibrocystic disease of the pancreas is usually the result of chronic staphylococcal lung infection. Thrombi are found in relation to the infected lung foci only.

Case 58. (R.H.S.C. 2667/59. June M. 9 months.)

Admitted on 23.3.59 with gross hydrocephalus, a sacral meningocoele and pyrexia. General condition poor. Deteriorated and died on 10.4.59.

Postmortem Examination (R.H.S.C. 9670). Sutures widely patent, skull bones very thin, four pints of cerebro-spinal fluid in ventricular system, aqueduct of Sylvius is forked, both foramina of Luschka non-existent, mild left hydronephrosis with hydroureter.

Histological Examination. Findings quoted above are confirmed. No pneumonia. Thrombosis of the adrenal vein with distension of some tributaries.

Sections stained by P.T.A.H. show thrombi only in the adrenal gland (Fig. 206). Here laminated thrombus occludes some major veins but sparing others, whilst affecting a few sinusoids as they pass through the medullary tissue. The cortex is spared. The thrombi are mixed, containing platelets, fibrin, red and white

corpuscles.

Comment. The cause of this thrombosis is not apparent.

Case 59. (R.H.S.C. 8587/59. Elizabeth K. 10 months.)

Admitted to Royal Hospital for Sick Children, Glasgow, at age of one month with umbilical hernia. Had whooping cough at 4 months. Had rectal prolapse at 5 months. Admitted to Belvidere Fever Hospital at 7 months with pneumonia. Well till day of re-admission to Royal Hospital for Sick Children (24.5.59) when refused all feeds, very warm, irritable, petechial rash over trunk and behind ears. Lumbar puncture revealed clear fluid. Given large doses of penicillin. Died on following morning (25.5.59) with a more widespread rash.

Postmortem Examination (R.H.S.C. 9692). Petechial rash widespread, both suprarenal glands are haemorrhagic but not enlarged (Fig. 207). Congestion of other organs. Bacteriology of spleen - large numbers of pus cells but no organisms seen on smear: no growth on chocolate agar.

Histological Examination. Bronchial cuffing by round cells; round cells and polymorphs in duodenal villi with development of lymphoid tissue and germinal follicles.

Sections stained by P.T.A.H. show widespread antemortem

thrombi in the duodenal mucosa and between the Brunner's glands while the pyloric mucosa of the stomach is unaffected (Fig. 208). These are pure fibrin thrombi. Antemortem mixed thrombi are present in the spleen, in small numbers (Fig. 209).

Comment. The presence of mucosal fibrin deposits in the duodenum together with the development of much lymphoid tissue there may suggest the presence of a low grade enteric infection although no organisms have been cultured, or seen on section. The splenic thrombi may suggest a bacteraemia. It is unfortunate that the adrenal glands had been mislaid for no histology has been made. It is unfortunate also that the skin rash was not studied histologically to determine if the petechiae were due to a purpura, or if they were due to vascular thrombi. The sudden onset of the terminal illness together with the rapid deterioration and death with the postmortem finding of bilateral adrenal haemorrhages suggest that an overwhelming septicaemia occurred.

Case 60. (R.H.S.C. 7171/58. Margaret L. 11 months.)

Admitted in July 1958 and found to have lymphatic leukaemia. Treated initially with delta-dehydro-hydrocortisone ("prednisolone"). Remission resulted, but relapse occurred in September. Readmission and treated with combination of "prednisolone" and 4-aminopteroyl glutamic acid ("aminopterin") -

the clinicians being fully aware of the potential risks with such therapy. A partial remission resulted. Readmitted on 25.10.58 with gross melaena and died on 29.10.58.

Postmortem Examination (R.H.S.C. 9592). Very pale, scanty purpuric spots, pulmonary oedema, widespread intestinal mucosal haemorrhages, little areas of haemorrhagic necrosis in the liver, 0.5 cm. infarct in the spleen, marrow resembled aplasia, but it was in fact leukaemic on histology.

Histological Examination. Leukaemic infiltration present in all thoracic and abdominal organs, and in marrow. Skin shows purpura only. Central nervous system normal. Sections stained for fibrin show mixed thrombi of an antemortem nature in the spleen only (Fig. 210). Even at low magnification it is possible to appreciate that these thrombi show signs of retracting to the wall of the sinusoid and thus appear to be about two weeks old.

Comment. The cause of the splenic sinusoidal thrombi cannot be stated with certainty. It is well to note however that the child had a chronic otitis media which yielded abundant staphylococcus aureus sensitive to achromycin and streptomycin, moderately sensitive to chloramphenicol, and resistant to penicillin.

Case 61. (R.H.S.C. 5321/59. Philip M. 1½ years.)

Admitted on 27.5.59 with a history of fever and vomiting

of one day's duration in association with a left ischiorectal abscess. Given penicillin, streptomycin, and chloramphenicol. Oxygen therapy was necessary because of the degree of collapse. On the following day the abscess was pointing and was incised without anaesthesia. The pus yielded abundant staphylococcus aureus sensitive to novobiocin and erythromycin. Later in the evening, the child developed peripheral circulatory failure with hypothermia, and he died on the following day.

Postmortem Examination (R.H.S.C. PC/8/59.). 1.0 cm. linear surgical incision over left ischiorectal fossa, abscess draining well, walls nearly cleared of sloughs, basal pulmonary oedema, spleen (89 grams), large, dark, firm with mild perisplenitis. Bacteriology of spleen: some gram-positive cocci and gram-negative bacilli on smear. Two colonies of staphylococcus albus and moderate growth of coliforms on culture.

Histological Examination. Early suppurative lymphangitis in portal tracts of liver, congestion of spleen with hyperplasia of Malpighian corpuscles.

Sections stained with P.T.A.H. show antemortem thrombi in the spleen only.

The perisplenitis is found to be due to an early serosal reaction. Widespread antemortem thrombosis is present (Fig. 211)

at the periphery of the Malpighian corpuscles and in the sinusoids, and higher power shows these to be mixed thrombi rich in fibrin. On studying areas where the changes are less advanced the impression is gained that these fibrin clusters are formed in relation to cocci (Fig. 212).

Comment. While antemortem in nature, the thrombi have been present for less than two weeks and this agrees with the clinical history.

Group D. IV. Thrombi Associated with Congenital Lesions

Case 62. (R.H.S.C. 10,688/58. Jacqueline M. 9 weeks.)

Admitted on 24.10.58 with a history of breathlessness and difficulty in feeding since birth. Not active. Pale complexion. No cyanosis noted until two days before admission. Cyanotic attack on admission. Loud systolic murmur over all areas. X-ray chest: enlarged heart and pulmonary plethora. E.C.G. - left ventricular preponderance. Gained weight until 1.11.58 when developed fever, dyspnoea, and died on 2.11.58.

Postmortem Examination (R.H.S.C. 9594). Mild cyanosis, pulmonary plethora with haemorrhagic areas, heart 52 grams, greatly enlarged, hypertrophy of both ventricles, capacity of left ventricle is twice that of right ventricle. Dilatation of both auricles, 1.25 cm. diameter atrial septal defect, 0.75 cm. ventricular septal defect

of membranous portion, mild congestion of other organs. Histological Examination. Early pneumonia with tracheitis, venous congestion.

Sections stained for fibrin show antemortem thrombi only in the liver. The thrombi lie in the sinusoids and are located in the mid- and central zones of the lobules (Fig. 213). The thrombi (Fig. 214) are mainly of fibrin composition, are antemortem in type because the fibrin strands lie along the direction of blood flow in the centre of the lumen and because there is evidence of dissolution and necrosis of the liver cells near the central vein.

Case 63. (R.H.S.C. 5982/59. Judith H. 13 weeks.)

Admitted on 12.6.59 with cyanosis during the last four days with refusal to take meals. Systolic murmur in all areas. X-ray chest - no cardiac enlargement but left ventricular preponderance, oligaemic lung fields. E.C.G. - left axis deviation in standard leads, P pulmonale, left ventricular preponderance. Condition deteriorated. Died on 20.6.59. Postmortem Examination (R.H.S.C. 9699). Cyanosis, pus in trachea, major and minor bronchi, heart normal in size, tricuspid atresia with rudimentary right ventricle, foramen ovale widely patent, left ventricular hypertrophy, ventricular septal defect, ductus arteriosus closed. Bacteriology - pus from trachea -

abundant coliform organisms, few alpha-haemolytic streptococci, and scanty staphylococcus aureus resistant to penicillin, achromycin, chloramphenicol and streptomycin.

Histological Examination. Patchy bronchitis, mild congestion.

Sections stained for fibrin show antemortem thrombi in a kidney only. Here, glomerular capillary thrombosis is found without any arteriolar or venous involvement. The thrombi are mainly fibrinous in character and select some loops in glomeruli while sparing others and affect about one quarter of all the glomeruli studied. Figure 215 gives an indication of the various features. The thrombi have been present for sufficiently long to cause collapse of affected capillary loops, compensatory dilatation of others, and in occasional loops the fibrin shows signs of settling out from the axial stream to lie against the endothelium. This suggests a duration of about two weeks in some instances.

Case 64. (R.H.S.C. 6159/59. Alex M. 15 weeks.)

Heart murmur heard at 4 days. On 1.6.59 the child had an illness resembling measles and since 8.6.59 has had flatulence. Admitted on 16.6.59 and loud systolic murmur heard at lower end of sternum. Screening of chest - prominent left ventricle with broadening of mediastinum. E.C.G. - right axis deviation. Large deflections in V4 such as those described in ventricular

septal defect. Cyanotic attacks persisted when being fed. Tetracycline 50 mg. 6 hourly. Became dyspnoeic on 8.7.59 with cyanosis, rales at both bases and was given 0.1 mg. digoxin intramuscularly. Died on 9.7.59.

Postmortem Examination (R.H.S.C. 9707). Cyanosis, pulmonary oedema, heart not enlarged, hypertrophy of both ventricles, defective foramen ovale, high ventricular septal defect, supernumerary left superior vena cava draining via the oblique vein into the coronary venous sinus, congestion of abdominal organs.

Histological Examination. Pulmonary oedema, no infection, congestion of organs.

Sections stained for fibrin show antemortem thrombi in the liver only. Here, the fibrin is more diffusely distributed throughout the lobules and is not very apparent with low magnifications, but with the higher magnifications, thrombi are easily identified (Fig. 216). They lie in the centre of the sinusoids, and being more scattered, they have not caused the same degree of parenchymal damage as illustrated in some earlier cases, but scanty foci of incipient centrilobular necrosis are present nevertheless (Fig. 217).

Case 65. (R.H.S.C. 3224/59. Catherine C. 16 weeks.)

Admitted on 7.4.59 with congestive cardiac failure. Found

to have a heart murmur five weeks after birth, with slight cyanosis. Dyspnoea appeared two months later. Given oral tetracycline 25 mg. 6 hourly and digoxin ("lanoxin") 0.1 mg. intramuscularly to be followed by 0.1 mg. orally 6 hourly. Deteriorated and died on 10.4.59.

Postmortem Examination (R.H.S.C. 9671). Mild ankle oedema, marked pulmonary congestion and oedema with areas of haemorrhage, heart (66 grams) greatly enlarged, massive right ventricular hypertrophy with dilatation, rudimentary left ventricle, large ventricular septal defect, transposition of great vessels, foramen ovale and ductus arteriosus closed, abdominal organs pale, brain 645 grams (cerebrum 580 grams, cerebellum 65 grams) mild superficial congestion, gross haemorrhagic leuco-encephalopathy throughout with large 6.0 x 4.0 x 4.0 cm. haemorrhagic subcortical softening in the right temporal lobe extending into the occipital lobe (Fig. 218).

Bacteriology and virology of trachea, lung and brain: - no pathogens isolated.

Histological Examination. Terminal inhalation of gastric contents, no pneumonia, severe pulmonary congestion, oedema and haemorrhage, fatty change in liver, numerous intravascular thrombi in the cerebral capillaries and venules with numerous haemorrhages and softenings, not infected but antemortem with reactionary gliosis (Figs. 219, 220 and 221).

Sections stained by P.T.A.H. show antemortem thrombi in the cerebral hemispheres, kidney and adrenal gland. In the brain some of the features have been illustrated already. In many areas widespread antemortem capillary and venous thrombosis is present (Fig. 222). This is essentially composed of fibrin thrombi but in some vessels, both large and small, "mixed" thrombi are readily identified (Fig. 223). In this last figure, lamination is well shown and there is a tendency for the fibrin to cover the endothelium and leave the central channel free. From evidence illustrated previously, it would appear that the thrombotic state has been in existence for almost two weeks. This case illustrated also (Fig.224) how little fibrin is present in the regions of haemorrhage. The kidney shows widespread glomerular capillary thrombi (Fig. 225), and the adrenal gland shows widespread deeply staining cortical sinusoidal thrombi with strands lying parallel to one another between the columns of cortical cells (Fig. 226).

Case 66. (R.H.S.C. 2149/59. Dorothy M. 17 weeks.)

Admitted when 8 weeks old because of repeated vomiting. Small and thin. Systolic murmur at apex and along left sternal border. Very orthopnoeic, minimal cyanosis. Given digoxin ("lanoxin") and chlorothiazide ("saluric") with much benefit.

Still had feeding difficulties. Developed two scalp abscesses. Culture grew staphylococcus aureus sensitive to chloramphenicol and streptomycin, resistant to penicillin and achromycin. Went into cardiac failure for the second time. Treatment without effect. Died at 18 weeks.

Postmortem Examination (R.H.S.C. 9706). Cyanosis, pulmonary oedema, enlarged heart with left and right ventricular hypertrophy, widely patent foramen ovale, 1.0 cm. ventricular septal defect, ductus arteriosus closed, liver congested.

Histological Examination. Pulmonary capillary congestion and pulmonary oedema, possible early pneumonia, mild fibro-elastosis of left ventricle, liver shows fatty change and congestion.

Sections stained for fibrin show antemortem mixed thrombi in the liver only. These thrombi (Fig. 227) are rich in fibrin nevertheless, are located in the midzones of the lobules, and show collapse of the affected sinusoids with compensatory dilatation of the unaffected ones. It may be that the latter have been subjected to venous congestion and have responded to this while the former are unable to respond. Further examination shows that these thrombi are migrating from the central axial position to the periphery of the sinusoid (Fig. 228), and since the majority of

thrombi show this feature it is believed that they are about two weeks old. The only incident in the patient's history occurring two weeks before death is the presence of the scalp abscesses, but these hepatic thrombi are not typically infected thrombi although they are similar to thrombi illustrated previously, which are seen in association with infection.

Comment. It is difficult to give an explanation for the occurrence of thrombosis in these five cases of congenital heart disease. The thrombi are too recent in appearance to have any connection with birth in any of the cases. The liver is affected in 3 cases, the renal glomeruli in two, and the brain and adrenal gland in one case. The thrombi are different from those described in the earlier cases in Sections A - C, being mainly "mixed" in character, although the renal glomerular thrombi in Case 63 resemble pure fibrin thrombi in many instances. If an attempt is made to correlate some incident in the history with the formation of the thrombi, the following result is obtained:-

Case 62 :- onset of heart failure.

Case 63 :- "unwell" with refusal of food, and cough.

Case 64 :- already experiencing intermittent cyanotic attacks.

Case 65 :- already experiencing severe cyanotic attacks.

Case 66 :- appearance of scalp abscesses.

Rich (1948) recorded a high incidence of pulmonary thrombosis in patients with the tetralogy of Fallot, and while unable to explain the full basis for this lesion, he considered that polycythaemia with increased viscosity played a part and possibly a sluggish pulmonary flow which was much less in volume than normal as a result of pulmonary stenosis. None of these patients fit into this category although they have congenital heart disease. Could anoxia play a part ? If so, other factors must be involved, for there must be other explanations for the selection of affected organs.

Group D. V. Thrombi Associated with Surgical Conditions

Case 67. (R.H.S.C. 10,778/58. Thomas P. 1½ years.)

Admitted as an acute abdominal emergency. Laparotomy - complete volvulus of small intestine found. Untwisted. Bowel viable. Died within 24 hours postoperatively. Incidental history - blind in right eye for last 14 months, because of retinoblastoma.

Postmortem Examination (PC/38/58). Nothing unusual found to account for death. No ileus. Bowel suffused but viable.

Histological Examination. Right retinoblastoma (Fig. 229), left fundus normal.

Sections stained for fibrin show thrombosis of the basilar artery at the midbrain level (Fig. 230). It is a mixed thrombus. Since this is a chance finding, it is not possible to discuss the origin or consequences of this solitary finding.

Group D. VI. Allergic Lesion of the Vascular System

Case 68. (R.H.S.C. 11,281/58. Carol B. 6 years, 10 months.)

Admitted with 3 days history of cramps in both legs, swelling of the ankles, right hand, fever and lethargy. On admission had a purpuric rash and later had melaena stools accompanied by coffee grounds vomiting. Three weeks later, albumin, casts, red blood corpuscles in urine, blood urea 130 mg. per 100 ml., mild hypertension. One month later developed ascites with marked oedema, hypertension worse, degree of renal failure worse. Muscle biopsy - polyarteritis nodosa. Died with convulsions.

Postmortem Examination (R.H.S.C. 9638). Polyarteritis nodosa of coronary arteries, gross pulmonary oedema, pericardial and pleural effusions, patchy intestinal haemorrhages, periportal haemorrhages in liver, both kidneys show confluent wedge-shaped cortical haemorrhages, subarachnoid haemorrhage, small cerebral haemorrhage in region of left external capsule.

Histological Examination. Typical chronic periarteritis nodosa

of coronary arteries, hepatic and pancreatic arteries, arteries of small intestine, suprarenal arteries, renal arteries, and arteries of psoas muscle.

Sections stained by P.T.A.H. for fibrin show thrombi in many of the affected arteries (Figs. 231 to 235).

Comment. The aetiology of the arteritic lesion in this condition is imperfectly understood. It is apparent that thrombosis is part of the arteritic process. In the more chronic lesions illustrated it is noted that the fibrin once incorporated into the thickened intima begins to lose its customary staining properties. Since the total clinical duration of the illness was eleven weeks, and since one or two intimal fibrin deposits have almost lost their staining properties, it would seem that these changes start much earlier than eleven weeks, but it is unfortunately not possible to state with any certainty how soon in the disease this change is first detectable. It is possible however to suggest that, about 11 or 12 weeks after the onset of such lesions, the customary staining reaction of fibrin is totally lost.

## E. THROMBOSIS IN RELATION TO TUMOURS

In the course of this study, thrombi were found in three patients in relation to tumours, once in a stillbirth, and twice in children of $1\frac{3}{4}$ years and $8\frac{3}{4}$ years. It is considered that these cases merit separate attention and have not been considered in sequence in the previous sections for that reason.

### Case 69. (S.R.I. 6/33. Baby G.)

This female infant was stillborn after 35 weeks gestation. At postmortem examination, she was pale and showed such gross anasarca that hydrops foetalis was considered to be the probable diagnosis. Histologically there was intense extramedullary haemopoiesis, more than could be explained by the moderate degree of prematurity.

The liver was greatly enlarged to three times normal because the whole left lobe was replaced by a diffuse subcapsular vascular tumour. On section there were cavernous areas and haemorrhagic areas so that naked-eye examination suggested a massive cavernous angioma. Histological examination however showed an adenoma of liver composed of cords of liver cells, wide sinusoidal channels and the absence of portal tracts (Fig. 236). Many areas are necrotic and sections stained by P.T.A.H. show massive antemortem thrombi with parallel streaming

strands of fibrin, with lamination and with "sedimentation" of the fibrin against the walls of the sinusoids (Fig. 237).

Comment. These features recall the appearances noted in the liver of Case 3. The appearances are very similar in the two cases, but Case 3 shows the features in the liver itself while the present case shows them in a simple adenoma of liver.

Case 70. (R.H.S.C. 7490/58. Carol A. 1 year 9 months.)

Terminal admission because of retention of urine due to massive pelvic metastases of sacro-coccygeal tumour. Suprapubic cystostomy performed. Died two months later.

Postmortem Examination (R.H.S.C. 9580). Enormous pelvic mass of grey necrotic tumour tissue, sacrum totally destroyed, liver riddled with grey secondary tumour nodules, also present in the lungs. No cerebral metastases.

Histological Examination. A columnar cell myxo-papillary tumour which some pathologists consider to be a variety of chordoma while others consider that they belong to the myxo-papillary ependymoma group of tumours; these latter however are not as highly malignant as the type of tumour under discussion (Fig. 238). Professor D.F. Cappell, Western Infirmary and Glasgow University, and Dr. A.M. MacDonald, Pathologist to Royal Hospital

for Sick Children, Glasgow, however consider this to be unlikely and that it is best regarded as being of teratoid origin until further information is available.

Sections stained for fibrin show numerous mixed thrombi, some of long duration, not only in the main mass but also in the hepatic and pulmonary metastases (Figs. 239 and 240). It is of interest to note that in spite of intense pressure on the normal liver tissue adjacent to a metastasis this shows no evidence of thrombosis (Fig. 241).

Case 71. (R.H.S.C. 12,724/58. James S. $8\frac{3}{4}$ years.)

Admitted on 25.12.58 complaining of listlessness, anorexia, joint pains and vomiting for 7 weeks. The anti-streptolysin "O" titre was normal. Treated however as rheumatic fever, but after one month, condition I.S.Q.. X-rays of long bones revealed cortical erosions suggestive of early leukaemia. Peripheral blood examination normal. Bone marrow - infiltrated by primitive cells suggestive of neuroblastoma, but not like leukaemia. X-ray - I.V.P. - lateral and downward displacement of left kidney due to enlargement of left adrenal gland. No response to Vitamin $B_{12}$ therapy. Multiple skull secondaries appeared. Died on 10.5.59.

Postmortem Examination (R.H.S.C. 9687). Marked weight loss. 8.0 cm. diameter left adrenal gland replaced by haemorrhagic necrotic tumour, para-aortic lymph nodes contain numerous secondary grey nodules, which are also present in the liver, skull, ribs, sternum, vertebrae and pelvis.

Histological Examination. Typical neuroblastoma, rosettes being best seen in the lymph node metastases (Fig. 242).

Sections stained for fibrin by P.T.A.H. show it to be present intravascularly only in the tumour deposits. In the primary mass and in the metastases too, it is found not only intravascularly but also interstitially and this makes it difficult to reproduce on photography. Figures 243 and 244 are an attempt to do so.

Comment. It is difficult to understand why some tumours should show intravascular thrombosis while others do not do so. The best known example of this is the glioblastoma multiforme. In addition, there may now be added this example of so-called myxo-capillary sacro-coccygeal tumour, and some cases of neuroblastoma for I have another case which is negative. Other tumours encountered which do not show this tendency are lymphatic leukaemia, myeloid leukaemia, chloromata, Letterer-Siwe disease, and medullo-blastoma.

## F. THROMBOSIS AND THE ANTEMORTEM BLOOD FIBRINOGEN LEVEL

Another method of studying the problem of thrombosis is to compare that seen histologically by special stains with the blood fibrinogen levels determined before death. In the course of biochemical studies, reported later in Section H, this situation occurred 16 times. Two cases (numbers 13 and 23) have been discussed in detail in Sections B and C respectively. A third case has been followed very closely for the first five months of her life and the child died in the Royal Hospital for Sick Children, Glasgow, aged 8 months, without any recent fibrinogen estimation having been made, and therefore this case was excluded. The remaining 13 cases are summarised in Table I. The interval between the cord blood sample and column one of heel blood samples was about 12 hours. Thereafter, there are 24 hours between each column. At postmortem 13 routine blocks of tissue were selected for histology, namely 3 of lung and one each of heart, liver, pancreas, spleen, kidney, adrenal gland, skin, brain stem, pituitary and salivary gland. Often a block of trachea with thyroid gland was taken. Any additional lesion meant that additional blocks of tissue were taken. The histological sections of these thirteen cases were re-examined for fibrin

deposits and each one was graded in this manner:- 1 point for a small wisp, 3 points for a moderate sized deposit (about three times the size of a wisp) and 6 points for a large strand (on the average about six times the size of a wisp). Occasionally a very large strand was encountered which was equivalent to two large strands as defined and was counted as being equivalent to two of these. Examples are shown in Figures 245 - 247. These arbitrary values were added to give a total for each case, and the cases were grouped in accordance with the last available fibrinogen value (Table II). It is seen that as the fibrinogen value rises so does the "points" value. Cases 76, 82 and 84 are out of alignment and an explanation was sought for each of these. Case 76 lived for only 2 hours but on microscopic examination showed an early intrapartum bronchopneumonia with intra-alveolar fibrin exudation. This has not been assessed in the points system because I was concerned only with intravascular (including intra-lymphatic) fibrin. It would seem therefore that in the 2 hours of life, this infant lost about two-thirds of its circulating fibrinogen into the lung alveoli. Case 82 lived for 2 days after its heel blood fibrinogen had been estimated. Microscopic examination shows well marked hyaline membrane formation which is moderately rich in fibrin. This is another case which has lost about two-thirds of its

fibrinogen from the circulation. Case 84 lived for $1\frac{1}{2}$ hours and death resulted from blood loss in the intrapartum period from an unsuspected vasa praevia. This situation is similar to any variety of acute blood loss, and the cord blood value was probably a reasonably accurate assessment of the true value, but the low points value from histology would seem to be a measure of the severe haemodilution occurring after birth. The haemoglobin before death was about 30 per cent (Sahli). Explanations are therefore available for these three cases not showing correlation between the fibrinogen level and the fibrin found histologically after death. The mean points values at the foot of Table II are therefore the means of the other values, and in the case of the last column the value of ? 174 is obtained by extending the series of means which seem to be forming a simple arithmetic series with a difference of 40 points between each mean. It would also appear that one "point" on this basis is equivalent to about 2.5 - 3.0 mg. of fibrinogen.

One conclusion to be drawn from these results is that the assessment of the fibrin in histological sections gives a reasonable assessment on a broad basis of the blood fibrinogen level immediately before death.

Another point can be discussed at this stage. Earlier it was stated that by using the P.T.A.H. staining method routinely only a small proportion of all cases show fibrin which can be classified by certain characteristics into antemortem, agonal, and postmortem forms. In this section however, I have discussed 13 random cases which all show fibrin on histological examination. Obviously an explanation is necessary. In this latest small series the high power (1/6 inch, 4 mm.) objective lens was used throughout in order to detect the smallest and finest strands of fibrin. In the earlier survey, I was concerned only with those cases showing obvious fibrin deposition when using the low power (2/3 inch, 16 mm.) objective lens, and only when thus detected was the fibrin classified according to its characteristics. Fortuitously, this microscopic division can be applied to Table II, and shows that my 'positive' cases, whether the thrombi are antemortem, agonal, or postmortem in character, have nearly all had blood fibrinogen levels before death above 200 mg. per 100 ml. (the normal mean level, See Section H). This rather crude method therefore confirms that the 71 cases recorded earlier must all have had high blood fibrinogen levels before death, a fact which could be deduced previously on other grounds - namely that the finding of numerous thrombi on histology is an uncommon finding rather than a common one.

G. RABBIT FOETUSES

In 1956, Doctors J.R. Anderson and J.M. Johnstone reported from this Department the death of an iso-immunised doe rabbit during labour due to intravascular fibrin formation.

Through the courtesy of Dr. Anderson, I have been able to study the tissues of the four non-macerated rabbit foetuses carried by this doe. The tissues examined consist of lung, heart, liver, spleen, pancreas, kidney, adrenal gland, lymph node and placenta. Antemortem fibrin thrombi are not present in any one of these animals.

## H. FIBRINOGEN VALUES IN NEONATES

This part of the work was performed with the aid of a grant from the Dr. David Foulis' Memorial Fund, to the trustees of which the writer is greatly indebted. This part of the work was carried out at the Royal Maternity and Women's Hospital, Rottenrow, Glasgow.

Experiment 1. Cord blood was obtained from 53 normal babies at birth by the procedure described earlier under the section on "Material and Methods". The fibrinogen content of the plasma was determined by the micro-Kjeldahl method, and the optical density by the one per cent. sodium chloride rapid method. A regression equation was calculated and a graph was produced (Fig. 248). There is a close correlation between the two methods. A small error is due to the rapid method estimating protein which is not fibrinogen.

Experiment 2. The cord blood fibrinogen value of 39 normal babies was compared with the value in plasma obtained from heel stab blood immediately after the cord had been tied and cut, both specimens being tested by the micro-Kjedahl method. A regression equation was calculated and a graph constructed from the values obtained (Fig. 249). There is a high degree of correlation between the two sets of values. This shows that heel blood

fibrinogen values reflect accurately those obtained in blood from the cord almost simultaneously. It also implies that blood from the heel gives a reasonable assessment of the fibrinogen level in the circulation.

Experiment 3. In 12 normal babies, the plasma obtained from cord and heel blood sources was subjected to the one per cent. sodium chloride rapid fibrinogen method. The mean difference between the pairs of optical density readings was 0.003, the greatest being 0.007 in two cases, and the readings being identical in three cases. Therefore the optical density readings of heel stab plasma reflect closely those obtained from cord blood plasma.

It would appear to be established by these three experiments that blood obtained by heel stab of the neonatal infant may be used to determine the fibrinogen concentration in the circulation.

Main Series of Results. The above experiments formed the pilot trial and through them the accuracy of the rapid method was determined, and a regression equation was calculated from which a graph could be drawn correlating optical density readings with fibrinogen values.

Thereafter, 366 babies were screened. Their cord blood was not always obtained as described above. On the average,

their heel stab blood was tested 12 hours after birth. Heel stabs were done on all admissions to the Sick Nursery irrespective of their cord blood being obtained or not. Every day, one normal baby, in a Unit Nursery, had a heel stab fibrinogen estimation done, and this was done on a baby for whom a cord blood sample was available. It was possible to follow up the Sick Nursery babies by performing heel stabs daily or on alternate days when it was felt necessary.

1. General. There are three main groups:- (1) Premature (sick) babies, (2) Mature (normal) babies, and (3) Mature (sick) babies. The mean cord blood and heel blood values are shown in Table III. A statistical analysis of these results has been made with the three conclusions that:-

(a) there is no significant difference between the cord blood values of premature infants and of mature (normal) babies;
(b) there is a significant difference between the cord and heel stab values in premature (sick) babies; and
(c) there is a significant difference between the cord blood values of mature (normal) babies and mature (sick) babies.

Even if the premature babies' cord blood values are tabulated according to the infant's birth weight, the level is constant throughout and within normal limits of the mean value. Thus, the premature infant's liver is not deficient in fibrinogen-forming properties, irrespective of the other functions which may be deficient at this period. This finding agrees with those of Rapoport, Rubin and Chaffee (1943).

There may be three explanations for the significant difference between cord and heel blood values in the case of premature (sick) infants. Firstly, it is less likely that the heel blood value was obtained within 12 hours of birth in such babies, because their general condition is precarious and it was the practice to allow them at least 24 hours to become adjusted to extra-uterine existence. This only applies to those who were less than 4 lb. (1.82 kg.) and these babies formed 33 per cent of all premature babies examined. Secondly, the longer the interval before testing the heel blood fibrinogen the more chance was there of the infant becoming infected. Infection is known to cause a rise of fibrinogen concentration (Gram 1922, Foster 1924, and Taylor 1957). Thirdly, premature babies tend to become oedematous after birth, and the rise of fibrinogen concentration may be a measure of the degree of haemoconcentration.

No explanation can be offered at this stage to account for the significant difference between the cord blood values of mature (normal) babies and mature (sick) babies. One possible explanation, which can be discounted by the clinical courses taken by the babies, is the occurrence of antepartum and intrapartum infection. While, statistically, this result is significant in its own right, it would be desirable to enlarge these two series in the future so that the difference is verified further.

These mean results are much lower than those obtained by Crane and Sandford (1936) from ten babies. They confirm the mild postnatal rise noted by these authors.

2. Twins. At every available opportunity, irrespective of the babies being admitted to the Sick Nursery or to the Unit Nursery, twins were studied. There were seven pairs of dissimilar (binovular) twins and eight pairs of identical (uni-ovular) twins.

The mean cord blood fibrinogen of the second twin was lower than that of the first twin. The differences were not statistically different.

The mean heel blood fibrinogen of the second twins (irrespective of their being uni-ovular or binovular), taken on the average 12 hours after birth, was higher than those of the first twins which showed less of a fluctuation from the cord

blood values obtained earlier. The differences were not statistically significant however.

The results suggest that the fibrinogen level of the second twin tends to be unstable, irrespective of that level being low, normal, or high at the time of birth. Further observations are necessary to support this suggestion.

3. Babies Recording Low Fibrinogen Values. Twenty-one babies gave fibrinogen values of less than 100 mg. per 100 ml., at some point during the course of the investigation. None died. None showed haemorrhagic manifestations. Prematurity occurred in 20 per cent only. Nine were born by spontaneous vertex delivery; five were delivered by mid- or low-cavity forceps; five were assisted breech deliveries and two were delivered by lower uterine segment Caesarean section. The incidence of assisted deliveries is abnormally high, being nearly 60 per cent, while for the whole series of 320 babies with normal fibrinogen values assisted deliveries of any variety occurred in 57 instances (18 per cent).

4. Babies Recording High Fibrinogen Values. These babies gave fibrinogen values of over 400 mg. per 100 ml. There were 25 cases. One died within $1\frac{1}{2}$ hours of birth as a result of blood loss from a ruptured vasa praevia, found in retrospect (see Section F. Case 84). None showed haemorrhagic manifestations. Five cases (20 per cent)

were premature. Twenty were born by spontaneous vertex delivery; three were delivered by mid-cavity forceps; one was an assisted breech delivery and one was delivered by lower uterine segment Caesarean section. The babies with high fibrinogen values compare favourably in respect of the proportion of assisted deliveries (20 per cent) with the normal series (18 per cent). Concerning the babies with high fibrinogen values, an offensive vernix caseosa was encountered in 3 cases. It was decided to study this aspect.

5. Babies with Offensive Vernix Caseosa or Liquor Amnii

There were eight babies in the series showing one or other of these states at birth. Only two were premature. The mean heel blood fibrinogen was available in 7, and the mean value being 460 mg. per 100 ml., was compared with the mean heel blood fibrinogen value of the mature (sick) babies. The difference was statistically significant.

Foul-smelling liquor or vernix is accepted as one guide for the presence of intrapartum infection of the foetus. For this reason such infants are admitted to the Sick Nursery. Infection is known to cause a rise of blood fibrinogen which was found in this small series. The difference was statistically significant from the mean heel blood value of mature (sick) babies.

Nevertheless, the clinical course in all eight cases was favourable. None died. Only one baby showed an elevation of temperature which required antibiotic therapy, and indeed all made good progress. In two instances, the mother had a mild postpartum pyrexia.

What are the causal organisms ? If infection has occurred, it is surely not simply cutaneous, in the sense that the vernix is foul smelling, in order to be capable of arousing a significant fibrinogen response. If the infection has caused the high fibrinogen levels, it would at least suggest the occurrence of latent respiratory infection and at the worst a septicaemia. Why then, was the progress of these infants so smooth postnatally ? It is not possible to supply answers to these questions.

6. Babies of Rhesus Negative Mothers with Antibodies

The cord blood of thirteen of these babies was available for fibrinogen estimation. The mean value was 211 mg. per 100 ml. This value was compared both with the mature (normal) and the mature (sick) babies' mean cord blood values. In neither case was there any significant statistical difference. It may be suggested, since labour tends to be induced early in these cases, that the mean value should be compared with that of the premature

a relative immaturity, for the liver is not inefficient at manufacturing fibrinogen.

8. "Physiological" Jaundice in Mature Babies. In this series, four mature babies showed "physiological" jaundice. The cord blood fibrinogen value was available in one case only, but heel blood values were available in all four cases, and the mean value was 308 mg. per 100 ml. This value was compared with the mean heel blood value of all mature (sick) babies, and the difference was not statistically significant. It is apparent that "physiological" jaundice in mature babies occurs much less frequently than does jaundice in premature babies.

9. Babies Whose Mothers had Ante-Partum Haemorrhages. There were 15 of these babies, and one of them died at 19 hours from prematurity associated with atelectasis. The cord blood fibrinogen level of this baby was 260 mg. per 100 ml., the heel blood level at 12 hours was 140 mg. per 100 ml., and a sample taken from the polythene catheter inserted into the umbilical vein in order to give a small blood transfusion at 18 hours, gave a level of 180 mg. per 100 ml. Microscopic examination of P.T.A.H. stained tissue sections of postmortem material reveals only faint strands of fibrin in postmortem thrombi (see Section F. Case 78).

The mean cord blood fibrinogen level of seven cases was 190 mg. per 100 ml. Since six of these seven cases are premature babies, the level is not significantly different from the mean of all premature babies in this series.

Heel blood fibrinogen levels are available in 13 cases and the mean value is 285 mg. per 100 ml. Seven of these cases were premature babies and six were mature. The mean value is not significantly different from the mean heel blood value either of the premature (sick) babies or of the mature (sick) babies.

10. Babies Whose Mothers Had Toxaemia of Pregnancy. There were seven of those babies admitted to the Sick Nursery. Five were premature babies. Three died. One (Case 23) died from massive bilateral adrenal haemorrhages. A second (Case 74) died from congenital heart disease. Postmortem examination was refused in the third case. Cord blood fibrinogen values are available for only two of these infants.

Heel blood fibrinogen values are available for all seven babies and the mean value is 280 mg. per 100 ml. This value is not significantly different from the mean heel blood value of all premature (sick) babies.

# V. DISCUSSION

"It is not to see something first but to establish solid connections between the previously known and the hitherto unknown that constitutes the essence of scientific discovery. It is this process of tying together which can best promote true understanding and real progress" (Selye).

While the results presented above throw some light on thrombotic conditions occurring in the stillborn and neonatal infant and in the child, they present an incomplete picture. In this section, the results will be brought together under various headings in an effort to present a more composite picture.

## 1. Incidence and Distribution of All Varieties of Thrombi

Before considering the antemortem thrombi separately, it will be useful to consider briefly the incidence and distribution of all thrombi in the whole series of 755 cases, and these are shown in Table IV. It is apparent that the numbers of these thrombi vary not only from case to case but also from organ to organ. It is also clear that this has no bearing upon the number of specimens of each organ examined, the numbers being so large overall. While the thyroid gland is highest in the list, due mainly to the high incidence of postmortem thrombi found in this site, the incidence of thrombi in the lungs is higher than in the thyroid gland in the two columns of neonatal infants. At the other extreme, it is clear that thrombi are found seldom in the coronary vessels of the heart or in the skin, while no thrombi were found in 110 pancreases or in 97 pituitaries among stillbirths.

It would appear therefore that the presence of thrombi, (and by this I mean intravascular clots containing fibrin which are visible with the two thirds inch (16 mm.) objective lens of the microscope), has some significance irrespective of the variety of thrombus. It is difficult at the present state of knowledge to suggest a probable explanation for this.

Table IV also shows that the incidence of thrombi of all varieties increases with age. This is to be expected, for the blood volume increases with age, and even if the fibrinogen level remains constant at 200 mg. per 100 ml., the absolute amount of circulating fibrinogen increases in direct proportion with the blood volume. Thus, even if all the thrombi used to compose this Table were postmortem thrombi, the amount of fibrinogen available for clotting in the older child is so much more than that available in the younger child that thrombi are larger, or more numerous, or both. It could be argued that the capacity of the circulatory system is also proportionately greater, but the Table shows that thrombosis does not occur evenly and equally throughout all organs after death, but is selective. For that reason the plasma proteins seem to concentrate in certain areas, which vary from case to case, before clotting takes place and the greater bulk of the resulting fibrin is responsible for the greater

incidence of recorded thrombi in the older child. This selective coagulation may be due to patchy agonal increased capillary permeability with loss of electrolytes and resulting concentration of the plasma. This possible mechanism may also occur postmortem during the process of hypostasis.

2. Varieties of Thrombosis

In the adult, thrombi tend to be large, and all varieties tend to be readily visible and they reveal characteristic naked-eye features. There is no doubt however that antemortem thrombi of significant number, even in the adult, may be microscopic in size; one example of this being seen histologically in fatal hypofibrinogenaemia associated with pregnancy (Johnstone and McCallum 1956), and another being Moschcowitz's thrombotic micro-angiopathy (Stuart and McGregor Robertson 1956).

In infants and children widespread antemortem thrombosis is seen frequently on naked-eye examination in relation to the renal veins and the cerebral venous sinuses. Microscopic study shows however that thrombi can be found in many organs, and that occasionally these too appear to have been formed antemortem. By histological study, it is possible to classify such thrombi in infants and children as antemortem, agonal or postmortem in character. This thesis is concerned primarily with antemortem

thrombi which are rich in fibrin. A classification of antemortem thrombi, and the cases illustrating these varieties are listed in Table V. From this it is clear that 43 out of 71 cases (61 per cent) show pure fibrin thrombi. Seven of these cases show no apparent connection between the thrombotic episode and the presence of the foetus in utero, or with delivery. Fibrin thrombosis in the latter cases appears to be related to some condition which appeared post-natally. No conclusive explanation is possible for these seven cases in the state of present knowledge. One or two suggestions are possible and will be discussed later. The other varieties of thrombosis are well known and they require very little amplification here. The two cases illustrating thrombi of unknown aetiology are only "unknown" in retrospect because of inadequate postmortem technique. It is difficult to cover all possible eventualities when microscopic thrombosis is being considered.

The general incidence of antemortem thrombi is shown in Table VI. This shows that the incidence of antemortem thrombosis in stillbirths and in early neonatal deaths is constant, about 3 - 4 per cent. If the series is broken into retrospective material and current material, the incidence of antemortem thrombosis is 3 - 4 per cent in each group. This would suggest

that, every year, there is a steady 3 - 4 per cent incidence of stillbirths and of early neonatal deaths associated with antemortem thrombosis. Of a rather smaller series of infants and children coming to postmortem 20.25 per cent show antemortem thrombosis. (More than 95 per cent of all children dying in the Royal Hospital for Sick Children come to necropsy). The late neonatal deaths show the highest incidence of antemortem thrombosis of all groups, namely 27.73 per cent. It would appear that these infants, while still demonstrating the same 3 - 4 per cent incidence of thrombosis encountered in stillbirths and early neonatal deaths, also become liable to the conditions which give rise to antemortem thrombosis in infants and children. Table VI is very revealing in this connection. One in every four late neonatal deaths shows antemortem thrombosis. This adds further weight to the well known aphorism which states that:-

"the neonatal period is the most dangerous period of one's life."

Table VII details the distribution of these antemortem thrombi by organs. Among the stillbirths, the liver is the organ affected most frequently. The spleen and adrenal gland are affected next in order of frequency. Among neonates dying

within 48 hours of birth, the adrenal gland is the most frequently affected organ (57 per cent), and the liver and lung followed with almost equal incidence. Among late neonatal deaths, the lungs and the spleen are affected most frequently (30 per cent), to be followed by the liver (22 per cent) and then by intestine, kidney, adrenal gland and brain in equal incidence in third place. Deaths among infants and children show that antemortem thrombi affect the spleen and kidney most frequently (30 per cent), followed by the intestine and liver (25 per cent), and thirdly by the lungs, brain and adrenal gland (20 per cent).

This distribution is important when the question of aetiology is considered later.

It will be clear from a study of the case reports quoted earlier that antemortem thrombosis was not believed to be the cause of death in every case in which this feature was recorded. It is important however to have an assessment of this, and Table VIII shows my assessment of the relationship between antemortem thrombosis and death in the 68 cases. This reveals that 15 (22 per cent) of these 68 cases (or 2 per cent of the 755 cases) are considered to have died primarily from thrombosis, while in 25 (37 per cent) of the 68 cases (or 3.3 per cent of the whole series) thrombosis is believed to have played some major part

in causing death. Therefore, 40 out of 755 deaths (5.2 per cent) are due directly or indirectly to thrombosis.

If these figures are assessed in another way, it is found that

6 out of 331 stillbirths (1.7 per cent),

7 out of 226 early neonatal deaths (3.1 per cent),

19 out of 119 late neonatal deaths (16 per cent), and

8 out of 79 infant and children deaths (10 per cent)

are due partly or entirely to thrombosis.

3. Incidence and Distribution of Fibrin Thrombosis

Table V shows that 43 (83 per cent) of the 68 cases relevant to this thesis had fibrin thrombi. Thirty-six of these were encountered in stillborn infants and in early and late neonatal deaths. Seven were encountered in late neonatal deaths, infants and children and the features of these latter thrombi suggested that they had no connection with the child's delivery.

Fibrin thrombosis is a condition which has been encountered previously in the postpartum period in adults (Johnstone and McCallum 1956) and in rabbits under various experimental conditions (Schneider 1950; Anderson and Johnstone 1956; Smith and Johnstone 1958). Thrombosis is well known in infancy and childhood, but I have been unable to find any

published report prior to my own (Boyd 1958) which records the possible occurrence of fibrin thrombi in the neonatal infant. In the present 68 cases, fibrin thrombi were found in 9 of the 10 stillborn infants to show antemortem thrombi, in 8 of the 9 early neonatal deaths and in 20 of the 33 late neonatal deaths. In view of these figures, it would appear that, if thrombosis is going to be responsible for the intra-uterine, intrapartum, or early neonatal death of a foetus or infant, it is more likely to be fibrin thrombosis which will be found histologically than any other kind. Fibrin thrombosis may be responsible for late neonatal deaths but the incidence among all cases showing antemortem thrombosis drops rapidly after the first four days, antemortem mixed thrombus becoming the dominant variety thereafter.

The distribution of fibrin thrombi by organs is shown in Table IX, and is virtually the same as that given for antemortem thrombi in Table VII.

4. Aetiology of Fibrin Thrombi

When considering the aetiology of these thrombi, it is necessary to note that the thrombi, by the histological features described and illustrated, have been formed only to a limited extent at the sites where they are demonstrated histologically. If they had been formed totally at the sites illustrated they

would demonstrate some point of attachment to the vessel wall and they would have shown a tendency to lamination. The cases illustrated demonstrate beautifully the appearance of thrombosis in a moving stream of blood while the thrombus is still held within this stream. This accounts for the features of these thrombi, described in detail earlier, and illustrated fully. These microscopic thrombi continue to move in vessels carrying oxygenated blood until their further progress is prevented by the fibrin embolus forming a saddle thrombus, or by the smaller diameter of the vessel lumen. In some instances, for example in the pulmonary or glomerular capillaries, it appears as if the thrombi had formed in these sites, but at the very instant when the blood was passing through these narrow vessels, the initiation of thrombosis having occurred elsewhere. In the case of thrombi in veins, these appear to be formed by the union of smaller thrombi in venules and capillaries, so that the antemortem streaming character results from the firm "anchorage" of the thrombus in the smaller vessels.

Since this involves time and motion studies of blood clotting in a moving stream, the answer is not likely to be obtained easily.

The group of stillbirths is the most consistent of the whole series and it is important to note that in these babies, the liver is the organ to be affected most frequently. The thrombotic episode must have been initiated proximal to this structure and this leads us to the placenta. Could thrombosis be initiated at this site to cause hepatic damage ? The answer to this question requires a knowledge of (a) the circulation time of the foetus in utero, and (b) the average time required in vivo for clotting to occur from the time that it has been initiated. There is only indirect information available if an attempt is to be made to answer these two points.

With regard to (a), Barclay, Barcroft, Barron and Franklin (1939) complained of the sluggish umbilical vein flow for the injection of radio-opaque dyes for their studies on the functional closure of the ductus arteriosus. Barcroft (1946) states that the blood flow through a lamb's placenta is 100 cc./kg./min. In 1958, Dawes states that the flow in the umbilical vein of the umbilical cord of the lamb is 100 - 180 ml./kg./min., and Adams and Lind (1957) calculate the value to be about 187 ml./kg./min. in humans. There is a certain rough consistency in these figures so that for the sake of this argument we may accept the figure of

150 ml./kg./min. Applying this value to a full term infant of 3.0 kg., the umbilical vein flow is 450 ml./min. If it is accepted that the umbilical vein has a cross-sectional area of 1.0 sq. cm., on the average, and a length of 80.0 cm. (average length of cord = 50.0 cm., + 10.0 cm. to allow for the spiral form assumed by the vein, + 15.0 cm. from chorionic villi to attachment of the cord to the placenta, + 5.0 cm. from umbilicus to liver), the vascular conducting system from chorionic villus to foetal liver carries 80.0 ml. of blood in the full term infant. The figure of 450 ml./min. quoted above suggests that the blood in this system is changed about 5 - 6 times/min., and thus it takes 10 - 12 seconds for blood to travel from the conducting vessels arising in the placenta to the liver. This is obviously a hypothetical mean figure which is liable to great variations.

The answer to (b) above is available indirectly from the experiments of Schneider (1950), Tager (1954), and Smith and Johnstone (1958). Those workers were concerned with the intravenous injections of thromboplastin-rich extracts. If their extracts were too strong the animal died "promptly", or "immediately" and in order that the more long term effects of these extracts could be studied they had to be diluted.

To correlate these two sets of findings depends on whether "promptly" or "immediately", and 10 - 12 seconds are

synonymous. They are not incompatible and it appears therefore that there is no need to seek further than the placental site to account for the thrombi found in the livers of the stillborn foetuses. If the rate of circulation is slightly more rapid, the thrombi may not form until the blood has passed through the liver, and thus involve other organs. One possible aetiological mechanism is therefore a thrombo-embolic episode in the region of the placental site and affecting part or all of the foetal blood which is present in the placenta at that time. Under such circumstances it is possible to appreciate why one of twins may be affected and not the other. It also explains why the lungs are more often affected in the neonatal infant than in the stillborn infant. This suggestion is similar to Schneider's (1951) which he made in order to explain certain cases of obstetric shock associated with abruptio placentae. Sharp, Howie, Biggs, Methuen (1958) have studied this condition from the haematological aspect, and their results support Schneider's explanation.

This may not be the only mechanism involved. For example, Quastel and Racker (1941) and Stoner and Green (1947) have shown that ischaemia of muscle increases the clot-promoting activity of 0.9 per cent sodium chloride extracts made from it later, and that

this increased activity is due to thromboplastin, normally stored in an inactive form, becoming mobilised. If this finding has a general application, is it not possible that arterial disease or spasm, chronic bronchitis with emphysema, anaemia, or cardiovascular disease etc., in the mother may lead to a certain degree of placental ischaemia ? It is known from Schneider's work (1950) that the placenta and decidua are much richer in thromboplastin than is any other known tissue, including muscle. If the placenta is rendered ischaemic, may it not release thromboplastin into the maternal or foetal circulations or into both ? Further, retroplacental haemorrhage or widespread intervillous fibrin deposition may have a similar effect. Again, these situations may equally well cause foetal asphyxia as well as placental ischaemia, and may the musculature of the foetus as a whole not release thromboplastin in a fashion similar to that in the limb clamping experiments of Stoner and Green (1947) ? Under such circumstances, thromboplastin of placental origin would cause fibrin thrombosis in the liver primarily, but thromboplastin of foetal muscle origin would enter the right side of the heart, and, in a foetus <u>in utero</u> whose lung alveoli are yet unexpanded, would pass through the ductus arteriosus to affect either the intestinal tract, pancreas

spleen, adrenal glands, kidneys, gonads or the placental vessels themselves. The vessels of the lower limbs may not escape such an incident. Theoretically therefore, placental ischaemia and foetal ischaemia (or asphyxia) may initiate thrombo-embolic episodes. It would appear unlikely from the results detailed in Table IX that generalised foetal asphyxia plays much part in this process of foetal thrombosis. Nevertheless it may be responsible occasionally. It is difficult to explain the high incidence of adrenal gland thrombi except on a basis such as this in some cases, for these organs are very far removed from the source of oxygenation of foetal blood (i.e. the placenta). Only the genito-urinary tract, the distal half of the large intestine and the lower limbs are further removed from the oxygen supply than the adrenal glands are in the foetus in utero. In spite of this, the adrenal glands show antemortem thrombosis in much higher incidence than does any of these other organs mentioned above in stillbirth and neonatal deaths. One possible explanation for this will be made later.

In this connection, the brain may be considered as a potent source of thromboplastin. It may be expected that damage in any form would cause release of thromboplastin from it. This may initiate local or distant thrombosis. The cases

of cerebral damage illustrated above show that the thrombi were probably brought to the brain as thrombo-emboli rather than having formed there — except in one case, number 65. It is naturally not possible to say when a distant thrombus has been initiated in the brain unless some of the thrombus remains attached there, and under these circumstances the distant lesion is really an embolus. Even the presence of frank cerebral damage in an infant whose ductus arteriosus is yet patent does not permit one to say that an adrenal thrombo-embolus arose in the brain.

Infection is a third possible explanation for the occurrence of these fibrin thrombi. It has long been known that infection and thrombosis are very closely related in certain circumstances. At least two possibilities exist however to explain this coincidence, (a) the thrombosis is the direct result of the properties of the infecting organism, e.g. the coagulase property of staphylococcus aureus, or (b) the infecting organism causes tissue necrosis which, in turn, causes thrombosis either as a result of the local release of thromboplastin as mentioned above, or as a result of direct damage to the vessel wall and endothelial lining e.g. the histolytic activity of certain clostridia. Aschoff (1913) was quite certain in his own mind that what generally occurs is the

secondary infection of an already existing simple thrombus. This has been confirmed several times in this series. There are two cases (numbers 43 and 48) showing probable primary infective arteritis and phlebitis respectively, in which thrombosis is probably secondary. In this connection it is notable how often thrombosis was associated with staphylococcal infections — even when staphylococci were not cultured, but were identifiable histologically in the tissues at the site of damage. It seems certain that the thrombi at the site of infection were non-infected in the first instance, but the puzzling feature is the occurrence of metastatic fibrin or mixed thrombi also apparently non-infected in the first instance in many of the late neonatal deaths and in the infants and children. These metastatic thrombi were seen most frequently in the spleen, but were also noted on the aortic endothelium. What do they represent ? Do they indicate a low grade bacteraemia ? If this is so, the thrombi arise probably in relation to a nidus of organisms and this would convert these to infected thrombi even although the vast majority show no histological evidence in favour of this. Could they represent the result of spontaneous entry of staphylococcal coagulase into the circulation since there is no histological evidence in favour of these being

infected thrombi ? I consider that this is unlikely, for, as mentioned above, these thrombi are seen most frequently in the spleen —— an organ which is well recognised for its capacity for destroying or immobilising organisms in association with the reticulo-endothelial system in general. If these thrombi were the result of the entry of coagulase into the circulation, the spleen would not be selected particularly as the site for their deposition. There is no doubt however that splenic sinusoidal thrombosis is connected in some way with infections, and particularly with staphylococcal infections, sometimes of a rather minor nature clinically. Aschoff (1913) noted that dead cultures of staphylococci cause widespread fibrin thrombosis in the capillaries of the lung when injected intravenously and occasionally in other organs. This finding may supply part of the answer to this problem.

A fourth aetiology of fibrin thrombi is concerned with congenital disease of the heart and great vessels. Rich (1948) reported the finding of pulmonary thrombosis (of veins as well as arteries) in 18 (90 per cent) of 21 cases dying with Fallot's tetralogy. This feature had been unrecognised hitherto, and was not necessarily the result of operation. No other viscera were involved. Rich suggested two explanations for this finding:-

(a) the polycythaemia accompanying this condition leads to increased viscosity, and (b) the pulmonary stenosis causes a sluggish flow of blood through the lungs. In the present series there are seven babies with congenital heart disease and who show fibrin thrombi in various organs. One case (number 26) had dextrocardia and showed fibrin thrombi in the liver and spleen. The others, having various forms of atrial or ventricular septal defect, showed thrombosis in various organs including liver (4 cases), kidney (2 cases), adrenal gland and central nervous system (1 case). It is difficult to say whether or not these cases are similar to the condition which Rich (1948) described.

Fifthly, it is well known that arterioles become spastic when a vaso-constrictor agent such as oxytocin is administered. Is it possible for the thrombotic process to be secondary to an initial episode of vasospasm ? I consider that this possibility is unlikely, otherwise some of the striking lesions illustrated in capillaries and venules would not have been seen. If arteriolar spasm was the essential lesion, thrombosis in capillaries, sinusoids and venules would assume an agonal or postmortem character on account of the reduced rate of flow.

Lastly, it is interesting to consider some of Aschoff's

(1913) observations on thrombosis. He recognised the existence of fibrin thrombosis in contradistinction to thrombosis of any of the other cellular elements of the blood including the platelets, but he believed that fibrin thrombosis occurs only secondarily to the previous existence of one of the other forms of thrombi. He did not believe that endothelial damage or direct coagulation of the blood played any role in thrombosis. He recognised that intravenous injection of dead cultures of S. typhi, dysentery bacilli or staphylococci caused widespread fibrin thrombosis in the lung capillaries and in other organs. These points have to be considered with regard to the thrombi described here. For example, if the thrombo-embolic episode is of placental origin, it is implied that thromboplastin of placental origin initiates the thrombotic process. If that were so, it may be reasonable to expect that thromboplastin of platelet origin need not be required — and indeed that the infant's platelets themselves may be unnecessary for the evolution of this thrombo-embolic process. Under these circumstances the infant's own platelets should be identifiable in the blood within the vessels in the tissue sections as easily as one can identify them in blood films. Since platelets have been prominent by their

absence in most of the cases described in this thesis, (Case 15 being the exception), it would imply that they are necessarily implicated in the condition of disseminated fibrin thrombo-embolism. That being so, is not Aschoff (1913) correct when he stated that fibrin thrombosis is always secondary, as a sequel of other forms of thrombosis, for the platelet is involved in the earlier stages of coagulation ?

In this section, five processes have been discussed which may play a part in producing fibrin emboli, (a) a thrombo-embolic process initiated in the region of the placenta similar in nature to that causing the syndrome of hypofibrinogenaemia of pregnancy in the mother, (b) placental or foetal asphyxia, (c) infection, (d) congenital heart disease, and (e) the pre-existence of platelet thrombosis.

5. Consideration of these Findings with Regard to our Knowledge of the Circulation of the Foetus in Utero

The high incidence of thrombi in the liver of foetuses dead in utero and in stillbirths suggests very strongly that the process initiating this thrombotic process occurs in the region of the placenta.

Observation of the occurrence, incidence and distribution of these thrombi becomes therefore an observation of Nature's

experiment with emboli in the foetus, and this is likely to be more satisfactory than any experiment designed by humans, but it will be of some interest to be able to compare the results described in this thesis with those obtained by Barcroft and his team, who were followed later by Dawes and others (1958).

(a) The Circulation of the Liver in the Foetus. In former years, the ductus venosus was considered to be a very important structure for conveying oxygenated blood from umbilical vein to the heart and brain and thereby short-circuiting the liver (Hamilton, Boyd and Mossman 1945). Since there was a connection with the portal circulation it was appreciated that some of this blood may be deviated to the liver, but this was a feature of secondary importance. During studies of the functions of the ductus venosus by Franklin, Barclay and Prichard (1940 - 41), Barclay, Franklin and Prichard (1942), and Barron (1942), it was realised that the size of the ductus was incapable of containing the majority of the umbilical vein blood flow, and that indeed the greatest proportion of this blood did in fact pass through the liver; eight ninths at the most according to Dawes (1958). This is quite understandable once it is pointed out, for, in addition to oxygen, the blood in the umbilical vein is rich in

many other substances for the nourishment and growth of the foetus, and the foetus surely must possess its own intermediary metabolism. It would appear logical for the umbilical vein blood to pass through the liver before being distributed elsewhere. Further, some animals such as the horse, do not possess a ductus venosus (Barcroft 1946). These studies of the Oxford and Cambridge team under Sir Joseph Barcroft receive support from my histological observations.

(b) The Ductus Venosus. The ductus venosus cannot be ignored, for it provides a suitable route whereby a proportion of the oxygenated blood may reach the coronary arteries and cerebral circulation earlier than it would do otherwise. Here is one "link" which will help to answer some of the outstanding questions; for instance why a thrombo-embolic process, presumably of placental origin can affect the liver and spleen simultaneously (Cases numbers 4, 21 and 26), liver and adrenal gland (Case number 13), liver, heart, lung and kidney (Case number 15), and liver, brain and adrenal gland (Case number 20). Blood, in which clotting is imminent may be split into two portions at the start of the ductus venosus, a larger portion which passes relatively slowly through the liver and a smaller portion which passes more rapidly through the ductus venosus to the posterior (inferior) vena cava.

(c) The Foramen Ovale. The work of Barcroft and his team (Barclay, Franklin and Prichard 1944, Barcroft 1946), has established that the major proportion of the blood from the posterior (inferior) vena cava passes through the foramen ovale into the left atrium. Here it is diluted to a small extent by pulmonary venous flow (roughly 1 part of the latter to 3 of the former), before proceeding to the left ventricle, and ascending aorta, to the coronary arteries and to the cranium. A small proportion passes over the aortic isthmus into the descending aorta. It is possible therefore for blood which is due to clot to enter the descending aorta by this route, rather than by taking a long circuitous route through the head, neck and fore-limbs, the right ventricle and through the ductus arteriosus. That most of the posterior (inferior) vena cava blood passes through the foramen ovale is supported by the absence of antemortem fibrin thrombi in the lungs of all stillborn infants.

(d) The Ductus Arteriosus. Even if a large proportion of posterior (inferior) vena cava blood were diverted into the right auricle and ventricle by sudden alteration of the circulatory mechanics, and if this volume of blood were due to clot, it is still unlikely that it would do so in the lungs of the foetus in utero, for the larger proportion of the pulmonary

artery flow passes through the ductus arteriosus into the descending (thoracic) aorta.

(e) The Adrenal Gland. The high incidence of fibrin thrombi in the adrenal glands remains difficult to explain. Table IX shows that one stillborn infant, four infants dying early in the neonatal period, and four infants dying later in the neonatal period show thrombi in the sinusoids of the adrenal gland. If blood which clots in the adrenal glands had the clotting process initiated in the placental area, that blood could have taken one of several routes through the foetal circulation before reaching the foetal adrenal glands. The first is the common route taken by the greater volume of the circulating blood, namely:- umbilical vein, liver, inferior vena cava, foramen ovale, left auricle and ventricle, ascending aorta, head and neck, superior vena cava, right auricle and ventricle, pulmonary artery, ductus arteriosus, descending aorta, suprarenal arteries. This is a very unlikely route. Other possibilities exist, which necessitate the blood taking the "minority" route at one or more bifurcations, and by selecting these routes the blood could reach the adrenal glands much more rapidly than by the "common" route. For instance, (i) by passing through the ductus venosus rather than by passing through the liver, (ii) by passing into the right auricle and

ventricle with the superior vena cava flow rather than by passing through the foramen ovale, and (iii) if the blood did pass through the foramen ovale, then by passing over the aortic isthmus into the descending aorta rather than by entering head and neck. The chances of these channels being selected rather than the more usual are (i) the ductus venosus — 1 in 9 (Barclay, Franklin and Prichard 1944), (ii) the right auricle rather than the left auricle — 1 to 1, or 1 to 2 at term (Barron 1944, Dawes 1958), and (iii) the aortic isthmus rather than by the head and neck, 1 to 1, or 1 to 2 at term (Barron 1944), or 3 to 1 according to Dawes (1958).

It appears to me that, if blood is to reach the adrenal glands rapidly it must by-pass the liver and thereafter it has the choice of two routes. The overall chances of this are (a) for the route via the right auricle and ductus arteriosus 1/9 x 1/2 = 1/18 at the worst, or 1/9 x 1/1 = 1/9 at the best, and (b) for the route via the foramen ovale, left ventricle and aortic isthmus 1/9 x 1/2 = 1/18 at the worst, and 1/9 x 3/1 = 1/3 at the best. Now the actual incidence recorded for the adrenal glands in Table IX for stillbirths and neonatal deaths only is 30 per cent, but it must be noted that the intestines and spleen

are in a similar anatomical-physiological position in the foetus and their incidences of thrombi are 17 per cent and 28 per cent respectively, while the kidneys show a 7 per cent incidence. The mean incidence therefore among these four organs supplied by the descending aorta is about 20 per cent. From this, is it permissible to suggest that the oxygenated blood to these organs is purposely channelled through the ductus venosus, foramen ovale, left auricle and ventricle, ascending aorta and aortic isthmus, or via the right auricle, right ventricle and the ductus arteriosus ? The point being stressed however is that it does seem possible from my findings among stillbirth and neonatal deaths for blood, coming from the placenta, to reach these abdominal organs earlier than at first seems possible, and this may explain the apparently anomalous findings in the adrenal glands.

Why is there a different incidence of thrombosis in the four organs mentioned above, and particularly between the adrenal glands and kidneys whose embryonic development is so closely connected, and whose vascular supplies are even partly connected ? It is my opinion that this difference is an indication of the relative sizes of the blood supplies to these various organs in

the foetus. The kidneys require a blood supply for growth and development, but function *in utero* is minimal since the placenta performs the excretory functions of the foetus. Likewise the intestines have little function to perform while the foetus lies *in utero*, and thus they require relatively little blood. The spleen on the other hand is an organ which is the seat of haemopoiesis in early development and which retains some of these functions even at term. Its blood supply is necessarily greater. The functions of the adrenal glands *in utero* are virtually unknown. Indeed some authors have declared that they have no function in the foetus for all necessary hormones are supplied by the mother. I find this view very difficult to accept, for if these organs had no function they would never retain such a size in the foetus relative to the kidneys which are dwarfed by them. I believe that their size alone is a sufficient indication that they perform some essential functions during foetal life. The functional activities of the gland demand an increased vascularity, and the increased vascularity allows the glands to become more exposed to thrombo-embolic processes and the high incidence of these affecting the adrenal gland is further evidence, in addition to the size of the organs, that they are functioning actively.

6. The Organisation of Thrombi

It is apparent now that many cases of stillbirth and of neonatal death show thrombo-embolism dating from about the time of birth, with one or two exceptions. The longer that these infants survive after such episodes, the greater will be the opportunity for studying the organisation of aseptic thrombi. This subject has been studied intensively in recent years from several departments (Duguid 1948, Duguid and Anderson 1952, Crawford and Levene 1952, Lendrum A.C., 1955 and Dible 1958). If the stillbirths, and early and late neonatal deaths are selected, and grouped according to the infant's age, a certain rough classification of the duration of these thrombi becomes possible in most of the cases where there is little doubt. For example,

Cases 1 - 2, 4 - 8, 10 - 13, 14 - 18, 20 - 31, and 45 are aged 0 - 14 days, and they all show thrombi of one form, situated centrally in the lumen;

Cases 33 - 35, and 46 are between 14 and 21 days; they show thrombi which are retracting towards the intima of the vessel and are vacating the axial or central position;

Cases 37 - 38 are between 21 and 28 days old and the thrombi in these cases show endothelial proliferation and recanalisation of

the retracted thrombi;

Case 68 had polyarteritis nodosa, an illness which lasted for 12 weeks. Histological examination has revealed that the thrombi of the oldest lesions which are now completely incorporated into the intima of the vessels affected have lost completely their conventional staining properties. From all this information an incomplete timetable with regard to the organisation of aseptic pure fibrin thrombi in the neonate and stillbirth can be prepared, and this is shown in Table X.

In this table there are now placed five cases (numbers 3, 13, 50, 9 and 32) whose thrombi show features which are not compatible with the child's age. Case 3 was a foetus dead in utero for four weeks and which showed massive antemortem hepatic necrosis. The liver thrombi showed complete retraction to one side of the vessel wall. This could have occurred within these three weeks while the foetus was dead, and thus it is my opinion that retraction of fibrin is a property of this substance which does not require a vital stimulus. This is well known from the in vitro occurrence of clot retraction. On account of the probable age of these thrombi, one should expect an endothelial reaction and this is lacking because the foetus was dead. Case 13

died at 12 hours from bilateral interventricular haemorrhages. Fibrin thrombi are present in one adrenal gland which conform more to the appearances of thrombi of 14 - 21 days duration, i.e. were laid down while the foetus was in utero. Case 50 died when 5 days old from fibro-elastosis of the heart and shows thrombi in the liver sinusoids of 2 - 3 weeks duration and which must therefore have been laid down in utero. Case 9 was an intrapartum stillbirth whose placenta showed laminated organising thrombi in two umbilical arteries with early endothelial proliferation, i.e. consistent with those of 3 - 4 weeks duration. Case 32 died at 13 days from suppurative pneumonia, superior sagittal sinus thrombosis with subdural haemorrhage and bilateral interventricular haemorrhage. In addition, histological examination revealed a well organised renal vein thrombosis, the thrombi being well covered by endothelium and therefore of nearer 4 weeks duration. They must have been laid down in utero.

My small experience of thrombus organisation suggests that organisation does not occur very much more rapidly in veins than in arteries. The timetable given in Table X is rather slower than those given by Harrison (1948) and Heard (1952) for experimental fibrin thrombi in rabbits.

7. The Conditions Necessary to Produce the Histological Pictures Described in These Cases

(a) Fibrinogen. The infant's fibrinogen level in the circulating blood must be very high before the thrombotic process is initiated. This is certain from a study of these cases. What causes an infant's fibrinogen to rise, particularly when it is still in utero ? This question has yet to be answered. It is well known that infection, particularly pneumonia causes a rise of the fibrinogen level, but it is equally certain that few of these babies were infected in the first instance. The answer may be that the conditions which cause the infant's fibrinogen to rise are the conditions present in the mother which are responsible for maintaining her fibrinogen at high levels.

(b) Thromboplastin. An episode is required in the region of the placenta which causes the release of thromboplastin which enters the foetal circulation to initiate a thrombo-embolic process. If this is to be fatal, the quantity of thromboplastin must be relatively massive, but the same quantity entering the maternal circulation may be insufficient to produce any clinical upset because of the great differences in circulating blood

volume (e.g. 500 ml. and 6,000 ml.). Smaller quantities may likewise be fatal if the thrombus lodges in vital spots, or in areas where secondary effects will be fatal. This thesis has also illustrated that lesser grades of this process occur and may be survived.

The nature of these episodes is uncertain and indeed they may be symptomless for the mothers of Cases numbers 3, 6, 9, 10, 17, 22, 25 - 30, 34, and 36-38, and others, could give no guide in their history to account for these deaths.

(c) The Lack of Fibrinolysins. If these babies had possessed fibrinolysins, there is a reasonable chance, especially in the cases of those infants who died in utero, of the fibrin deposits being lysed before the birth of the infant. This does not imply that all newborn babies are lacking in these enzymes. Indeed I have observed the presence of fibrinolysins in several babies in very high titre, although this is uncommon.

(d) Platelets. It has been mentioned in an earlier section that platelets may play an essential part in the production of these thrombi even although thromboplastin is supplied from other sources in the region of the placenta. While this is important by itself, there is another point to be considered.

Smith and Smith (1955) have shown that experimental pulmonary emboli are rich in serotonin (5- hydroxytryptamine) and that certain of the clinical results of pulmonary embolism may be explained by the serotonin content, which may cause pulmonary hypertension and other effects. Serotonin and heparin are antagonistic and therefore thrombi which are very rich in serotonin may exhibit a certain stubbornness to being removed by natural or artificial methods.

(e) The Use of Refrigerated Postmortem Accommodation.

It may be little appreciated how important this has been in the present study. Refrigeration has been widely adopted for the storage of cadavers only since the end of the War (1945) or since the initiation of the National Health Service (1948). It has become widespread practice to use this means of storing cadavers primarily from the hygienic aspect, but also from the humanitarian angle. Relatives used to complain bitterly of the severe state of decomposition of the bodies of deceased persons and these factors were responsible for the introduction of this means of storage. Pathologists welcomed the move not only for the above reasons but also because the preservation of tissues was greatly improved for histological study, and

many far reaching results have come from this simple procedure alone. The body of the stillborn infant, or the neonatal death, or the child's, is ideal for refrigeration since it is so small that autolysis of the internal organs should be minimal. Further, Mole (1948) showed that fibrinolysins can be active after death, and tend to be present in high titre in sudden deaths of a violent nature. He showed that blood was often fluid at postmortem and was not capable of being made to clot. What he meant under these circumstances was, that the blood had already been clotted and had been lysed by fibrinolysins by the time that he came to study it. He seldom found fluid blood in babies. Although there is no mention of this point in his paper, it is likely that his observations were made on non-refrigerated cadavers. Fibrinolysins function best at 37°C. and refrigeration stops their activity. Therefore, if refrigeration had not been instituted, it is unlikely that this number of cases could have been presented in this thesis, and it is very likely that the standard of histology would have been much poorer.

8. Relation to Maternal States

It is important to consider maternal conditions during

pregnancy which may affect the foetus. Table XI details the conditions in the mothers of the 43 cases showing pure fibrin thrombo-emboli.

The first feature is that nearly 50 per cent of the mothers gave no history of abnormality during pregnancy or labour. In those four cases for which there is no information available it is known that the deliveries took place at home, and it can be assumed that there was no abnormality during pregnancy or labour. Of the remainder, uterine haemorrhages of one form or another, and toxaemia of pregnancy and eclampsia occur most frequently, forming one third of the total number.

In the previous section it was suggested that certain maternal conditions might be responsible for causing a high foetal fibrinogen level. In pregnancy the maternal fibrinogen is above normal levels. The mean value of 38 maternal plasma fibrinogen levels tested by the micro-Kjeldahl method was 400 mg. per 100 ml. Secondly, toxaemia of pregnancy has been shown to be accompanied by elevated fibrinogen levels (Foster 1924). Foster (1924) and Gram (1922) showed that acute infections showed raised fibrinogen values, particularly in lobar pneumonia, and less so in bronchopneumonia.

Investigation of this aspect of fibrinogen levels is incomplete and in Great Britain one would certainly wish to know what affects chronic bronchitis, pyelitis of pregnancy, chronic pyelitis and cardiovascular disease in general, have on the fibrinogen level of pregnant women, and then whether the results obtained are reflected in the infant's plasma. Gram (1922) seemed to be quite certain that iron deficiency anaemia has no effect on the plasma fibrinogen level.

9. Relation of Thrombo-Embolism to Other Conditions of Neonatal Life and of Childhood

The possibility that foetal death in utero, intrapartum stillbirth or neonatal death may be the result of disseminated fibrin thrombo-embolism in the foetal circulation is a relatively new conception, and it becomes important to prove or disprove an association between this entity and other well recognised diseases of foetuses in utero and stillbirth deaths. This is a very large task but shall be considered in this section. The conditions to be discussed will be considered in alphabetical order, with minimal reference to the previous literature concerning each.

(a) Adrenal Haemorrhage. Massive haemorrhage has been associated in the past with haemorrhagic disease of the newborn

(Arnold 1930), trauma as a result of strong uterine contraction (Corcoran and Strauss 1924), neonatal infection (Gunson 1914 - 15), and venous congestion (Talbot 1900, Hamill 1901). The present series has shown a high correlation between fibrin thrombo-embolism of the cortical sinusoids, red infarctions and haemorrhage which may be arterial, venous, or both, in individual cases.

(b) Acute Glomerular Thrombosis. In 1932, Blackman and Rake published under the title of "acute pneumococcal nephritis", nine cases of children showing glomerular capillary fibrin thrombi in association with infections by pneumococci of no constant pneumococcal type. Zuelzer (1951) reported two cases of acute glomerular thrombosis. One was in a 3 week infant with gangrene of the penis following circumcision. The second was in a 7 month infant dying from a pneumococcal meningitis. Cases 63 and 65 of the present thesis show the same lesions but in only one case was there evidence of infection and this appeared to be partly staphylococcal. Both cases had congenital heart disease and the aetiology of these thrombi has not been explained satisfactorily.

(c) Cavernous Transformation of the Portal Vein.

This condition was the subject of an article by Gibson and Richards (1955) and by Parker and Seal (1955). In these articles it was suggested fairly conclusively that the lesion was not hamartomatous in nature, but that it resulted from longstanding chronic pylephlebitis as a result of chronic appendicitis, or umbilical sepsis at birth. Fibrin thrombo-embolism is another possible aetiological factor.

(d) Fibro-elastosis. (Foetal Endocarditis: Endomyocardial Sclerosis). The aetiology of this condition is still obscure. It was considered formerly to be of infective origin, while the foetus was in utero with healing by fibrosis and was usually accompanied by atresia (or stenosis) of one or more valves. (e.g. Potter 1952). Many reports have appeared which illustrate many cases (Bellet and Gouley 1932; Sano and Anderson 1942; Cosgrove and Kaump 1946; Edmonds and Seelye 1951; Gowing 1953; and Still 1954). The condition has been described in siblings, and Fisher and Lloyd (1951) described the condition in association with an anomalous left coronary artery arising from the pulmonary trunk. More recently, Still and Boult (1956, 1957) have studied the tissue immediately underlying

the endocardium of these cases by electron microscopy, and conclude that it shows the features of fibrin rather than of collagen or elastica both of which appear to be abundant by conventional staining methods in the thickened endocardium. In addition to Case 50 I have other examples of fibro-elastosis without evidence of fibrin thrombi, and in no case does the endocardium give the staining reactions of fibrin, but it has been shown in Section 6 above that there comes a time, about 12 weeks after its formation when fibrin loses its conventional staining properties. Therefore fibrin which is older than this may stain as collagen does. Case 50 was one of the few anomalous cases, in that the fibrin in its liver must be of about 2 weeks duration while the infant lived for 5 days only. The fibrin in the liver was laid down while the infant was <u>in utero</u>, similar to Case 3. If an earlier episode had occurred, at least 12 weeks before delivery, and if this had lodged in the cavity of the left ventricle, there is plenty of time available for such a thrombus to become incorporated into the endocardium of the left ventricle and aortic valve, and to lose its staining properties so that the final picture of fibro-elastosis results. This is an hypothesis only, but it would explain

some cases of this unusual condition.

(e) Foetal Endocarditis. This term is often used synonymously with fibro-elastosis, but I prefer to apply the term to the condition where vegetations are found on the heart valve. Such a condition has been described by Plaut and Sharnoff (1935), Plaut (1939) and McDonald (1950). In all three cases the vegetations were sterile and there is a maternal history of influenza four weeks before delivery in the first case, mild pre-eclamptic toxaemia in the second, and a positive W.R. in the third case. The vegetations were rich in fibrin and two of the three cases showed blood "cysts" on the valves affected by the vegetation but the latter had no connection with the cysts. None of these authors noted fibrin in any other organs, but there is no mention that special stains were used. Further, the second case (Plaut 1939) showed suprarenal haemorrhage, subarachnoid haemorrhage and atelectasis. These cases are not dissimilar to Case 15 above which may explain the aetiology of this particular form of foetal endocarditis. The authors mentioned above were uncertain of the aetiology and were stimulated to publish their cases firstly because they were so young, and secondly because they were examples of vegetations

arising on heart valves which were previously normal, apart from the "blood cysts" which are found frequently in the hearts of stillborn and neonatal infants (Levinson and Learner 1932).

(f) Foetal Hepatitis. This form of hepatitis appears in the foetus in utero and may affect siblings or one of twins. Reports of the condition have appeared since 1951. (Stokes, Wolman, Blanchard and Farquhar 1951; Bellin and Bailit 1952; Craig and Landing 1952; Dible et al. 1954; Krainin and Lapan 1956; Miller 1957, and Peterman 1957). It became necessary to study the livers in my series in order to determine the possible incidence of foetal hepatitis and also to find out if sinusoidal fibrin deposits could be responsible for a similar histological picture. I found no example of foetal hepatitis as described by the above authors in 573 livers examined, and fibrin thrombi do not seem to be capable of producing a similar histological picture. The two conditions appear therefore to be quite unrelated.

(g) Haemolytic Disease of the Newborn. In recent years the pathological histology of this condition as found in human foetuses and in stillbirths seems to have been neglected. I

was interested in this condition for the following reasons - (a) the blood group incompatibility stimulated the appearance of antibodies which, while showing their presence clinically by evidence of increased haemolysis, may also cause intravascular agglutination and thereafter, possibly thrombosis, as suggested by Wiener, Wexler and Brancato (1954), (b) the intensely oedematous state of the foetus with hydrops foetalis has not been explained satisfactorily, and it is possible that since hydrops foetalis is the worst form of haemolytic disease of the newborn, intravascular agglutination and thrombosis is worst in this form of the condition, (c) Rice and Eloise (1953) have reported a deficiency of prothrombin and fibrinogen in a fatal case of erythroblastosis foetalis with undue fluidity of the venous blood at necropsy. This could be explained equally by intravascular coagulation as by the presence of hepatic immaturity or insufficiency, and (d) Henderson (1942) and Gerrard (1952) have recorded the occurrence of cirrhosis of the liver in association with haemolytic disease of the newborn. My results show that Case 12, a baby with erythroblastosis foetalis, showed widespread fibrin thrombosis, but several examples of hydrops foetalis were

quite free from antemortem thrombosis. Therefore, I believe that intravascular thrombosis is unusual in association with haemolytic disease of the newborn, and that its occurrence has no direct bearing on this condition. The aetiology of hepatic cirrhosis remains unexplained.

(h) Haemorrhagic Disease of the Newborn. In 1955, Douglas and Davies re-studied this condition and reported that it is due to a deficiency both of factor VII and prothrombin. They also stated that water soluble Vitamin K would not produce normal levels of these coagulation factors, but would prevent deficiency which is normally present on the third day. It has become clear from the cases discussed above in this thesis, that thrombo-embolism in the neonatal infant may result in a temporary bleeding state so that if the infant dies the features seen at postmortem will be those of haemorrhage i.e. simulating haemorrhagic disease. Not only that, if the infant's blood is tested before death only for prothrombin and factor VII, without any tests for fibrinogen, the results obtained will be in favour of haemorrhagic disease. It is apparent therefore that a proportion of cases of haemorrhagic disease of the newborn are really examples of thrombo-embolism. In the future these

groups require separation for the treatment of the two conditions is different.

(i) Hepatic Necrosis. The first record which I am able to trace of venous infarction of the foetal liver was given to the Royal Society of Medicine by Palmer (1923 - 24). His example was from a mature stillborn foetus which died from prolonged pressure on the umbilical cord as a result of a prolonged second stage. The histological description, although brief, is comparable in many ways with Case 3. He could give no adequate explanation for these findings. An almost similar case in a neonatal death, at six days was recorded by Kaplan, Perlstein and Hess (1943). These reports and the two by Browne (1922) and Holland (1922) are the only ones on hepatic necrosis in foetuses and neonates apart from the recent series by Emery (1952, 1953 b. and 1956) who was concerned more with the normal involutionary changes in the left lobe after birth, and by Gruenwald (1949) who showed that the right lobe of the liver normally exists in the foetus on a very low oxygen concentration and may thus suffer severely when conditions make the foetus much more anoxic. Zimmerman (1930) showed that infarction seldom results from portal vein

thrombosis in adults if the arterial supply remains intact, while Parker (1955) showed that hepatic infarction probably occurs only as a result of arterial occlusion. This thesis shows, by the example of Case 3 in particular, that neither of these last mentioned authors is strictly correct.

(j) Hyaline Membrane. Hyaline membrane has a long and confused history dating from its first description by Wolbach (1919) in the lung alveoli of people dying during the influenza pandemic. Since then, it has been observed in the lungs of infants dying in the neonatal period. Its origin has been debated often. It is found most frequently in premature babies and in babies born by Caesarean section. Claireaux (1953) believed that the membrane was derived from amniotic squames. Others (Bruns and Shields 1954) associated them with the highly oxygenated atmospheres in which some prematurely born babies live. Wagner (1954) believed from his observations that they were derived from naso-pharyngeal and bronchial mucus. Hadders and Dirken (1955), Lendrum F.C. (1955) and Duran-Jorda, Holzel and Patterson (1956) believed that hyaline membrane was derived from the lung capillaries, and electron microscopy studies by van Breeman, Neustein and Bruns (1957) showed that the membranes were rich in fibrin. In my series, routine staining of sections

of lung with phosphotungstic acid haematoxylin not only shows the staining properties of fibrin in about one third of the cases, but shows actual networks of fibrin within the membrane. It then became important to decide whether these cases of hyaline membrane had suffered originally from pulmonary fibrin thrombo-emboli of the nature which is the subject of this thesis, and that ejection or extension of the thrombi from the capillaries into the alveoli may be one method by which the lung capillaries may re-acquire their patency. Histological study failed to uphold this idea.

(k) Hypothermia. Neonatal infants and in particular, premature babies are very susceptible to hypothermia. It is important to know if hypothermia is likely to be the result of, or the cause of, thrombosis as demonstrated in the cases discussed above. This would appear to be unlikely for some of the babies showing these lesions died *in utero*. Further, results from experimental studies on hypothermia (Knocker 1955), the application of hypothermia to patients undergoing cardiac surgery (Dundee, Scott, Mesham 1953, Drew and Anderson 1959), and the postmortem findings in cases of accidental hypothermia (Emslie-Smith 1958, Smith 1958) all show that thrombosis bears no connection with hypothermia.

(l) Intracerebral Haemorrhage. In 1919, Warwick drew attention to the high incidence of cerebral haemorrhage among the newborn in

her hospital — 50 per cent of 36 deaths. She believed that haemorrhagic disease of the newborn was a much neglected cause of such death. Later Craig (1938) reported a clinico-pathological survey of 126 deaths in which intracranial haemorrhage was found. Haemorrhage into the brain substance occurred only in six cases. He considered that haemorrhagic disease was responsible for four of these deaths. Cases 18, 29 and 31 above all show cerebral haemorrhages, and all show thrombi in the related vessel. Case 29 shows a microscopic softening in relation to a cerebral haemorrhage. My results suggest that a strong relationship exists between antemortem thrombo-embolism and intra-cerebral haemorrhage in the newborn.

(m) Kernicterus. Zimmerman and Yannet (1935) suggested a relationship between icterus gravis neonatorum and kernicterus, and that this was different from hepatolenticular degeneration. Since then kernicterus is known to arise in severe cases of haemolytic disease of the newborn (Vaughan 1946, Mollison, Mourant and Race 1948), and since then the condition has been recorded in association with prematurity (Aidin, Corner and Tovey 1950, Claireaux, Cole and Lathe 1953, Govan and Scott 1953), neonatal sepsis (Biemond and van Creveld 1937), and "spontaneously" (Butler and Spector 1952). Wiener, Wexler and Brancato (1954)

suggested that the neurological damage was the result of intravascular conglutination of red cells blocking the circulation. Cappell (1946) stated that he had never seen such a histological picture in kernicterus. My study of the basal ganglia and medullary centres of all cases dying of haemolytic disease of the newborn apart from in Case 12 above, fails to show thrombi of any variety.

(n) Neonatal Coronary Artery Thrombosis. Many examples of coronary artery disease with myocardial infarction or fibrosis have been recorded in infants who were several months old. It has been impossible to exclude completely in such cases the possibility that the arterial disease was the result of hypervitaminosis D or a hypersensitivity to Vitamin D. Ravich and Rosenblatt (1947) reported two cases of myocardial infarction in infants aged $10\frac{1}{2}$ hours, and 2 days, with thrombi in the related coronary arteries, and also in the coronary veins. Histology of other organs shows no remarkable features but specific stains for fibrin were not employed. It is possible that these two cases represent examples of thrombo-embolism affecting the coronary system.

(o) Neonatal Gangrene. This condition affects the lower limbs most frequently although the upper limbs and other parts of the

body may also be affected. Gross (1945) annotated the records of 41 published cases during the 20th century, and added six cases of his own. These incidents of gangrene are thought to be due to retrograde thrombosis of the hypogastric vessels, or to embolism from a thrombotic process affecting the ductus arteriosus which was shown in some cases to be of aneurysmal proportions.

It is accepted nowadays that these embryonal channels close without thrombosis in the great majority of cases after birth (Dawes 1958). The finding of antemortem thrombus in any of these channels postnatally is therefore significant. There is no reason why fibrin embolism should not lodge in the ductus arteriosus, at the bifurcation of the aorta, in the iliac, femoral, or hypogastric vessels to produce gangrene of various parts. It would seem however from a study of the material in this thesis together with a study of the cases in previous publications (e.g. Gross 1945, Morrison 1945, Perlmutter and Wagner 1950) that these cases of gangrene are really examples of infective thrombosis although evidence for this conclusion is not always apparent. Some examples (e.g. that of Lennox and McCarthy 1951) are clearly due to septic thrombi, while

a rarer example was published by Mills (1949) who suggested that intra-arterial injection of the umbilical cord, rather than intravenous injection, may be responsible for vasospasm and paralysis. My assessment of the literature and of my own material leads me to the conclusion that neonatal gangrene is more likely to be due to an infective thrombotic process than to the process of fibrin thrombo-embolism.

(p) Neonatal Hyperbilirubinaemia. Lathe, Claireaux and Norman (1958) have suggested that the jaundice of prematurity and "physiological" jaundice of mature infants may be due to temporary hepatic deficiency of glucuronyl transferase. My biochemical results have shown that this is a relative immaturity of the liver, for the fibrinogen levels of these babies is quite within normal limits, and it has been shown by Drury and McMaster (1929) that the liver is the main site of synthesis of fibrinogen. I have also shown however that hepatic sinusoidal fibrin is a relatively common finding at postmortem. This may be associated with jaundice (e.g. Cases 19 and 50), but there are also several other cases showing jaundice without intrasinusoidal fibrin (e.g. Cases 29, 32, 40, 44 and 51), and there are several cases showing intrasinusoidal fibrin but without jaundice (e.g. Cases 13, 15, 20, 21 and 26). The point which I wish to make is that

this is a mechanical block, reducing the ease of circulation through the liver and therefore capable of preventing removal of bilirubin from the blood by the liver. Thus, this factor by itself may be capable of causing neonatal jaundice, or in other circumstances, may be capable of enhancing the degree of jaundice which would have resulted.

(q) Neonatal Infection. This is mainly respiratory infection and is still a considerable problem in spite of improved knowledge, and improvements in care and treatment (Mac Gregor 1939, Rhaney and MacGregor 1948, Timbury, Wilson, Hutchison and Govan 1958). It will be apparent from some of the cases quoted above that the chances of pathogenic or non-pathogenic bacteria acquiring a foothold in a newborn baby may be enhanced by the presence of pulmonary infarcts as a result of fibrin thrombi lodged in the lung capillaries.

(r) Primary Pulmonary Hypertension. There have been numerous reports on this condition in childhood (Harvey and Hogg 1946, Herdenstam 1949, Berthrong and Cochran 1955, Carpenter and Prichard 1956, Rosenberg and McNamara 1957, Husson and Wyatt 1959). Recently, Evans, Short and Bedford (1957) described 11 cases, their youngest being 7 years at death. They stated that 'the theory that intimal proliferation is of embolic or

thrombotic origin is based partly on experimental evidence and partly on authenticated cases of pulmonary hypertension associated with recurrent embolism. Admitting that the histological distinction between intimal proliferation and organised thrombosis may be very difficult, we still believe it is unlikely that embolism can explain many cases of isolated pulmonary hypertension, especially when it occurs in young subjects." It appears that the condition of fibrin thrombo-embolism described in this thesis may provide the connecting link with this condition. It is my impression that once vascular damage of this form occurs, it may progress and become more widespread to result in the condition of primary pulmonary hypertension in childhood or adolescence.

(s) Pulmonary Infarction. In 1947, Ella Zuschlag described infarction of the lung in children and reported 38 cases. Most were due to infected thrombi from other sources and only one of her cases was less than one month old. Emery (1953a) discussed pulmonary thrombosis in fifteen children. Two of these children were neonates of $5\frac{1}{2}$ days and 9 days and both showed widespread thrombosis affecting several organs, and could be examples of the condition of fibrin thrombo-embolism as described in this thesis, although if they were, he failed to appreciate that the

thrombi were different from the other thirteen cases described. He also points out that many articles suggest that dehydration leads to haemoconcentration and then to thrombosis, but he remarks pointedly that many dehydrated infants never show thrombosis and therefore other factors are involved. This thesis has confirmed that aseptic pulmonary infarction can occur in the neonatal infant, in the absence of heart failure, and is the result of a thrombo-embolic episode affecting one or more parts of the lung.

(t) Renal Cortical Necrosis. Symmetrical renal cortical necrosis was described by Dunn and Montgomery (1941), Campbell and Henderson (1949), Zuelzer, Kurnetz and Charles (1951) and by Sheehan and Moore (1952). The ages of cases described by the first authors was 8 years to 67 years, by the second 9 weeks to $10\frac{1}{2}$ years, by the third authors 1 day to 12 years, while the fourth authors were concerned with the lesion as found complicating pregnancy. A satisfactory aetiology is yet to be found. Case 53 of this thesis shows a combination of renal cortical necrosis associated with renal vein thrombosis, but which could not be dated back to birth.

In summarising this section it appears that fibrin thrombo-embolism (i) plays an important part in some cases of adrenal haemorrhage, haemorrhagic disease of the newborn, hepatic necrosis, and intracerebral haemorrhage; (ii) may be important in the development of fibro-elastosis and foetal endocarditis; (iii) plays a less clearly defined role in some cases of acute glomerular thrombosis, cavernous transformation of the portal vein, coronary artery thrombosis, neonatal infection, primary pulmonary hypertension, pulmonary infarction, and renal cortical necrosis in childhood; and (iv) appears to play no part in the aetiology of foetal hepatitis, haemolytic disease of the newborn, hyaline membrane, hypothermia, kernicterus or neonatal gangrene.

10. Treatment.

Having now established the occurrence of disseminated thrombo-embolism in the foetus in utero and in the neonate, it may be permissible to make a few observations on proposed lines of treatment.

It is clear that the child may be suffering from internal haemorrhage as a result of utilisation of clotting factors in producing the thrombi, and this has to be stopped. This is best accomplished by giving transfusions of fresh blood

or fresh plasma which is rich in clotting factors. If this can be done by using double-, triple-, or quadruple-strength plasma, the better will the results be because the volume of blood lost is seldom important. The site which is damaged may be extremely important.

Secondly, there is the mechanical effect of widespread fibrin thrombi on the circulation. This aspect has not been considered up to the present when the mother is affected because in her case it is blood loss which primarily requires to be controlled. Further, the mother may have adequate circulating fibrinolysins (Phillips and Skrodelis 1958), but this is not necessarily the case; for Macfarlane and Biggs (1946) tested blood from 137 normal pregnant women and found no fibrinolytic activity. This was confirmed by Willson and Munnell (1946) who found fibrinolytic activity to be absent in normal pregnant women, but present when toxaemia of pregnancy occurred. It would seem therefore that present day treatment of the mother with the "defibrination syndrome" does not cover the widespread fibrin thrombo-emboli so that these are left to become incorporated in the intima of the blood vessels, and aggravating thereby any arterial disease already present. When the baby who has the same condition, is considered, it has been stressed repeatedly

that the ones who die possess no fibrinolysin and the intravascular fibrin deposits may provide a serious impediment to rapid, free circulation. It may be advisable to treat these patients with synthetic fibrinolysin preparations along the lines employed by Tillett, Johnson and McCarty (1955), and by Cliffton (1958) for treating thrombotic episodes in adults.

Thirdly, the appearance of pulmonary infarcts makes the child more susceptible than usual to respiratory infection and therefore, extremely careful nursing together with a prophylactic course of an antibiotic will be necessary in most cases.

Fourthly, if bilateral suprarenal haemorrhage is thought to be present as a result of a thrombo-embolic episode, substitution therapy with cortical hormones, and possibly with noradrenaline, may be necessary.

# VI. CONCLUSIONS

1. The incidence of thrombosis in 755 stillbirths, neonatal deaths, and deaths among infants and children, has been determined by staining sections of the tissues for fibrin with Lieb's phosphotungstic acid haematoxylin.

2. The thrombi encountered can be divided into three groups - antemortem, agonal and postmortem varieties. The antemortem thrombus which is the one discussed in this thesis was found in 71 cases (9.4 per cent) and in it the fibrin strands lie parallel to one another, lie parallel to the vessel wall, show a streaming effect which is evidence of a forceful blood flow at the time of their deposition, show a saddle embolus effect at the bifurcation of the vessels involved, cause ischaemic changes and sometimes necrosis of areas supplied or drained by these vessels, and may show signs of being incorporated into the vessel wall if they have persisted long enough.

3. Antemortem thrombi may be of different varieties — pure fibrin thrombi, or mixed thrombi. The pure fibrin thrombi are nearly always aseptic, although sepsis elsewhere in the body may appear to be responsible for their appearance in a few cases. Mixed thrombi may be aseptic, infected, traumatic or allergic, or may be of unknown aetiology.

4. Antemortem thrombi were recorded in 10 out of 331 stillbirths (3.02 per cent) and were responsible partly or wholly for death in 6 of these (1.8 per cent).

5. Antemortem thrombi were recorded in 9 out of 226 neonatal deaths within 48 hours of birth (4.0 per cent), and were responsible partly or wholly for death in 7 cases (3.1 per cent).

6. Antemortem thrombi were recorded in 33 out of 119 later neonatal deaths (27.73 per cent), and were responsible for death in 19 of these cases (15.96 per cent).

7. Antemortem thrombi were recorded in 16 out of 79 deaths among infants and children (20.25 per cent), and were never wholly responsible for death. The thrombi were partly responsible for 8 deaths (10.13 per cent).

8. Pure fibrin antemortem thrombi were encountered in 43 cases in all, and in seven of these it appeared to have a definite origin post-natally. In the remaining 36 cases the fibrin thrombi appeared to affect the infant either <u>in utero</u>, during birth, or immediately following birth.

9. Among stillbirths, the liver was the most frequently affected organ (7 out of 9 = 78 per cent). For this reason,

it is suggested that the thrombotic episode may have been initiated in the placental circulation. Among the neonatal deaths within 48 hours of birth, the adrenal gland is the most frequently affected organ (4 out of 6 = 67 per cent), and followed by the lungs (38 per cent) and liver (29 per cent). Among the later neonatal deaths, the spleen was involved most frequently (6 out of 14 = 43 per cent), to be followed by the lungs (35 per cent), central nervous system (27 per cent). It is important to notice that thrombosis in the liver occurs with a reasonably high incidence even among neonatal deaths. The incidence of pure fibrin thrombi among infants and children is too small to permit any real comparison with the figures given above, but they are quoted for the sake of completeness. The kidney is the most heavily involved organ (3 out of 4 = 75 per cent), followed by the liver (40 per cent).

10. These fibrin thrombi affect arteries, capillaries or veins, and it is typical of this condition to find the thrombi affecting all three types of vessel in the same organ of the one patient.

11. Several aetiological theories are suggested and discussed. The one which obtains the greatest support from the results as described is the occurrence of one or more thrombotic episodes

affecting the foetal blood as it flows through the chorionic villi of the placenta. Clotting takes place once the blood has returned to the foetus, most often in the liver, but occasionally in other organs such as the adrenal gland, brain, lungs, spleen and kidneys. This hypothesis is similar to the currently accepted one for the state of "obstetric shock" in the mother, also known as "hypofibrinogenaemia of pregnancy", and as "the defibrination syndrome of pregnancy". One of twins may be affected by this process and not the other.

12. Thromboplastin of placental origin appears to be capable of entering the foetal circulation.

13. Less thromboplastin should be required to cause death of the foetus than is required to cause maternal distress because of the differences in the circulating blood volumes.

14. Observations concerning the distribution of these thrombi are in effect observations on Nature's own experiment with emboli in the foetal circulation. The results obtained have been compared with those experiments made on other animals in order to determine the course of the circulation in the foetus. My results support these experimental results, and it may be added that these experimental results also support

my observations.

15. By placing the infants according to their ages, it is possible with a few exceptions to obtain a timetable concerning the organisation of fibrin. Little happens for the first two weeks. In the third week the thrombi retract to the vessel wall. In the fourth week, endothelial covering and recanalisation occur. The loss of staining properties of fibrin occurs some time after that, and is complete by the twelfth week at the latest. Ingrowth of new capillaries and fibroblasts from the intima into the thrombus appears to occur only where the thrombus is infected.

16. In order that such a histological picture of extensive fibrin thrombosis may be produced, it is necessary for the infant to have a previously high fibrinogen level, to be subjected to the sudden entry of a large quantity of thromboplastin into its circulation, to be deficient in circulating fibrinolysins, and when dead, to be accommodated in a refrigerated mortuary so that pre-existing thrombi may not be digested by fibrinolysins developed as a result of the presence of a thrombotic episode.

17. It has been shown that nearly half of the mothers

(49 per cent) gave no history of any upset which could be related to the fibrin deposition in the foetus. One fifth (19 per cent) gave a history of some form of antepartum, intrapartum or postpartum haemorrhage, and 12 per cent had toxaemia of pregnancy or eclampsia. The remainder had miscellaneous complications.

18. This syndrome of disseminated fibrin thrombo-embolism may, if not fatal by itself, leave the infant seriously depleted of blood clotting factors temporarily, so that a haemorrhagic state results.

19. The syndrome appears to be responsible for many of the examples of adrenal haemorrhage, intracerebral haemorrhage and hepatic necrosis, and for some of the examples of subcapsular haematoma of the liver, and haemorrhagic disease of the newborn.

20. In less severe cases, which are not fatal in the neonatal period, the syndrome may be responsible for disease later in infancy and childhood. Examples of such conditions may include primary pulmonary hypertension, fibro-elastosis and some examples of cavernous transformation of the portal vein.

21. The one per cent sodium chloride rapid fibrinogen method is almost as accurate as the longer micro-Kjeldahl method.

One reservation about the rapid method is that a small amount of protein other than fibrinogen is estimated. Since, in the first instance, I have been concerned only with gross differences in fibrinogen levels, this error may be dismissed in the present circumstances.

22. By employing a careful technique, heel blood is quite satisfactory for fibrinogen estimations and the results reflect those of the general circulation.

23. The mean cord blood fibrinogen value of premature babies is comparable with the mean value for mature normal babies.

24. The mean heel blood fibrinogen value of premature babies, taken on an average 24 hours after birth, is significantly higher than the mean cord blood value. This may be due to the longer interval than usual between the two samples, the increased opportunity of latent infection causing a rise of blood fibrinogen, or oedema causing a degree of haemoconcentration.

25. The mean cord blood fibrinogen level of mature (sick) babies is significantly higher than the mean value for mature (normal) babies. No adequate explanation can be offered for this finding at the present time.

26. There was an abnormally high incidence of assisted deliveries

among the babies with abnormally low fibrinogen values at birth.

27. The incidence of assisted deliveries among sick babies with high fibrinogen values was comparable with that for mature babies with normal fibrinogen values.

28. Babies with a foul vernix caseosa or liquor amnii had significantly high fibrinogen values, but the progress of all cases was satisfactory.

29. The mean fibrinogen value of babies with jaundice of prematurity is comparable with that of all premature babies.

30. The fibrinogen value of babies whose mothers had ante-partum haemorrhages and who had toxaemia of pregnancy were not significantly different from normal.

31. Further experience is necessary in this field before it will be possible to define clearly all the clinical syndromes which can be the result of the pathological process described herein.

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The scope of work covered by this thesis necessarily involved many other people and it is my wish that I should acknowledge here the help received from them in many ways. I shall try to detail them in a chronological fashion for otherwise I may omit someone. Indeed, in these days of subliminal advertisement, there seems to be little guarantee that any thoughts which one has are one's own, and it is necessary to remember discussions with colleagues who may not be mentioned specifically in this list, for little pieces of information here and there, which have played their part in building up this whole work.

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time, thought, and energy which most of one's teachers expend in preparing lectures, classes and demonstrations for us. There is no doubt whatever that their teaching moulds the thoughts and ideas of the student's brain. If there be any streak of brilliance in this thesis, then, to my former teachers, a large amount of credit is due.

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An apology is probably appropriate as a final remark. Any errors or deficiencies encountered in this work are entirely my own, while any favourable points are the results of the influence of my colleagues.

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"The process of ageing begins at birth." (Anon)

If one accepts the appearance of arterial disease as one of the manifestations of ageing, it is apparent from the substance of this thesis that vascular disease can commence in utero. The aphorism quoted above therefore becomes inaccurate.

VOLUME II

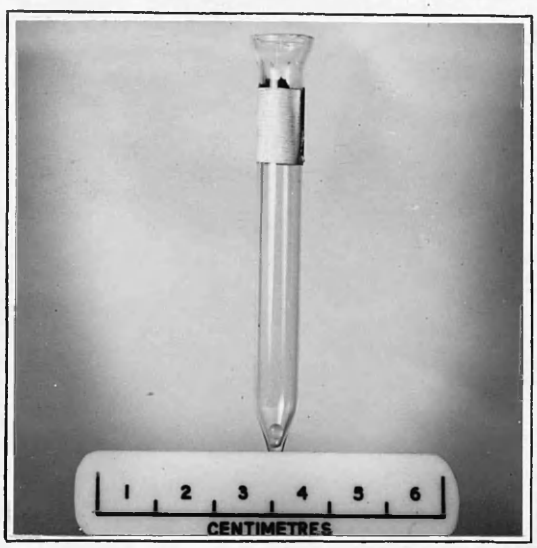



Fig. 1. Siliconed, heparinised Dreyer tube containing a glass bead before use. x $\frac{3}{4}$.

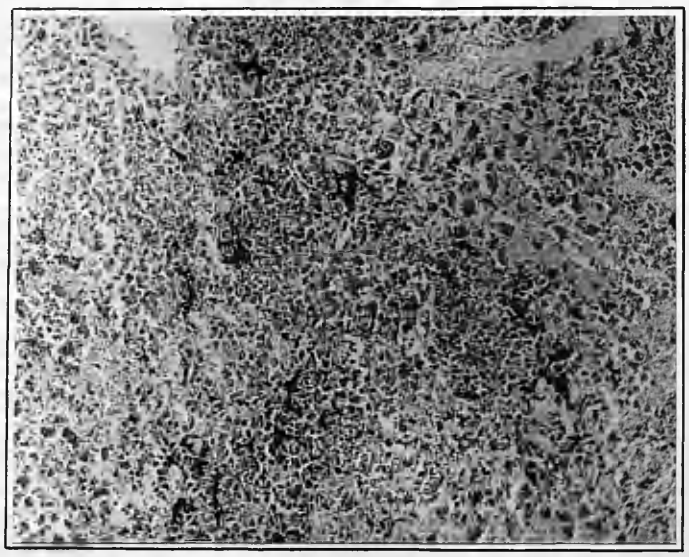


Fig. 2. Case 1. Macerated liver showing numerous sinusoidal fibrin thrombo-emboli (black) in relation to more advanced foci of cellular necrosis. P.T.A.H. x 95.

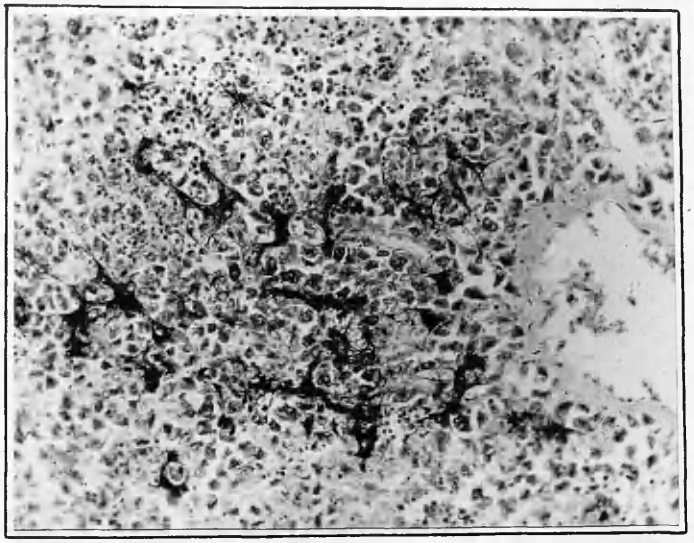


Fig. 3. Case 1. Focus of antemortem fibrin thrombo-emboli in centre of liver lobule. Linkages and streaming are shown. Focus of necrosis present. Early polymorph reaction. P.T.A.H. x 170.

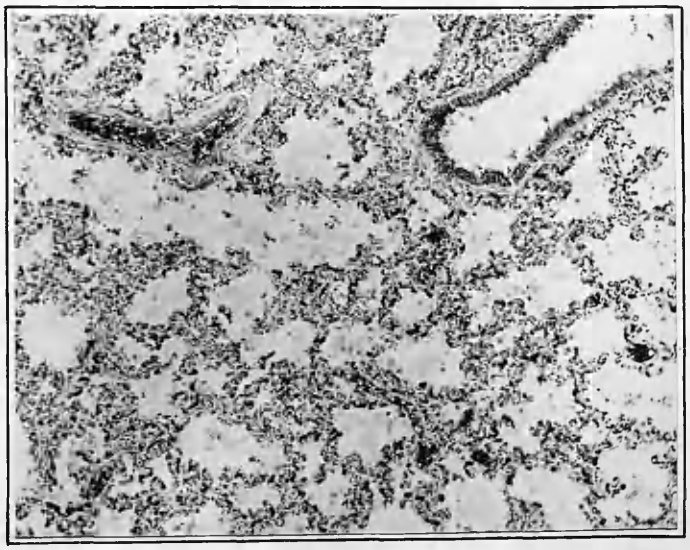


Fig. 4. Case 2. Moderate alveolar expansion of the lung, with capillary congestion and amniotic squamous cells in atrial duct and in alveoli. P.T.A.H. x 95.

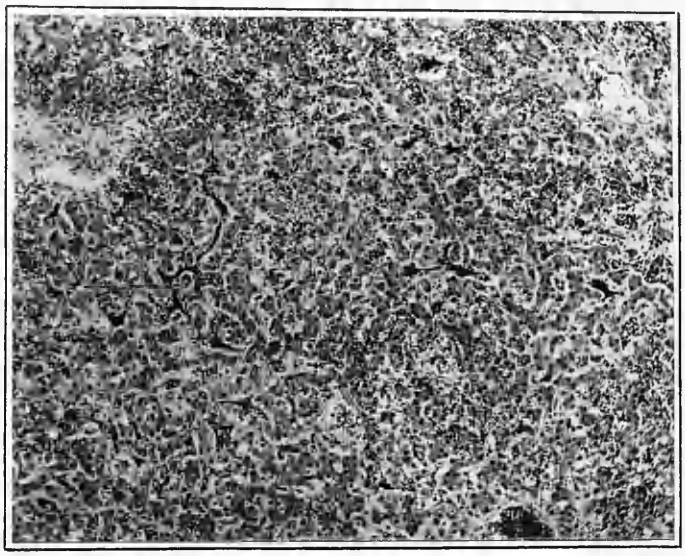


Fig. 5. Case 2. Antemortem fibrin thrombi in liver sinusoids, (black). Portal tract in top left corner, central vein in lower right. Streaming and linkages are evident. P.T.A.H. x 95.

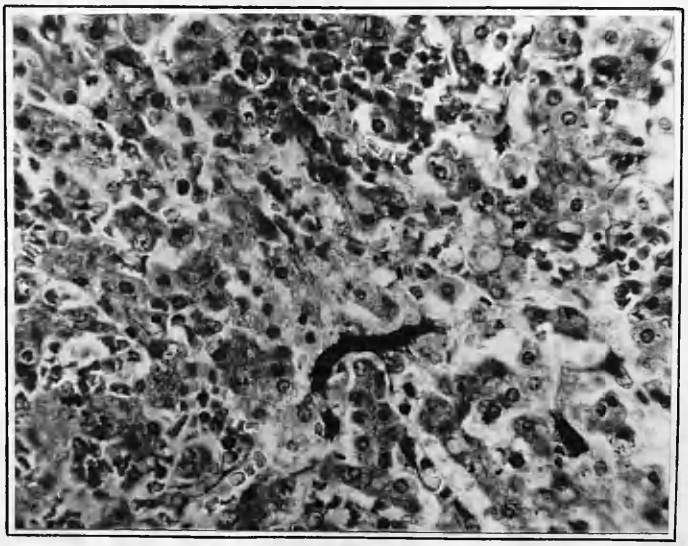


Fig. 6. Case 2. Antemortem fibrin thrombo-embolus in liver showing parallel strands, packed tightly together. P.T.A.H. x 310.

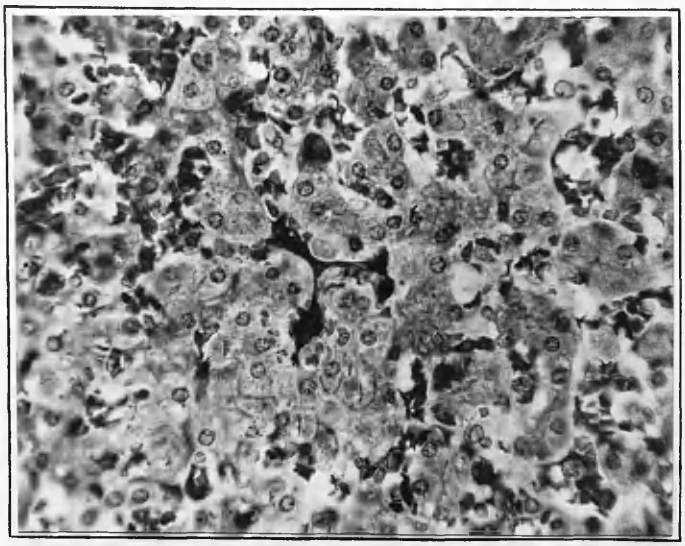


Fig. 7. Case 2. Tendency to linkage and saddle embolus effect of fibrin thrombo-embolus in liver. P.T.A.H. x 310.

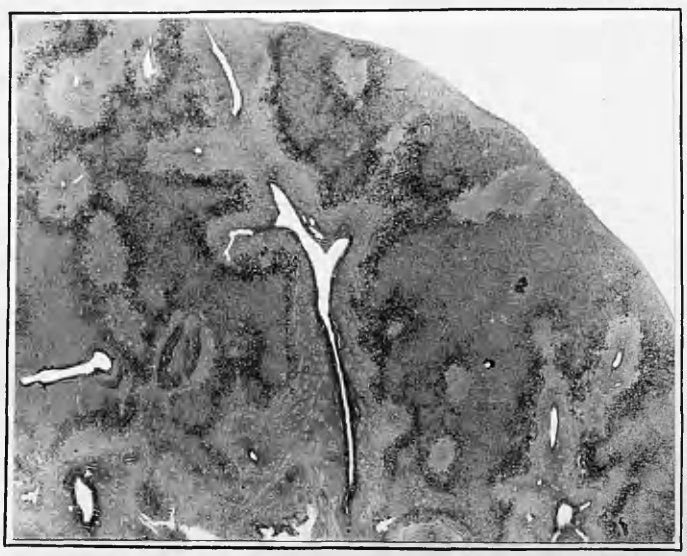


Fig. 8. Case 3. Section shows the irregular capsular surface, widespread confluent infarctions (dark grey) bordered by dense sinusoidal fibrin deposits (speckled black zones) and unaffected areas (light grey). P.T.A.H. x 7.

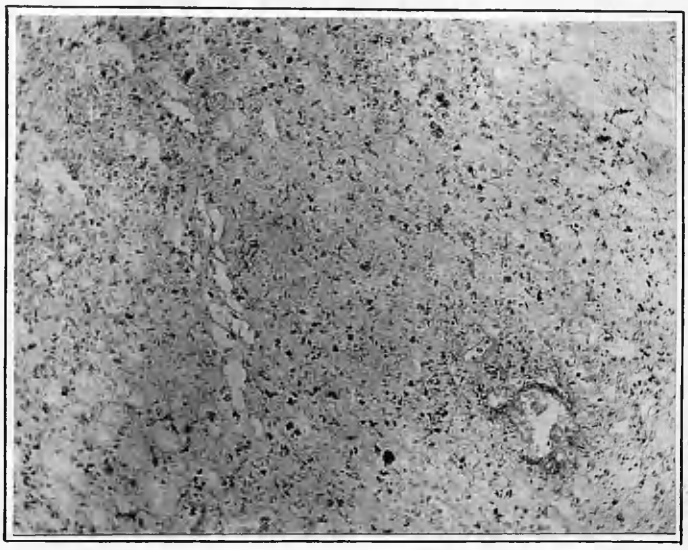


Fig. 9. Case 3. Macerated liver with nuclear debris only, and no fibrin deposition. P.T.A.H. x 95.

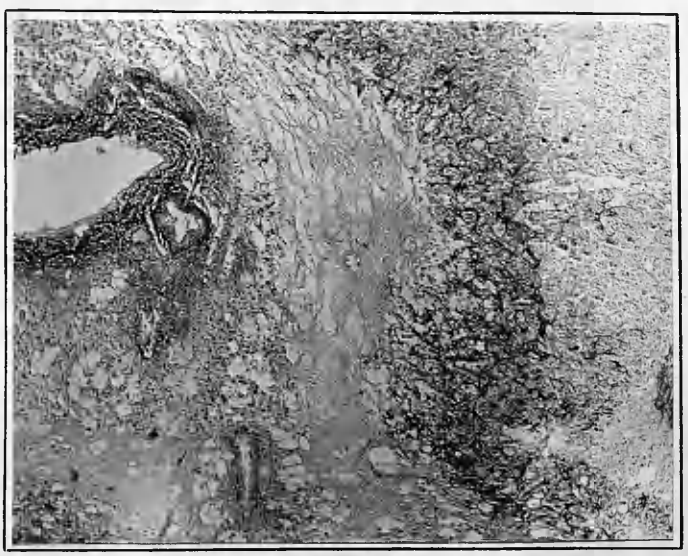


Fig. 10. Case 3. Large portal tract to the left, and macerated parenchymal tissue to the right, with sinusoidal fibrin deposited in the peripheral zones of lobules. P.T.A.H. x 45.

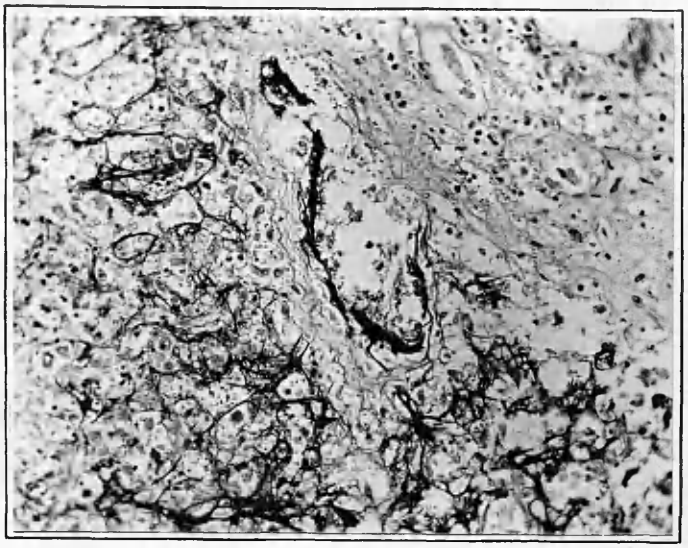


Fig. 11. Case 3. Small radicle of portal vein showing laminated fibrin thrombus. Laminated sinusoidal thrombus is also illustrated. P.T.A.H. x 170.

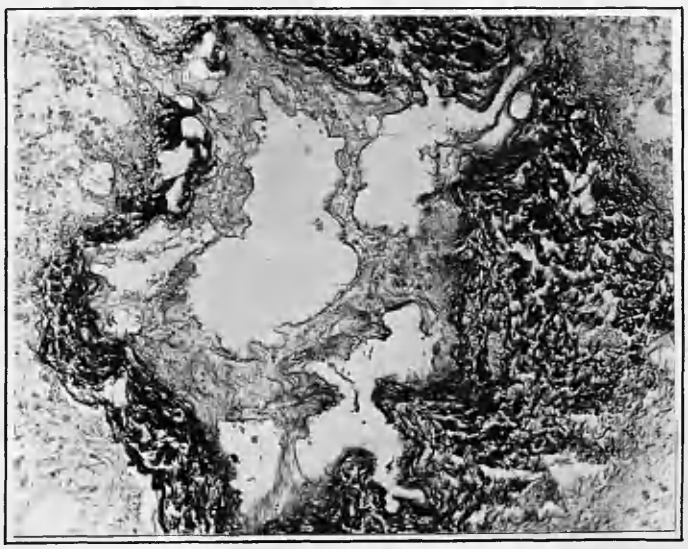


Fig. 12. Case 3. Part of a portal tract showing a portal vein with features resembling cavernous transformation. P.T.A.H. x 95.

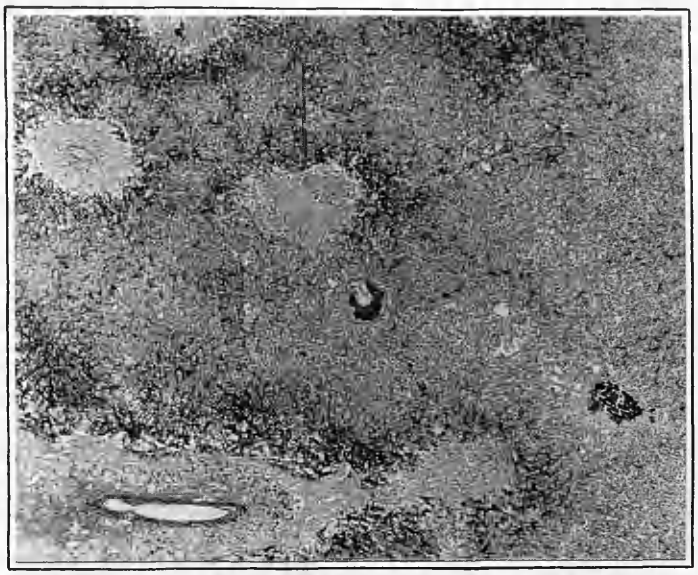
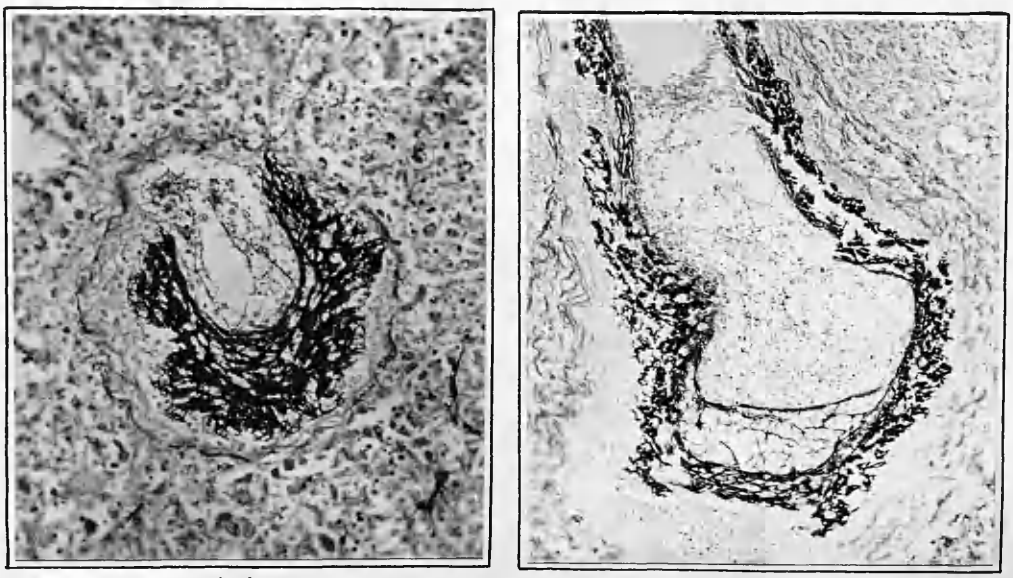


Fig. 13. Case 3. Subhepatic vein cut transversely, illustrating laminated fibrin thrombus. Scanty sinusoidal thrombus is also present. P.T.A.H. x 25.



(a) (b)

Fig. 14. Case 3. (a) Centre of Fig. 13 enlarged. P.T.A.H. x 170, and (b) subhepatic vein cut longitudinally to show laminated fibrin thrombus; no endothelial reaction. P.T.A.H. x 95.

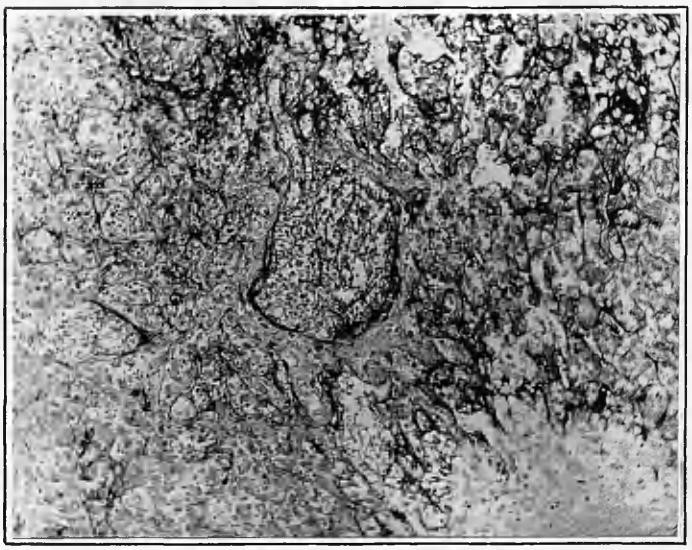


Fig. 15. Case 3. Centrilobular vein showing shallow layer of laminated thrombus against the endothelium. Sinusoidal thrombi also present. P.T.A.H. x 95.

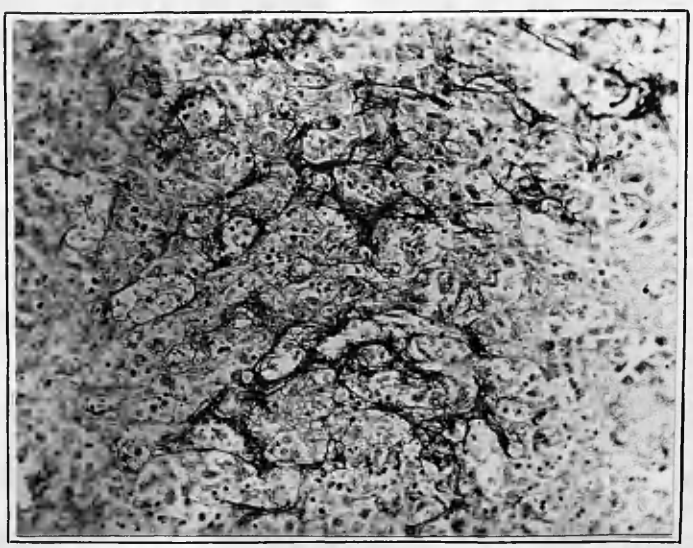
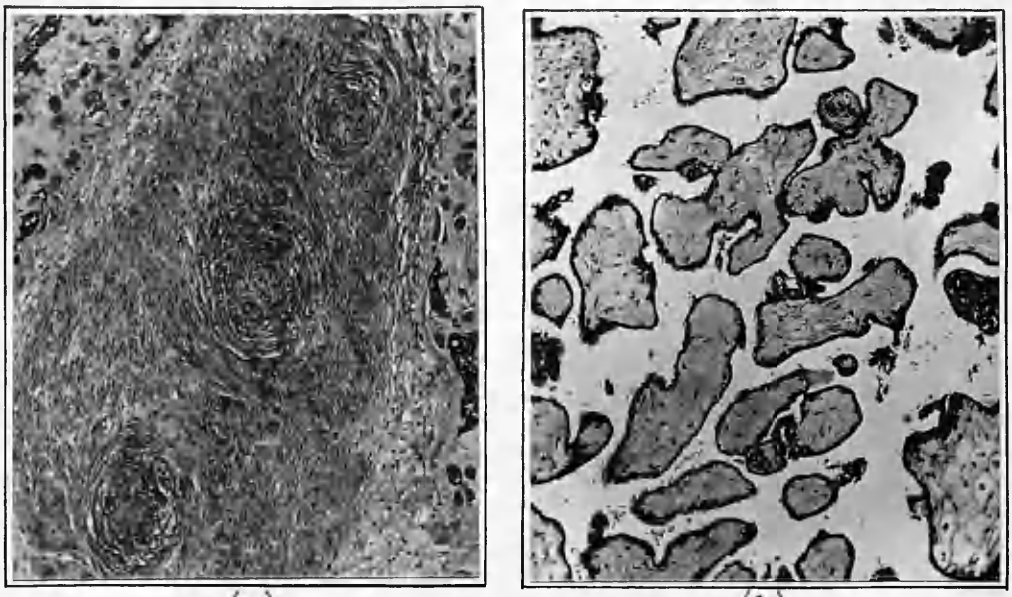
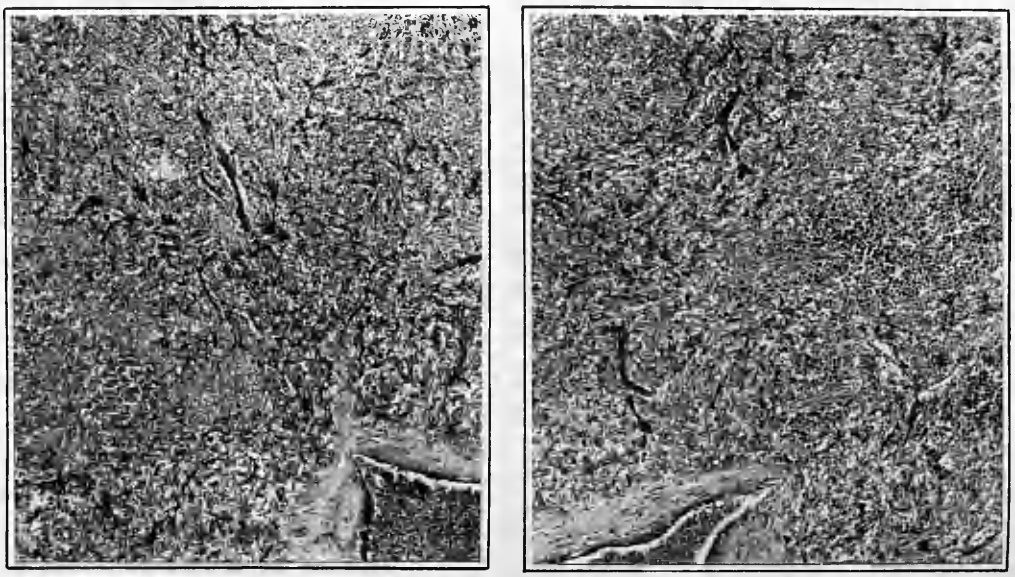


Fig. 16. Case 3. Sinusoids of liver lobule showing retracted laminated fibrin thrombus. P.T.A.H. x 170.



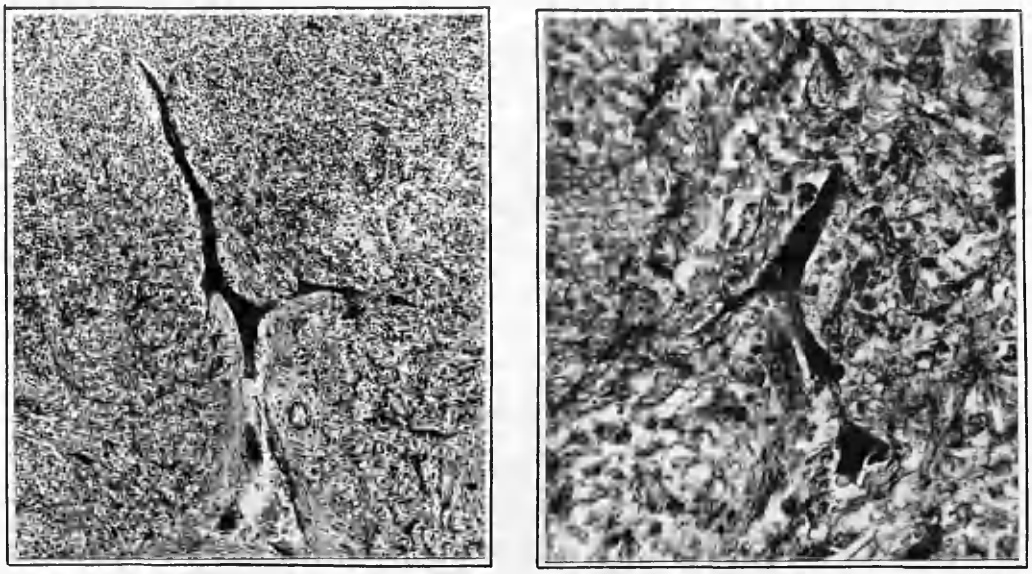
(a) (b)

Fig. 17. Case 3. (a) Placental vessels of cotyledon stalk showing endarteritis obliterans, and (b) avascular chorionic villi. P.T.A.H. x 170.



(a) (b)

Fig. 18. Case 4. Widespread antemortem sinusoidal fibrin thrombi in the spleen. The Malpighian corpuscles are unaffected. P.T.A.H. x 95.



(a) (b)

Fig. 19. Case 4. These photographs illustrate well the streaming and saddle embolus effects of these fibrin thrombo-emboli in the spleen. P.T.A.H. (a) x 95, (b) x 310.

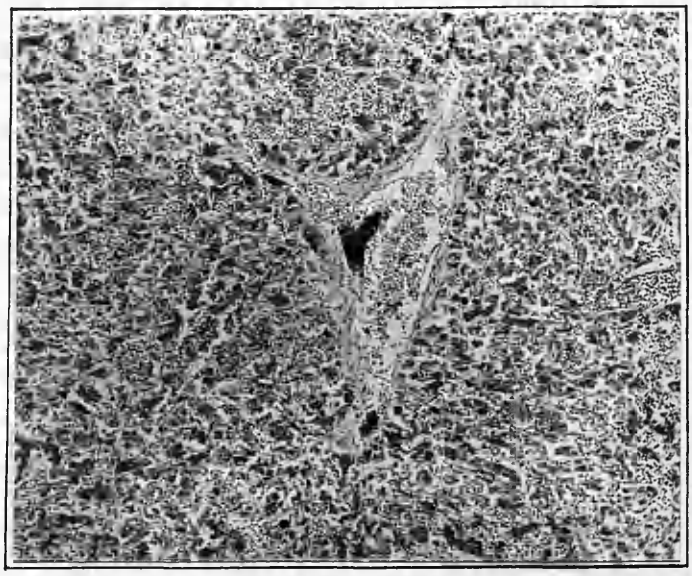


Fig. 20. Case 4. Scanty fibrin thrombi with parallel fibrin strands in central vein of liver. P.T.A.H. x 95.

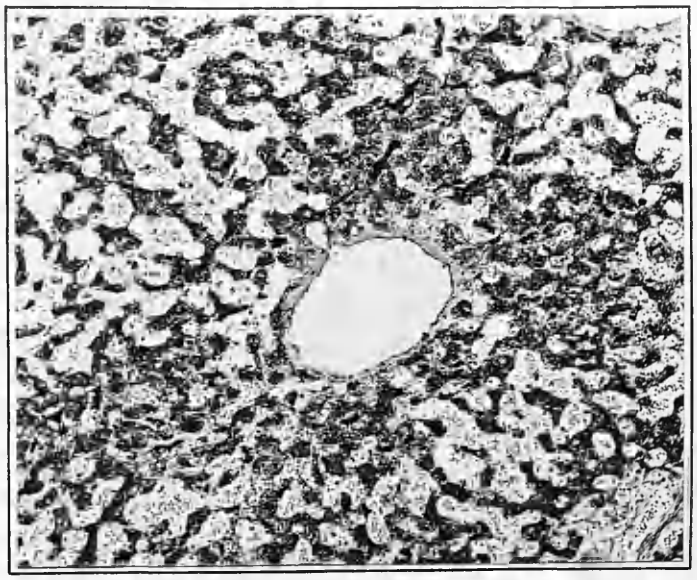


Fig. 21. Case 5. Liver lobule showing scattered antemortem fibrin thrombo-emboli. Sinusoids in relation to these are collapsed with distension of unaffected ones. P.T.A.H. x 95.

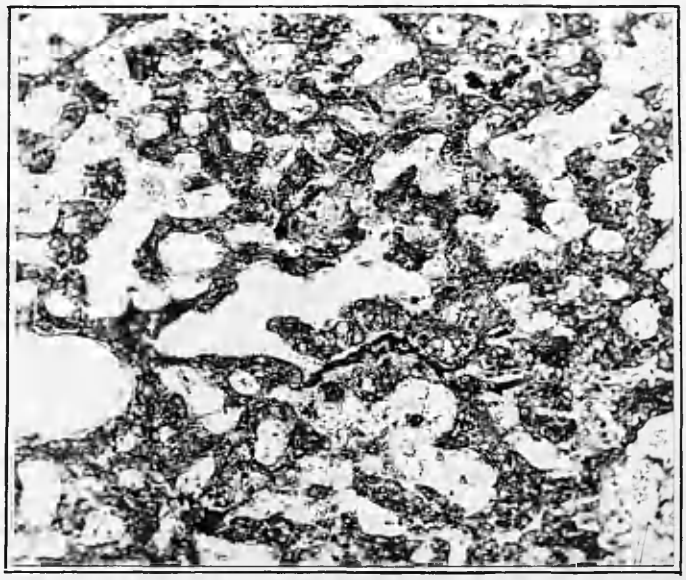


Fig. 22. Case 5. Streaming antemortem fibrin thrombo-emboli in sinusoids which are collapsed, with gross dilatation of adjacent ones from which most of the blood has drained. P.T.A.H. x 170.

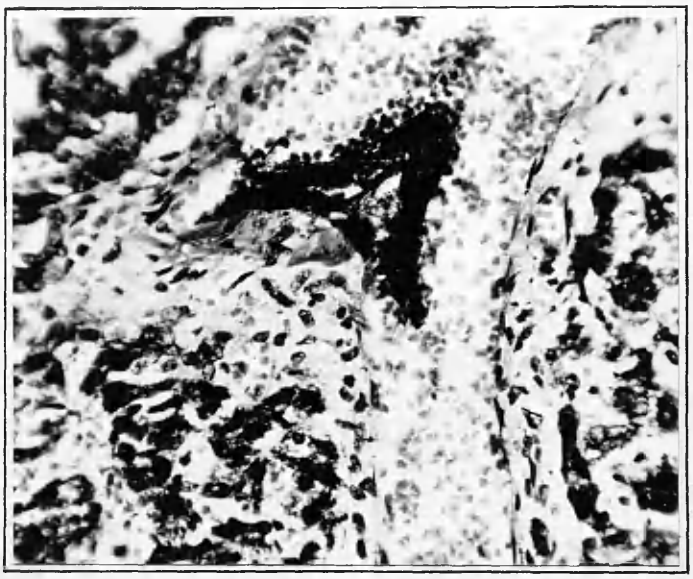


Fig. 23. Case 6. Solitary fibrin saddle embolus in a portal vein showing adhesion of platelets and red blood corpuscles. P.T.A.H. x 310.

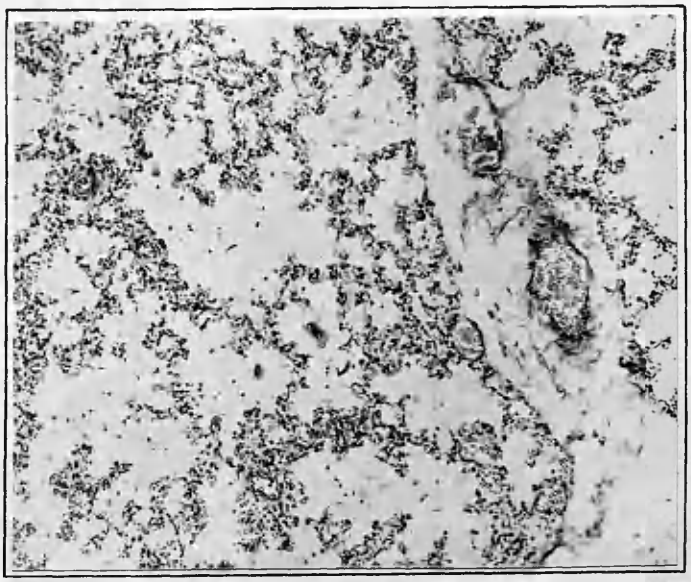


Fig. 24. Case 7. Lung showing well expanded alveoli bearing occasional amniotic squamous cells. P.T.A.H. x 95.

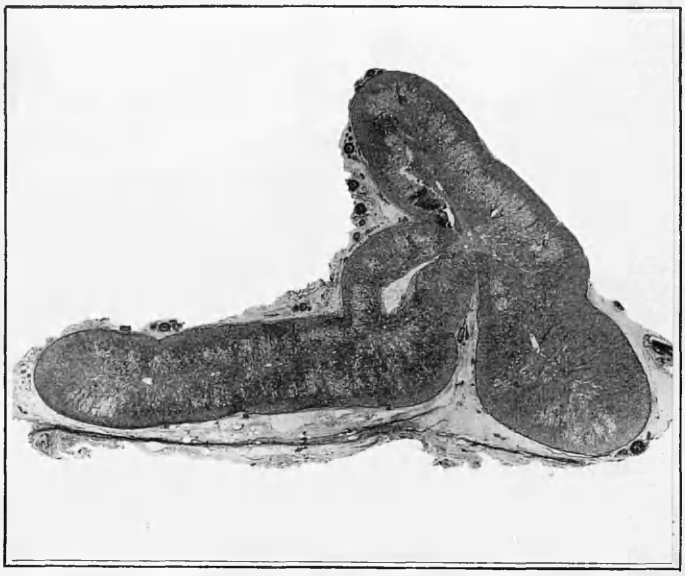


Fig. 25. Case 7. Adrenal gland showing confluent foci of vacuolation in the deeper cortex. Above the adrenal vein there is a dense area of fibrin thrombi. P.T.A.H. x 4.

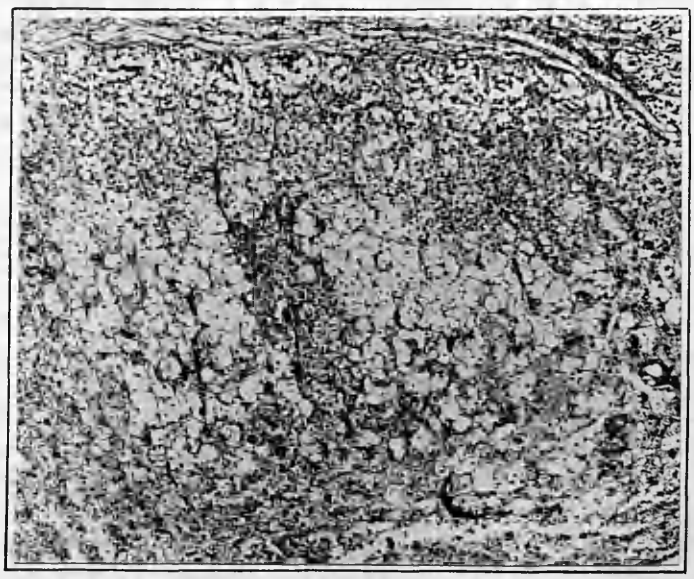
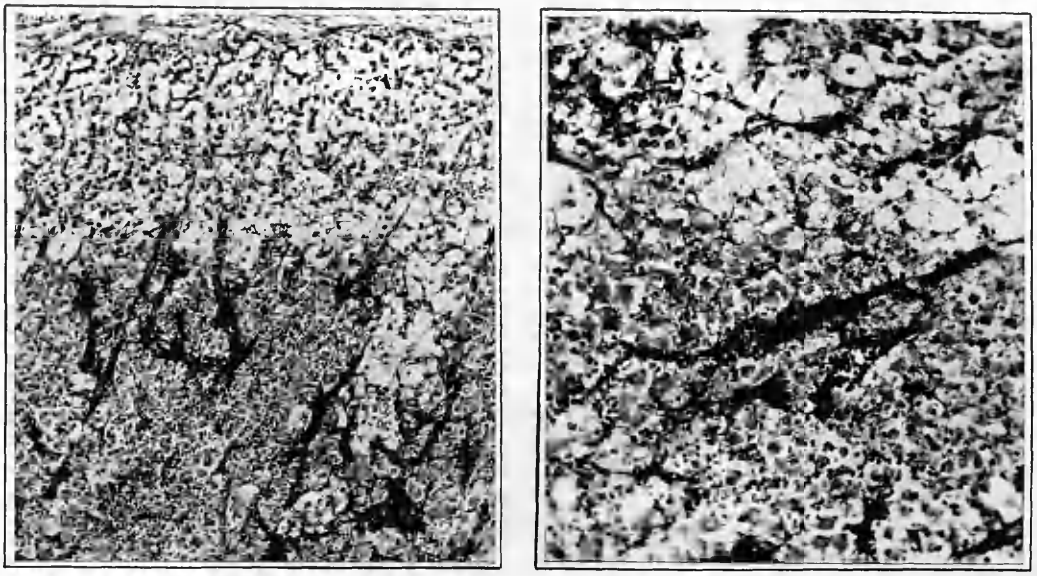


Fig. 26. Case 7. Small focus of adrenal cortical necrosis related to sinusoidal fibrin thrombo-emboli. P.T.A.H. x 60.



(a) (b)

Fig. 27. Case 7. (a) Larger focus of cortical necrosis with sinusoidal fibrin thrombi. x 95. (b) Streaming fibrin thrombi in focus of cortical necrosis with superadded more delicate fibrin. x 170. P.T.A.H.

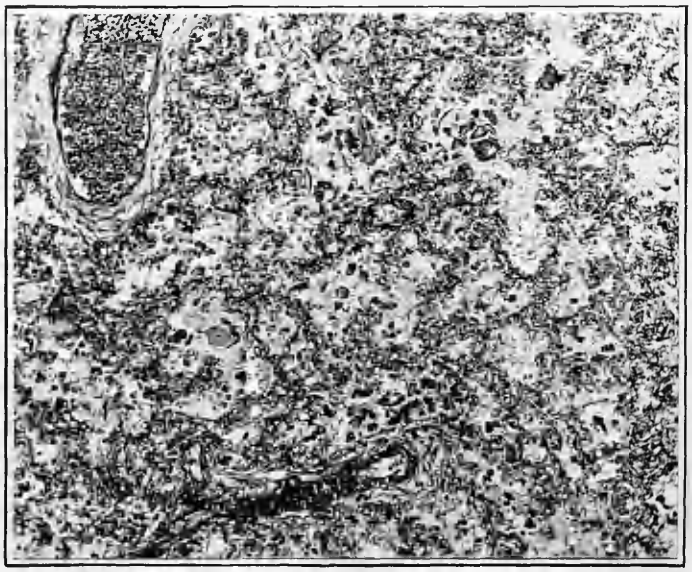


Fig. 28. Case 8. Moderately expanded alveoli containing moderate numbers of amniotic squamous cells. P.T.A.H. x 95.

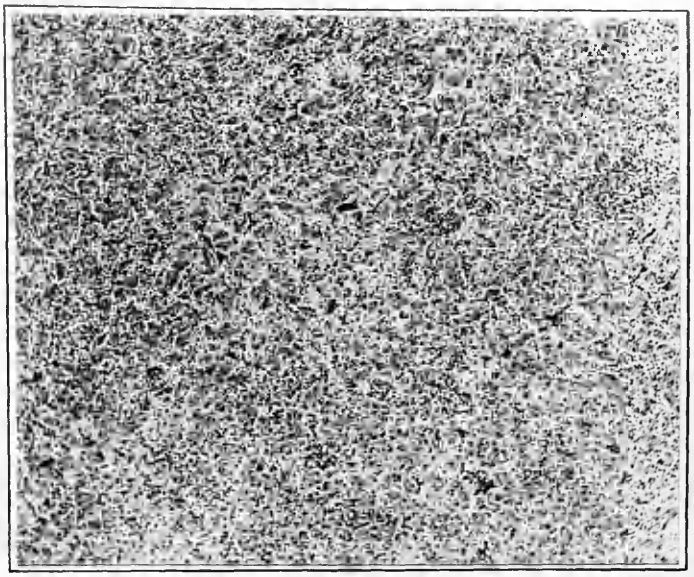
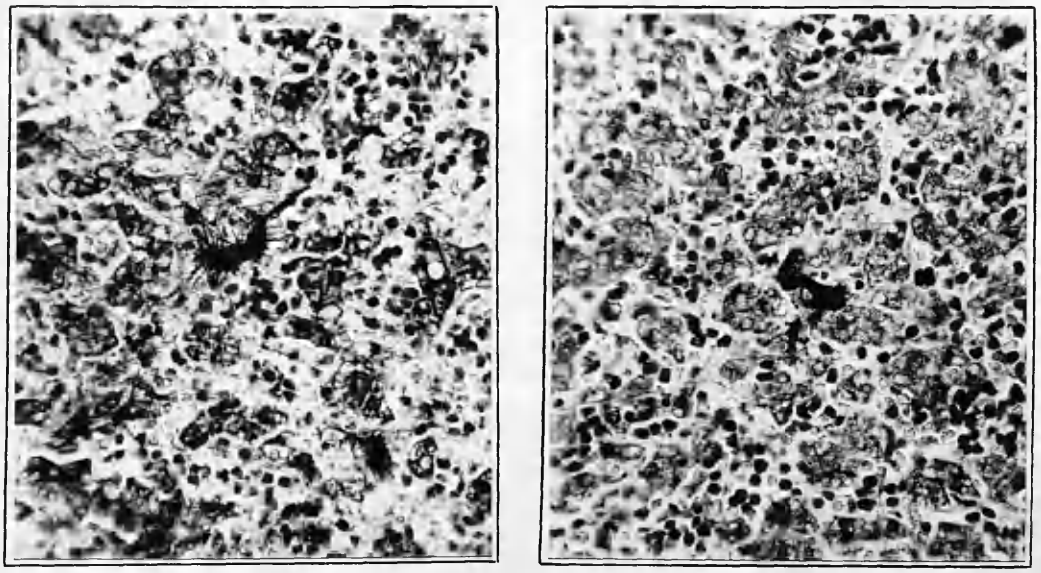


Fig. 29. Case 8. Low power view of liver showing numerous short fibrin thrombi scattered diffusely. P.T.A.H. x 95.



(a) (b)

Fig. 30. Case 8. (a) Streaming tendency of major strands with haphazardly distributed finer strands. (b) Tendency to streaming and linkage around columns. Both thrombi are out of the axial stream. P.T.A.H. x 310.

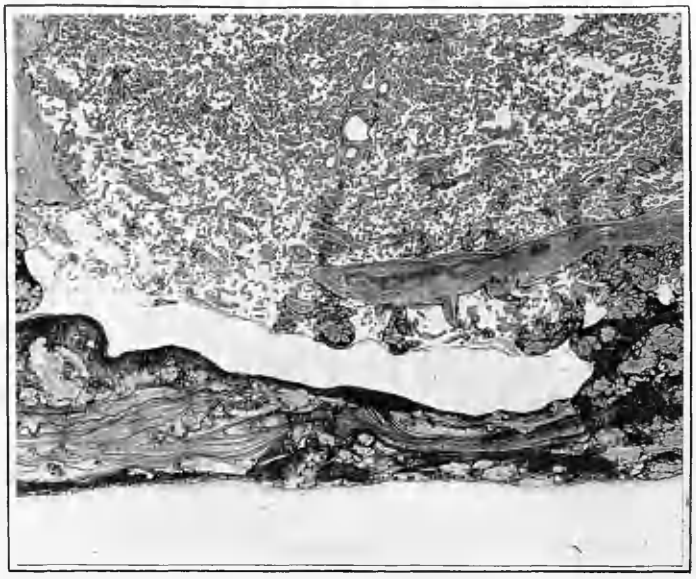
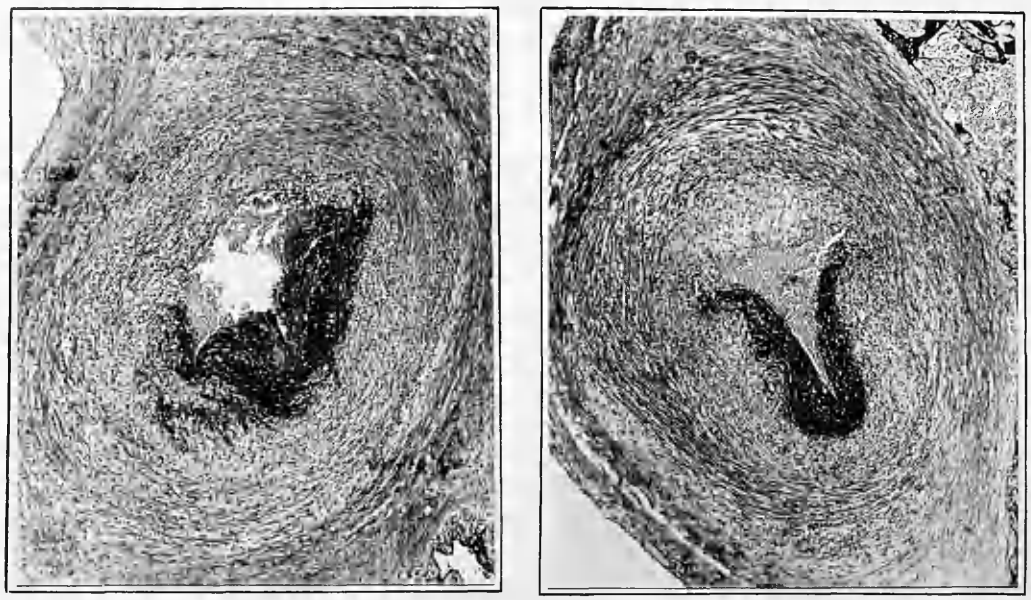


Fig. 31. Case 9. Placenta showing subchorionic haemorrhage with laminated deposits of fibrin. Maternal aspect is superior and foetal aspect is inferior. P.T.A.H. x 7.



(a) (b)

Fig. 32. Case 9. Placental arteries showing laminated organising fibrin thrombi. P.T.A.H. x 45.

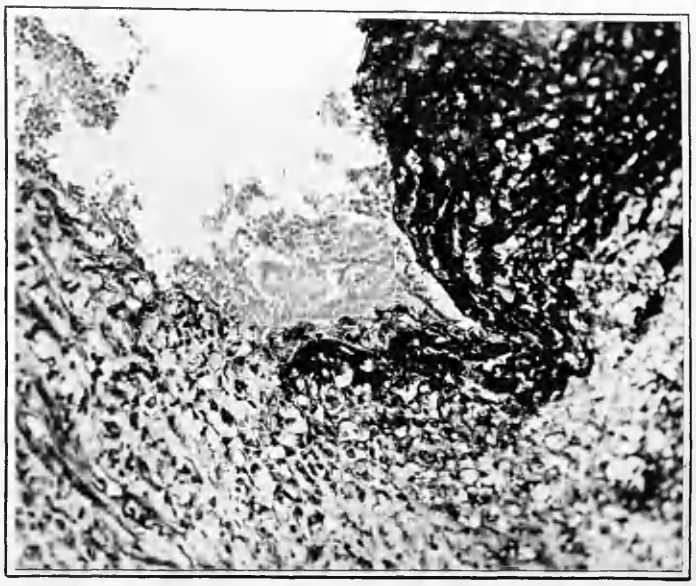
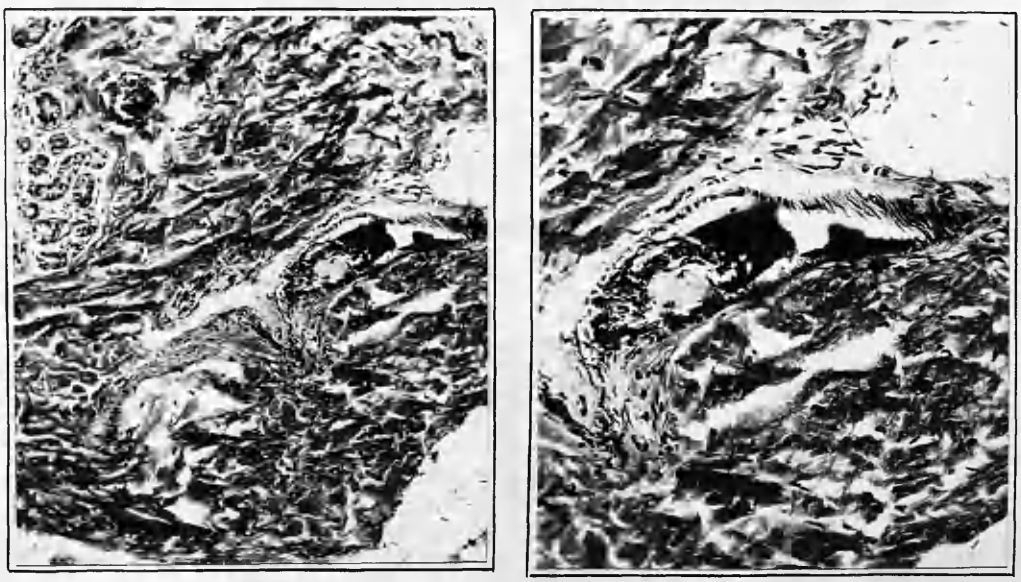


Fig. 33. Case 9. Enlarged section of Fig. 32 (a) showing three endothelial cell nuclei overlying the edge of the fibrin thrombus. No fibroblastic reaction. P.T.A.H. x 170.



(a) (b)

Fig. 34. Case 10. (a) Dark antemortem fibrin thrombus occluding vessel in dermis. x 95. (b) Antemortem fibrin thrombus with scanty platelets near the left. x 170. P.T.A.H.

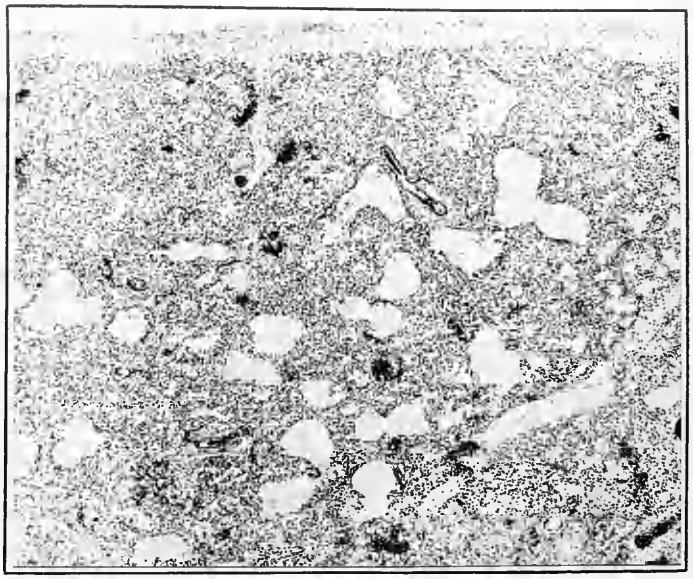


Fig. 35. Case 11. Lung shows patchy atrial and alveolar expansion, without evidence of infection. Fibrin thrombo-emboli are also visible. P.T.A.H. x 45.

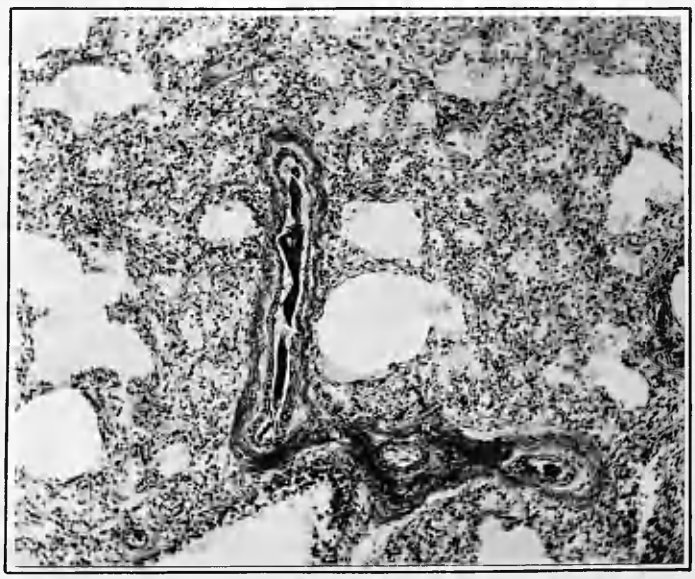
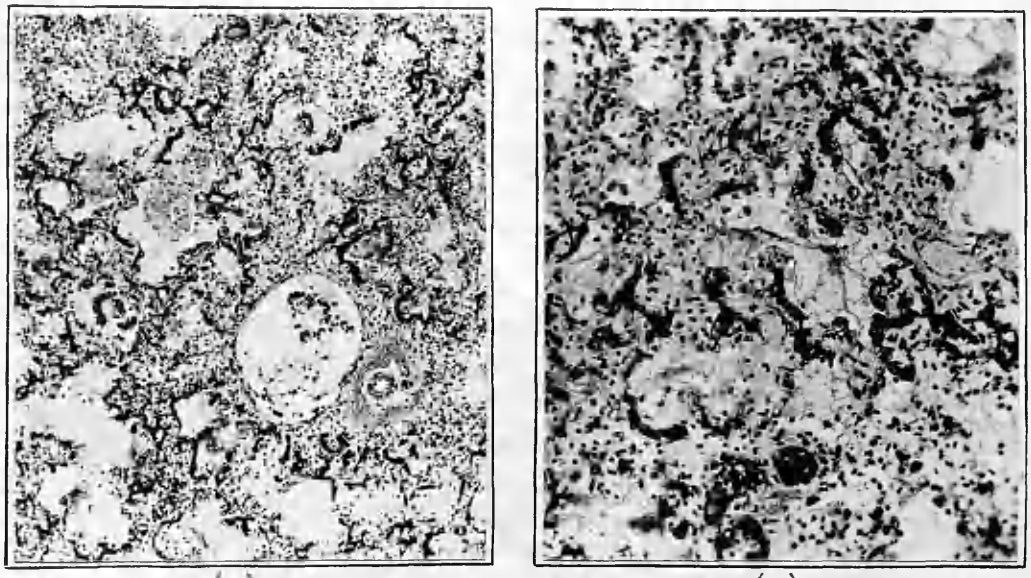
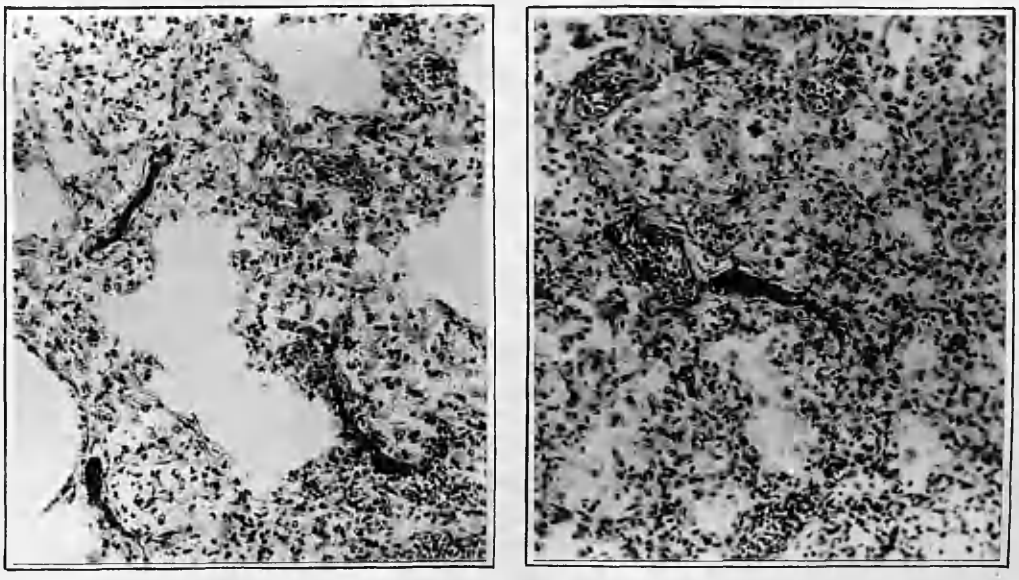


Fig. 36. Case 11. Pulmonary arteriole cut longitudinally, showing streaming antemortem fibrin thrombo-embolus. P.T.A.H. x 95.



(a) (b)

Fig. 37. Case 11. (a) Area of reasonable alveolar expansion showing widespread capillary fibrin thrombo-emboli. x 95. (b) Similar field, showing more delicate alveolar fibrin exudation. x 170. P.T.A.H.



(a) (b)

Fig. 38. Case 11. Pure fibrin thrombo-emboli in lung venules, showing streaming effect to advantage. P.T.A.H. x 170.

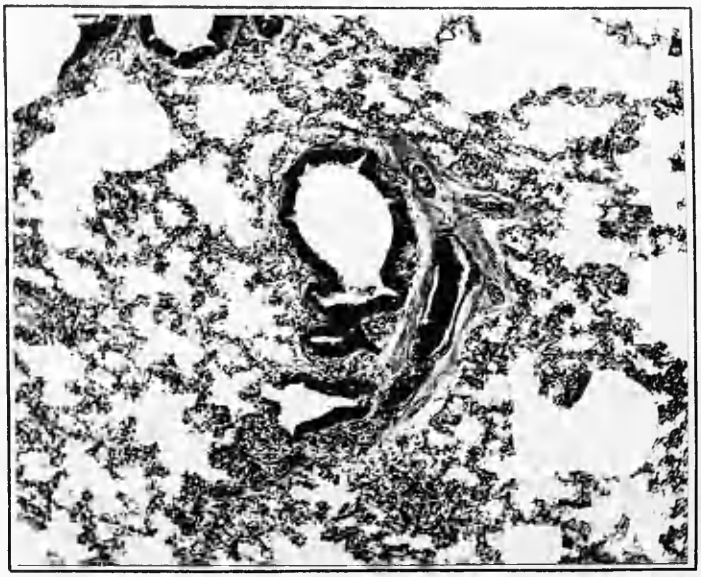


Fig. 39. Case 12. Dense fibrin thrombo-embolus in pulmonary arteriole. P.T.A.H. x 95.

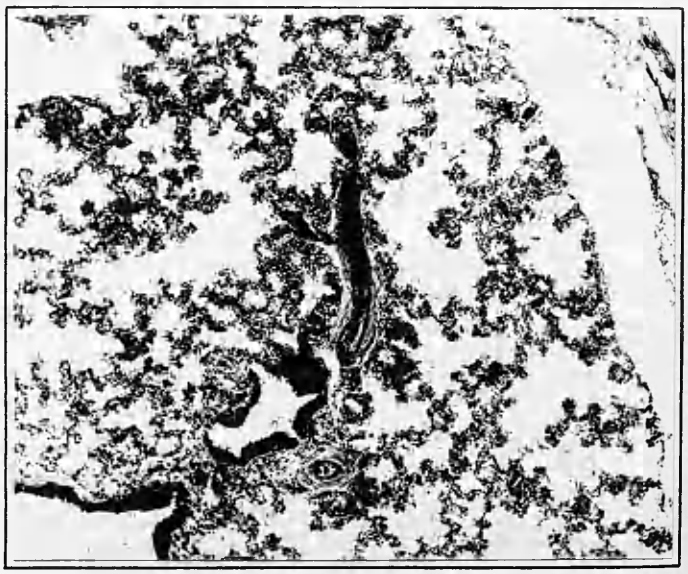


Fig. 40. Case 12. Dense fibrin thrombo-embolus in pulmonary arteriole. P.T.A.H. x 95.

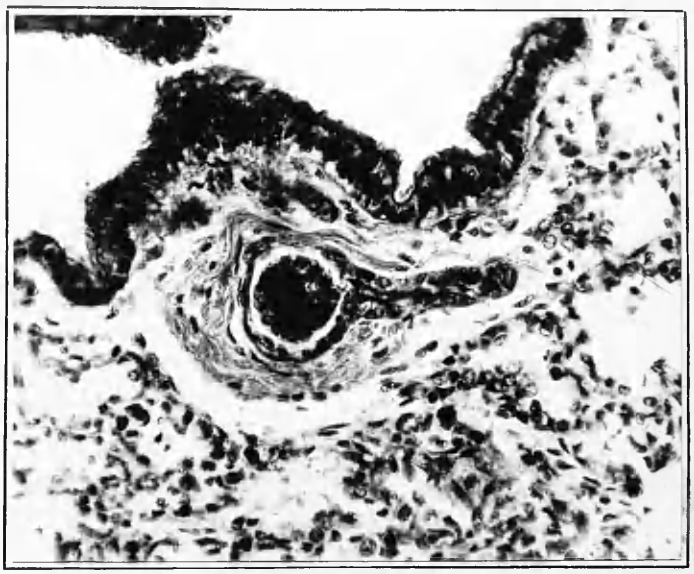


Fig. 41. Case 12. Pulmonary arteriole plugged with fibrin thrombus which is also rich in platelets. P.T.A.H. x 310.

Fig. 42. Case 12. Two venules in the liver bearing agonal mixed thrombus with delicate loosely-woven fibrin strands lying along the vessels. P.T.A.H. x 170.

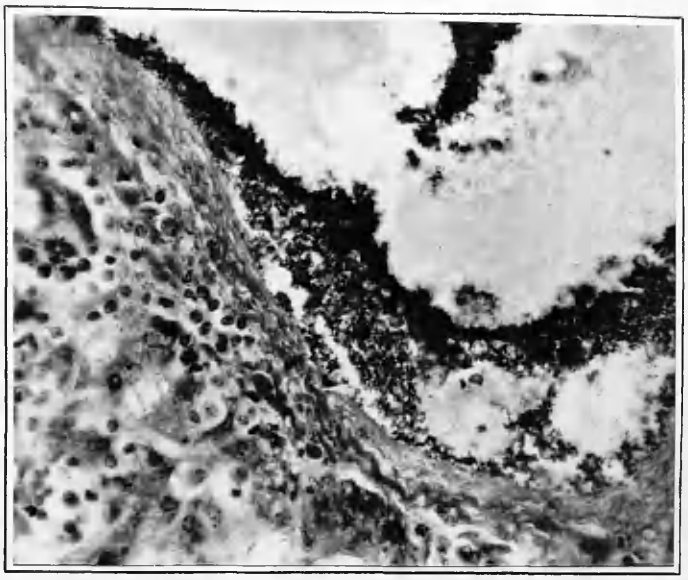
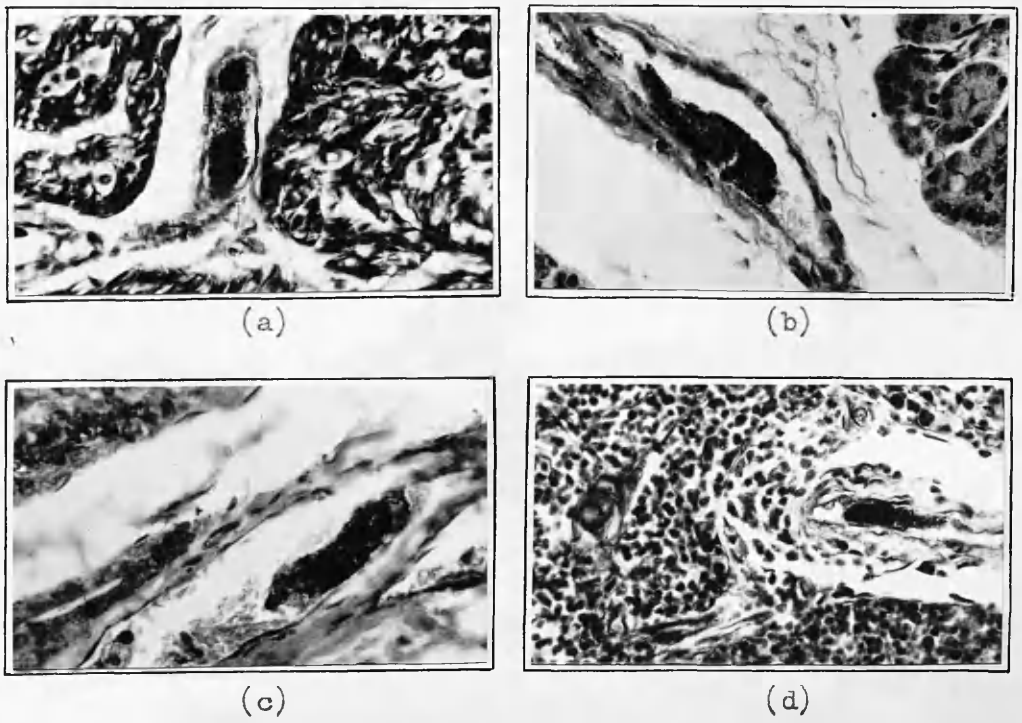


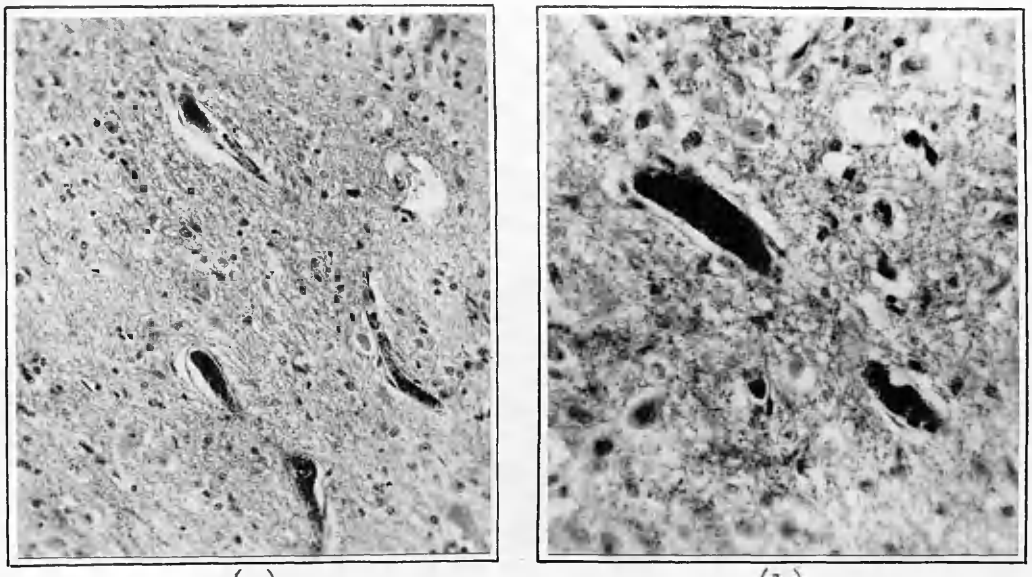
Fig. 43. Case 12. Hepatic vein bearing platelet thrombus in the lumen. P.T.A.H. x 310.



(a) (b)

(c) (d)

Fig. 44. Case 12. Platelet-fibrin thrombi in (a) the heart, (b) the pancreas, (c) the thyroid, and (d) the thymus. P.T.A.H. x 310.



(a) (b)

Fig. 45. Case 12. (a) Numerous fibrin-platelet thrombi in medulla of brain stem. x 170. (b) Dense thrombus showing a certain streakiness in favour of a fibrin basis. P.T.A.H. x 310.

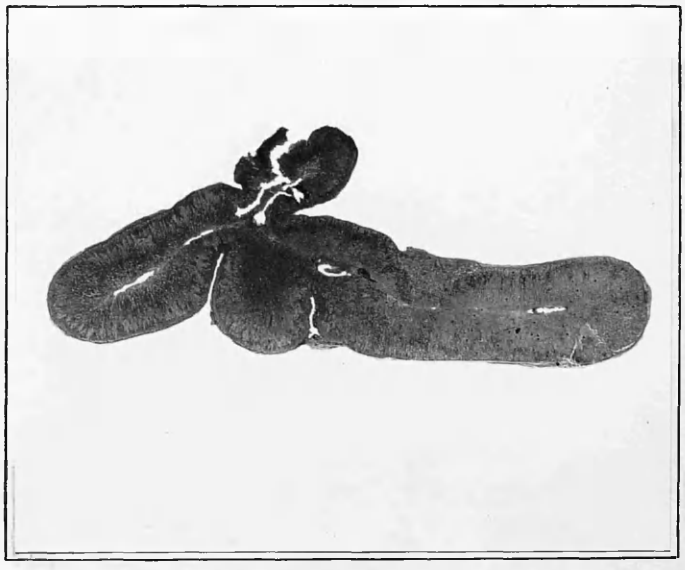


Fig. 46. Case 13. Adrenal gland showing infarction of the right-hand third, bordered by sinusoidal fibrin thrombi, and adrenal vein thrombosis nearer centre of specimen. P.T.A.H. x $3\frac{1}{2}$.

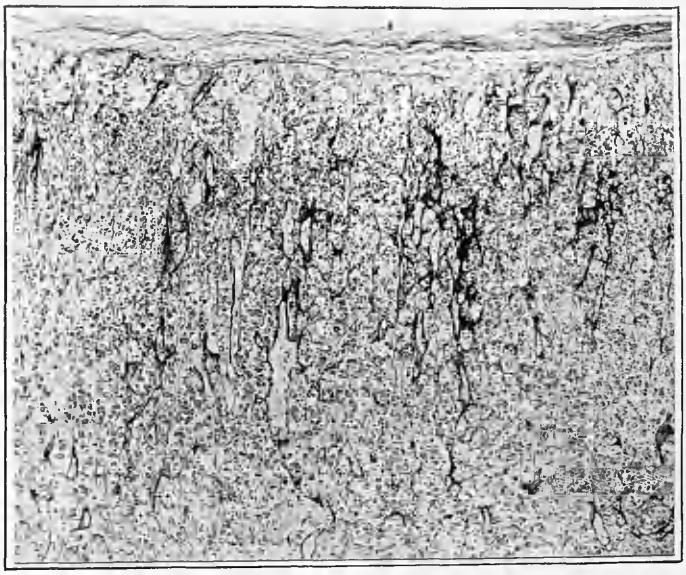


Fig. 47. Case 13. Adrenal cortex showing vertical zones of dense fibrin thrombi and collapsed sinusoids, alternating with areas of less dense thrombi and dilated sinusoids. P.T.A.H. x 45.

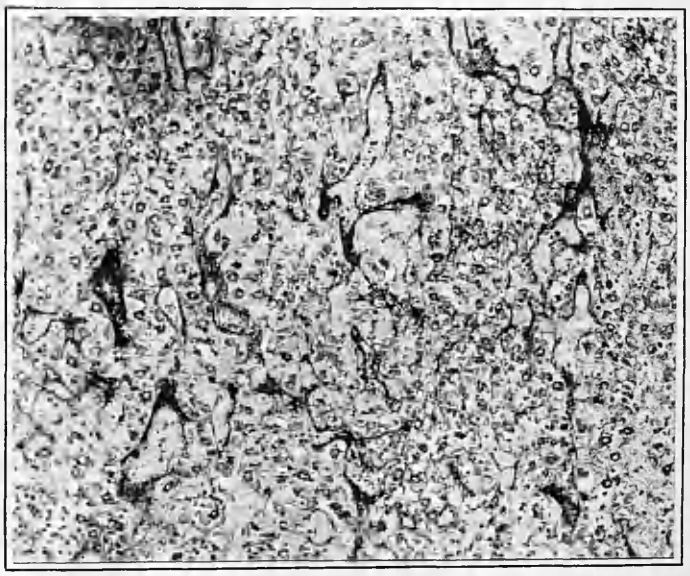


Fig. 48. Case 13. Region of adrenal cortex showing fibrin thrombi occupying the peripheral portion of the sinusoids, against the endothelium. P.T.A.H. x 95.

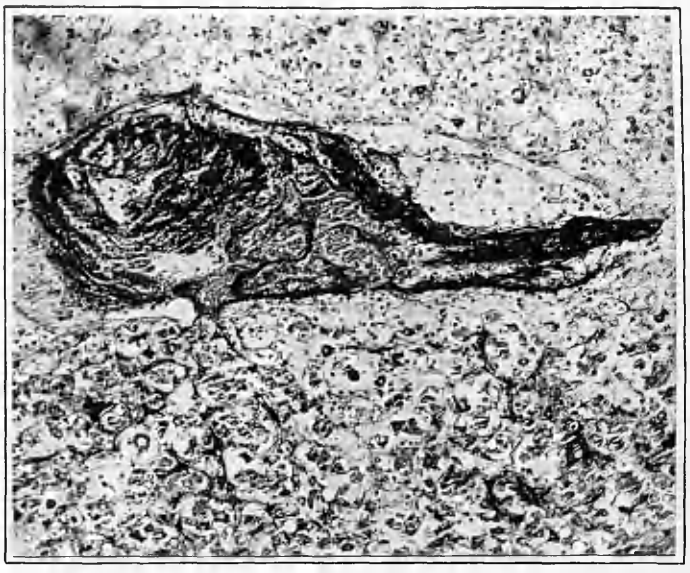
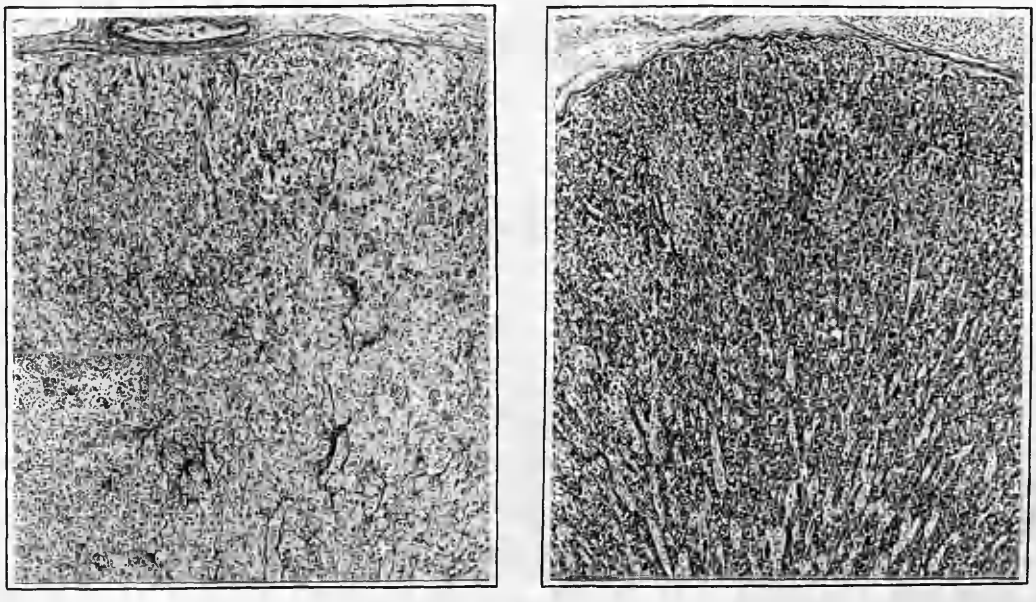


Fig. 49. Case 13. Adrenal medulla showing fibrin thrombi emanating from the sinusoids into the medullary vein, and inter-weaving to form a mixed thrombus. P.T.A.H. x 95.



(a) (b)

Fig. 50. Case 13. (a) Necrotic pole of adrenal gland, compared with (b) an unaffected pole of the same adrenal gland. P.T.A.H. x 45.

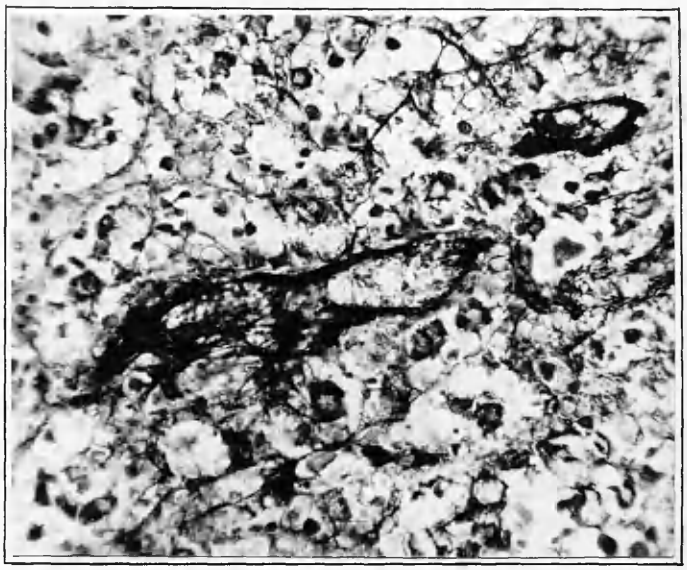


Fig. 51. Case 13. Dense antemortem fibrin deposits lying on sinusoidal endothelium, with more delicate strands of fibrin superimposed. P.T.A.H. x 310.

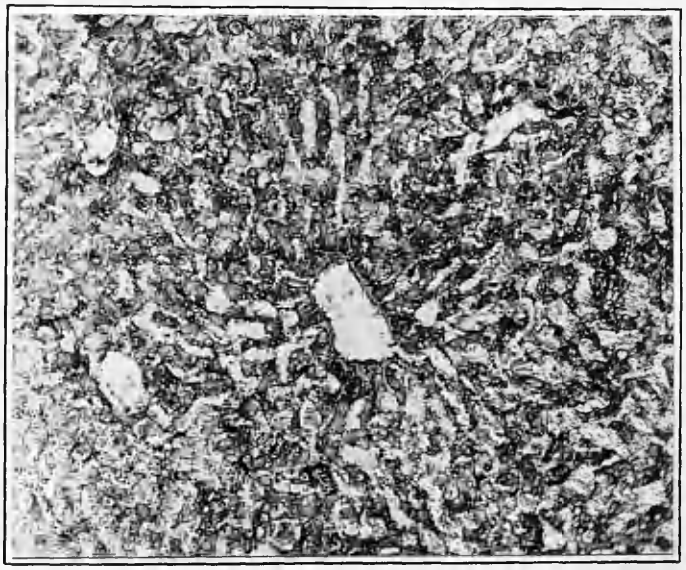


Fig. 52. Case 13. A liver lobule showing numerous midzonal sinusoidal fibrin thrombi, and loss of nuclear detail with patchy coagulative necrosis of liver cells. P.T.A.H. x 95.

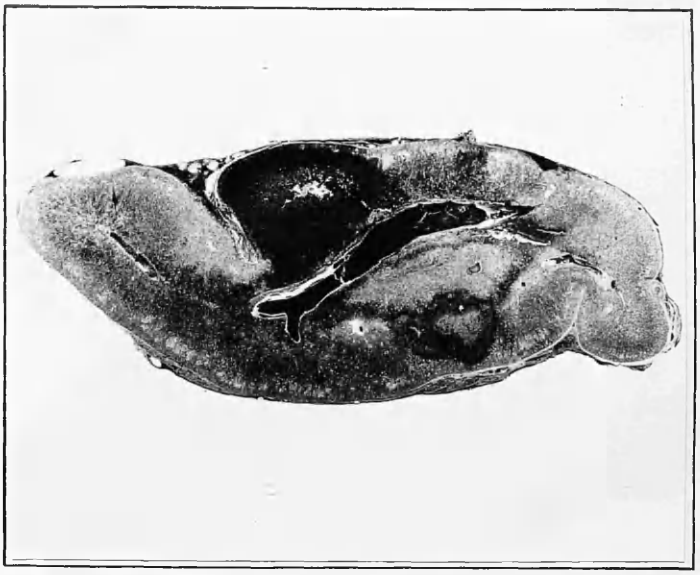


Fig. 53. Case 14. Section of adrenal gland showing two focal cortical haemorrhages as a result of infarction, and antemortem adrenal vein thrombosis. P.T.A.H. x3½.

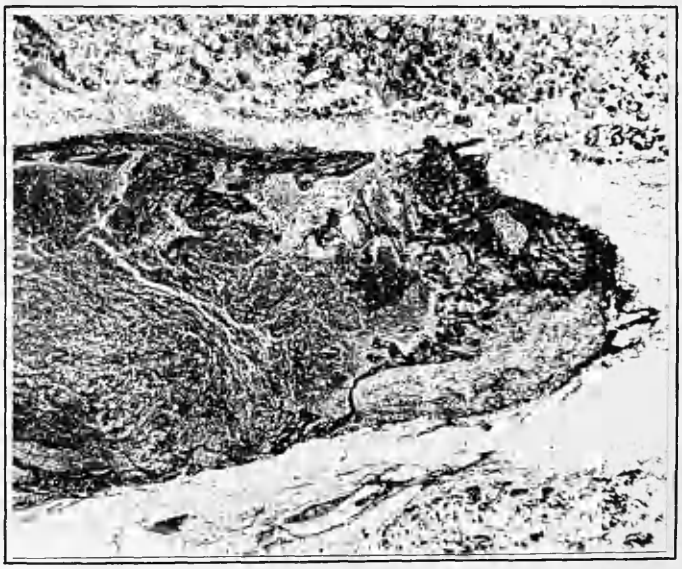


Fig. 54. Case 14. Mixed laminated adrenal medullary vein thrombus, rich in fibrin, and showing the typical blunt head of an antemortem thrombus. P.T.A.H. x 45.

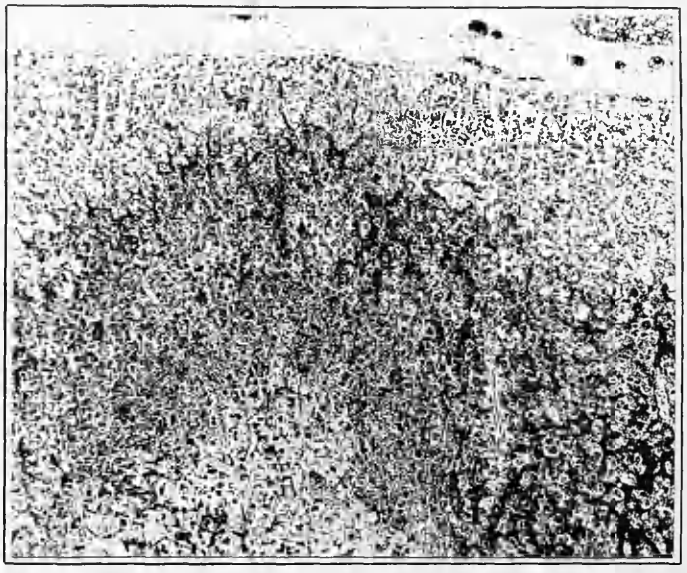


Fig. 55. Case 14. One adrenal cortical infarct. Necrosis of cortical cells with much interstitial haemorrhage and dense marginal deposits of sinusoidal fibrin thrombi. P.T.A.H. x 45.

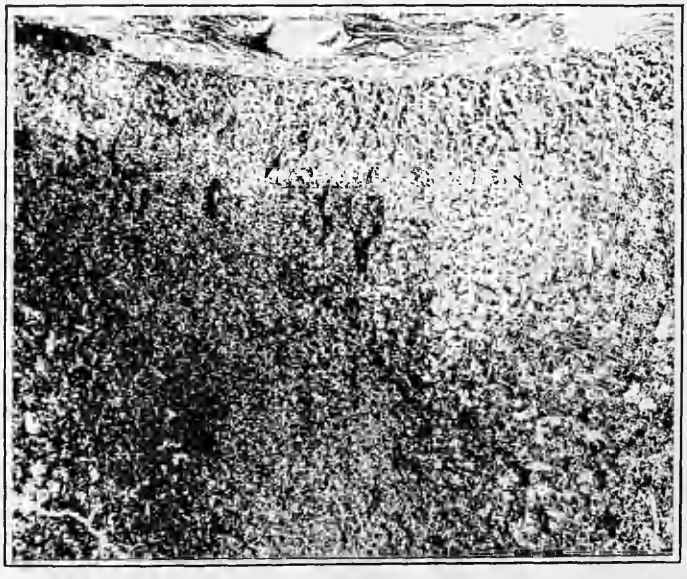


Fig. 56. Case 14. Second adrenal cortical infarct showing features similar to those in Figure 55. P.T.A.H. x 45.

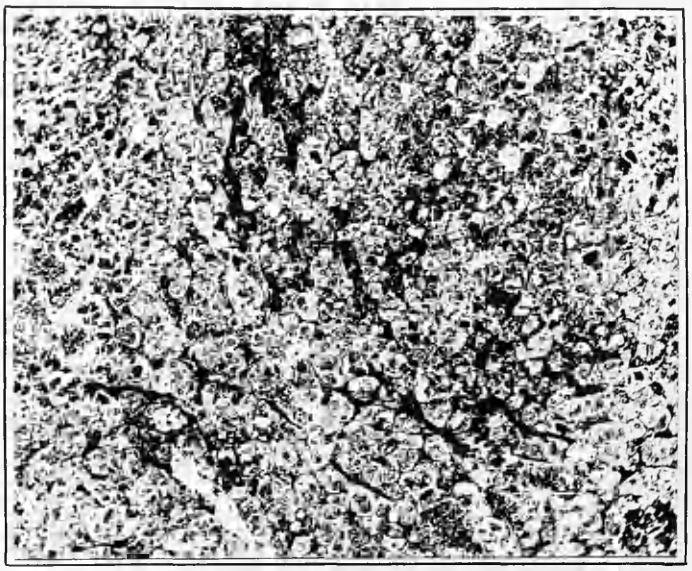


Fig. 57. Case 14. Another area of adrenal cortex showing dense antemortem sinusoidal fibrin thrombi with minimal necrosis. P.T.A.H. x 95.

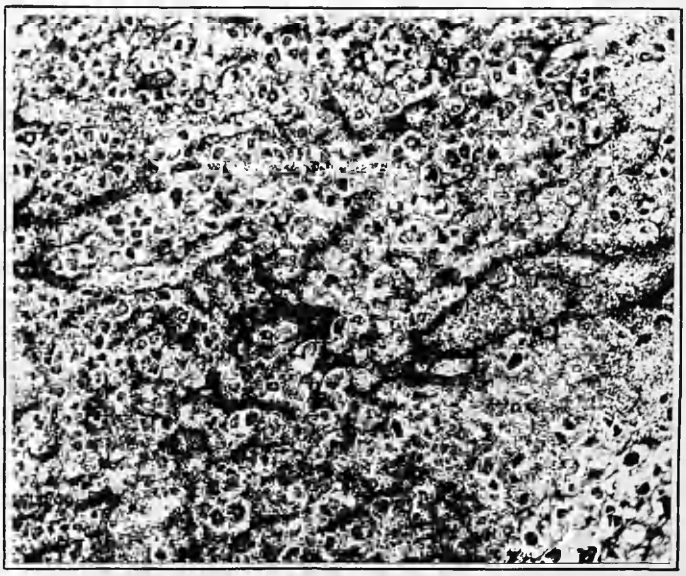


Fig. 58. Case 14. Adrenal cortex showing the only field in which sinusoidal fibrin thrombus has become laminated against the endothelial surface. P.T.A.H. x 95.


Fig. 59. Case 15. Oblique view of tricuspid valve showing one firm pale vegetation attached to the auricular aspect near the cusp margin. x 2.5.

Fig. 60. Case 15. Lung showing atrial expansion only, with moderately extensive hyaline membrane formation which contains fibrin in some areas and not in others. P.T.A.H. x 95.

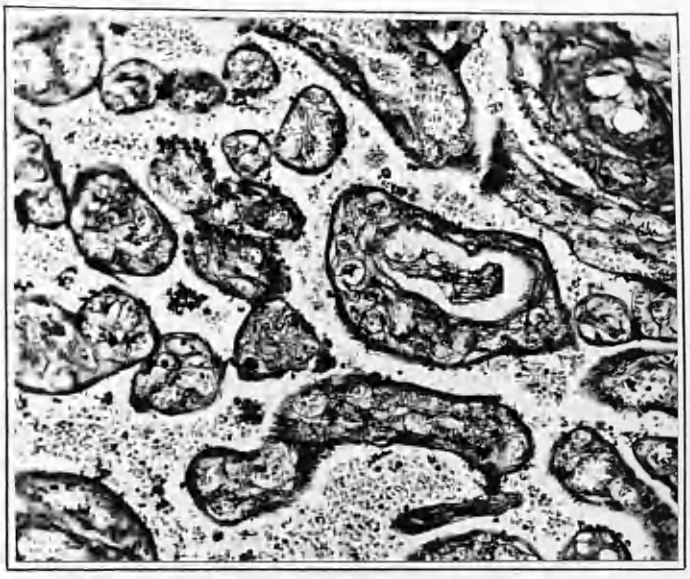


Fig. 61. Case 15. Placenta showing delicate agonal mixed thrombi in foetal vessels of chorionic villi. P.T.A.H. x 170.

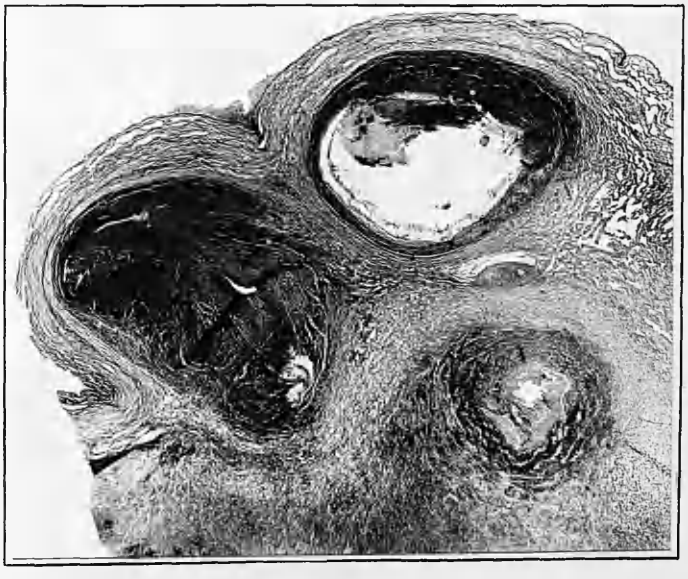


Fig. 62. Case 15. The two umbilical arteries are above, and the left one is cut obliquely. The umbilical vein is below. There is no evidence of thrombosis. P.T.A.H. x 12.

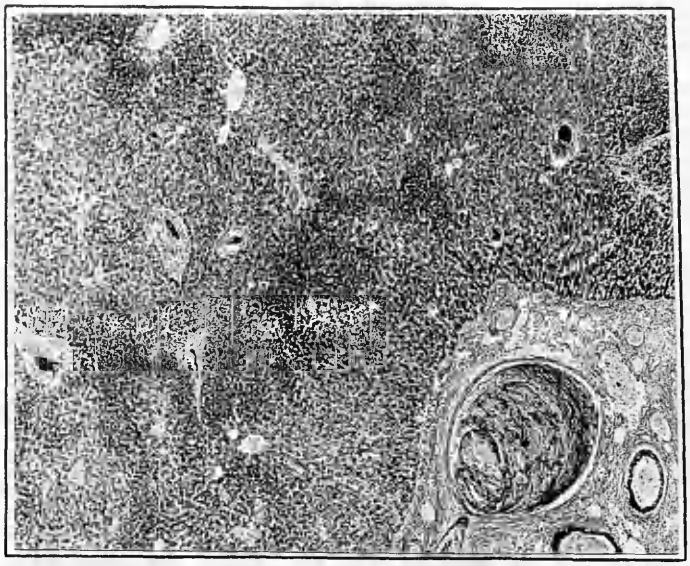


Fig. 63. Case 15. The left lobe of liver showing fibrin thrombo-emboli in several portal veins and laminated mixed thrombus in a large portal vein. P.T.A.H. x 25.

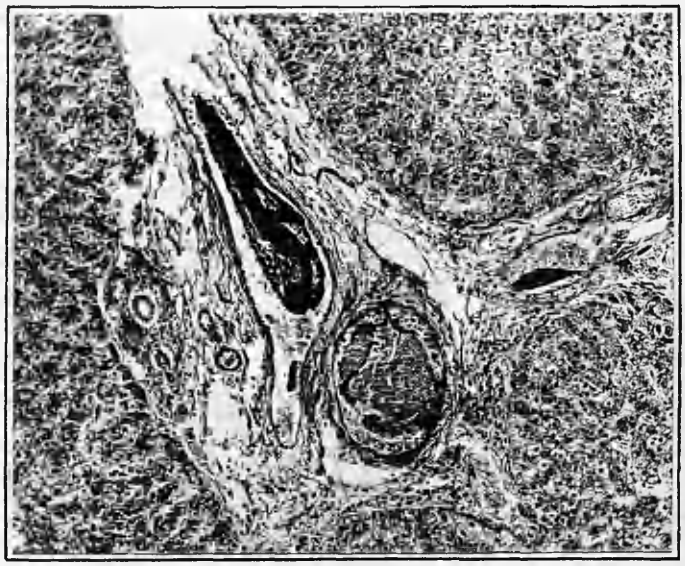


Fig. 64. Case 15. Portal vein branches in the left lobe of liver showing pure fibrin thrombus in one branch and mixed platelet-fibrin antemortem thrombus in the immediately adjacent branch. P.T.A.H. x 95.

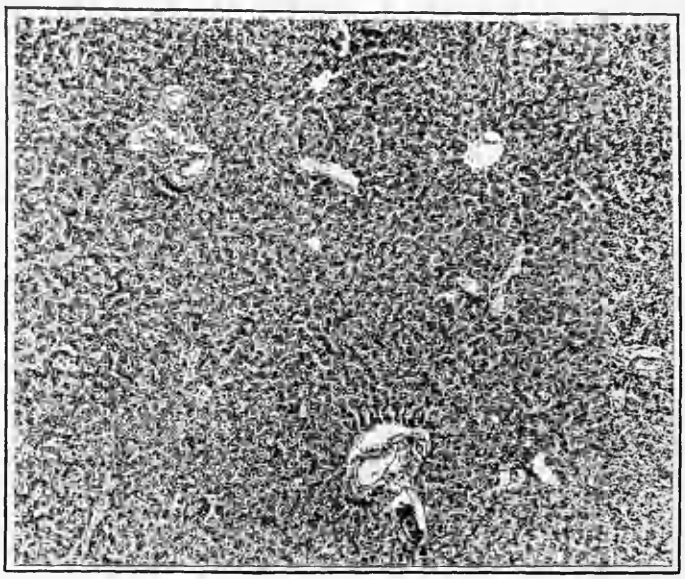


Fig. 65. Case 15. View of right lobe of liver showing absence of thrombi in portal tracts and in sinusoids. P.T.A.H. x 45.

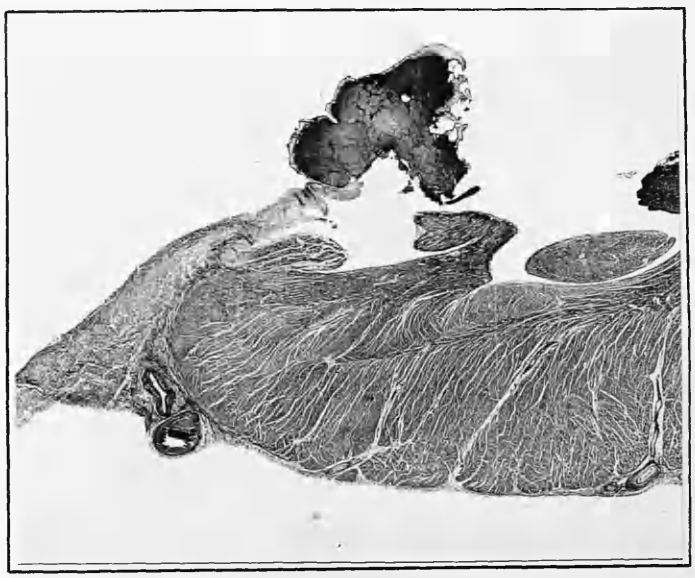
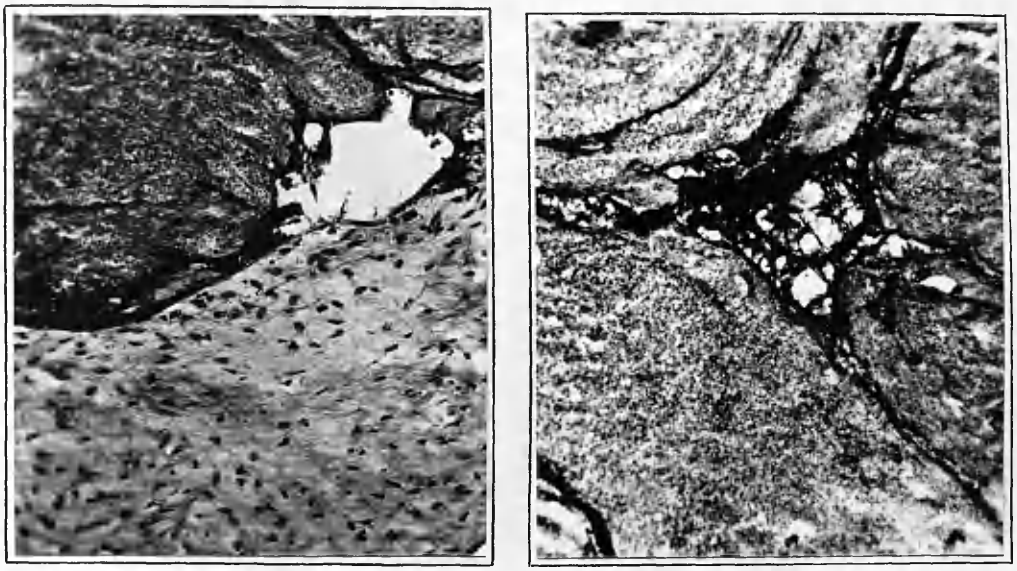


Fig. 66. Case 15. Section of tricuspid valve with one vegetation. The latter is rich in platelets but also contains fibrin networks. P.T.A.H. x 7.



(a) (b)

Fig. 67. Case 15. (a) Base of vegetation showing fibrin basis with platelets superimposed, lack of cellular response in cusp stroma, (b) centre of vegetation showing fibrin-platelet nature of these vegetations. P.T.A.H. x 310.

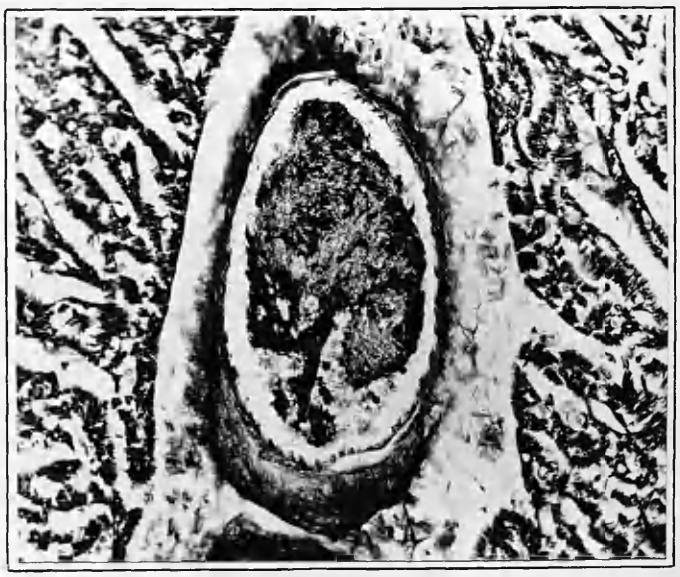


Fig. 68. Case 15. Small vessel in myocardium occluded by fibrin-platelet thrombus. P.T.A.H. x 170.

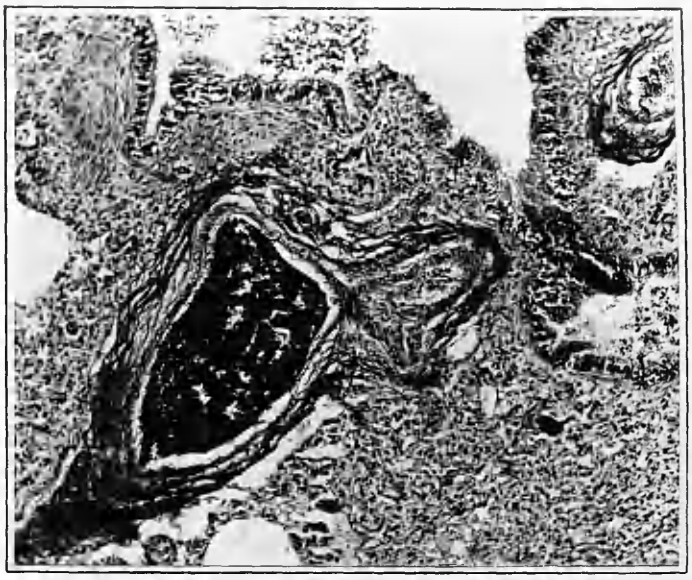


Fig. 69. Case 15. Pulmonary artery showing fibrin thrombus occluding it. P.T.A.H. x 95.

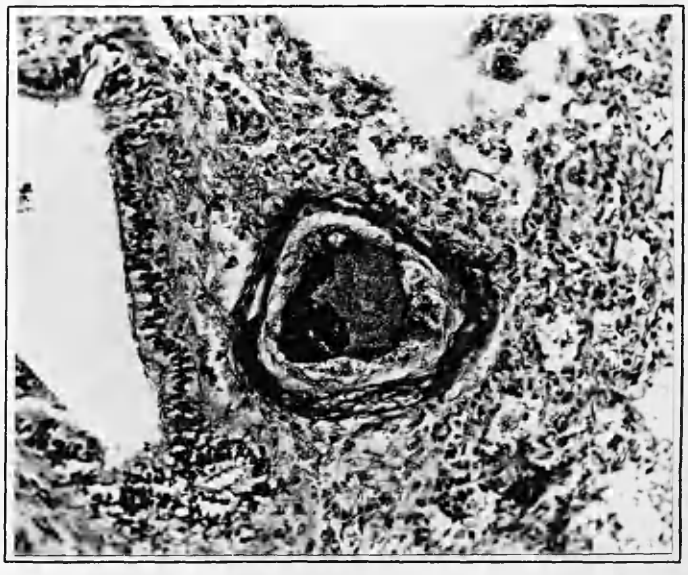


Fig. 70. Case 15. Pulmonary artery occluded by mixed fibrin-platelet thrombus, no doubt a seedling from the tricuspid valve vegetations. P.T.A.H. x 170.

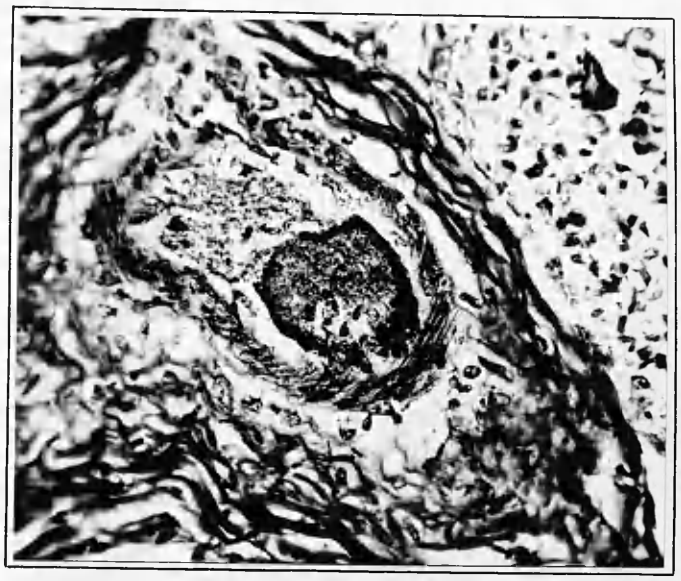


Fig. 71. Case 15. Mixed fibrin-platelet thrombus adherent to one side of the wall of a pulmonary artery. P.T.A.H. x 310.

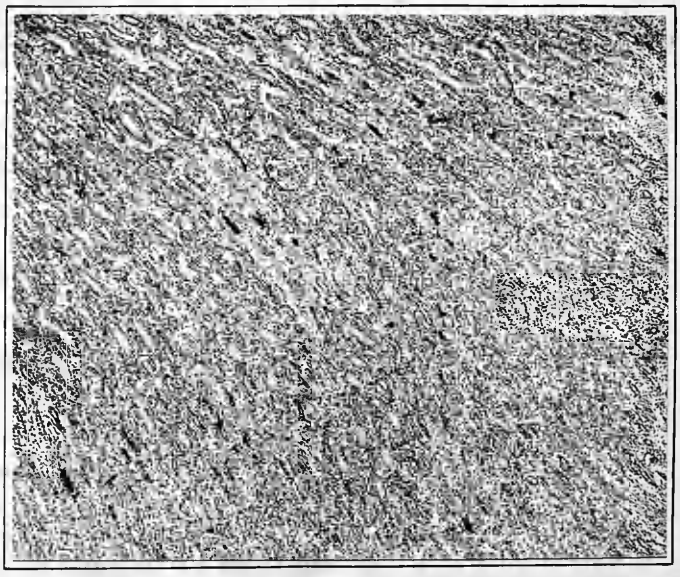


Fig. 72. Case 15. Extensive antemortem fibrin thrombo-emboli affecting a renal medullary pyramid. P.T.A.H. x 45.

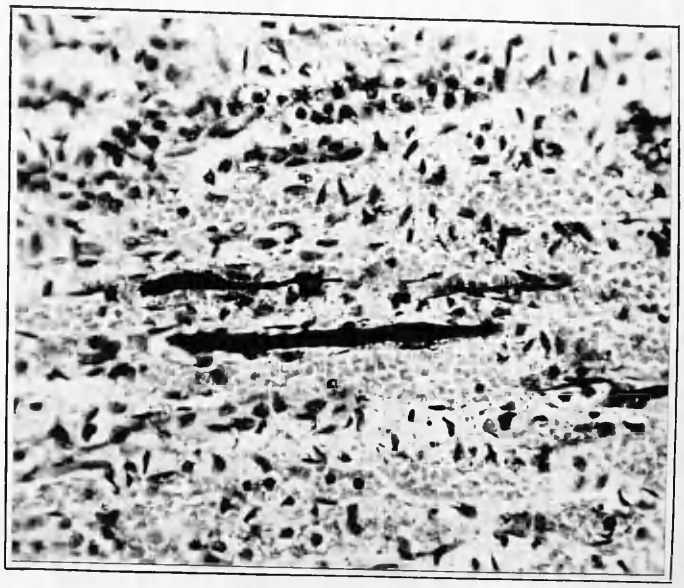


Fig. 73. Case 15. Antemortem fibrin thrombo-embolism affecting the vessels of the renal medulla. P.T.A.H. x 310.

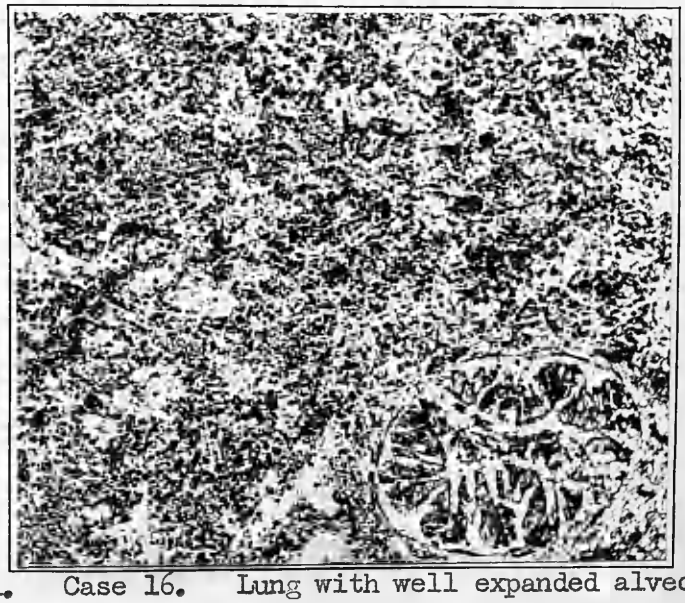


Fig. 74. Case 16. Lung with well expanded alveoli now the seat of well established haemorrhagic bronchopneumonia. P.T.A.H. x 95.

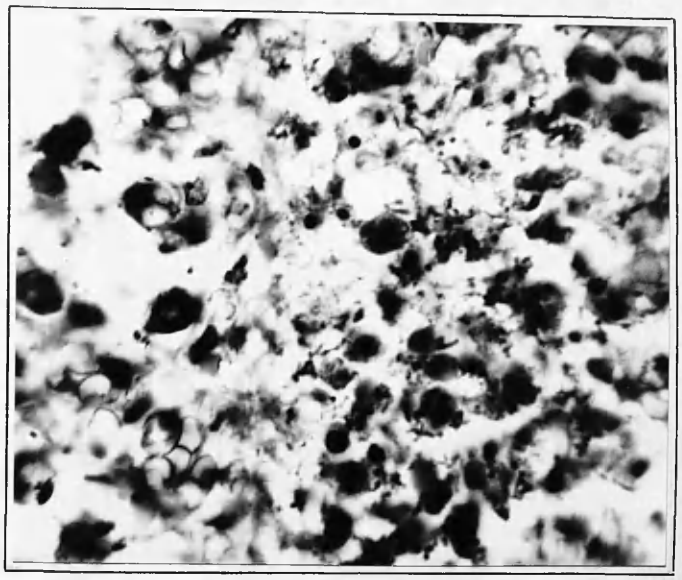


Fig. 75. Case 16. Distended pulmonary perivascular lymphatic containing degenerate pus cells and cocci in chains. Owing to the thickness of the section many of the chains are only partly in focus. P.T.A.H. x 700.

Fig. 76. Case 16. Umbilicus showing red blood corpuscles in an umbilical artery (above), and delicate agonal thrombus in the umbilical vein (right). There is no evidence of infection. P.T.A.H. x 12.

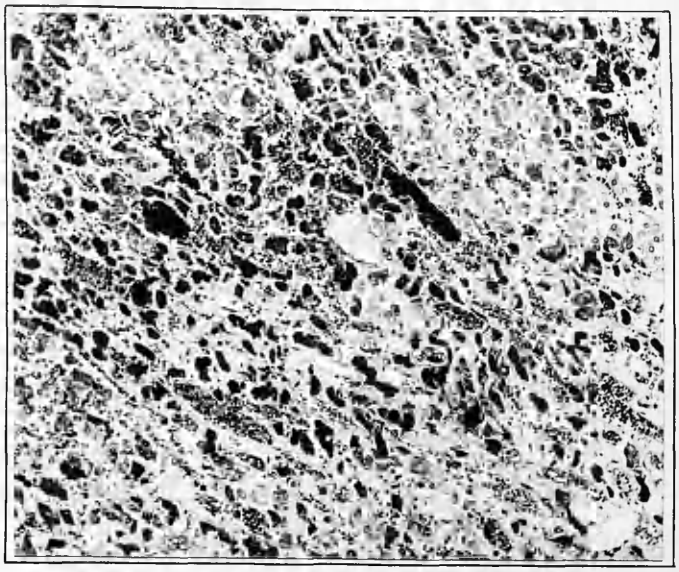


Fig. 77. Case 16. Scanty antemortem fibrin thrombo-embolus in the sinusoids of the adrenal gland. P.T.A.H. x 95.

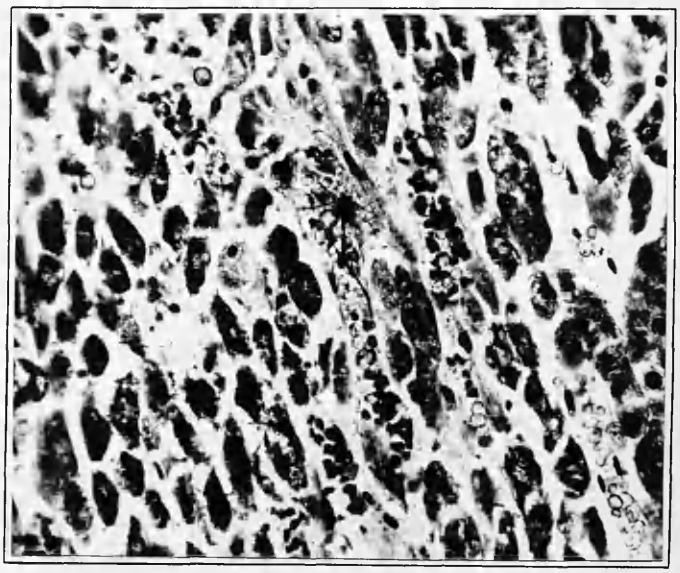


Fig. 78. Case 16. Delicate spidery network of fibrin in adrenal sinusoid. Long thick strand appears to be antemortem, with delicate superimposed agonal thrombosis. P.T.A.H. x 310.

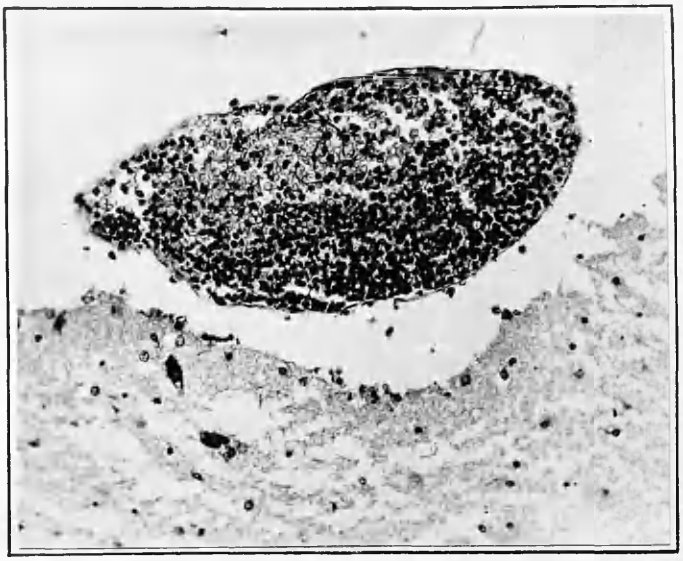
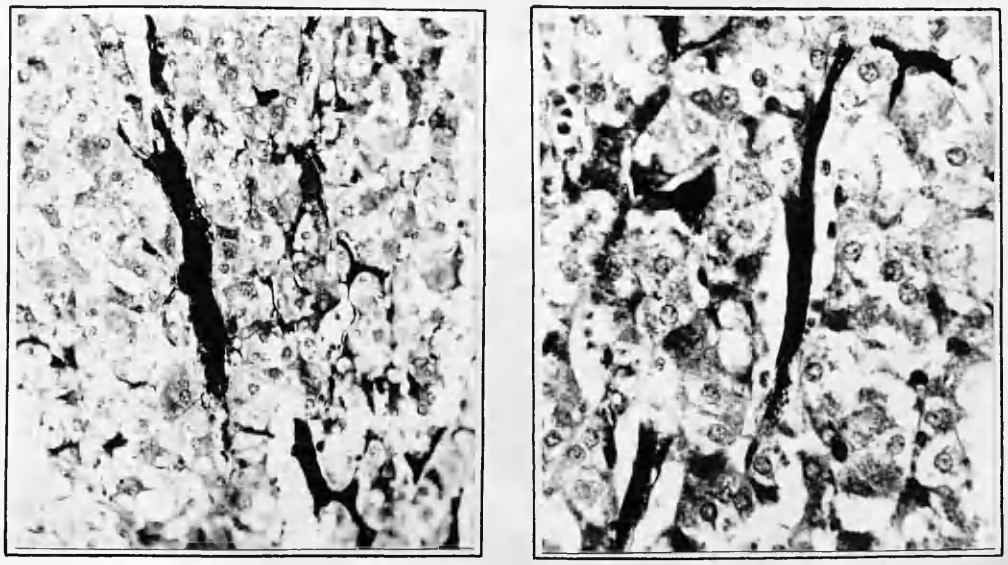


Fig. 79. Case 16. Sub-ependymal vein in floor of lateral ventricle showing delicate agonal clot. P.T.A.H. x 170.



(a) (b)

Fig. 80. Case 17. Two examples of fibrin thrombo-emboli in sinusoids of cortex of adrenal gland. P.T.A.H. (a) x 170 (b) x 310.

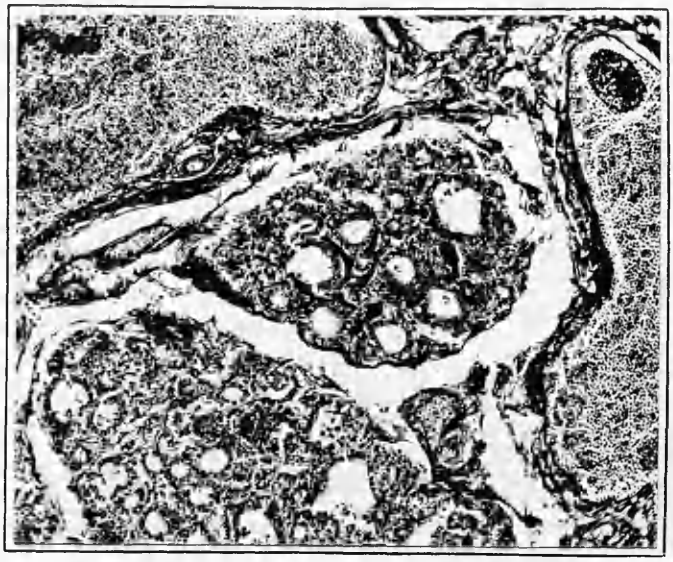


Fig. 81. Case 17. Central lobule shows numerous antemortem capillary fibrin thrombi. Adjacent lobule is negative. Postmortem thrombi are present in the upper corners of the print. P.T.A.H. x 95.

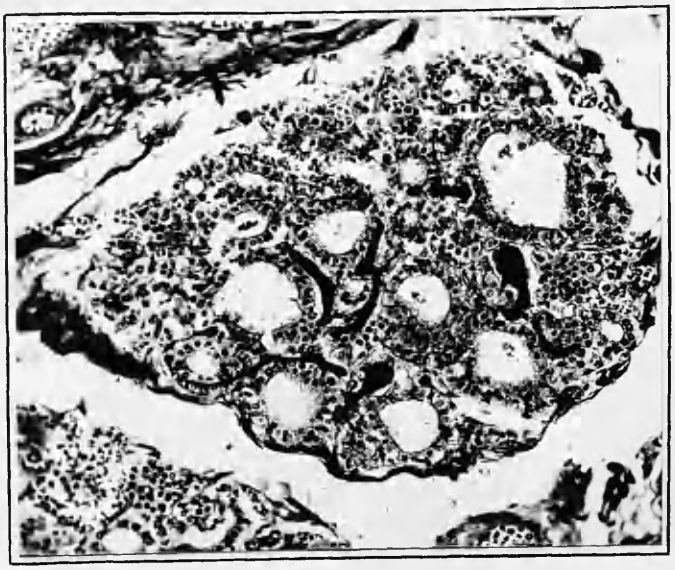


Fig. 82. Case 17. Higher power view of the centre of Fig. 81, to show antemortem capillary thrombosis. P.T.A.H. x 170.

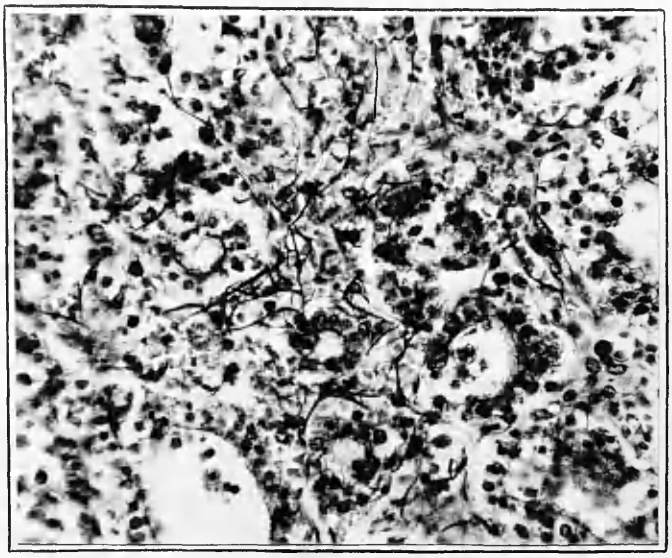


Fig. 83. Case 17. Scanty, delicate, deeply stained capillary fibrin strands, lying vaguely longitudinally along the capillaries. These may be agonal thrombi. P.T.A.H. x 310.

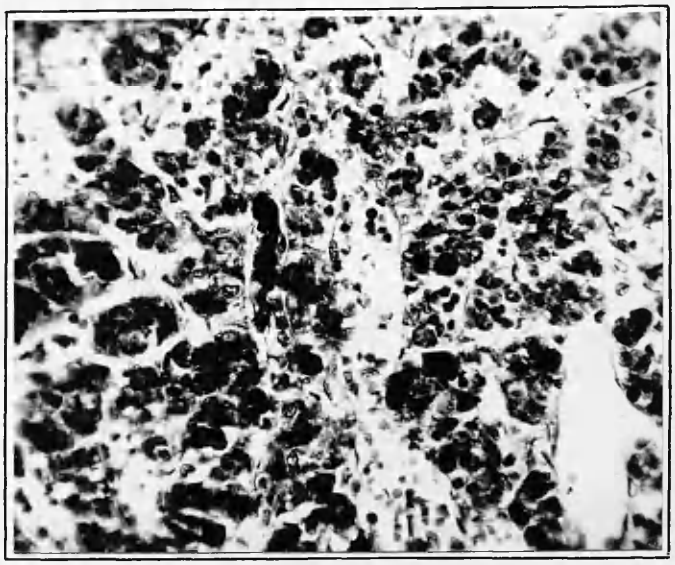


Fig. 84. Case 17. Pituitary gland showing one of several blunt fibrin thrombi which are probably agonal. P.T.A.H. x 310.

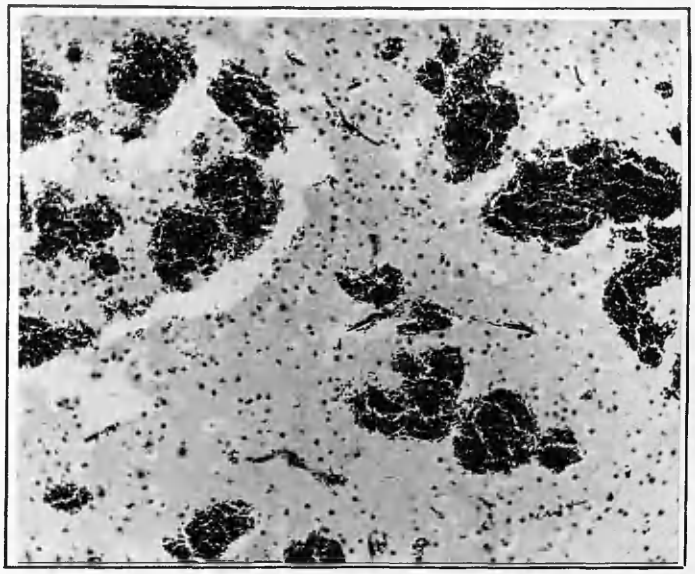


Fig. 85. Case 18. Moderate low power view of recent cerebral haemorrhage to show absence of clotting although blood is extravascular. P.T.A.H. x 95.

Fig. 86. Case 18. Vessel showing antemortem laminated fibrin thrombus. Vessel about to break up with early loosening of fibrin network at periphery. P.T.A.H. x 170.

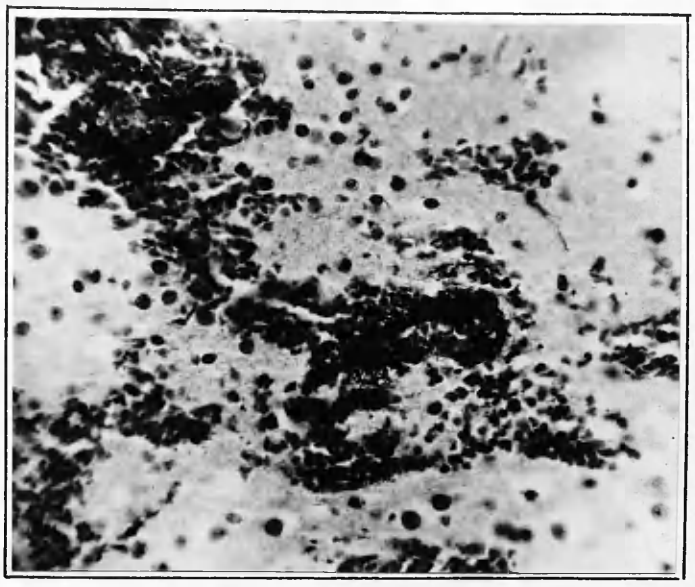


Fig. 87. Case 18. Haemorrhagic zone shows antemortem fibrin thrombus with parallel tightly packed strands as if it lay originally in a vessel, now destroyed. P.T.A.H. x 310.

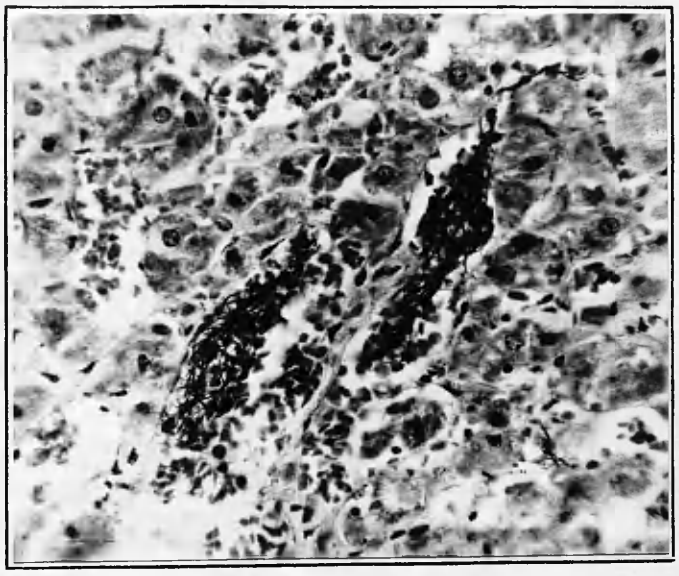


Fig. 88. Case 18. Loose fibrin thrombi (agonal) in the sinusoids of the cortex of the adrenal gland. P.T.A.H. x 310.

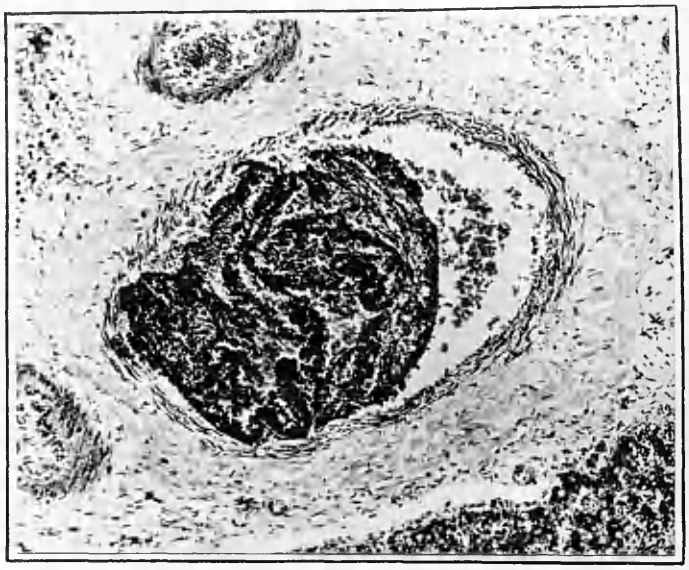


Fig. 89. Case 19. Antemortem laminated mixed thrombus in a portal vein. P.T.A.H. x 95.

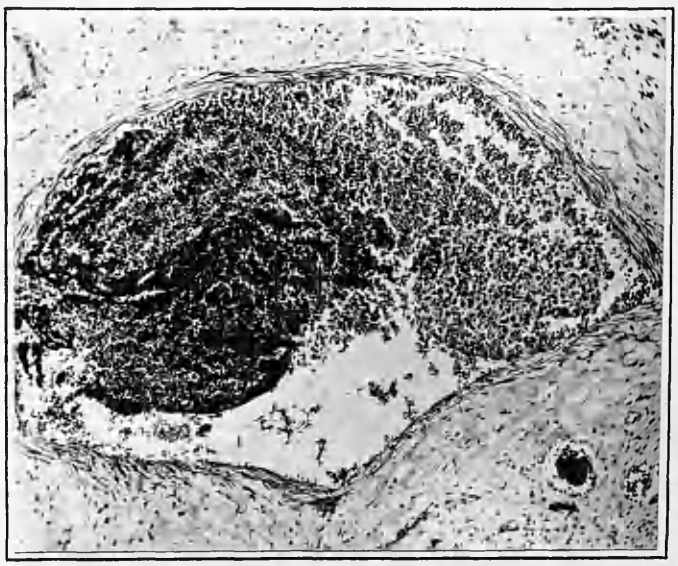


Fig. 90. Case 19. Portal vein showing antemortem mixed thrombus on the left, and a focus of early low grade suppuration in the same vessel, to the right. P.T.A.H. x 85.

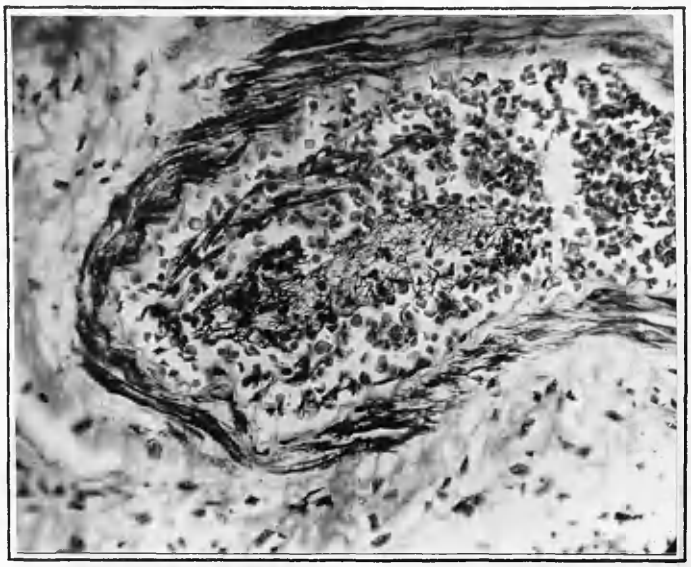


Fig. 91. Case 19. Renal arteriole containing postmortem thrombus. Delicate fibrin strands pass in all directions from fibrin "knots" (? platelets). P.T.A.H. x 290.

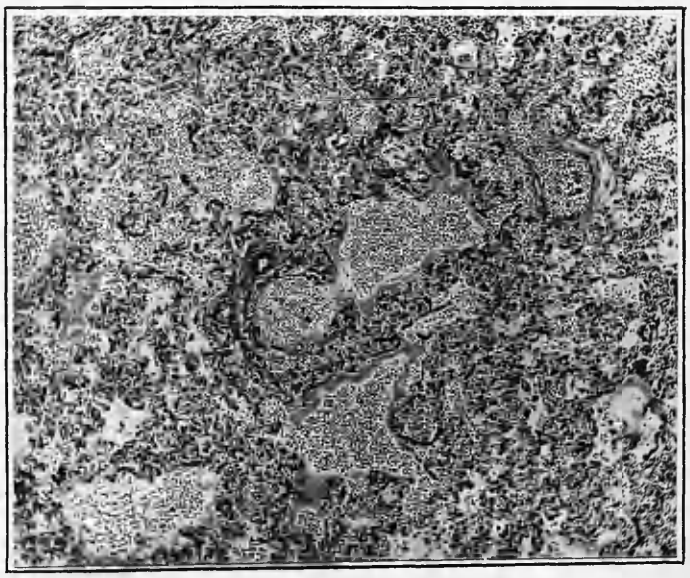


Fig. 92. Case 20. Haemorrhagic expanded lung showing well marked hyaline membrane disease and the latter is "negative" for fibrin. P.T.A.H. x 85.

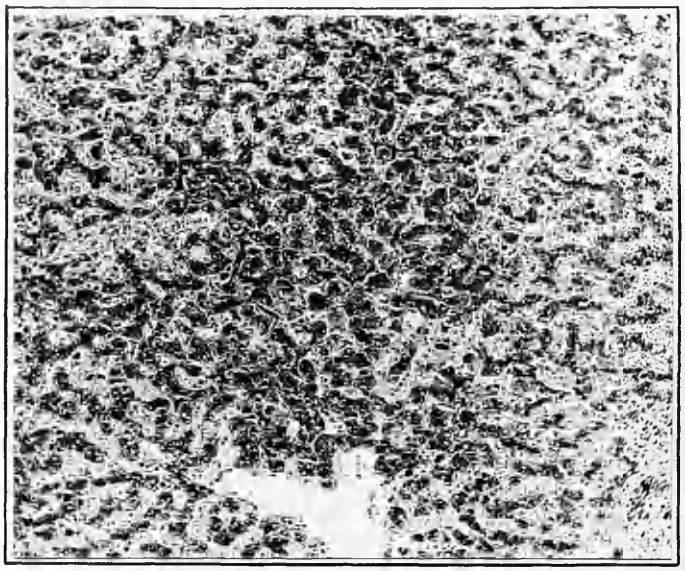


Fig. 93. Case 20. Sector of liver lobule showing mid- and centri-lobular fibrin thrombi in the sinusoids. P.T.A.H. x 85.

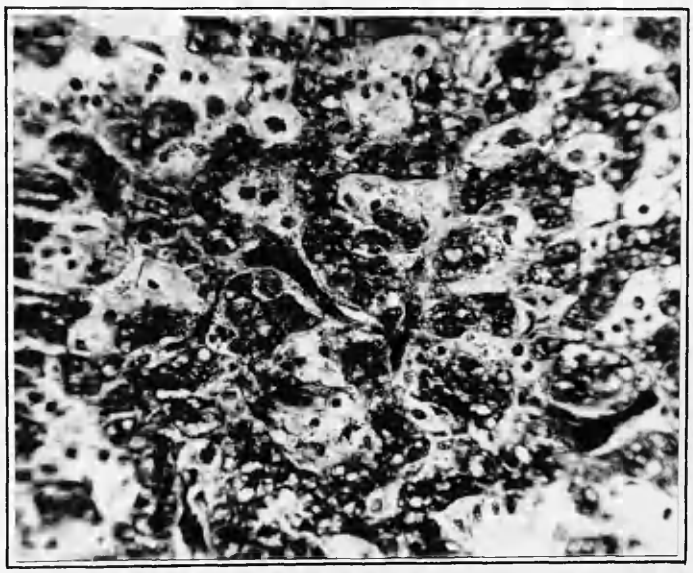


Fig. 94. Case 20. Hepatic sinusoidal fibrin thrombi showing a streaming effect and linkages. P.T.A.H. x 290.

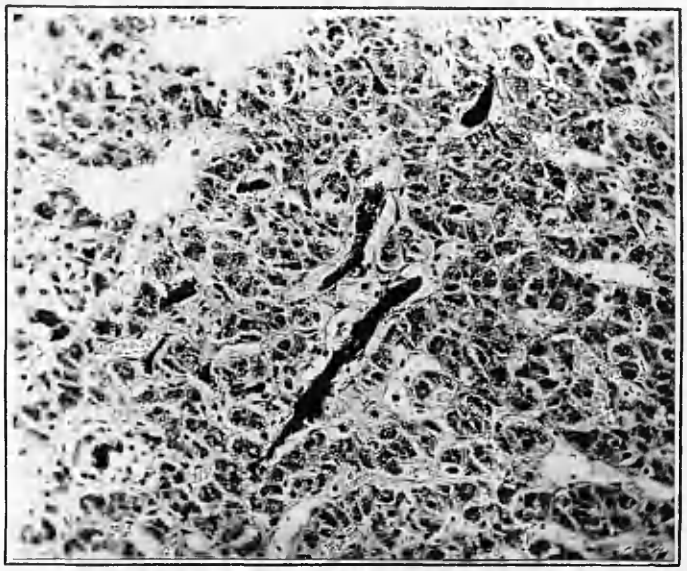


Fig. 95. Case 20. Solitary area of pure fibrin thrombo-emboli lodged in the sinusoids of the adrenal cortex. P.T.A.H. x 50.

Fig. 96. Case 20. Delicate fibrin strands lying mainly longitudinally in two vessels, but showing signs of entering the adjacent cerebral tissue because the vessel walls are ruptured. P.T.A.H. x 150.

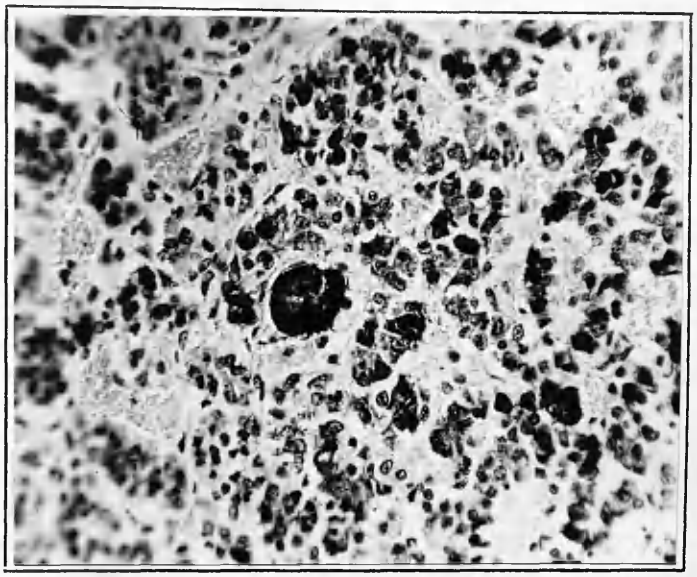


Fig. 97. Case 20. Solitary antemortem mixed fibrin-platelet thrombus in a sinusoid of the pituitary gland. P.T.A.H. x 290.

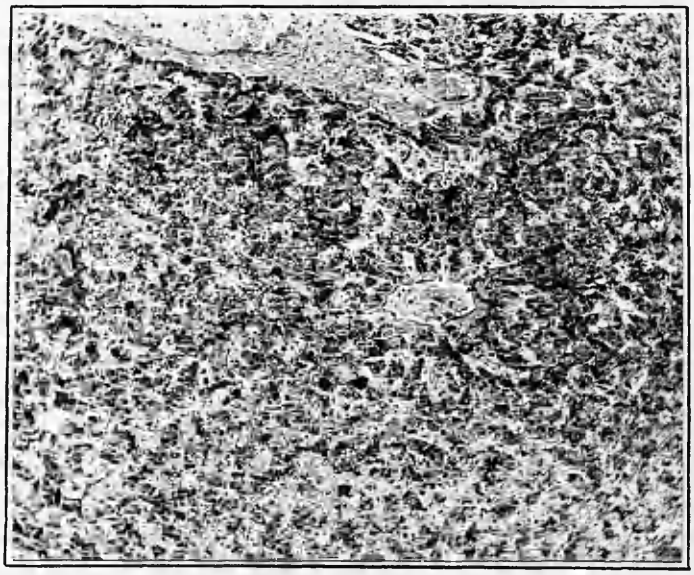


Fig. 98. Case 21. Liver showing numerous fibrin thrombi in the sinusoids, mainly in the mid- and central zones. P.T.A.H. x 85.

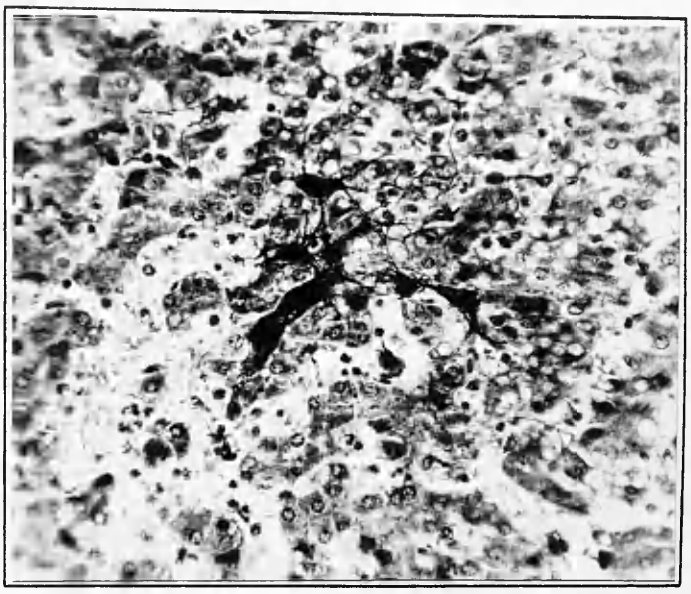


Fig. 99. Case 21. Antemortem fibrin thrombo-emboli in liver sinusoids showing linkages. P.T.A.H. x 290.

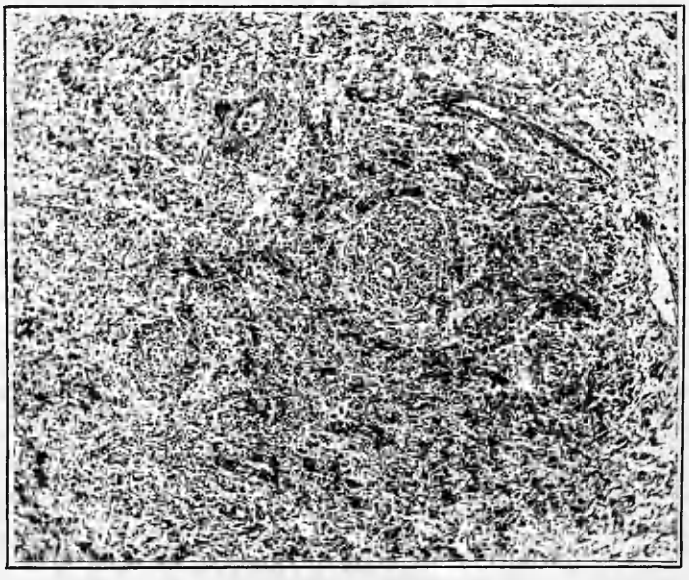


Fig. 100. Case 21. Multiple fibrin thrombo-emboli in the sinusoids of the red pulp of the spleen. P.T.A.H. x 85.

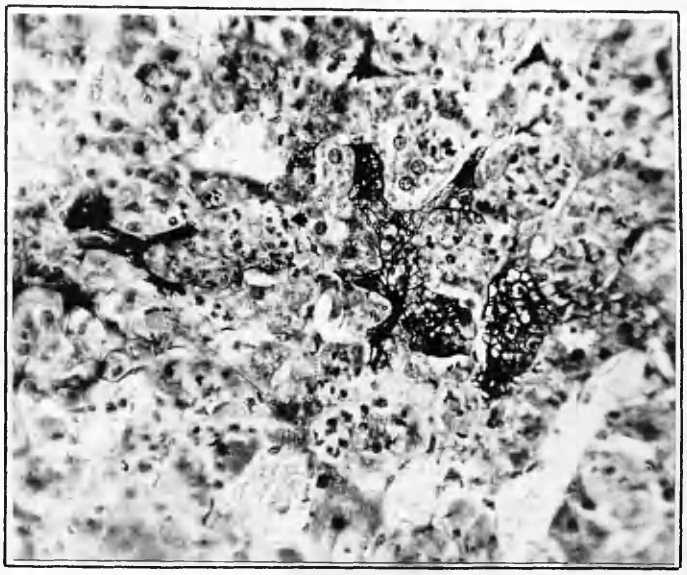


Fig. 101. Case 21. Possible agonal thrombi in sinusoids of one adrenal gland. Thrombi to the left however resemble antemortem fibrin thrombi. P.T.A.H. x 290.

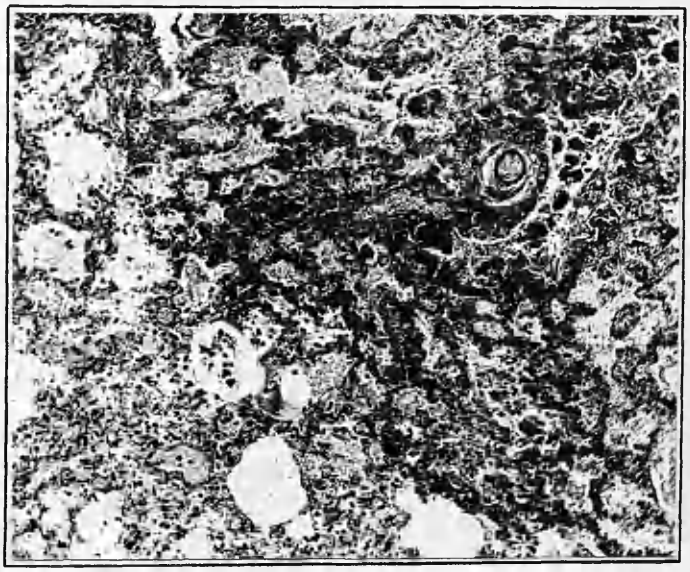


Fig. 102. Case 22. Total infarction of lung segment due to widespread capillary fibrin thrombo-embolism throughout it. Masson. x 95.

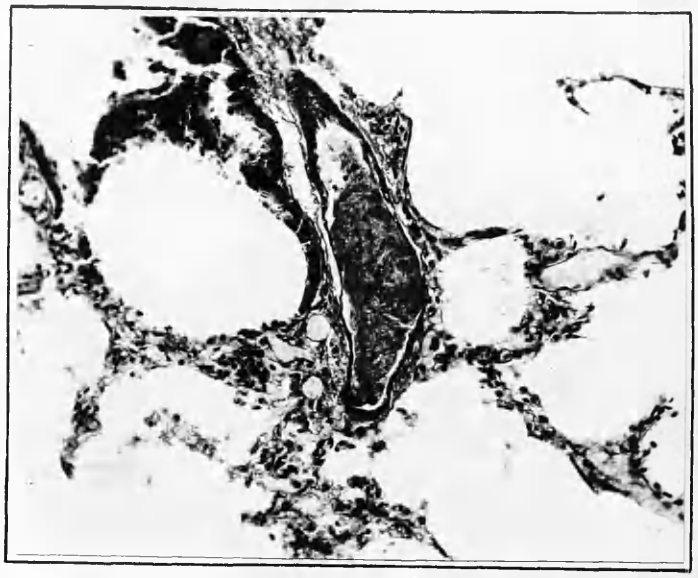


Fig. 103. Case 22. Fibrin thrombus occluding and ballooning branch of pulmonary artery. Masson x 170.

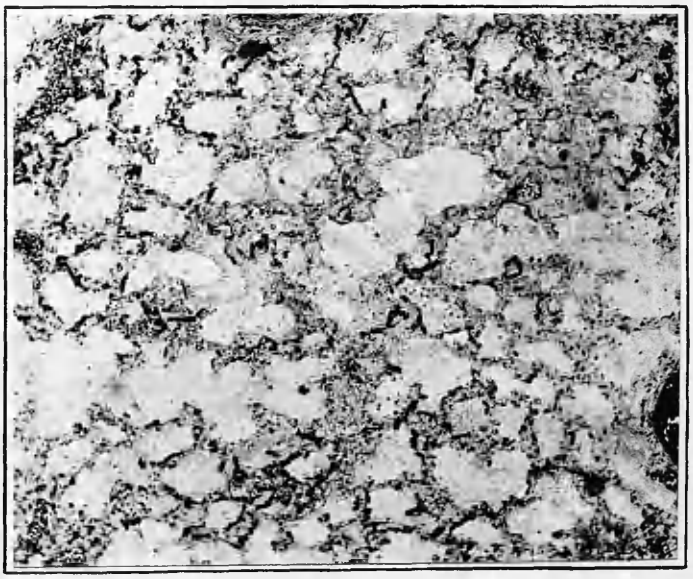


Fig. 104. Case 22. Widespread capillary fibrin thrombo-embolism with early pulmonary infarction, and no evidence of infection. P.T.A.H. x 95.

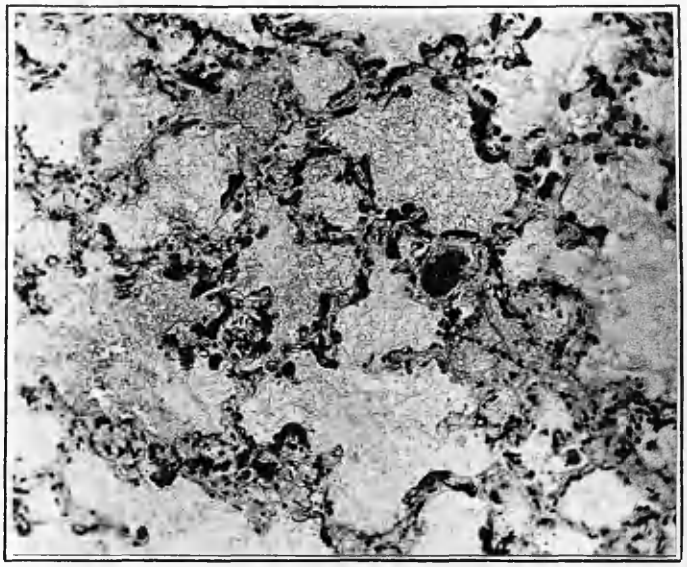


Fig. 105. Case 22. Widespread capillary fibrin thrombo-embolism with oedema of the atria and alveoli, and with a delicate alveolar fibrin network. P.T.A.H. x 170.

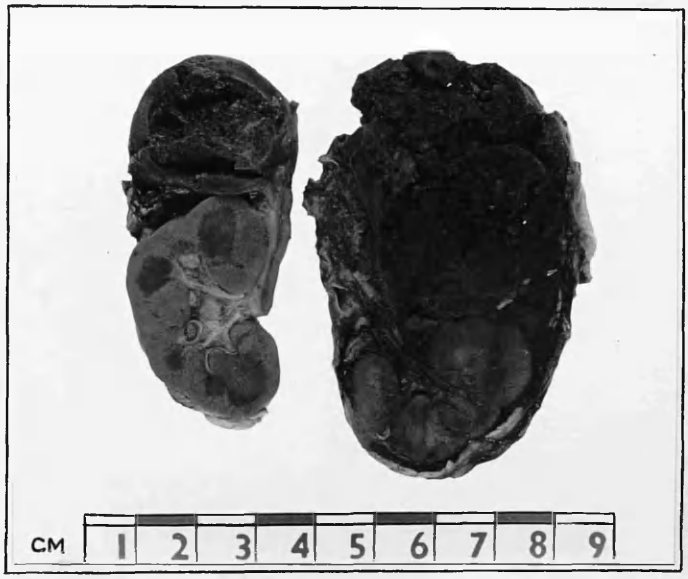



Fig. 106. Case 23. Gross specimen of bilateral adrenal haemorrhages seen from the posterior aspect. x $\frac{3}{4}$.

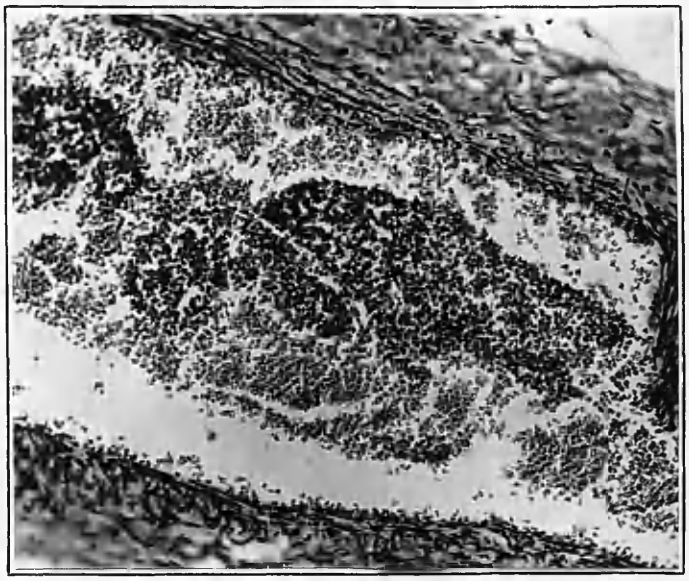


Fig. 107. Case 23. Postmortem thrombus in pancreatic artery. It shows the delicate criss-cross fibrin network and the heavy admixture of corpuscles. P.T.A.H. x 170.

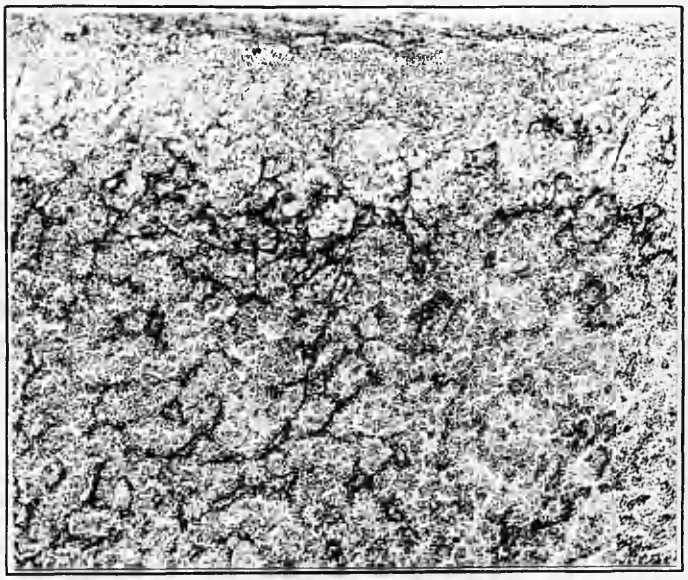


Fig. 108. Case 23. Total necrosis of cortex of right adrenal gland with widespread sinusoidal antemortem fibrin thrombo-emboli and interstitial haemorrhage. P.T.A.H. x 95.

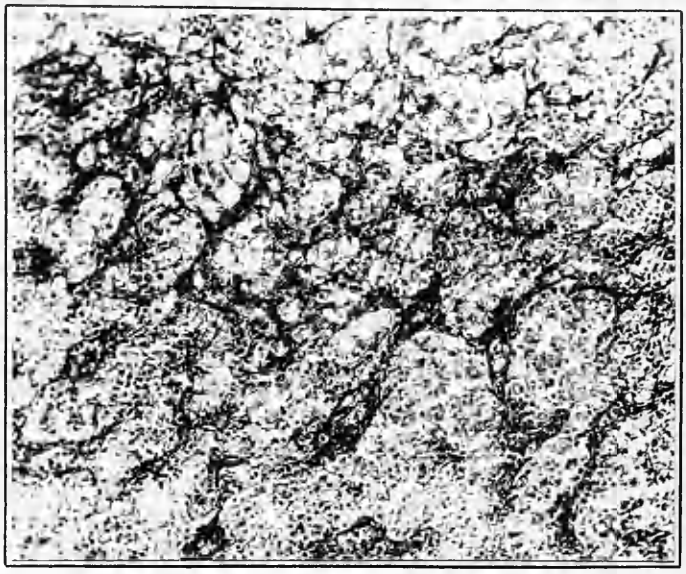
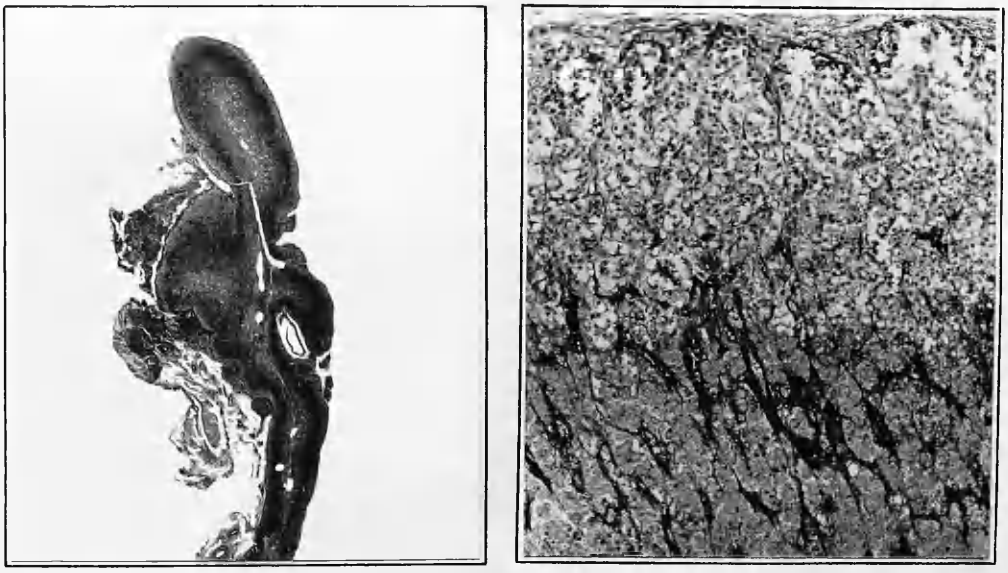
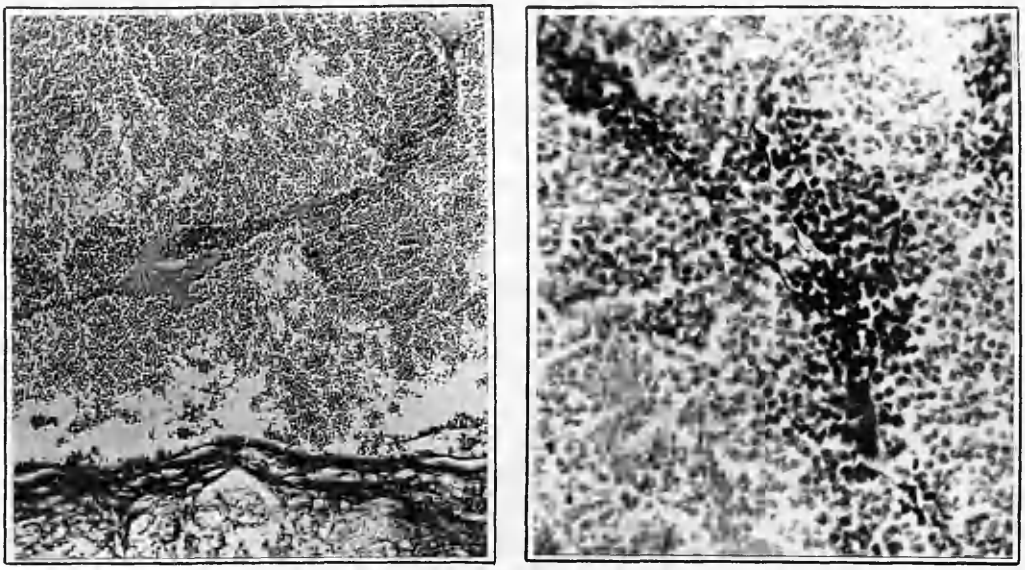


Fig. 109. Case 23. Haemorrhagic right adrenal gland with total infarction and antemortem sinusoidal thrombosis. P.T.A.H. x 170.



(a) (b)

Fig. 110. Case 23. (a) Left adrenal gland. Dark zone in the deeper cortex is due to sinusoidal fibrin thrombi. P.T.A.H. x 3. (b) Definitive cortex relatively spared and confluent sinusoid thrombosis with haemorrhage and necrosis in deeper (foetal) cortex. P.T.A.H. x 95.



(a) (b)

Fig. 111. Case 23. Typical appearance of haemorrhage surrounding the right adrenal gland. Remains of a gland capsule are present in the lower part of (a). P.T.A.H. (a) x 95. (b) x 310.

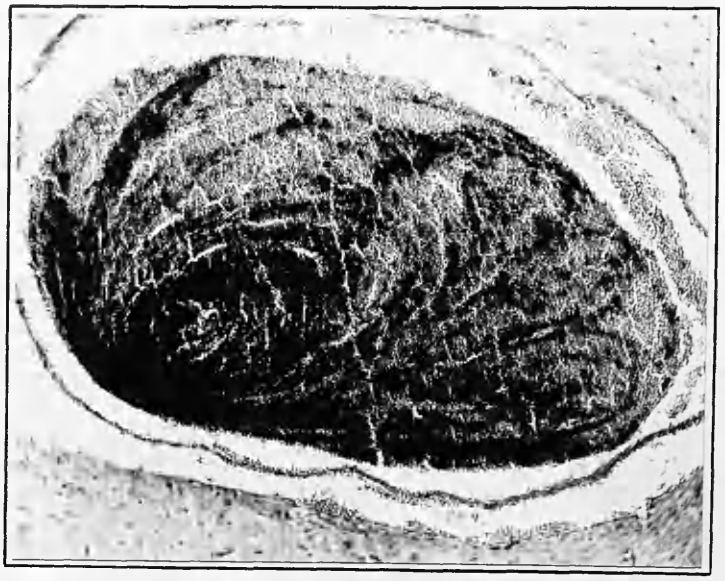


Fig. 112. Case 24. Transverse section showing antemortem mixed laminated thrombus in a tributary of the vein of Galen. P.T.A.H. x 85.

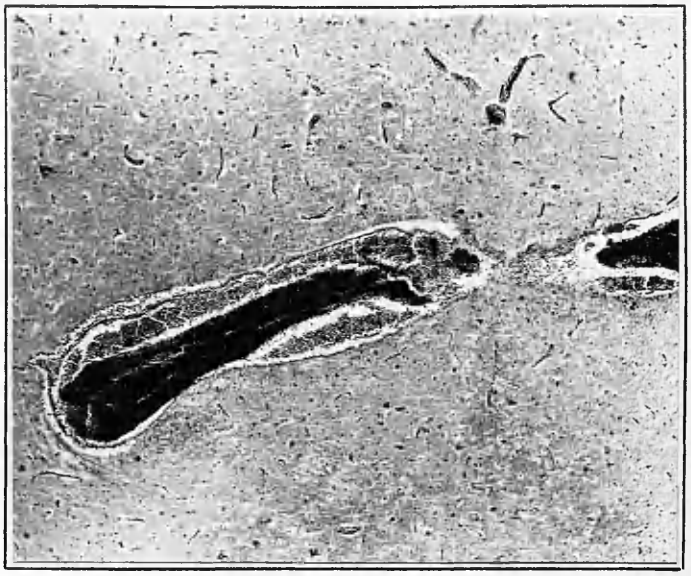


Fig. 113. Case 24. Longitudinal section of antemortem thrombosis of tributary of vein of Galen. Thrombus is rich in fibrin but trapped corpuscles can be seen. P.T.A.H. x 45.

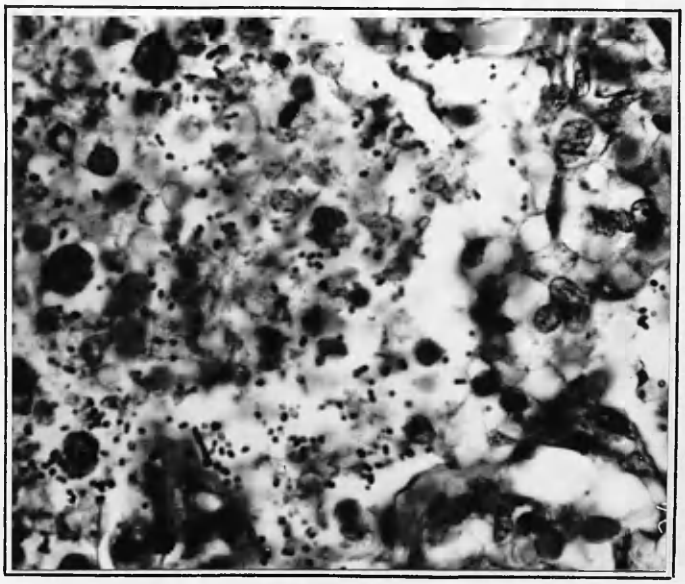


Fig. 114. Case 25. Lung alveolus filled with pus cells and an attempt has been made to illustrate numerous lanceolate diplococci. P.T.A.H. x 700.

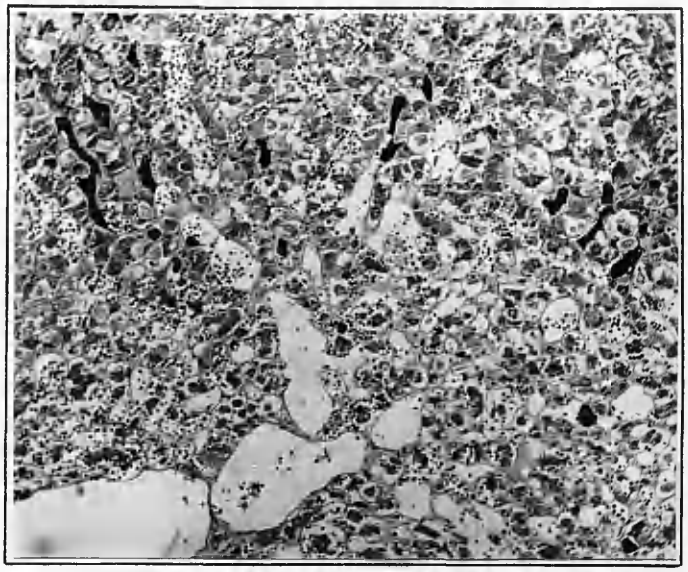


Fig. 115. Case 25. Multiple fibrin thrombo-emboli in the deeper layers of the cortex of an adrenal gland. P.T.A.H. x 95.

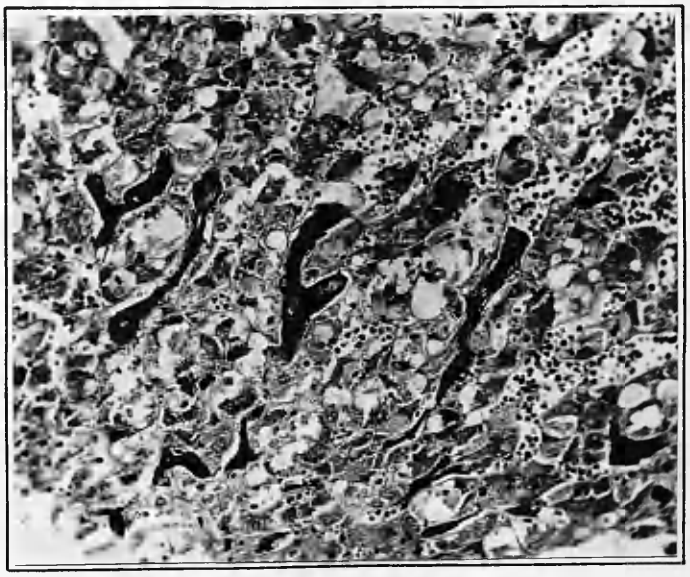


Fig. 116. Case 25. Fibrin thrombo-emboli in the sinusoids of an adrenal gland. P.T.A.H. x 170.

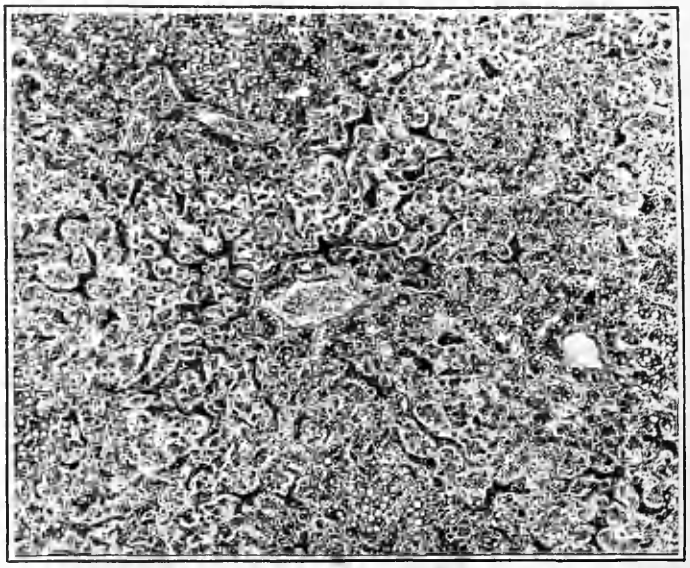


Fig. 117. Case 26. Widespread hepatic sinusoidal fibrin thrombo-embolism causing mid- and centrilobular fatty change and necrosis. P.T.A.H. x 95.

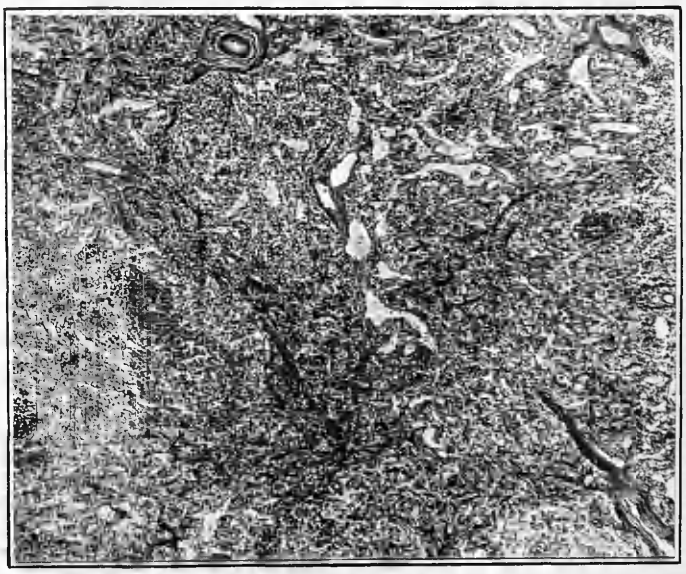


Fig. 118. Case 26. Antemortem fibrin thrombo-embolism affecting splenic sinusoids with compensatory dilatation of unaffected ones. P.T.A.H. x 45.

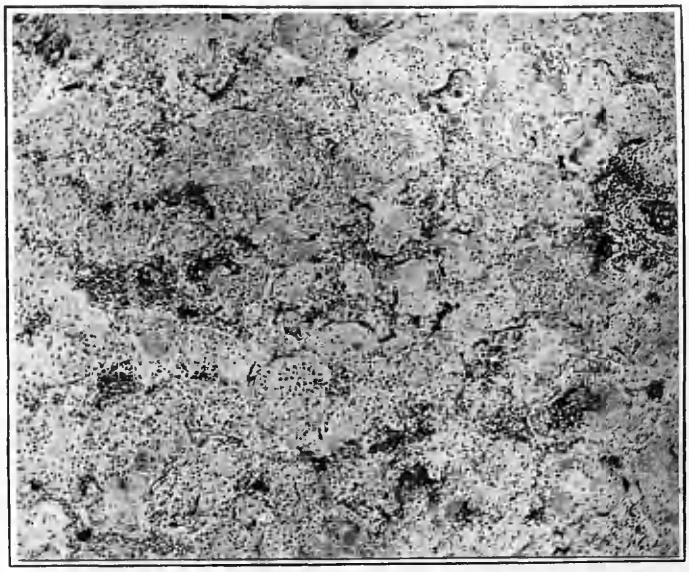


Fig. 119. Case 27. Moderately widespread capillary fibrin thrombosis. Expanded alveoli filled with plasma and mild polymorph infiltration associated with infarction and early infection. P.T.A.H. x 95.

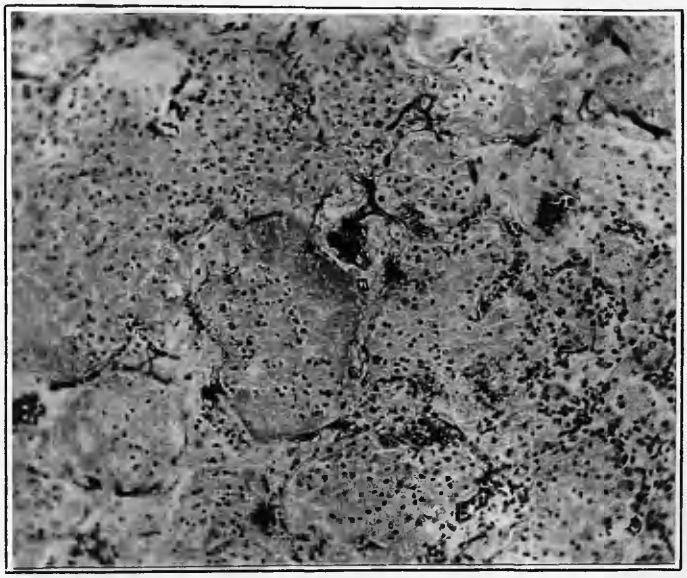


Fig. 120. Case 27. Thrombi in alveolar capillaries and mild infiltration of polymorphs in the alveoli. P.T.A.H. x 170.

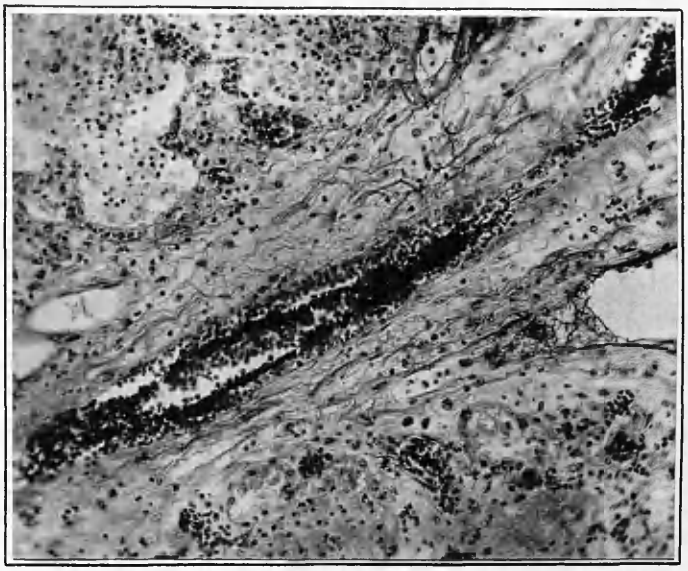


Fig. 121. Case 27. Fibrin thrombo-embolism affecting a pulmonary venule in a lung septum. There is a tendency towards lamination over the endothelial surface. P.T.A.H. x 170.

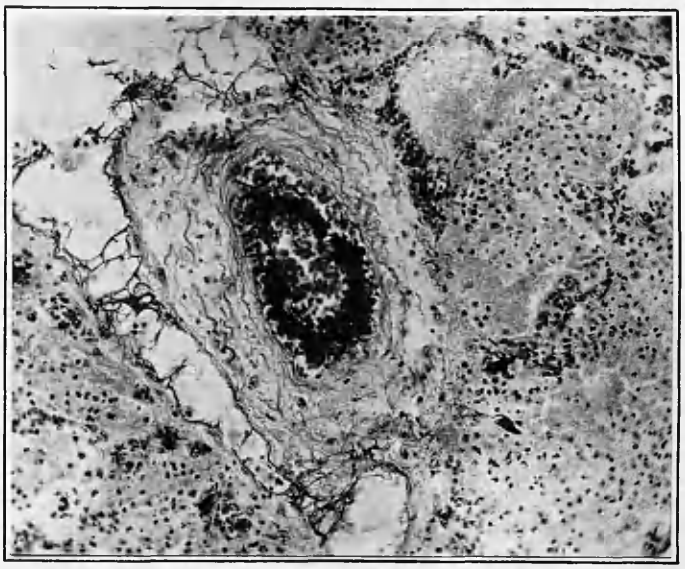


Fig. 122. Case 27. Transverse section of a pulmonary arteriole showing lamination of fibrin thrombus against the endothelium. P.T.A.H. x 170.

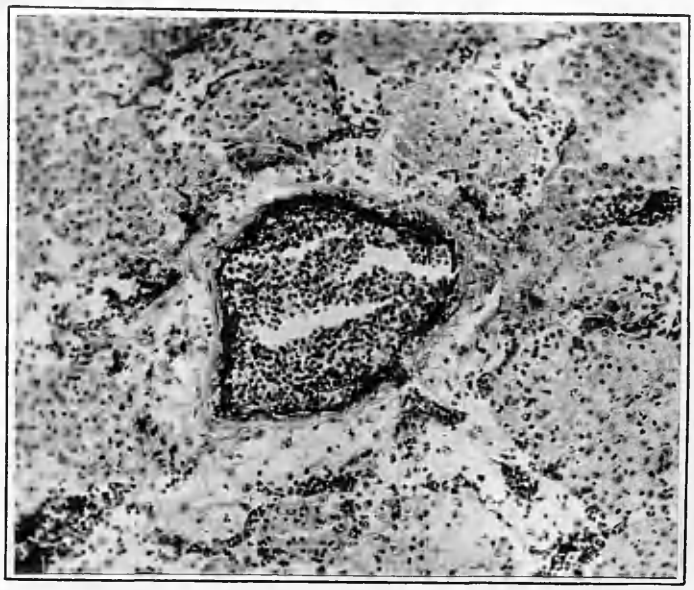


Fig. 123. Case 27. Similar laminated fibrin thrombo-embolism retracted against the endothelial surface. P.T.A.H. x 170.

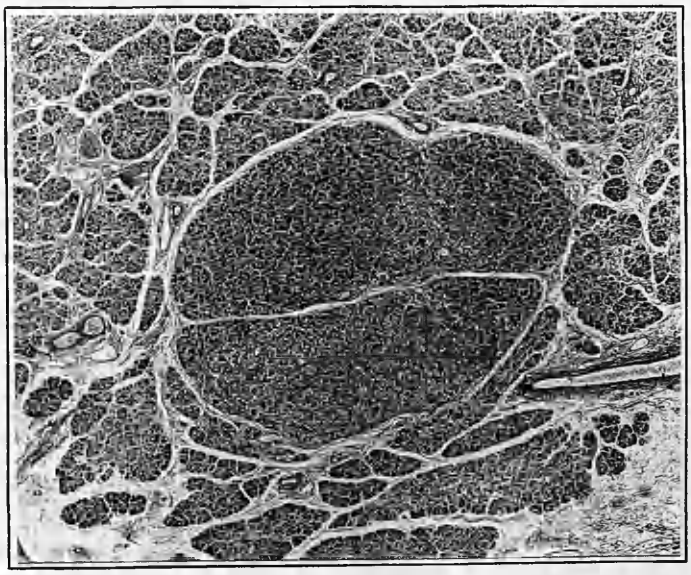


Fig. 124. Case 28. Small exocrine adenoma of pancreas. P.T.A.H. x 20.

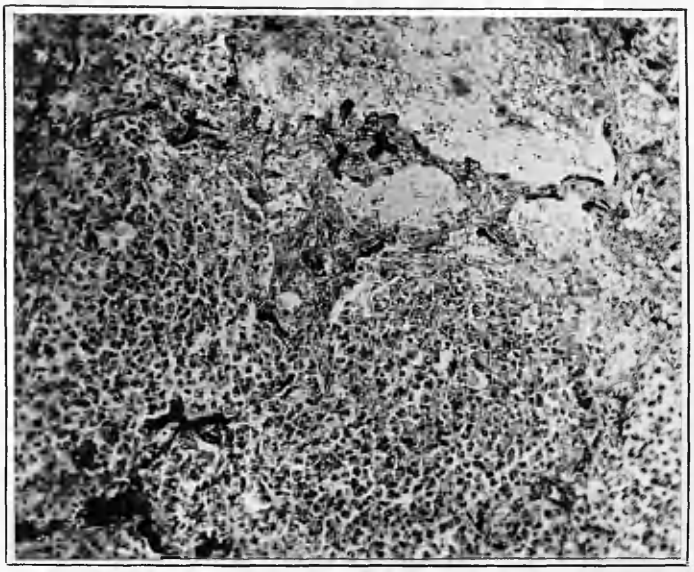


Fig. 125. Case 28. Area of lung, not yet totally destroyed by infection, showing capillary fibrin thrombosis. P.T.A.H. x 170.

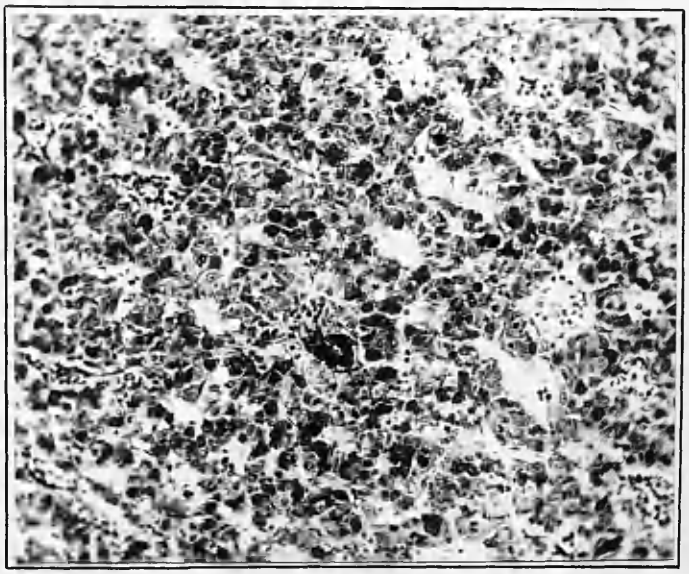


Fig. 126. Case 28. Rather loosely woven fibrin thrombus, probably agonal, in pituitary sinusoid. P.T.A.H. x 170.

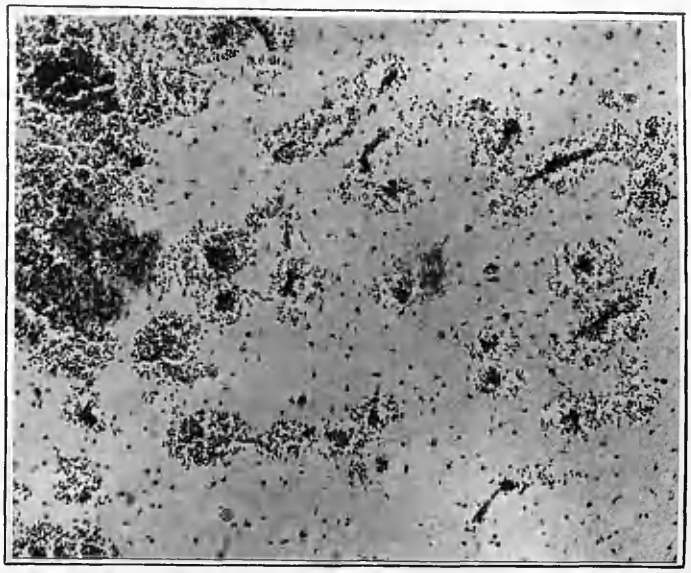
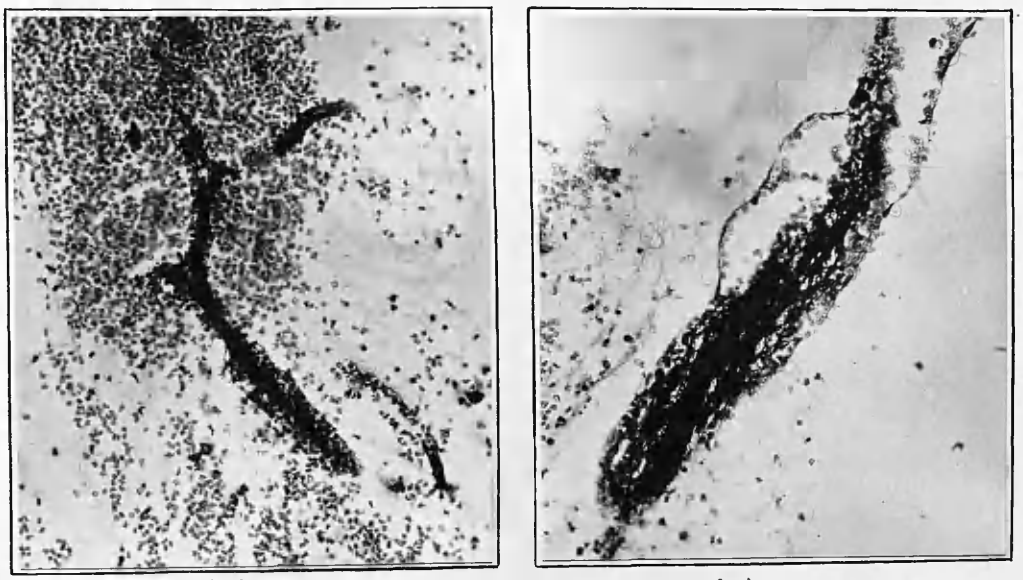


Fig. 127. Case 29. Margin of cerebral haemorrhage and scattered fibrin thrombi are apparent. These probably lay intravascularly at one stage. P.T.A.H. x 95.



(a) (b)

Fig. 128. Case 29. Two examples of antemortem fibrin thrombi in vessels. The viability of the vessel wall is doubtful in these examples. P.T.A.H. x 170.

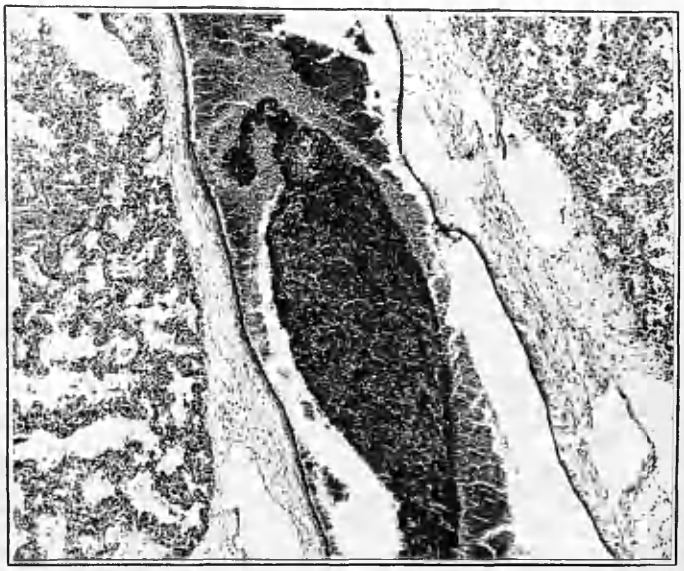


Fig. 129. Case 29. Postmortem thrombus in a pulmonary vein. P.T.A.H. x 45.

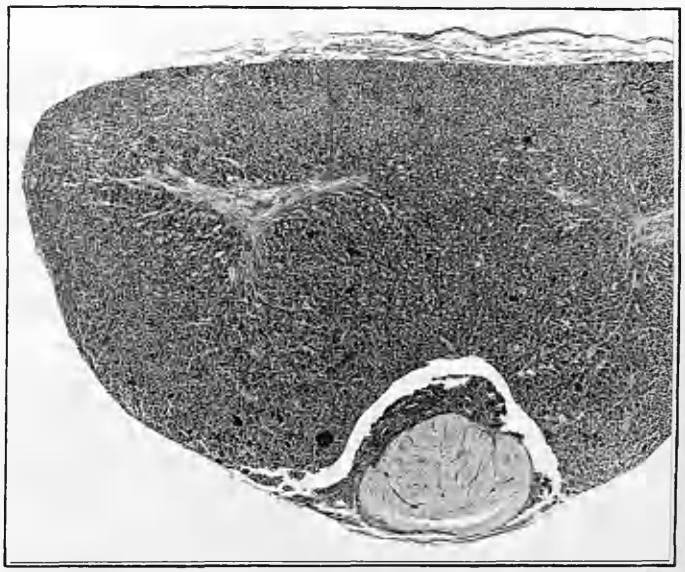
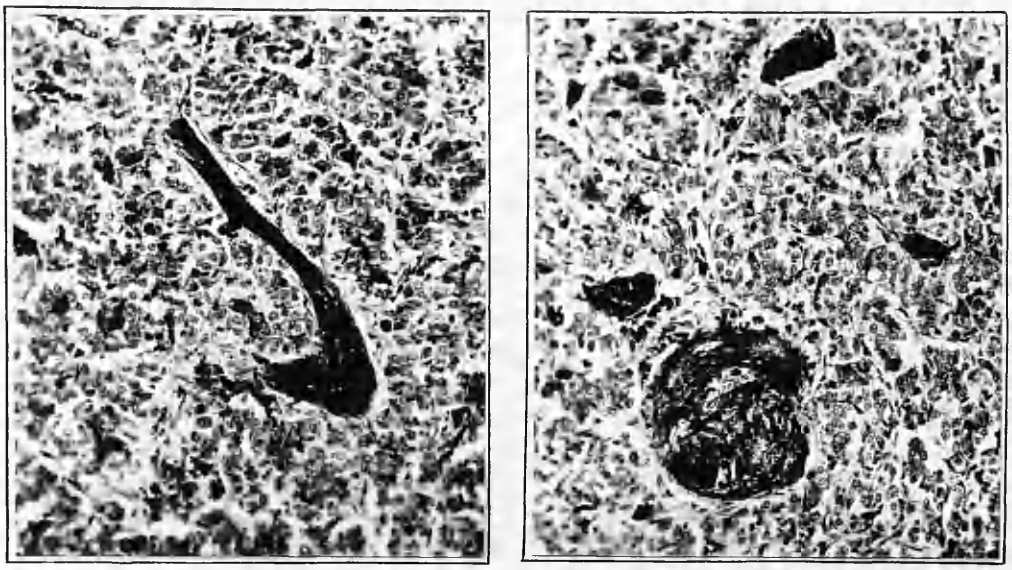


Fig. 130. Case 30. Pituitary gland showing widespread sinusoidal thrombi rich in fibrin. P.T.A.H. x 17.



(a) (b)

Fig. 131. Case 30. (a) Pituitary fibrin thrombo-embolus cut longitudinally and showing the streaming and saddle embolus effect. (b) Laminated fibrin thrombus cut transversely. P.T.A.H. x 170.

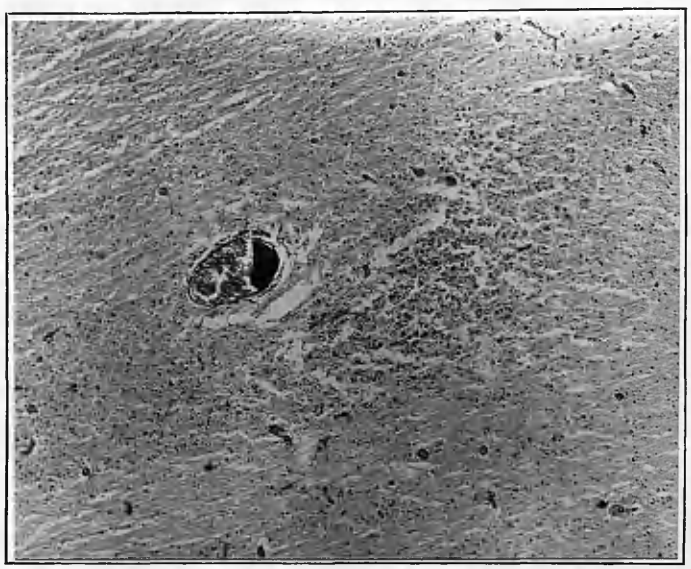
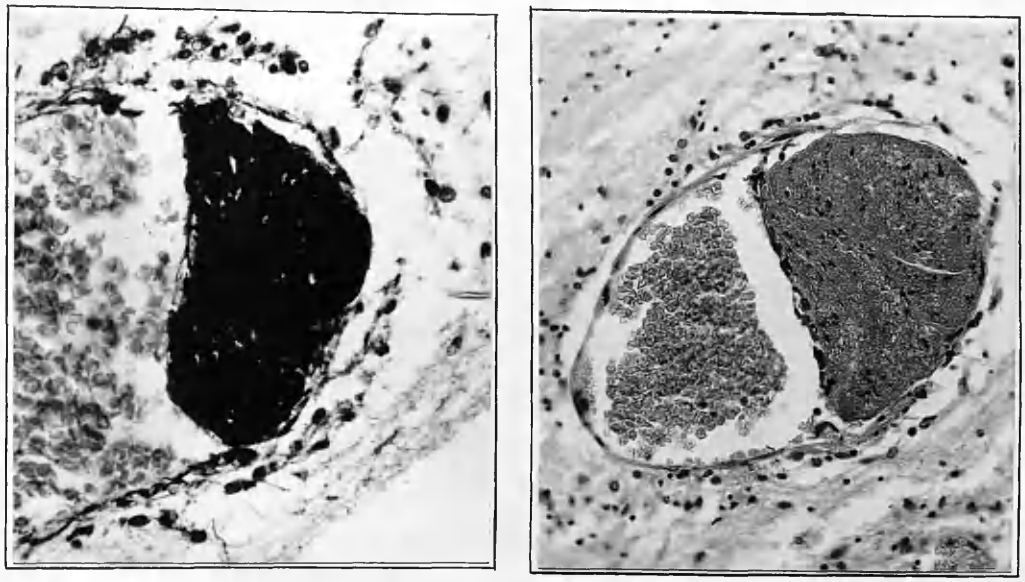


Fig. 132. Case 31. Pure fibrin thrombus lodged at the bifurcation of a cerebral vessel with early cerebral softening to the right (see Fig. 133). P.T.A.H. x 45.



(a) (b)

Fig. 133. Case 31. (a) High power view of vessel of Fig. 132 showing scanty endothelial nuclei "over" the thrombus. P.T.A.H. x 310. (b) The sixth serial section shows the double endothelial layer to an advantage. H. and E. x 170.

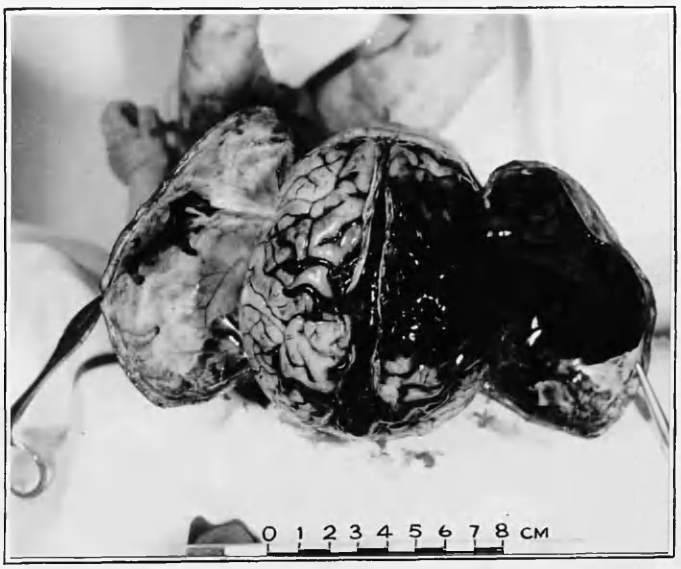



Fig. 134. Case 32. Thrombosis of the superior longitudinal sinus with extensive biparietal subdural haematoma. x $\frac{3}{8}$.

Fig. 135. Case 32. Capillary fibrin thrombosis in a relatively non infected area of lung. P.T.A.H. x 95.

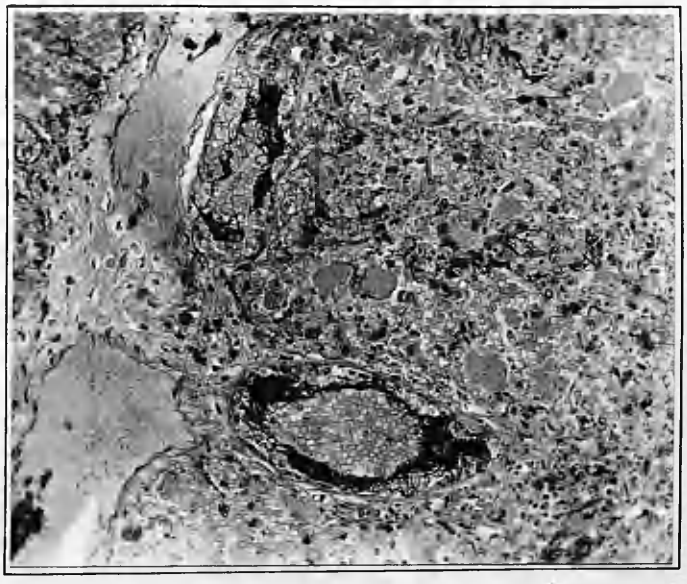


Fig. 136. Case 32. Antemortem fibrin thrombosis affecting a pulmonary venule with retraction and lamination towards the intimal surface. P.T.A.H. x 170.

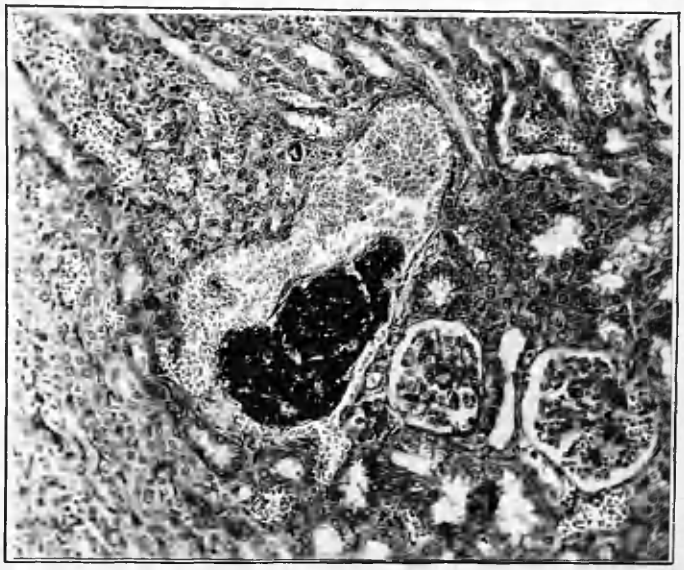


Fig. 137. Case 32. Fibrin thrombus in an arcuate venule, and it has retracted to one side of the vessel, and has been covered completely by endothelium. P.T.A.H. x 170.

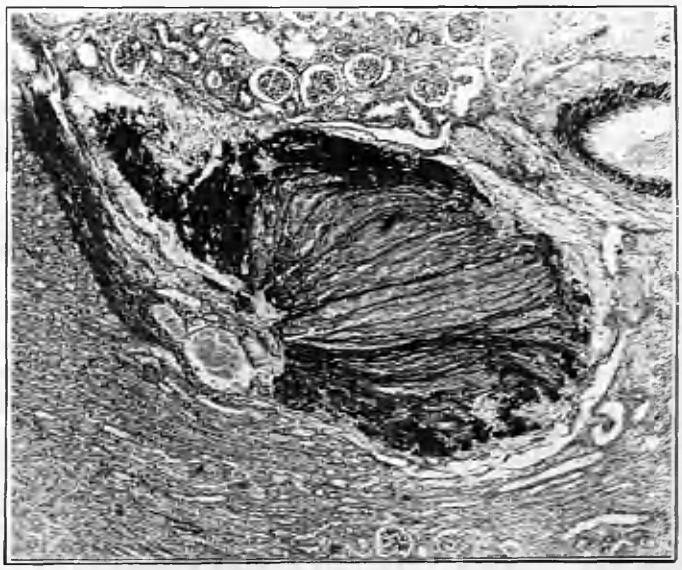


Fig. 138. Case 32. Recent laminated mixed thrombus affecting a large branch of the renal vein. P.T.A.H. x 45.

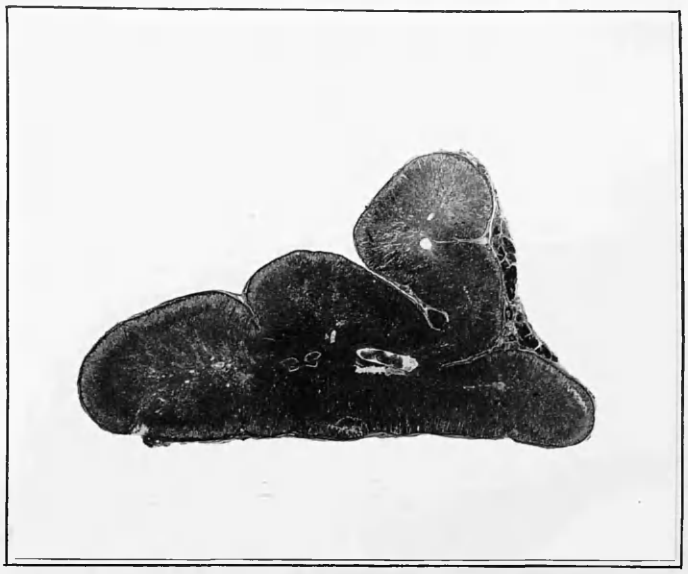


Fig. 139. Case 33. Right adrenal gland. Zone of increased density immediately deep to the adult (or definitive) cortex is due to sinusoidal fibrin. P.T.A.H. x 4.

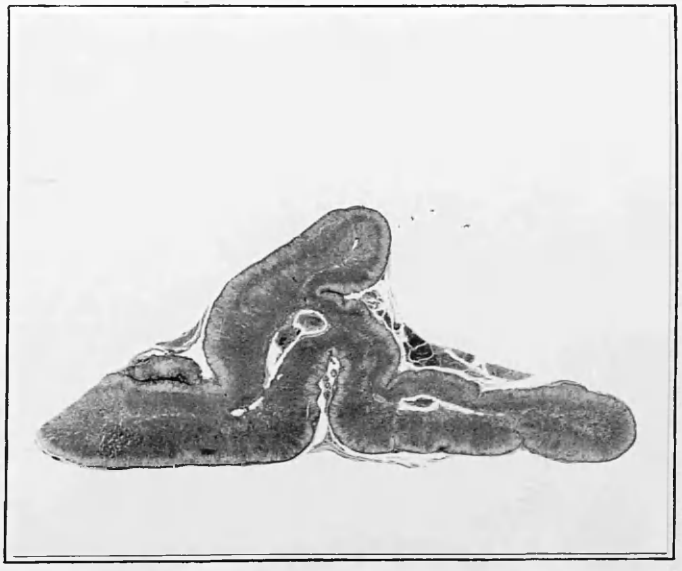


Fig. 140. Case 33. Left adrenal gland. P.T.A.H. x $3\frac{1}{2}$.

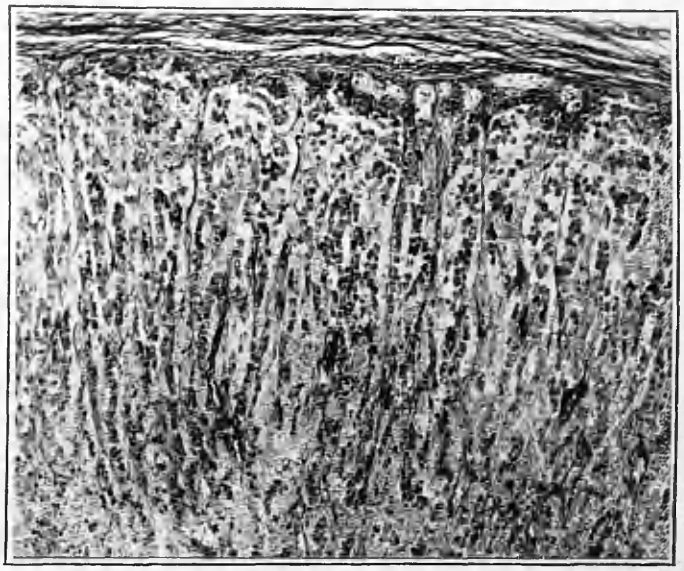


Fig. 141. Case 33. Sinusoids containing antemortem fibrin thrombi are narrow, whereas unaffected ones are stuffed with blood. P.T.A.H. x 45.

Fig. 142. Case 33. Fibrin thrombo-embolus now lying against endothelium of sinusoid, having vacated the axial stream. P.T.A.H. x 95.

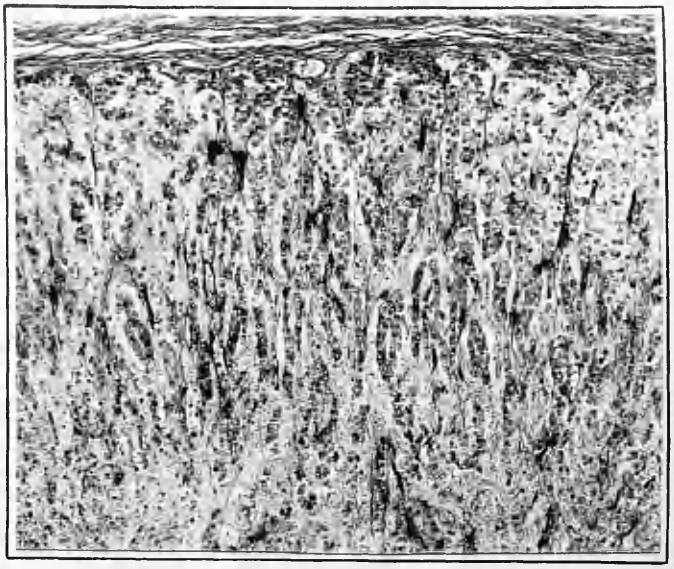


Fig. 143. Case 33. Definitive (or adult) adrenal cortex also showing antemortem fibrin thrombo-emboli. P.T.A.H. x 95.

Fig. 144. Case 34. Oesophageal arteriole near cardia showing laminated fibrin thrombus. P.T.A.H. x 45.

Fig. 145. Case 34. Gastric erosion, devoid of mucosa, showing laminated arteriolar fibrin thrombo-embolism, and capillary fibrin thrombus in the mucosa. P.T.A.H. x 45.

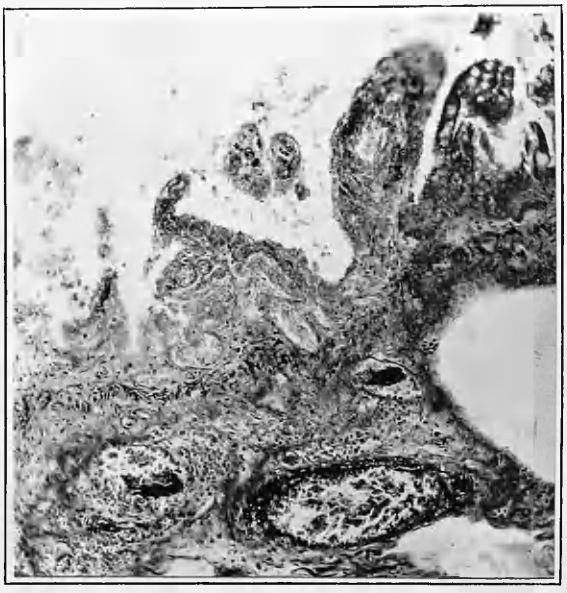


Fig. 146. Case 34. Ulcerated area of small intestine showing laminated arteriolar fibrin thrombi (below), capillary fibrin thrombi (left, in villus), and venous fibrin thrombi. P.T.A.H. x 95.

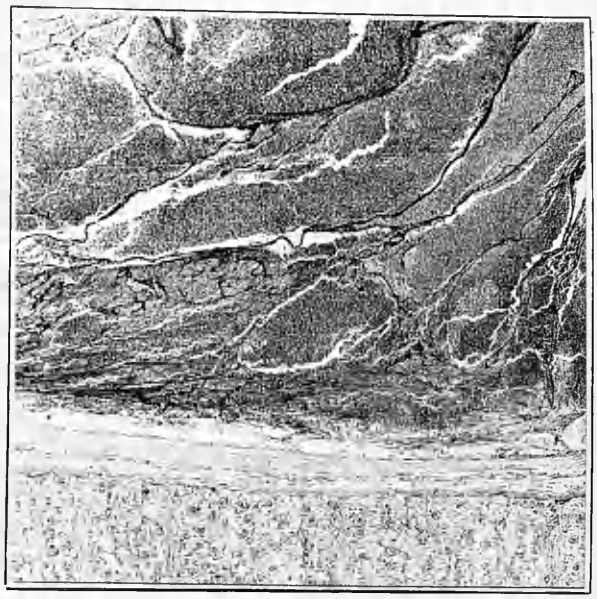
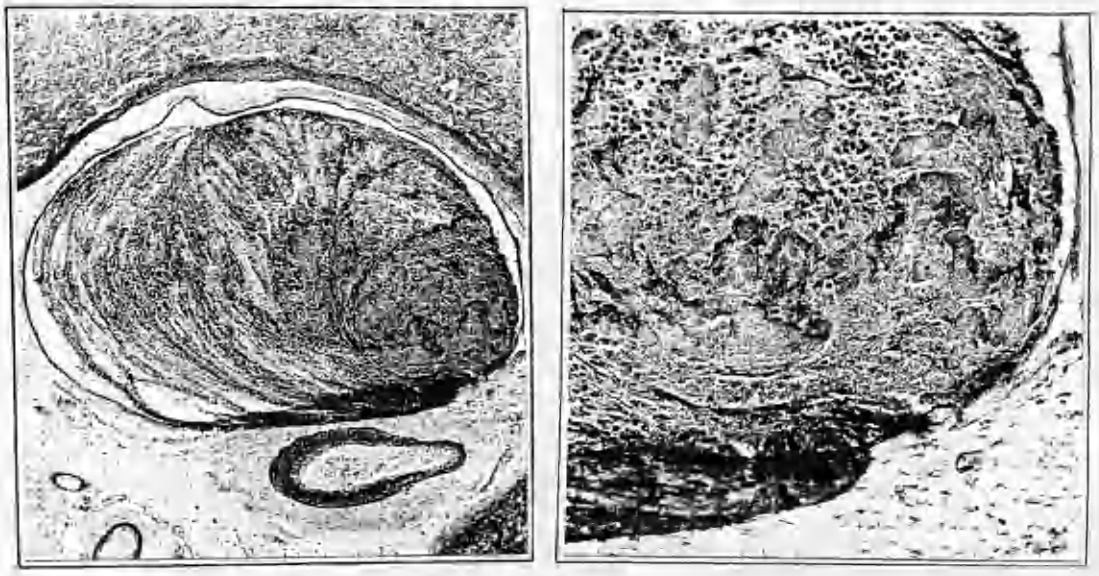


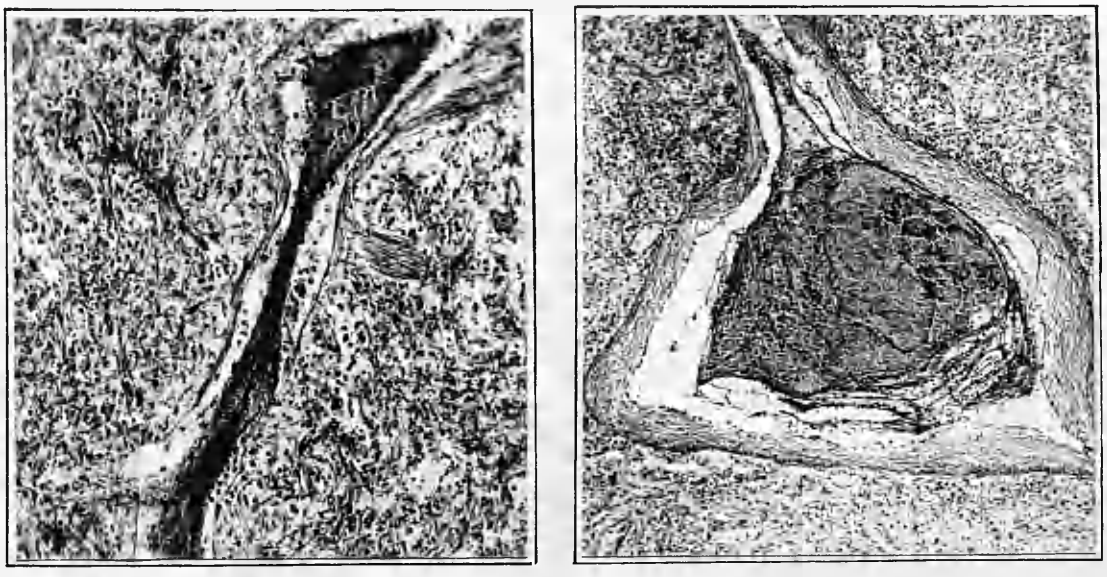
Fig. 147. Case 35. Intracapsular adrenal haematoma showing well stained strands of fibrin. P.T.A.H. x 21.

Fig. 148. Case 35. A small island of recognisable z. glomerulosa cells with antemortem fibrin thrombo-emboli in nearly every sinusoid. P.T.A.H. x 170.



(a) (b)

Fig. 149. Case 35. (a) Thrombosis of splenic vein at hilum. x 55. (b) Enlargement of bottom right hand corner. x 170. P.T.A.H.



(a) (b)

Fig. 150. Case 35. (a) Fibrin thrombus with early lamination of polymorphs on its surface. x 150. (b) Fibrin thrombus on section retracted towards wall with superimposed mixed thrombus internally. x 85. P.T.A.H.

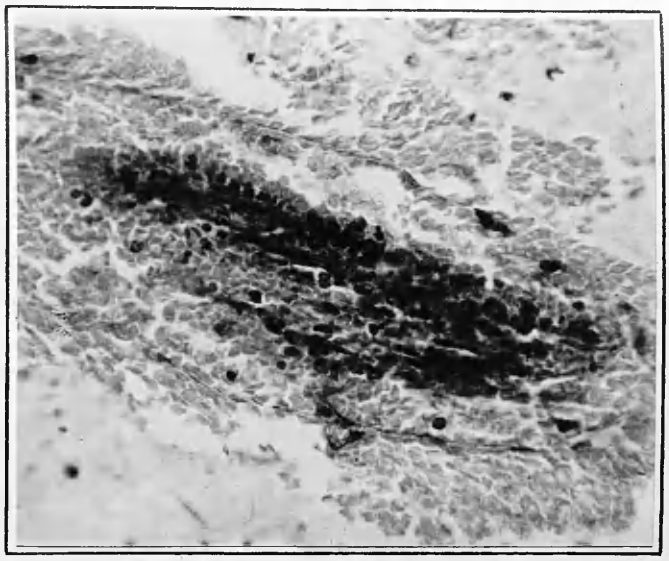
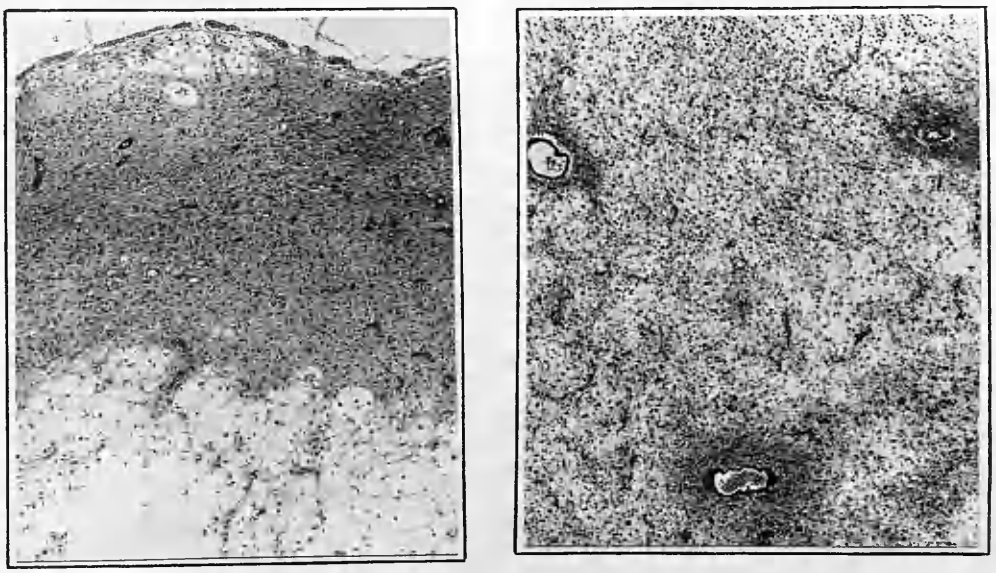
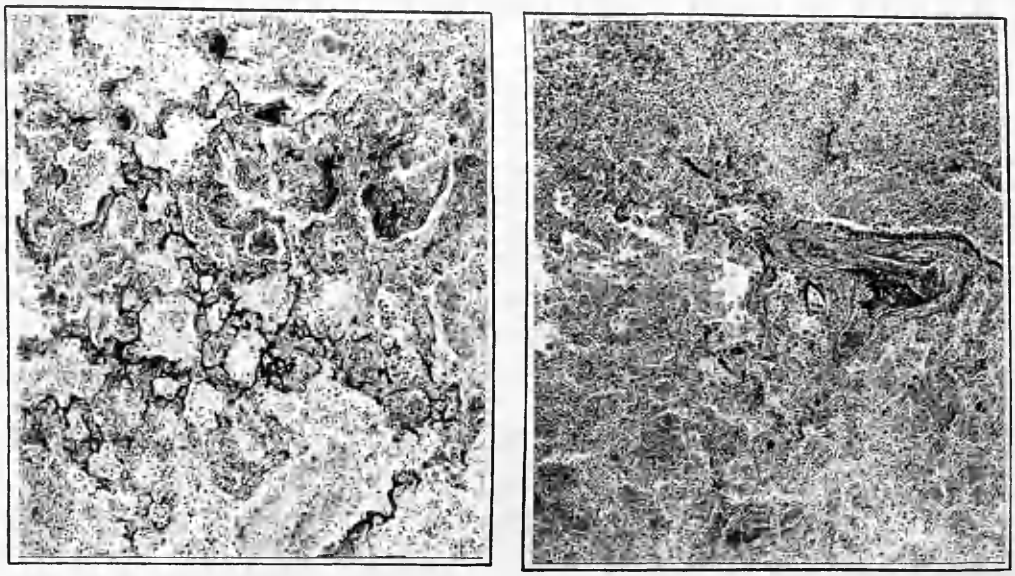


Fig. 151. Case 35. Thrombus in cerebral vessel cut almost transversely with scanty fibrin strands and numerous polymorphs. This thrombus is believed to be an infective thrombus. P.T.A.H. x 310.



(a) (b)

Fig. 152. Case 36. These illustrate the focus of subcortical encephalomalacia. In (a) the pia-arachnoid is above, with an adjacent focus of foam cells. The main lesion is subcortical and is also illustrated in (b). P.T.A.H. x 45.



(a) (b)

Fig. 153. Case 36. Pulmonary capillary fibrin thrombo-emboli, (a) in an infarcted relatively non-infected area, and (b) remains of thrombi in a heavily infected area. P.T.A.H. x 95.

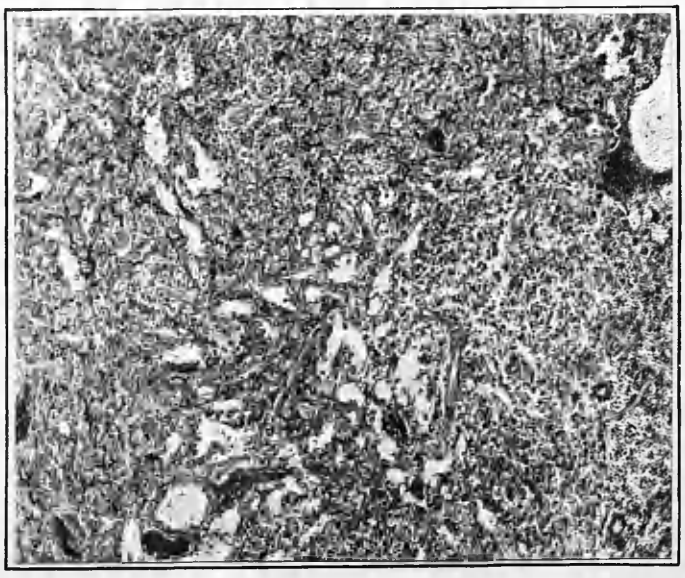
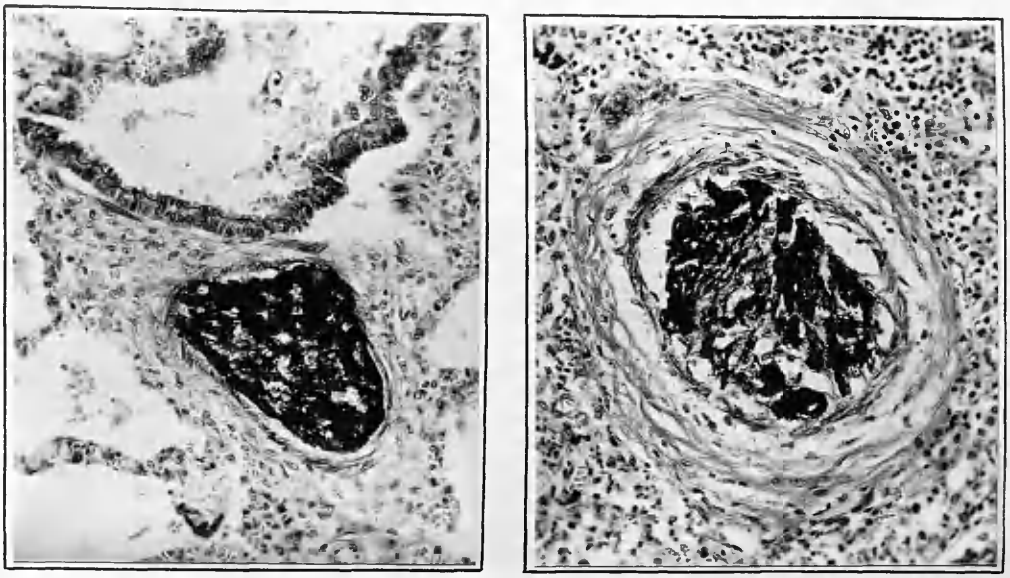


Fig. 154. Case 36. Spleen, showing fibrin thrombo-emboli (black) occluding collapsed sinusoids with compensatory dilatation of unaffected ones. P.T.A.H. x 95.



(a) (b)

Fig. 155. Case 37. Pulmonary arterial fibrin thrombo-embolism. In (a) not much retraction, but evidence of recanalisation. In (b) more retraction, several endothelial nuclei as evidence of recanalisation. P.T.A.H. x 170.

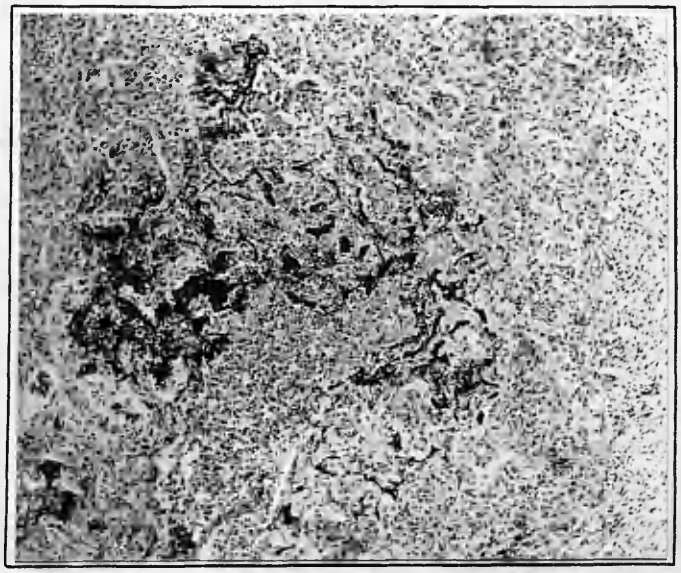


Fig. 156. Case 37. Focus of persisting capillary fibrin thrombosis in a suppurating area of lung; accompanied by marked alveolar fibrin exudation. P.T.A.H. x 95.

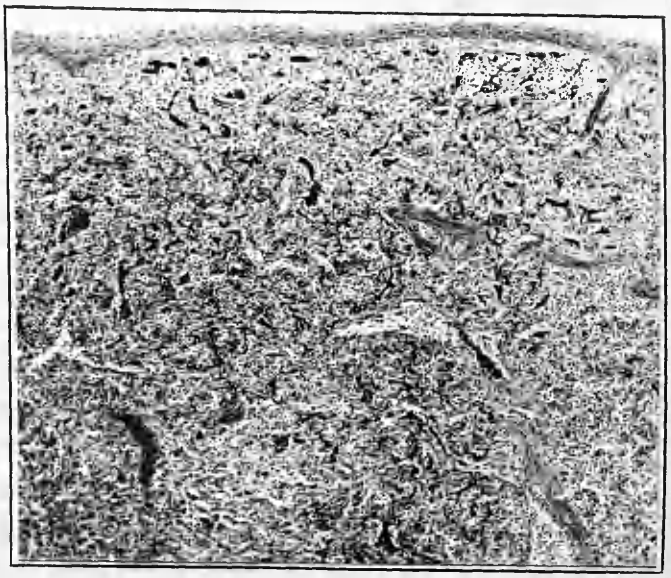


Fig. 157. Case 37. Widespread fibrin thrombo-embolism in splenic sinusoids. Evidence of retraction to one side of the sinusoid lumen is present. P.T.A.H. x 95.

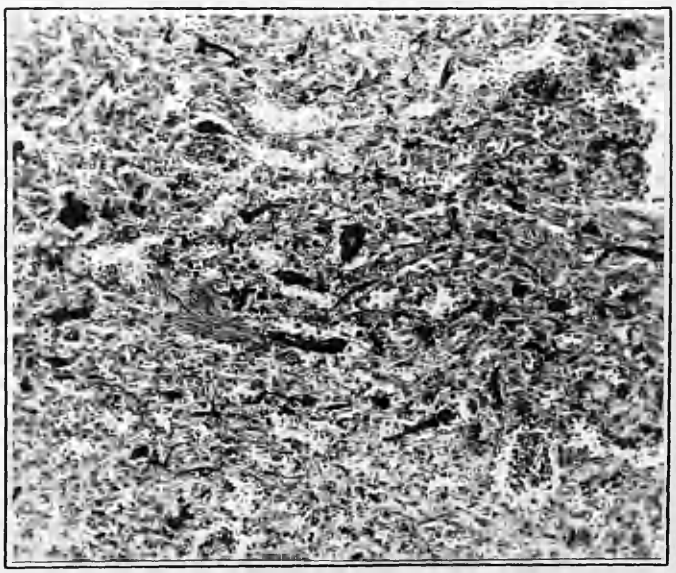


Fig. 158. Case 37. Splenic sinusoid fibrin thrombi showing adhesion and retraction to sinusoid walls with re-establishment of sinusoid lumen. P.T.A.H. x 170.

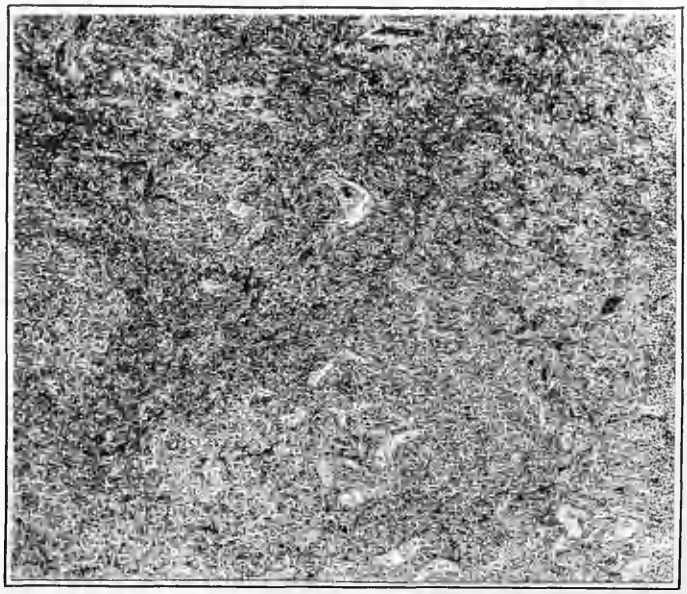


Fig. 159. Case 38. Zones of confluent sinusoidal fibrin thrombo-embolism are visible, with areas of compensatory sinusoidal distension. P.T.A.H. x 45.

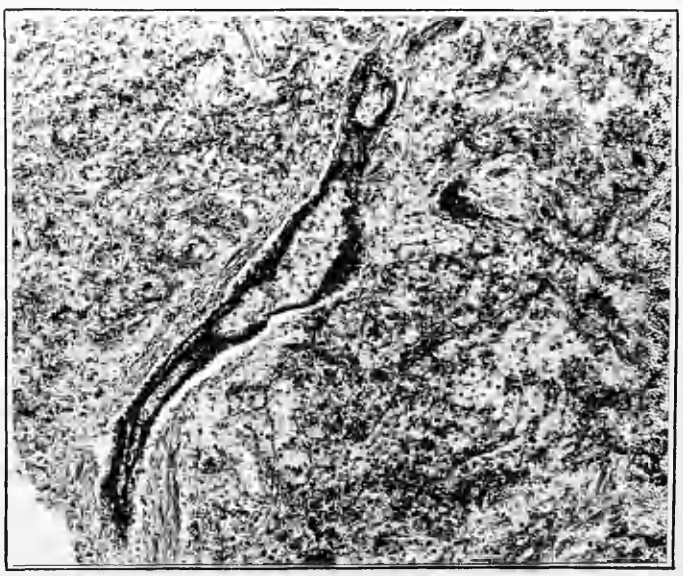


Fig. 160. Case 38. Splenic venule showing fibrin thrombus retracting against endothelial surface. This possibly dates from birth. P.T.A.H. x 95.

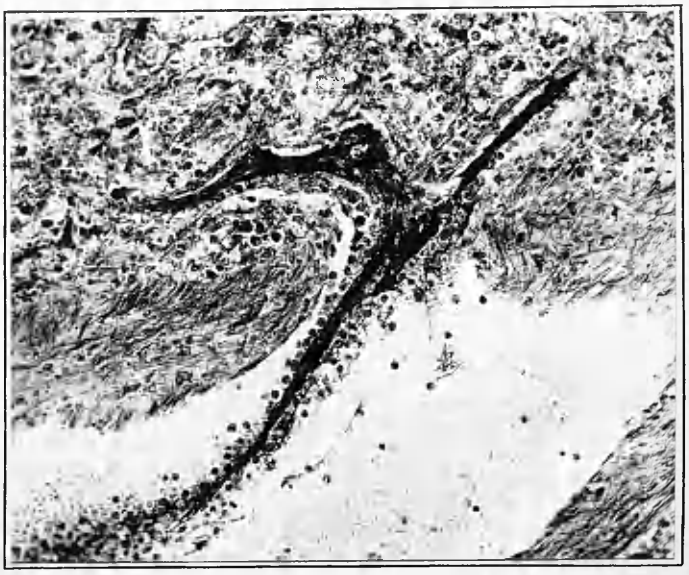


Fig. 161. Case 38. Antemortem thrombus entering splenic venule with core of fibrin and admixture of white and red corpuscles adherent to it. P.T.A.H. x 170.

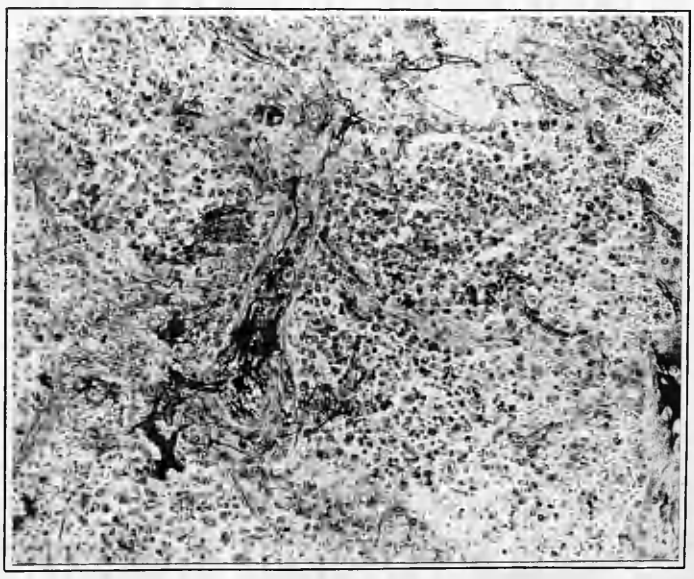


Fig. 162. Case 38. Delicate antemortem thrombi in pulmonary vessels at the margin of a suppurative area. Corpuscles are intimately mixed with the fibrin. P.T.A.H. x 170.

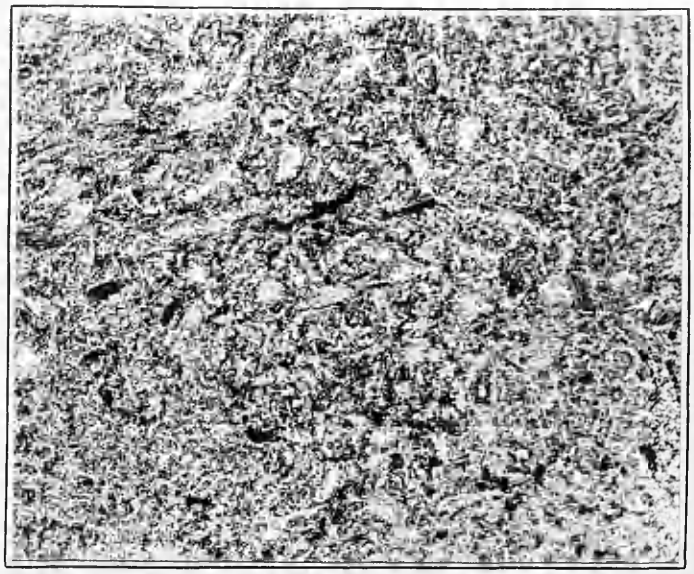


Fig. 163. Case 39. Antemortem thrombi, rich in fibrin, but probably of mixed composition, in splenic sinusoids, and showing compensatory dilatation of unaffected sinusoids. P.T.A.H. x 95.

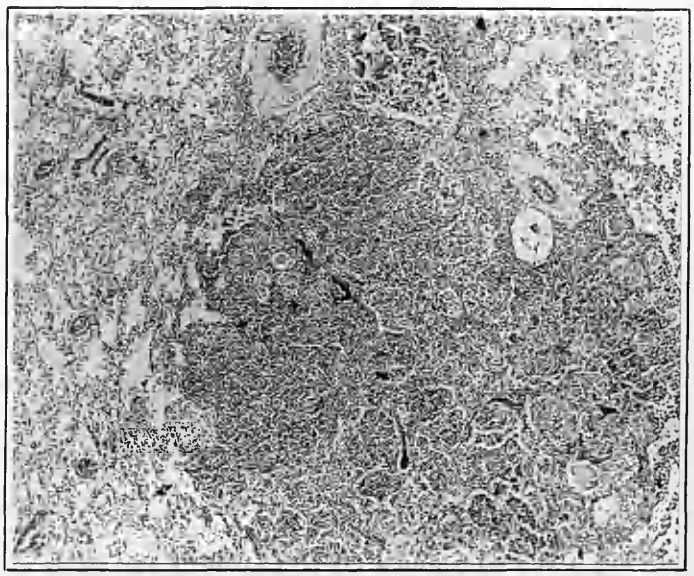


Fig. 164. Case 40. Suppurating area of lung showing scanty thrombi centred on this area only. P.T.A.H. x 45.

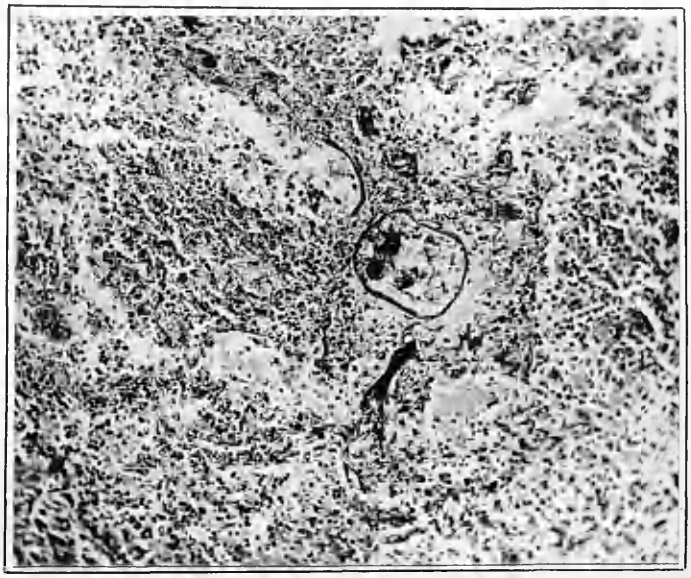


Fig. 165. Case 40. Antemortem thrombus cut longitudinally is rich in fibrin; others higher in the field are looser and contain corpuscles, i.e. they are mixed. P.T.A.H. x 170.

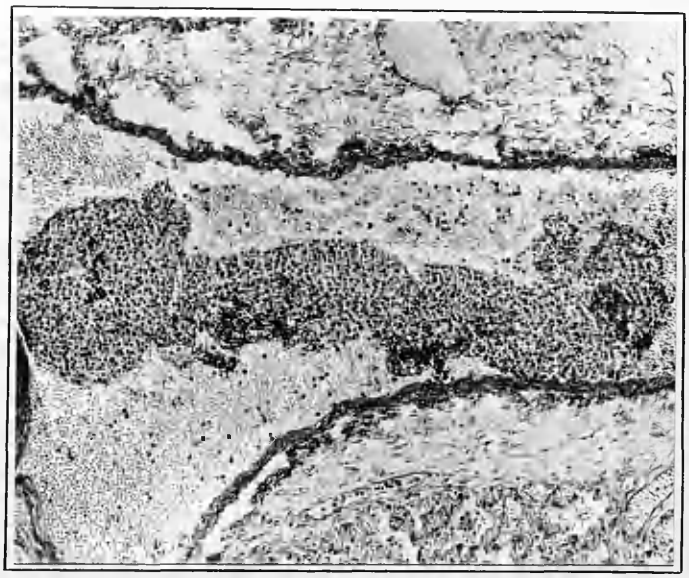


Fig. 166. Case 41. Thrombus in a pulmonary vein. It has the coiled appearance of a postmortem (or perhaps agonal) thrombus but it is very rich in polymorphs and may be a septic thrombus. P.T.A.H. x 95.

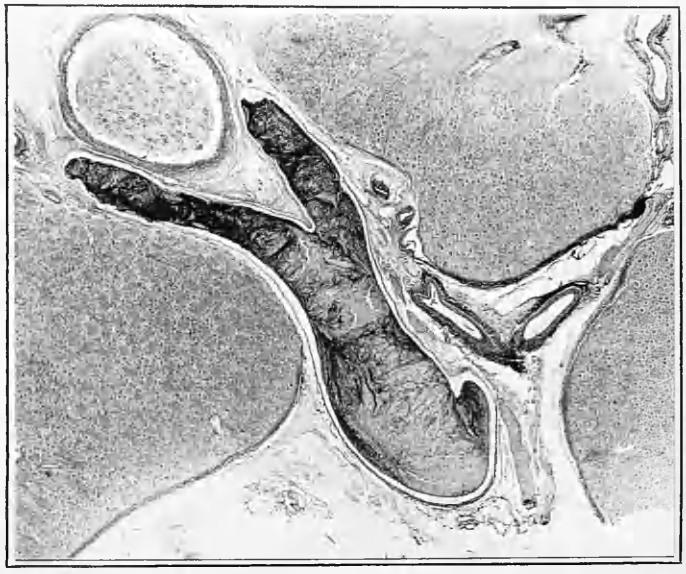


Fig. 167. Case 41. Antemortem laminated mixed renal vein thrombosis without infarction. P.T.A.H. x 7.

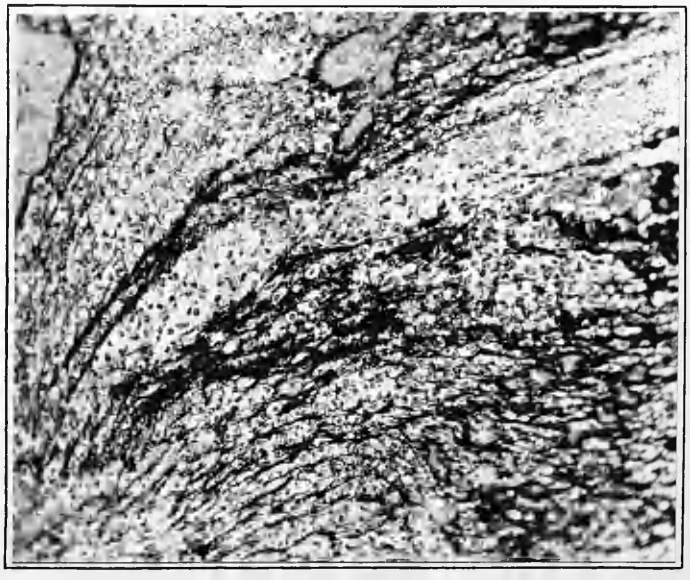


Fig. 168. Case 41. Area of renal vein thrombus moderately rich in polymorphs, and giving the appearance as if the fibrin laminae are breaking down due to early suppuration. P.T.A.H. x 170.

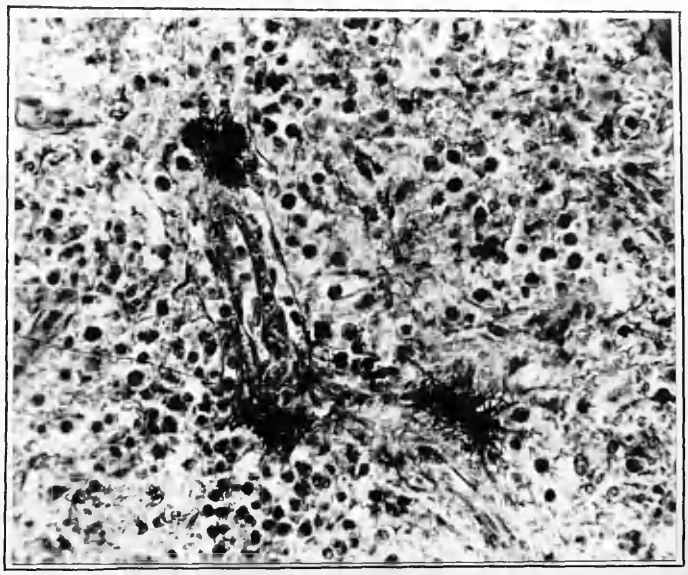


Fig. 169. Case 41. "Knots" of fibrin thrombi in the spleen. Fibrin strands pass centrifugally and give no suggestion of having formed while blood was flowing. P.T.A.H. x 310.

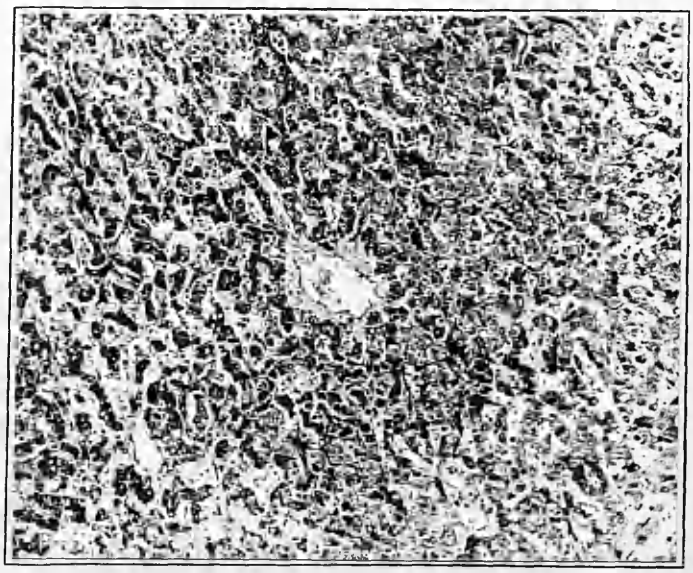


Fig. 170. Case 42. Fairly widespread liver sinusoid antemortem thrombi, and patchy fatty change. Darker liver cells appear to be potentially necrotic. P.T.A.H. x 95.

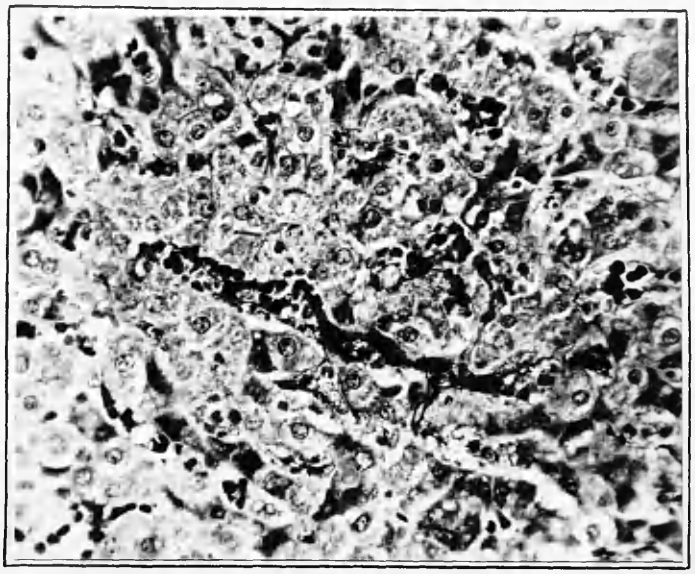


Fig. 171. Case 42. Antemortem thrombosis in liver sinusoid showing admixture of corpuscles. Patchy cytolytic necrosis is also distinguishable. P.T.A.H. x 310.

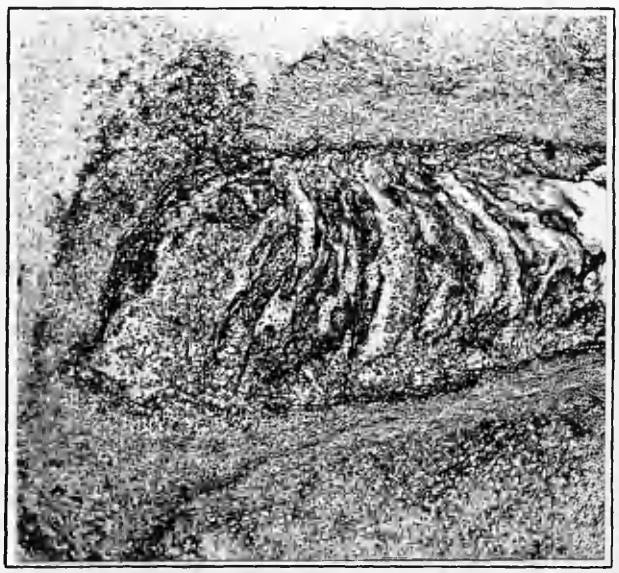


Fig. 172. Case 43. Laminated mixed thrombus in a pulmonary artery in the centre of a suppurating area in lung. P.T.A.H. x 38.

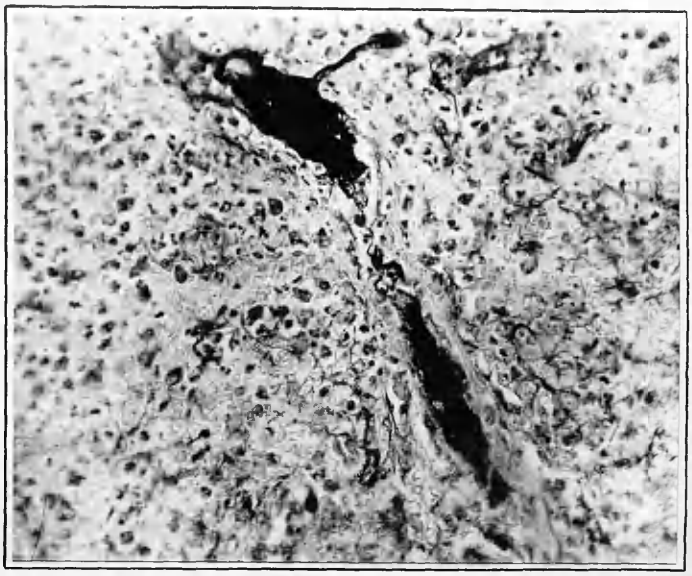


Fig. 173. Case 43. Thrombus rich in fibrin in relation to an area of infection in the lung. Some admixture of corpuscles and streaming is not marked. P.T.A.H. x 310.

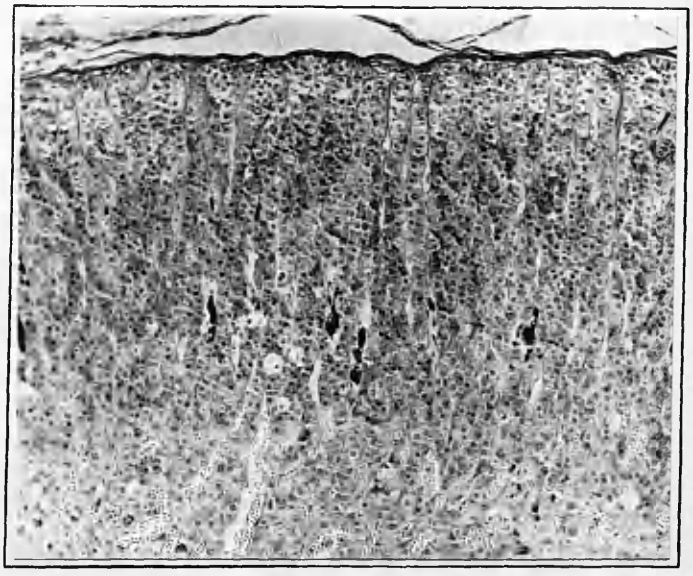


Fig. 174. Case 43. Scanty sinusoidal thrombi rich in fibrin in the adrenal cortex. These also show an admixture with corpuscles. P.T.A.H. x 95.

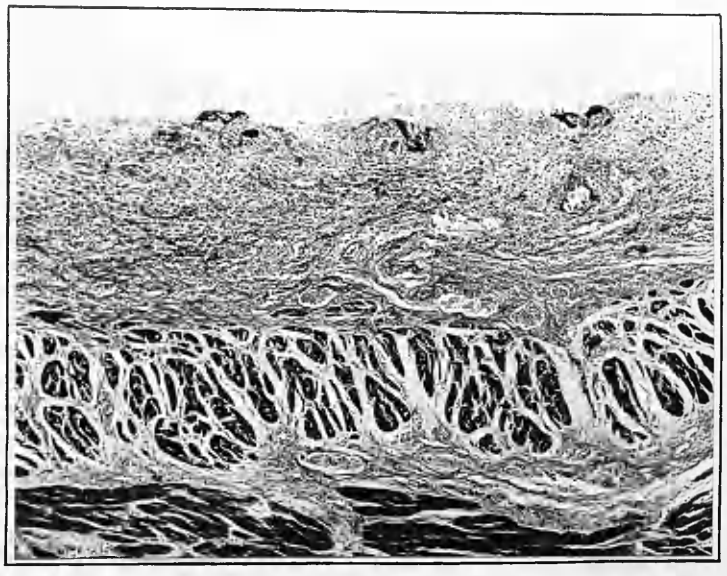


Fig. 175. Case 44. Capillary thrombi rich in fibrin exposed in the base of an area of stercoral ulceration in the duodenum. Evidence of infection is also present. P.T.A.H. x 45.

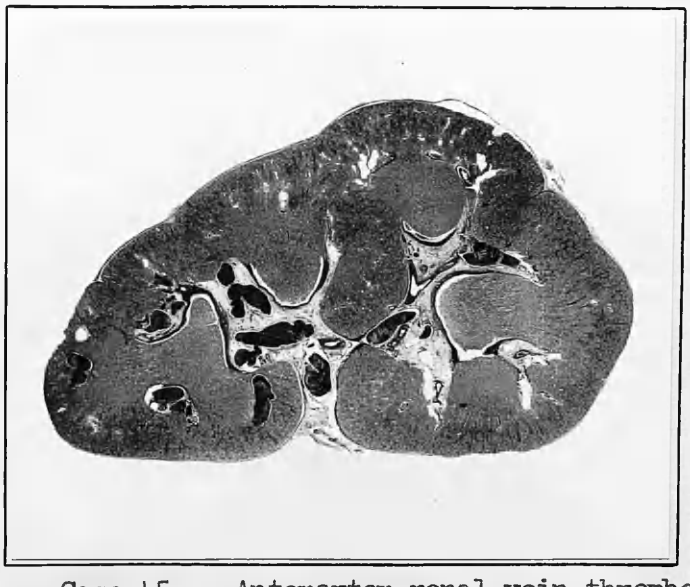


Fig. 176. Case 45. Antemortem renal vein thrombosis affecting the hilar vessels and a few arcuate veins. P.T.A.H. x $2\frac{1}{2}$.

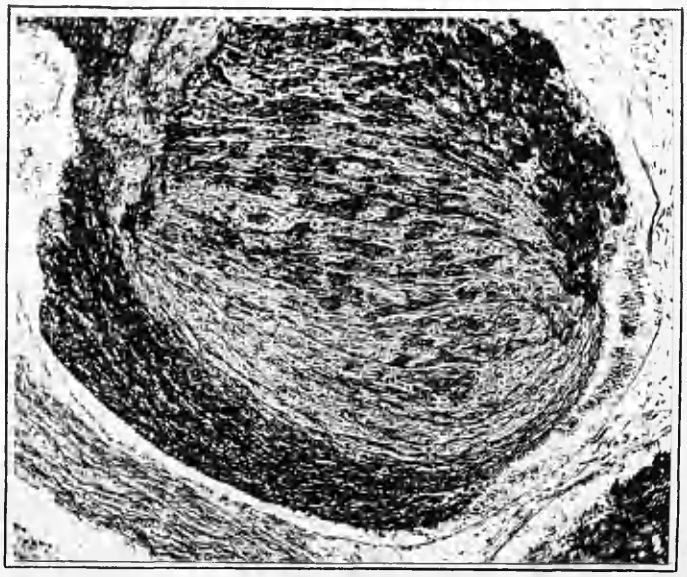


Fig. 177. Case 45. Renal vein thrombus showing the laminated structure of it. P.T.A.H. x 95.

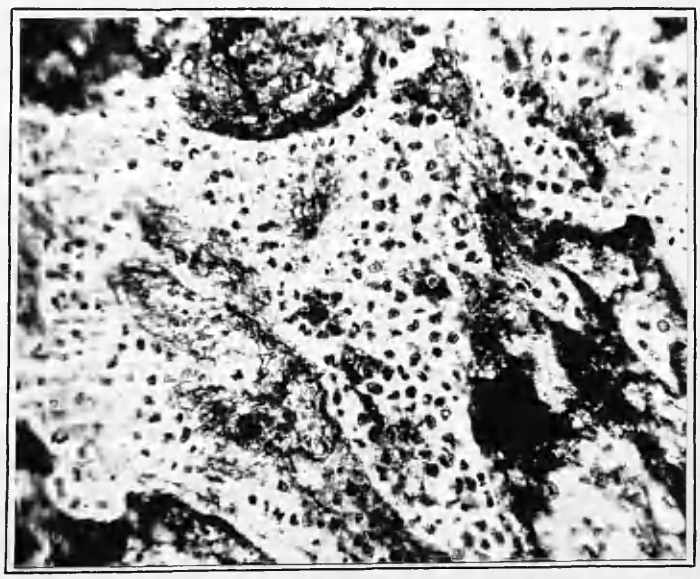


Fig. 178. Case 45. Clusters of polymorphs in the renal vein thrombus. They are partly degenerate, and the fibrin appears to be undergoing lysis. P.T.A.H. x 310.

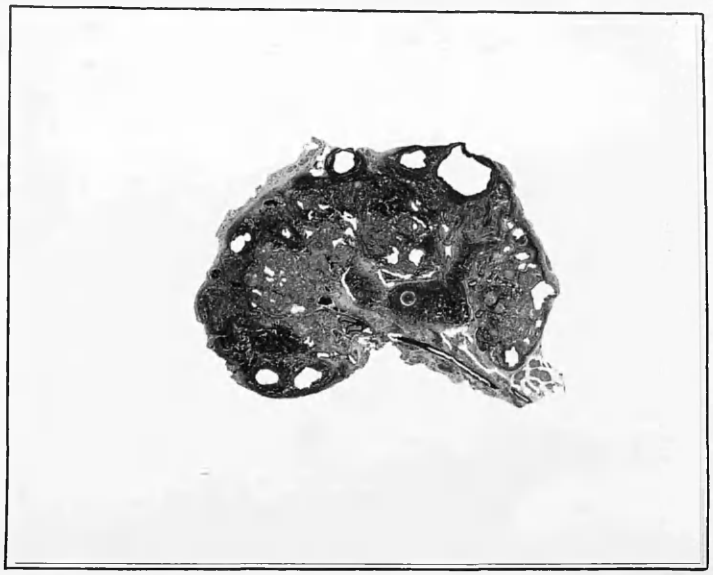


Fig. 179. Case 46. Hypoplastic cystic left kidney, showing no evidence of renal vein thrombosis. P.T.A.H. x 3.

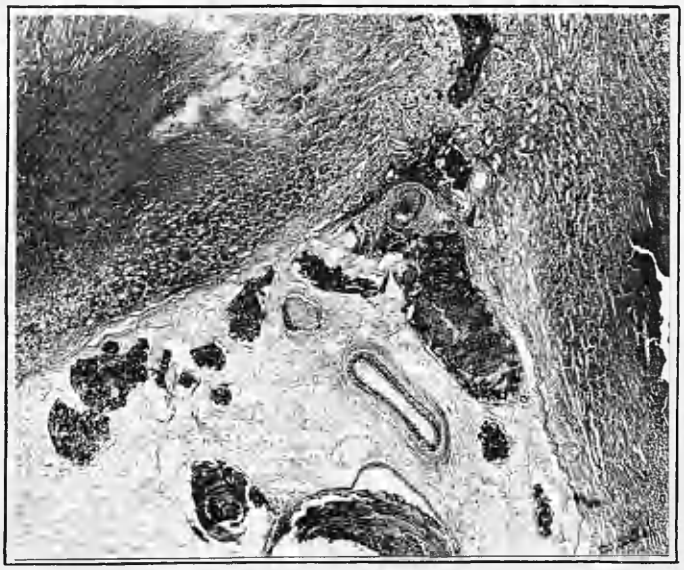


Fig. 180. Case 46. Laminated mixed renal vein thrombosis with haemorrhagic infarction of the right kidney. P.T.A.H. x 20.

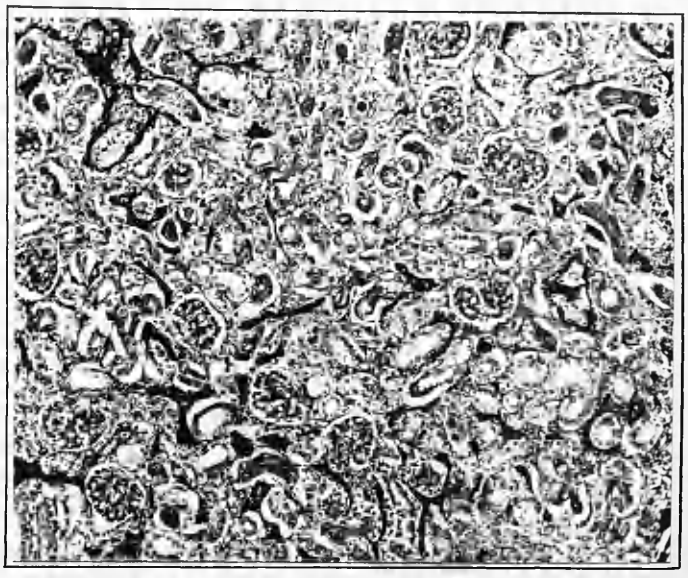


Fig. 181. Case 46. Widespread thrombosis in venules and inter-tubular capillaries. Evidence here and there of "mixed" constitution. P.T.A.H. x 95.

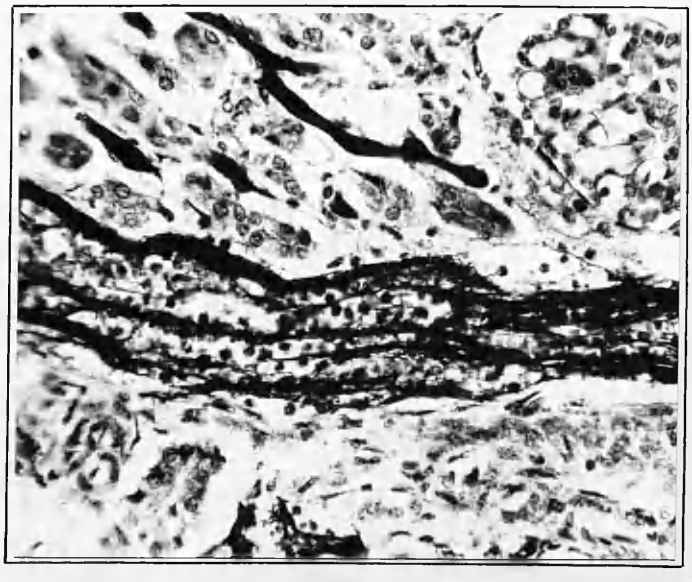


Fig. 182. Case 46. Antemortem renal thrombi, rich in fibrin in inter-tubular capillaries, but showing evidence of retraction in a larger vessel and with numerous polymorphs forming some laminae. P.T.A.H. x 310.

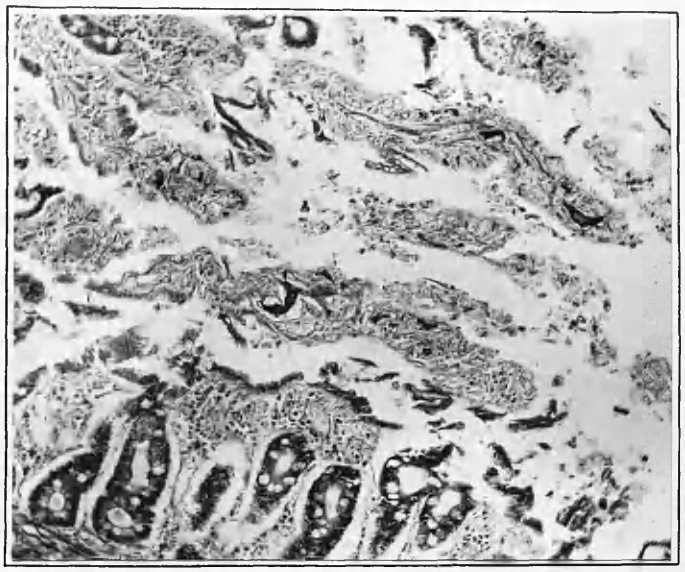


Fig. 183. Case 47. Capillary fibrin thrombi in intestinal villi denuded of their mucosa, but none where mucosa is reasonably intact. P.T.A.H. x 95.

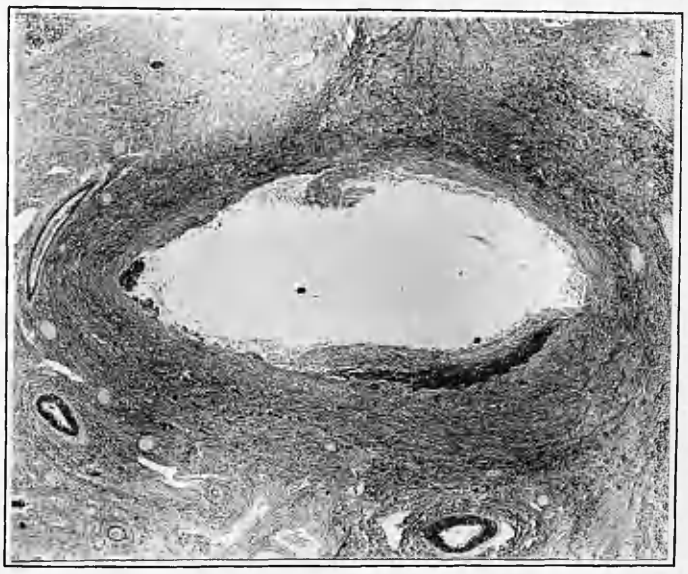
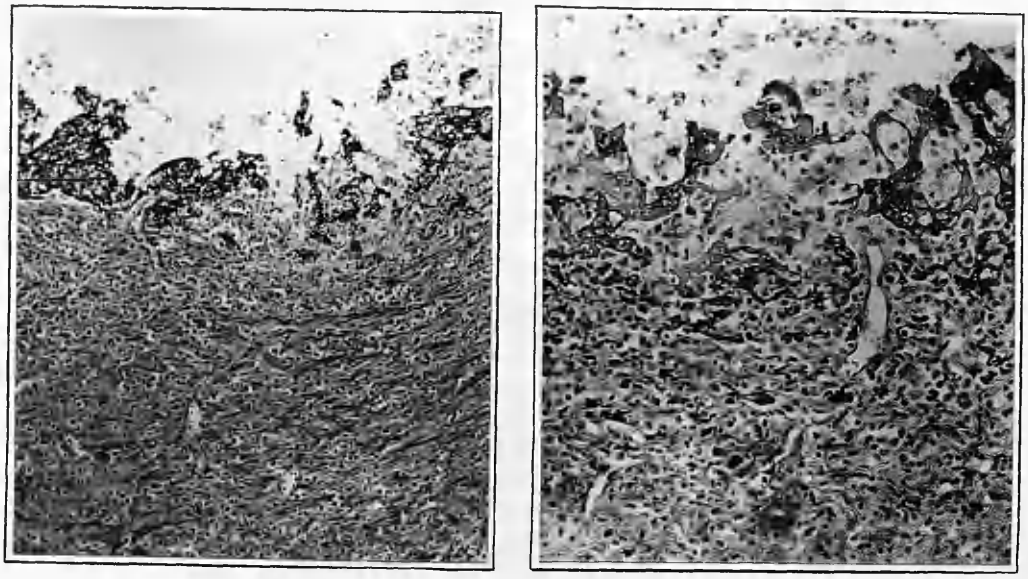


Fig. 184. Case 48. Low power view of portal vein showing tendency to laminated thrombus. P.T.A.H. x 20.



(a) (b)

Fig. 185. Case 48. Both (a) and (b) illustrate an acute pyogenic phlebitis of the umbilical vein with organisation of thrombus. P.T.A.H. (a) x 95. (b) x 170.

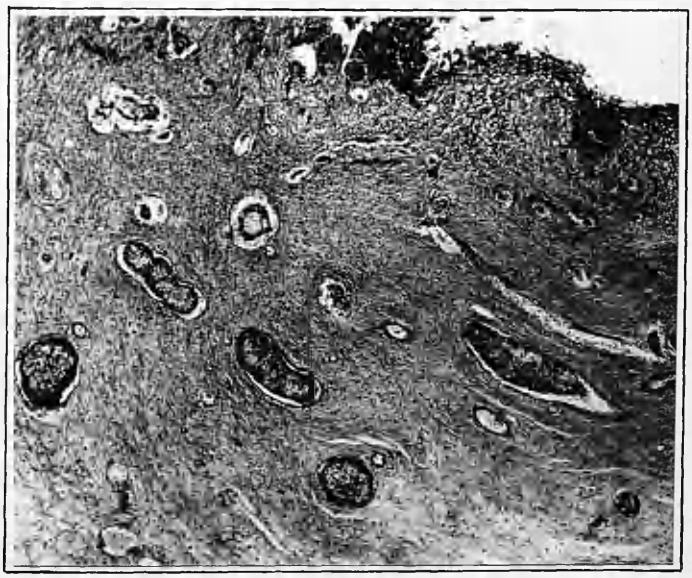


Fig. 186. Case 49. Wall of ectopia vesicae showing widespread antemortem mixed thrombi causing distension of vessels. P.T.A.H. x 45.

Fig. 187. Case 50. Wall of left ventricle showing the greatly thickened endocardium (fibro-elastosis). P.T.A. H. x 15.

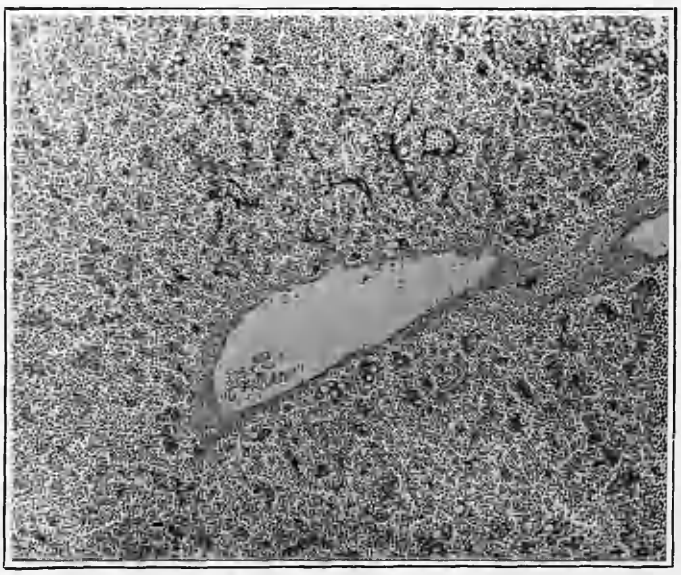


Fig. 188. Case 50. Liver showing intense venous congestion, marked fatty change, and scanty fibrin thrombi against the cords of liver cells. P.T.A.H. x 95.

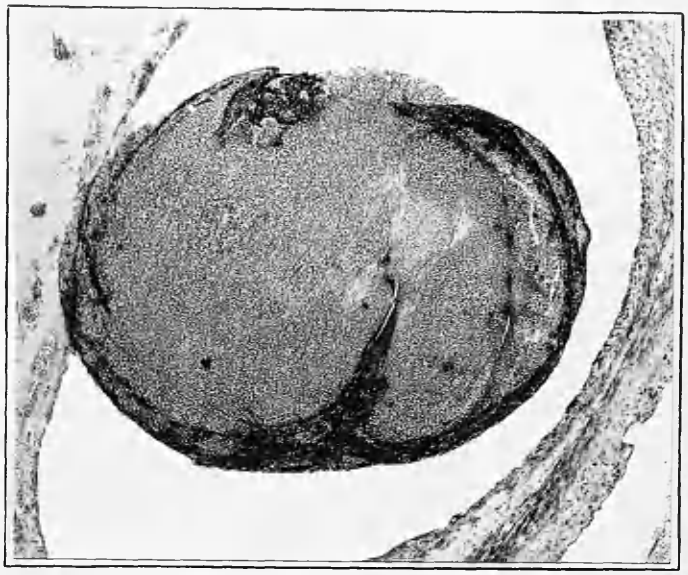


Fig. 189. Case 51. Antemortem mixed thrombus with laminated areas in superior mesenteric vein. P.T.A.H. x 45.

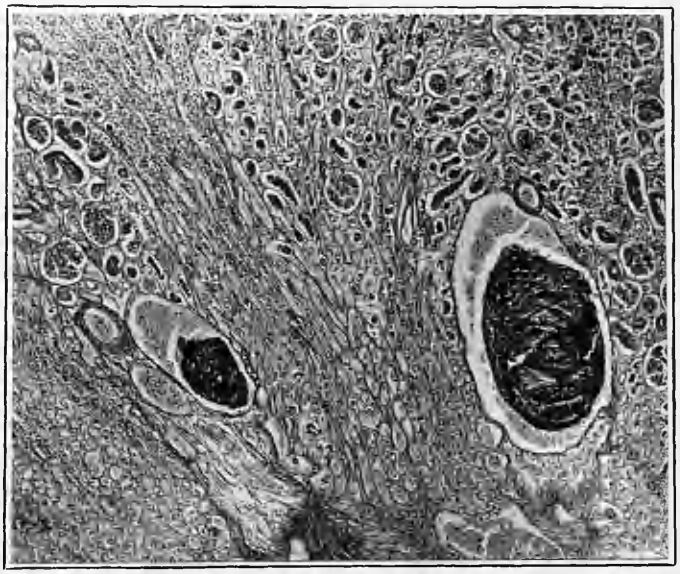


Fig. 190. Case 52. Laminated mixed thrombus rich in fibrin in arcuate veins of the left kidney. P.T.A.H. x 45.

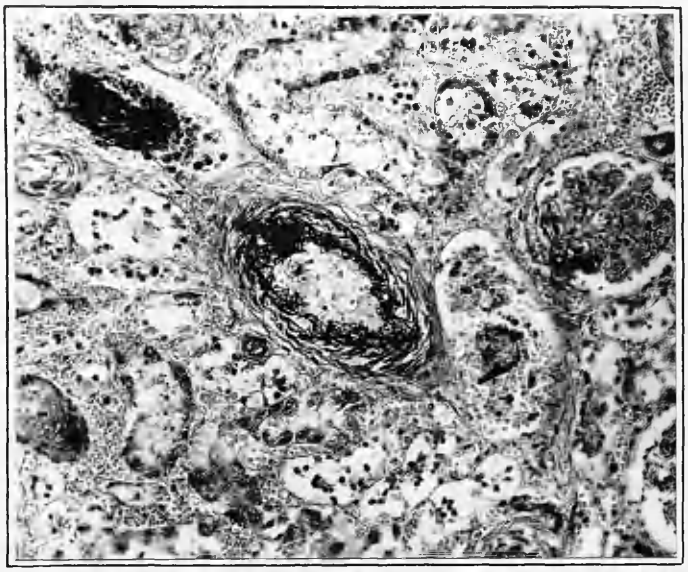


Fig. 191. Case 53. Renal arteriole cut almost transversely, and showing laminated fibrin thrombus against the endothelium. P.T.A.H. x 170.

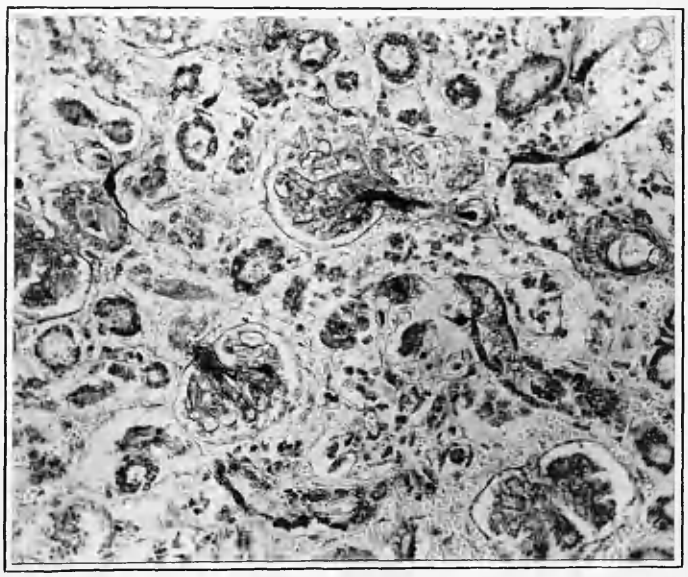


Fig. 192. Case 53. Renal glomerular fibrin thrombosis. P.T.A.H. x 170.

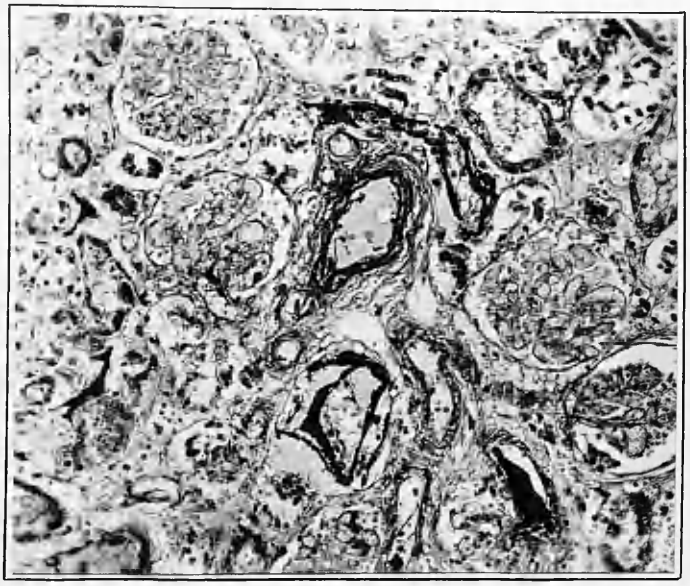


Fig. 193. Case 53. Interlobular vein cut transversely and showing retraction of fibrin thrombus from axial stream to peripheral stream. P.T.A.H. x 170.

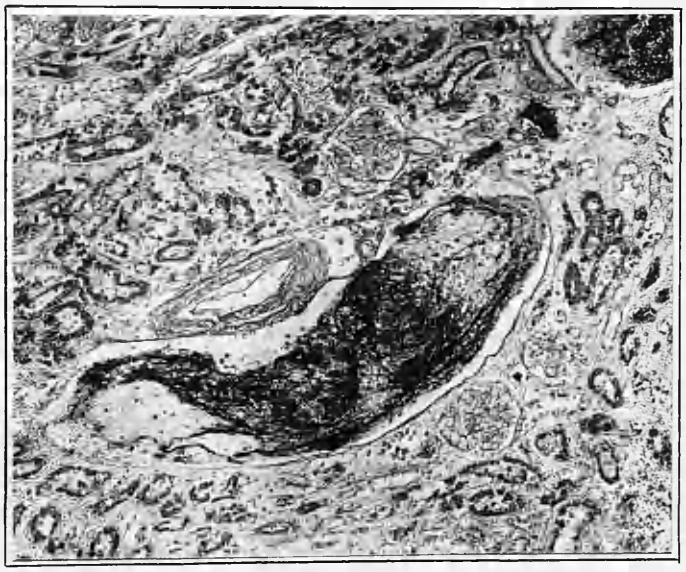
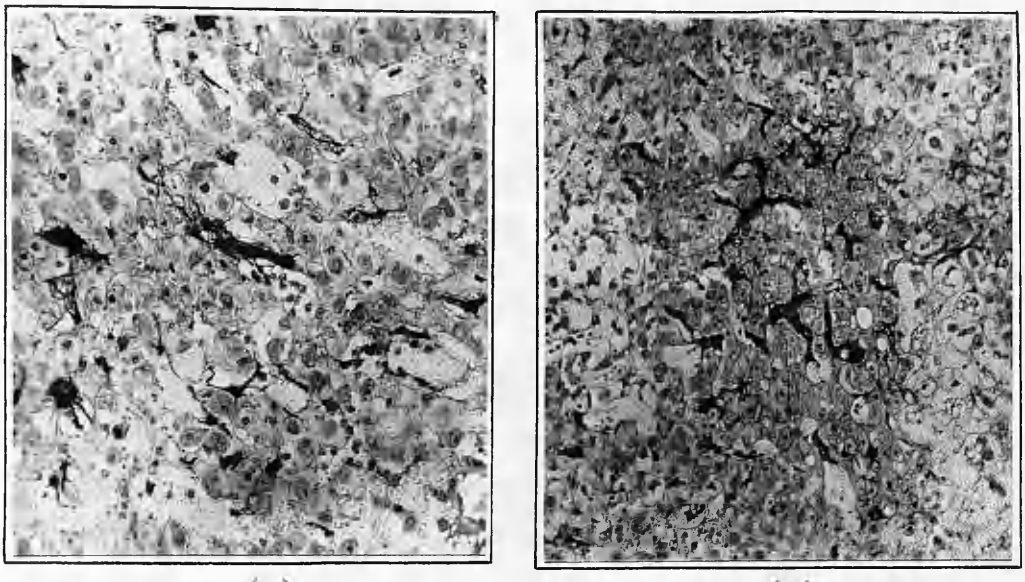


Fig. 194. Case 53. Recent mixed laminated renal vein thrombosis. P.T.A.H. x 95.



(a) (b)

Fig. 195. Case 53. (a) Fibrin thrombi in adrenal sinusoids retracted against sinusoid wall, and some with superadded recent thrombi. x 170. (b) More recent adrenal thrombi showing sinusoid collapse. x 95. P.T.A.H.

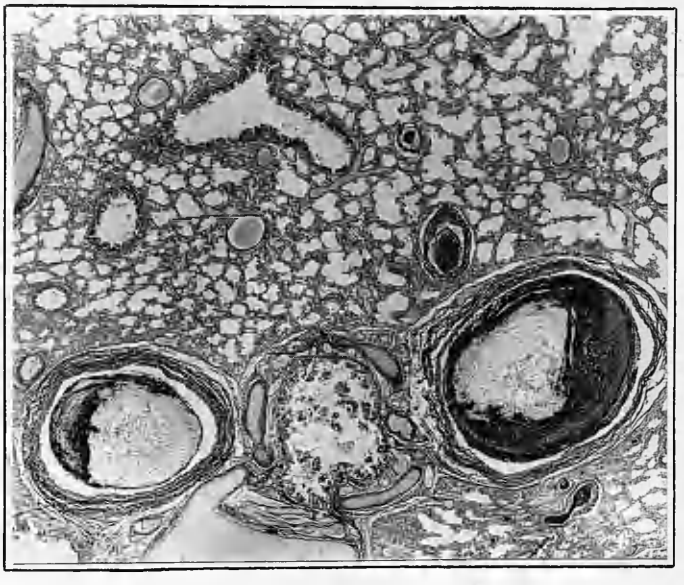


Fig. 196. Case 53. Mixed pulmonary embolism from the renal vein thrombosis. The emboli are in the axial stream. P.T.A.H. x 17.

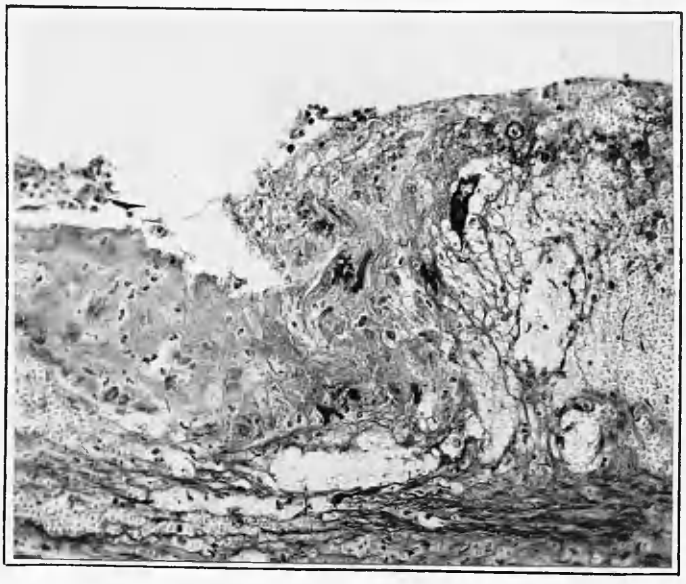


Fig. 197. Case 54. Capillary fibrin thrombi in gastric mucosa, and only in relation to the gastric erosion. P.T.A.H. x 170.

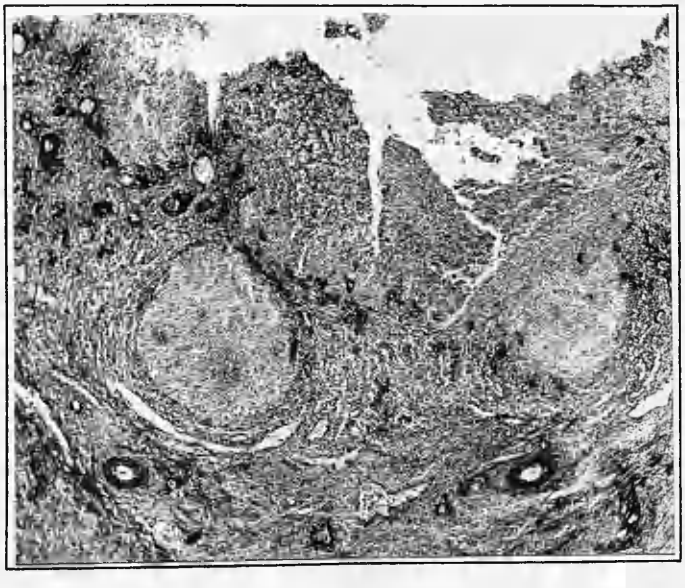


Fig. 198. Case 54. Sloughed mucosa near apex of intussusception, showing widespread fibrin thrombosis, some of considerable duration, and sparing the germinal follicles. P.T.A.H. x 45.

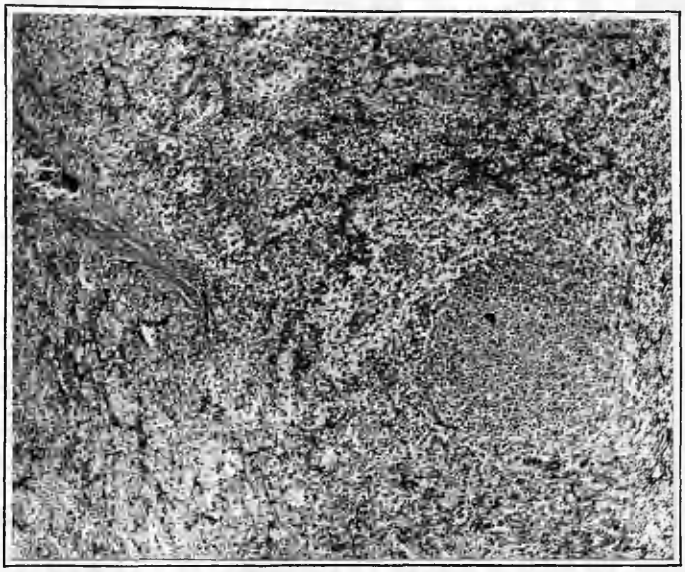
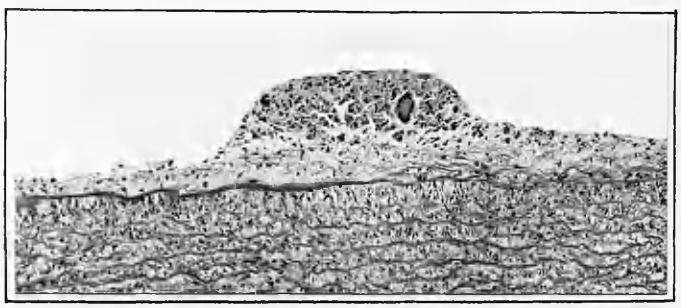
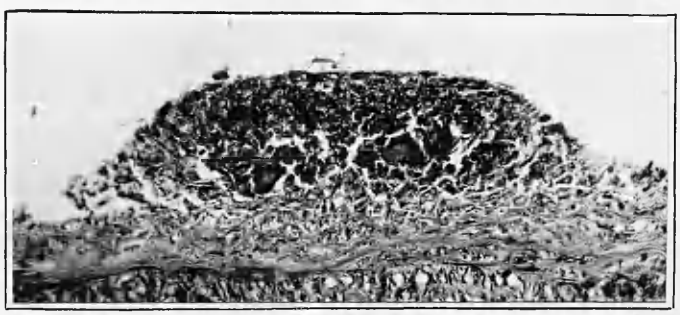


Fig. 199. Case 54. Splenic pulp showing widespread fibrin thrombosis, laminated at the left side, with moderate "softening" of the pulp. Malpighian corpuscles are spared. P.T.A.H. x 95.



(a)



(b)

Fig. 200. Case 55. (a) "Fatty" streak of the aorta. H. and E. x 95. (b) Duplicate section showing delicate fibrin network within the granuloma. P.T.A.H. x 170.

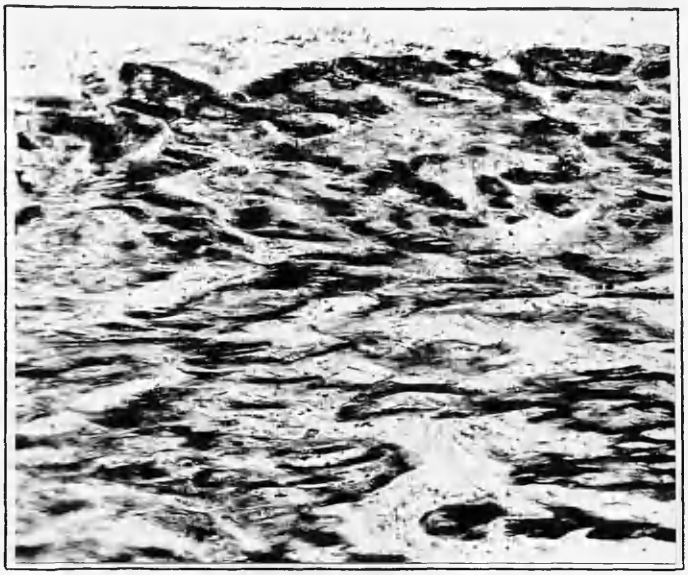


Fig. 201. Case 56. Severe loss of staining and striations, and "hyaline" change in myocardium. P.T.A.H. x 170.

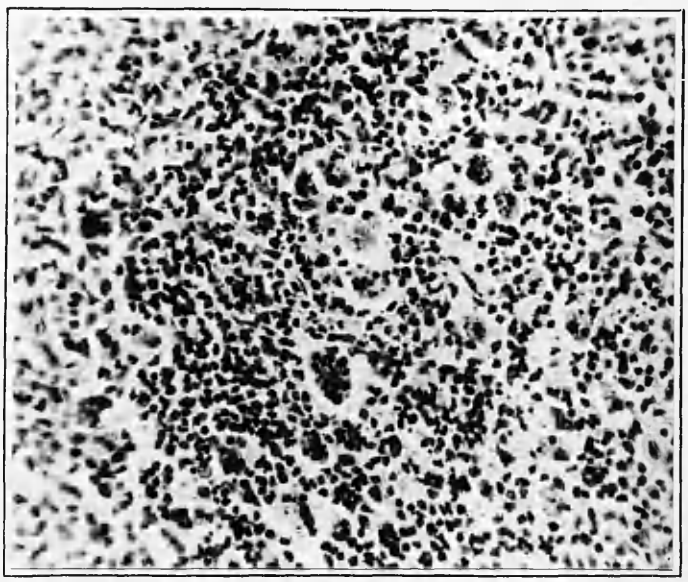


Fig. 202. Case 56. Warthin-Finkeldy giant cells of measles in Peyer's patch in ileum. H. and E. x 310.

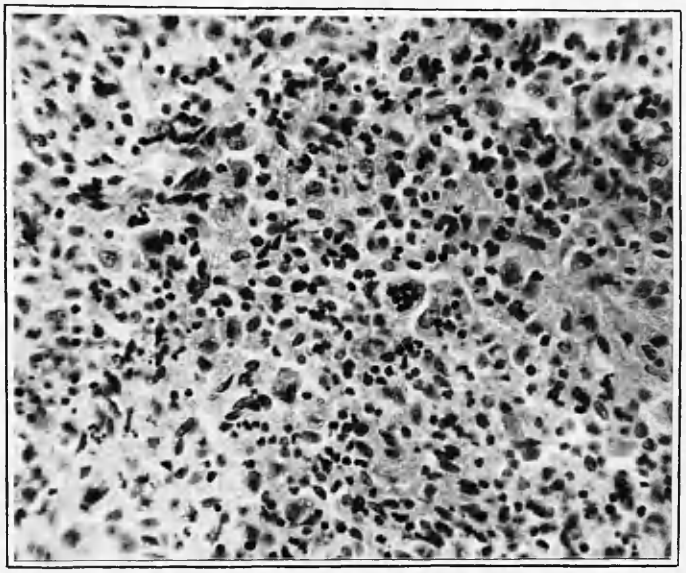


Fig. 203. Case 56. Warthin-Finkeldy giant cell in the spleen. H. and E. x 310.

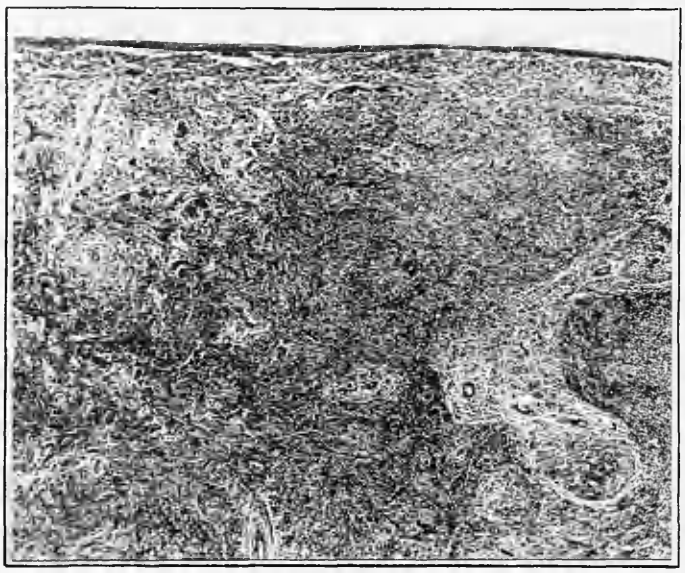


Fig. 204. Case 56. Spleen showing widespread sinusoidal fibrin thrombi (black), with sinusoidal collapse, and compensatory dilatation of unaffected ones. P.T.A.H. x 45.

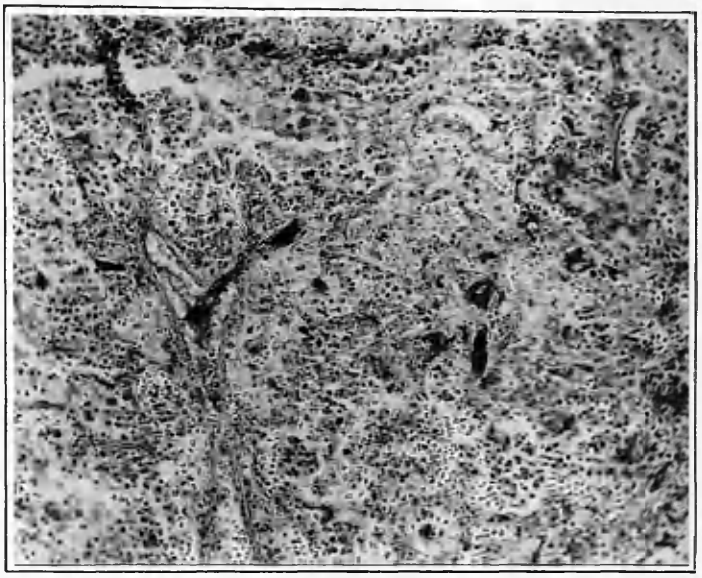


Fig. 205. Case 57. Mixed thrombi in lung vessels in relation to an area of suppuration. P.T.A.H. x 170.

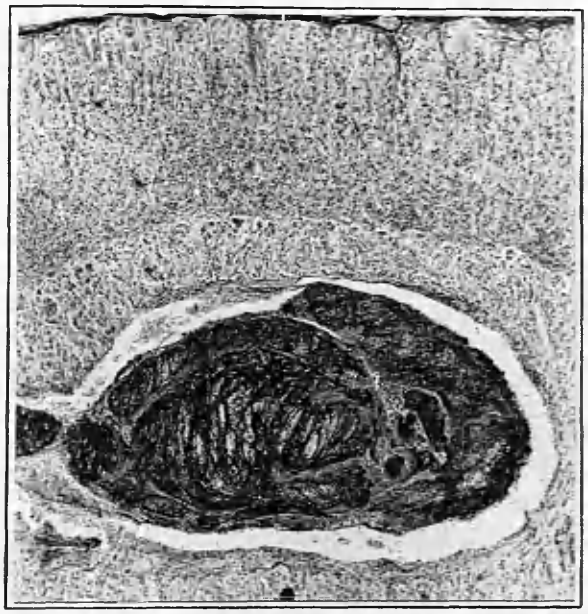


Fig. 206. Case 58. Mixed adrenal vein thrombosis, affecting medullary sinusoids in a patchy fasion. P.T.A.H. x 45.

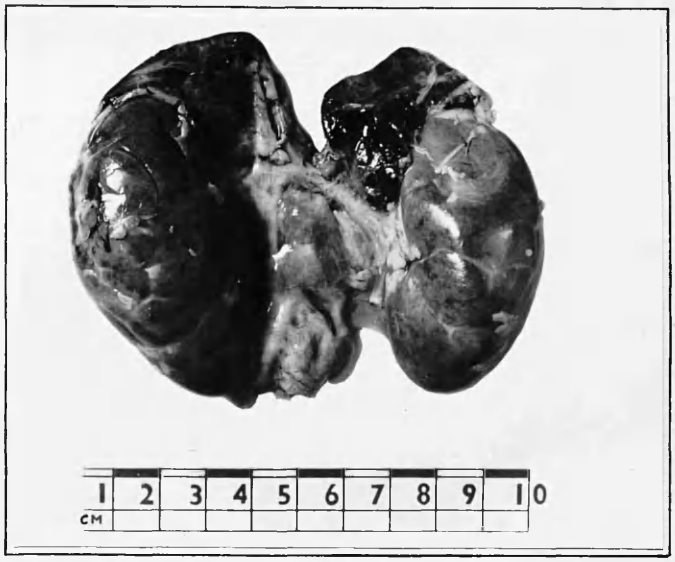



Fig. 207. Case 59. Haemorrhagic, but not swollen, adrenal glands. x $\frac{5}{8}$.

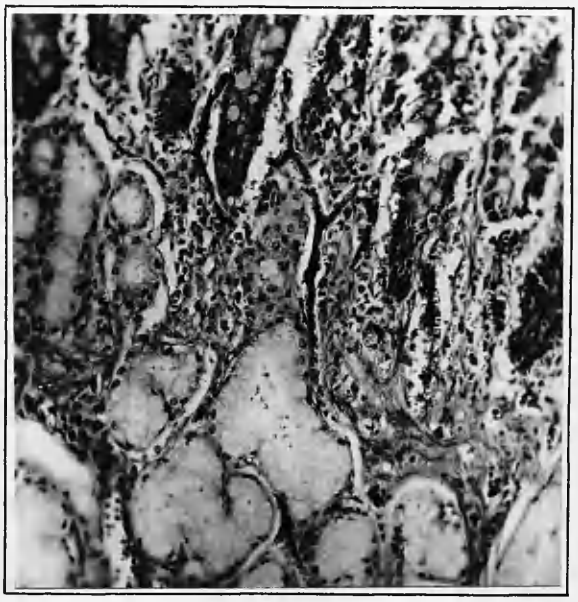


Fig. 208. Case 59. Fibrin thrombi of antemortem pattern in the vessels of the first part of the duodenum. P.T.A.H. x 170.

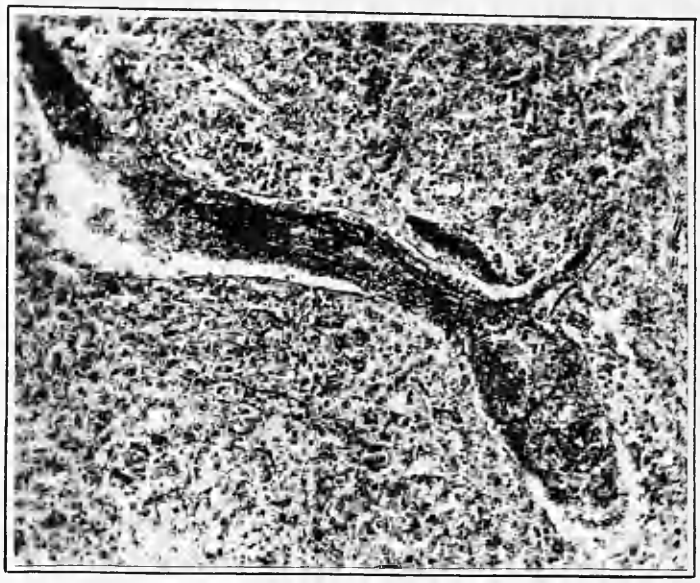


Fig. 209. Case 59. Antemortem mixed thrombus in a splenic sinusoid. P.T.A.H. x 170.

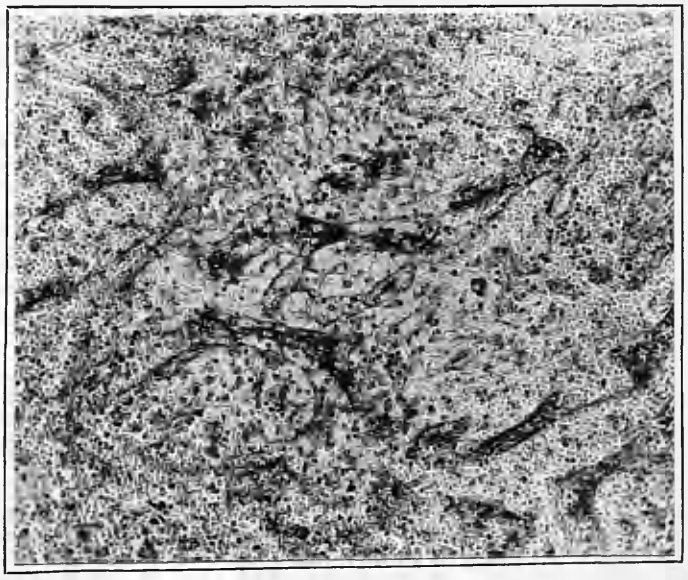


Fig. 210. Case 60. Antemortem thrombi in vessels of a very congested spleen. The thrombi show signs of retraction towards the vessel walls. P.T.A.H. x 170.

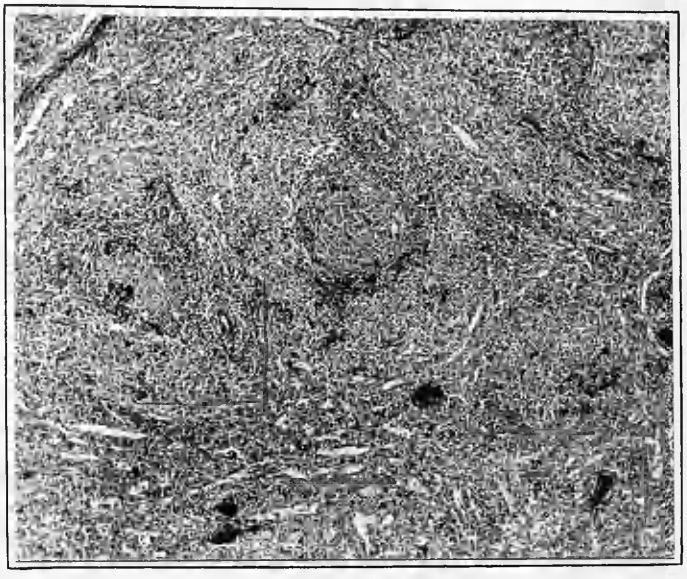


Fig. 211. Case 61. Thrombi in the spleen at the periphery of the Malpighian corpuscles, and occasionally in the sinusoids. P.T.A.H. x 45.

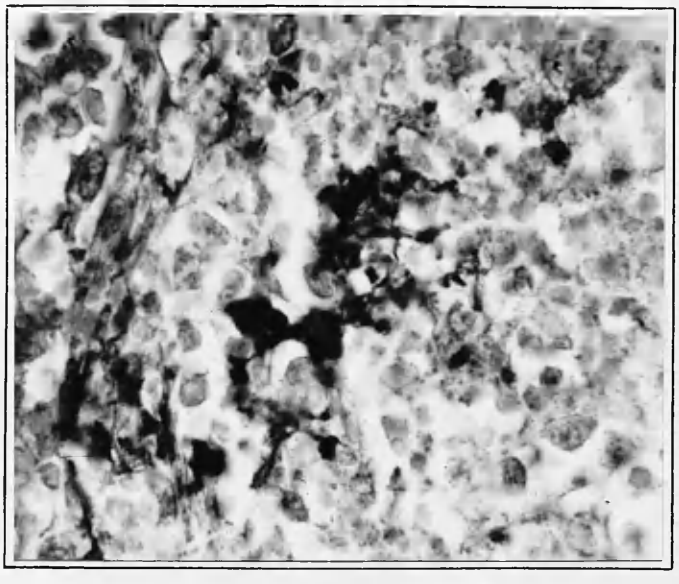


Fig. 212. Case 61. Fibrin thrombus with possible close association with haematoxyphil cocci. P.T.A.H. x 700.

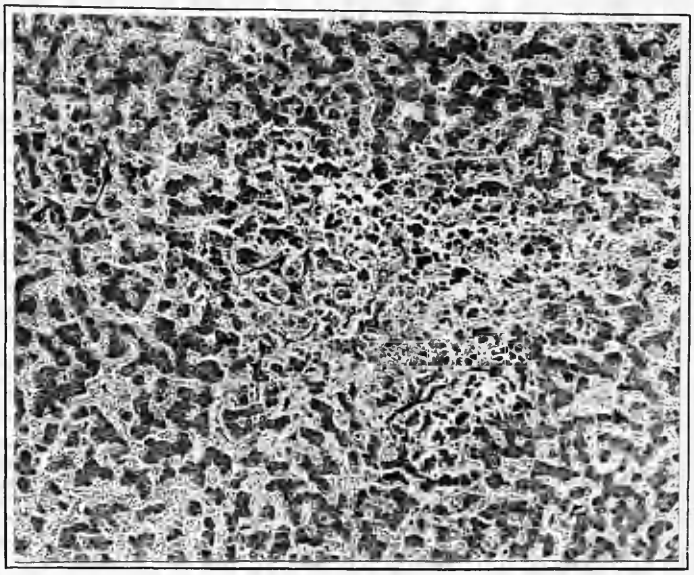


Fig. 213. Case 62. Centrilobular necrosis associated with antemortem fibrin thrombo-embolism in the liver sinusoids. P.T.A.H. x 95.

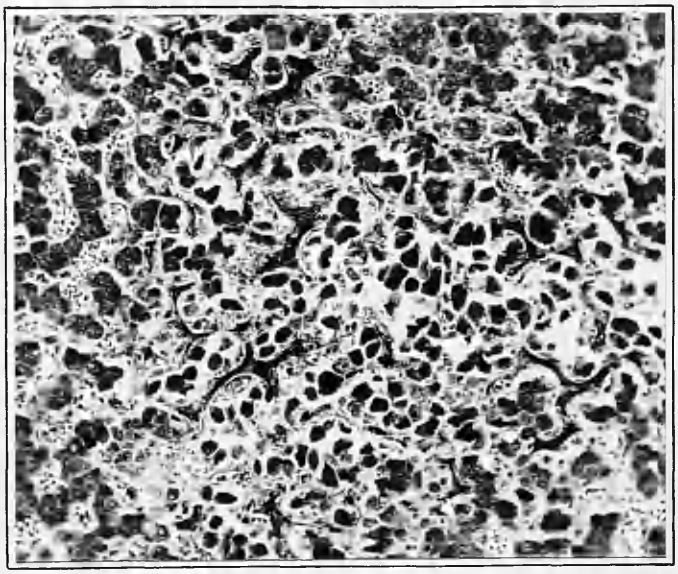


Fig. 214. Case 62. Antemortem liver sinusoidal thrombi rich in fibrin. P.T.A.H. x 170.

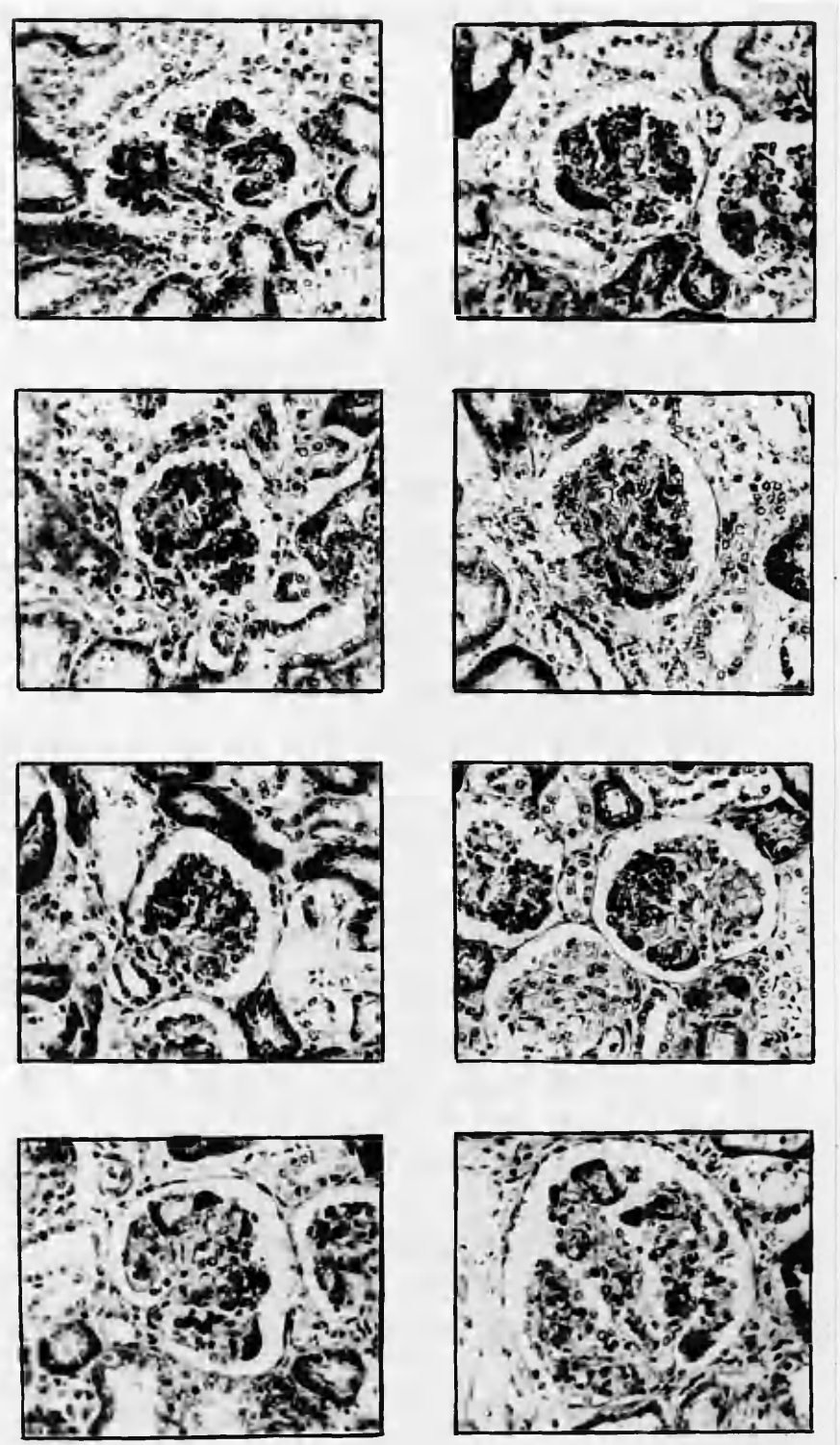


Fig. 215. Case 63. Renal glomerular capillary fibrin thrombi. P.T.A.H. x 206.

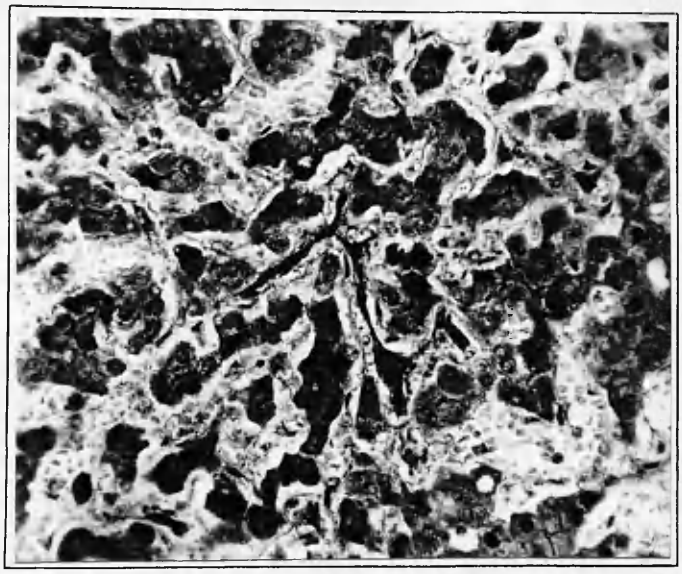


Fig. 216. Case 64. Delicate liver sinusoidal fibrin thrombi. P.T.A.H. x 310.

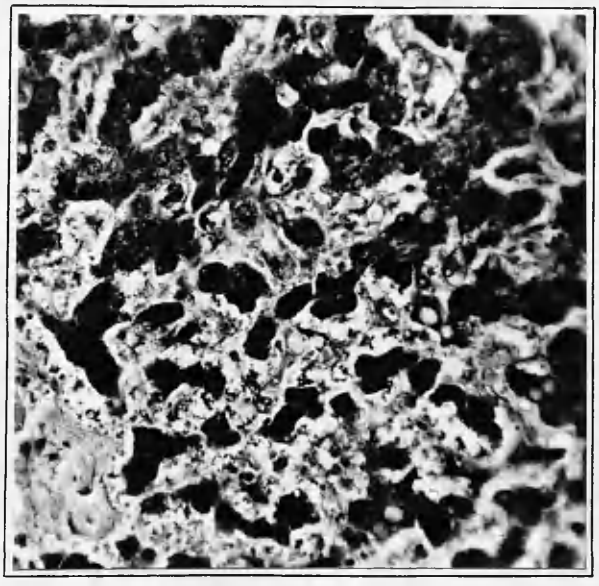


Fig. 217. Case 64. A focus of early centrilobular necrosis in relation to sinusoidal thrombi. The dark cells appear to be practically necrotic. P.T.A.H. 310.

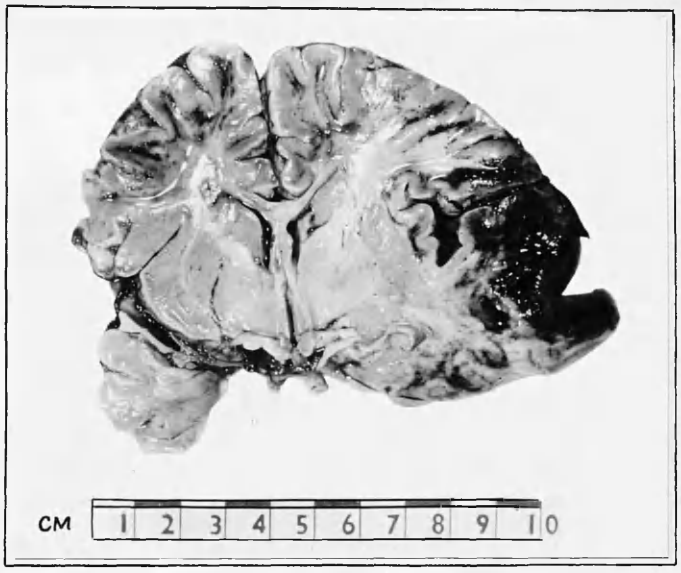



Fig. 218. Case 65. Haemorrhagic sub-cortical leuco-encephalopathy with large right temporal lobe red softening. x $\frac{5}{8}$.

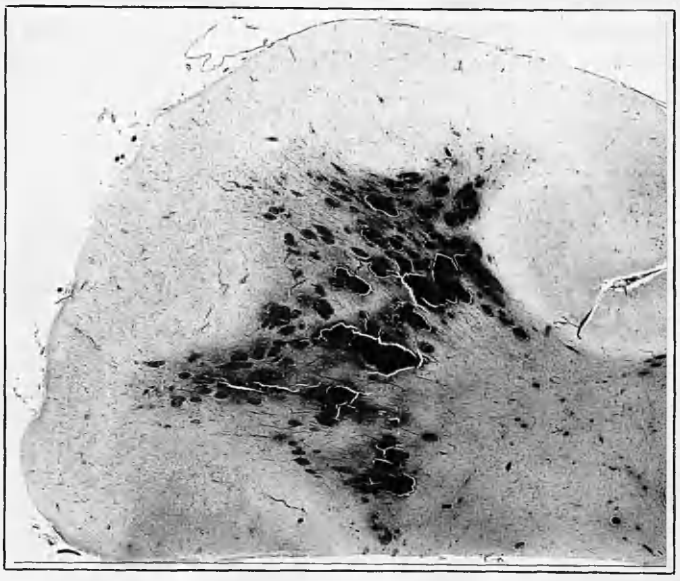


Fig. 219. Case 65. Many of the punctate haemorrhages (dark grey) show central fibrin thrombi (black). P.T.A.H. x $4\frac{1}{2}$.

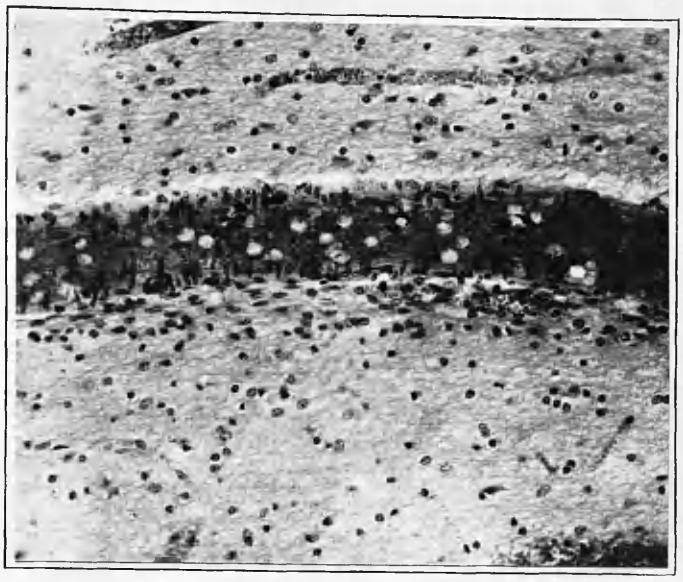
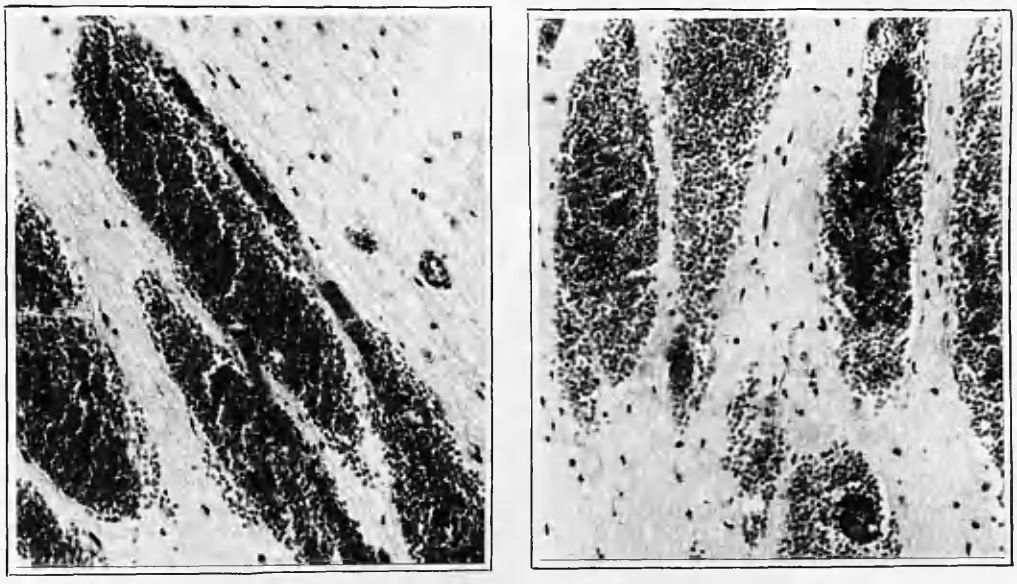


Fig. 220. Case 65. Early reactive gliosis in the neighbourhood of a cerebral arteriole. H. and E. x 170.



(a) (b)

Fig. 221. Case 65. (a) Fibrin strands visible because they are haematoxyphil (as are platelets), (b) others are visible because of formalin deposit. H. and E. x 170.

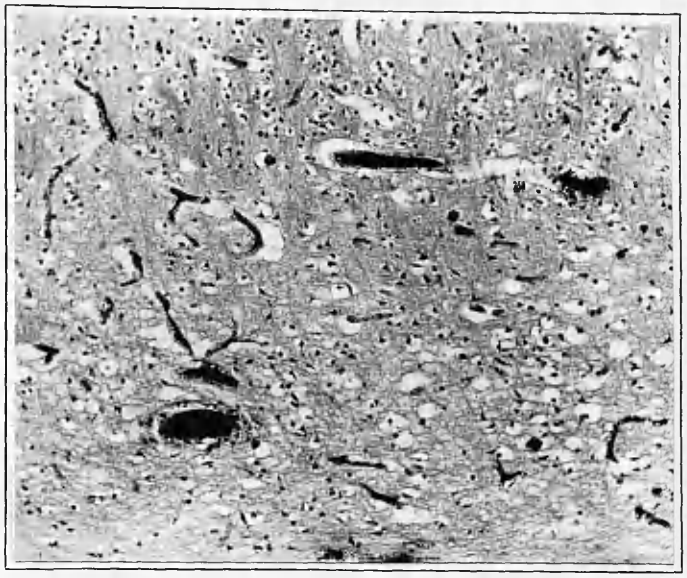


Fig. 222. Case 65. Widespread cortical and sub-cortical fibrin thrombosis. P.T.A.H. x 95.

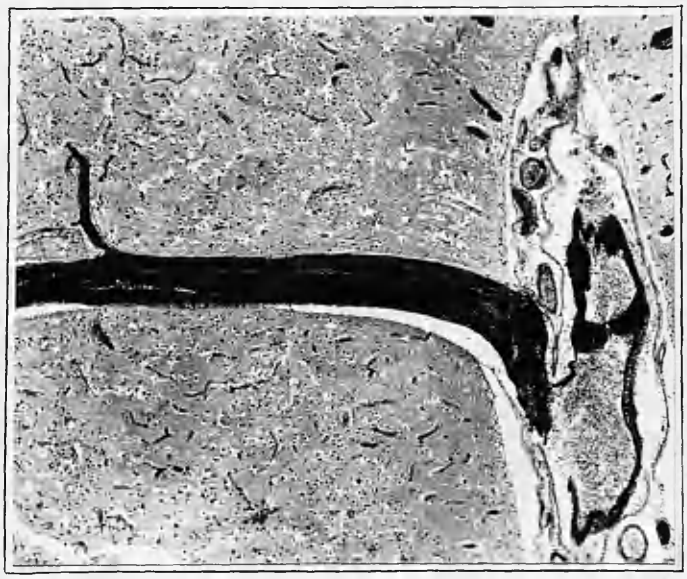


Fig. 223. Case 65. Laminated mixed thrombus rich in fibrin entering a cortical venous sinus. P.T.A.H. x 45.

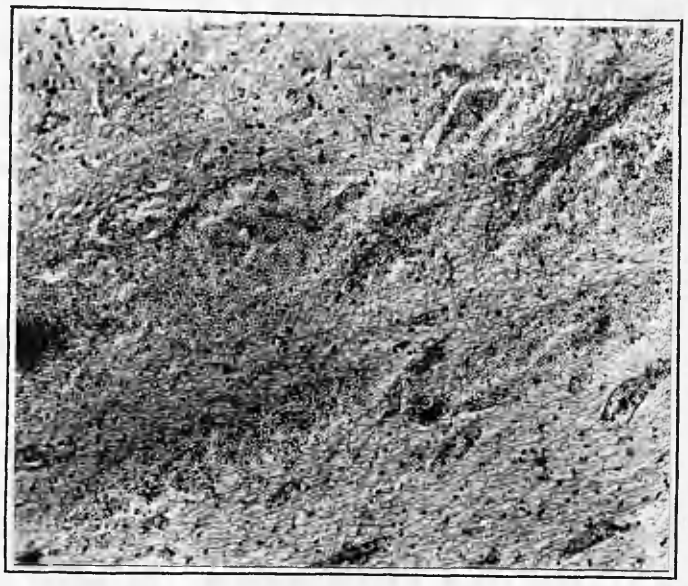
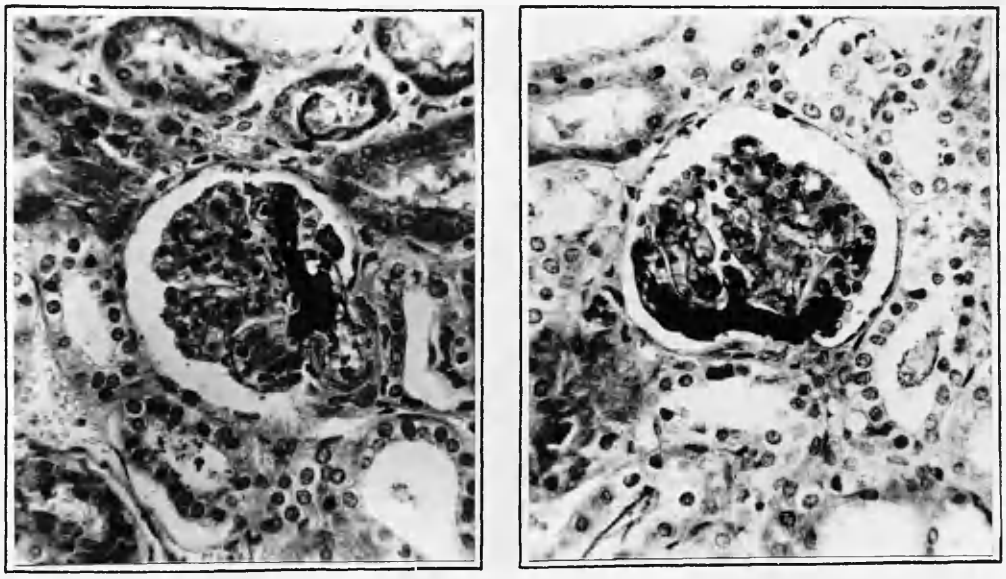


Fig. 224. Case 65. Margin of a cerebral haemorrhage elsewhere in this case, showing the absence of a fibrin network. P.T.A.H. x 95.



(a) (b)

Fig. 225. Case 65. Renal glomerular capillary fibrin thrombosis. P.T.A.H. x 310.

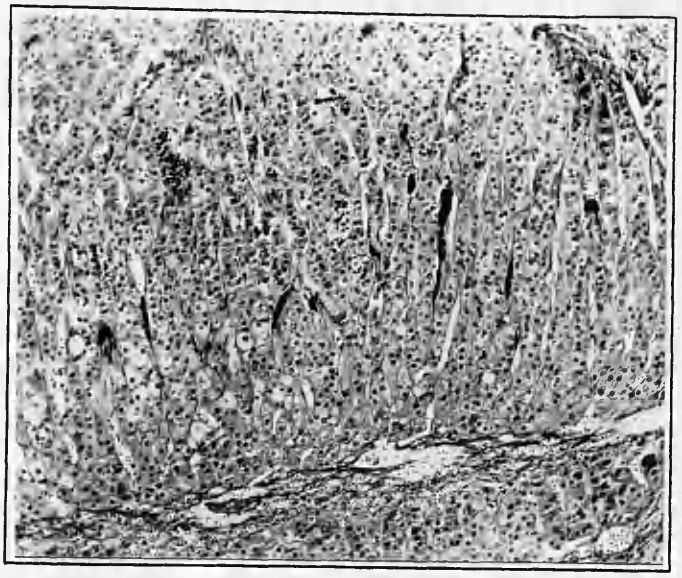


Fig. 226. Case 65. Antemortem fibrin thrombi in the adrenal cortical sinusoids. P.T.A.H. x 95.

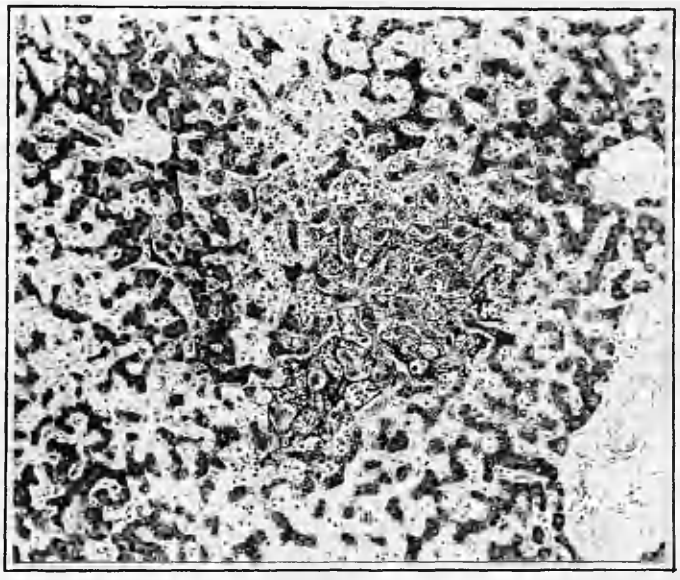


Fig. 227. Case 66. Liver sinusoid thrombi of mixed composition with focus of early necrosis. Unaffected sinusoids show great distension. P.T.A.H. x 95.

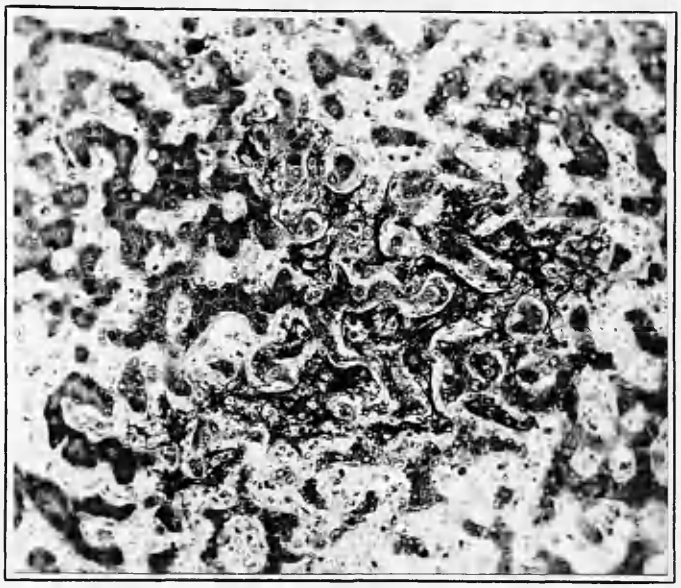


Fig. 228. Case 66. This shows the tendency of the main strands to vacate their axial position, and to lie against the sinusoid endothelium. P.T.A.H. x 170.

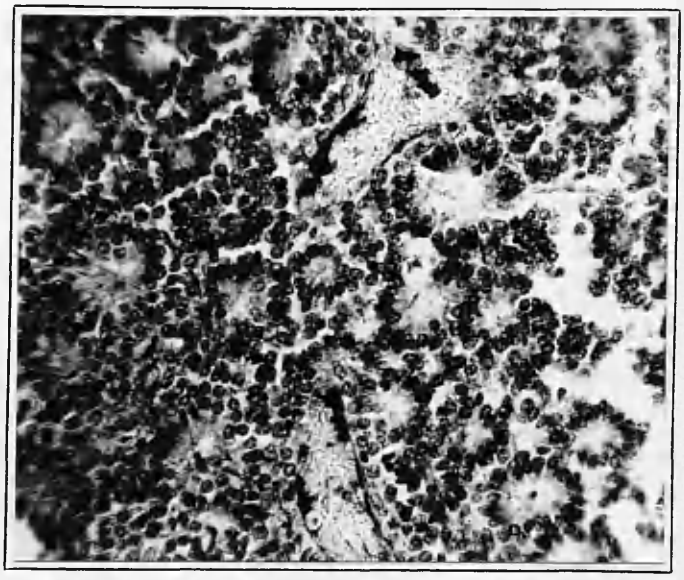


Fig. 229. Case 67. Retinoblastoma of right orbital fundus. Vessel along the middle field shows patchy calcification of its wall. P.T.A.H. x 310.

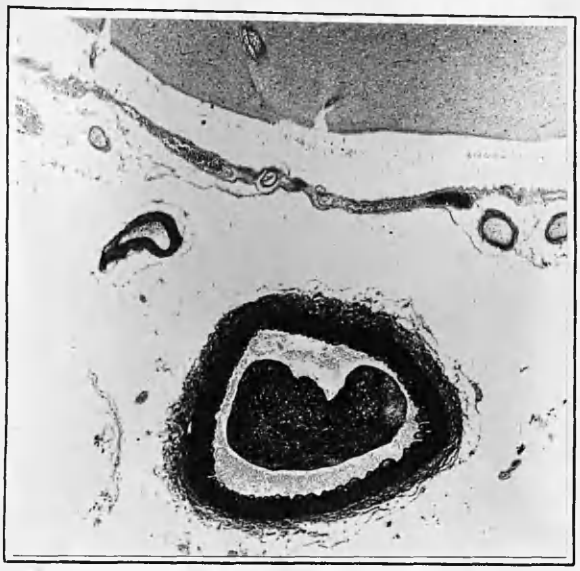


Fig. 230. Case 67. Antemortem mixed thrombosis of the basilar artery. P.T.A.H. x 25.

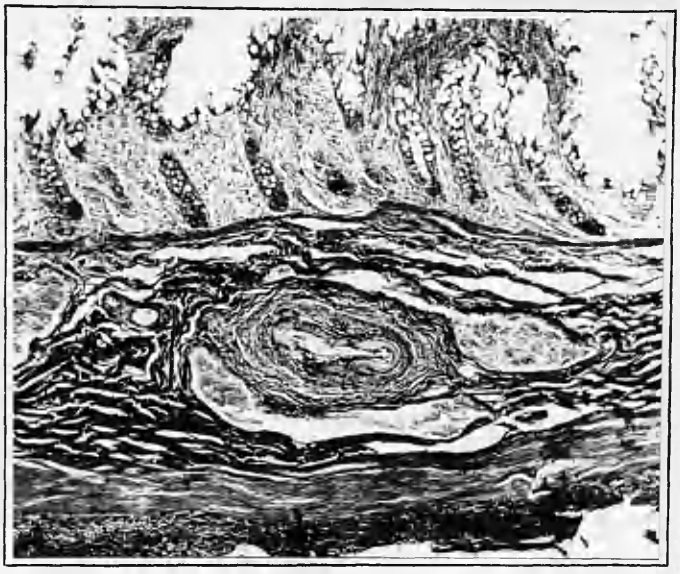


Fig. 231. Case 68. Intramural intestinal artery (centre) showing thickened intima with hyaline change, i.e. fibrin which has lost its staining properties. P.T.A.H. x 95.

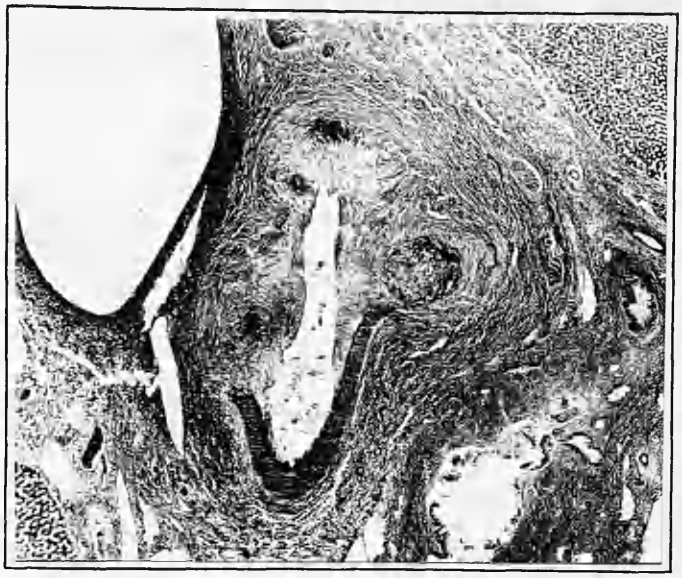


Fig. 232. Case 68. Hepatic artery showing more recent polyarteritis nodosa. Fibrin is stained deeply. P.T.A.H. x 25.

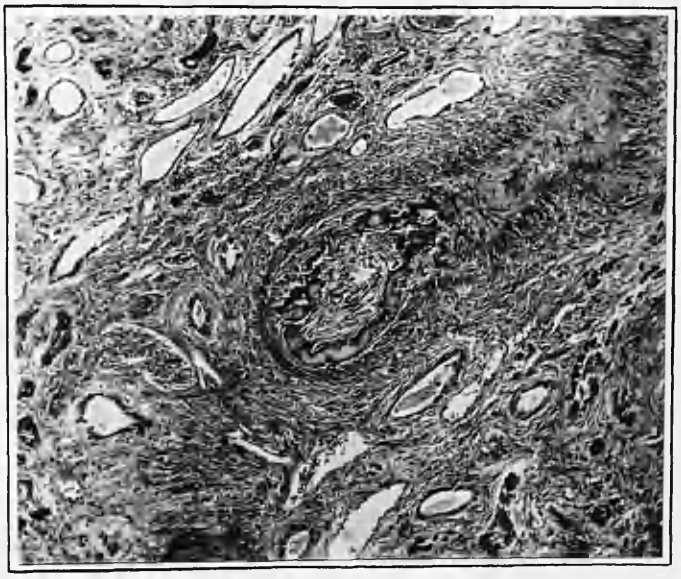


Fig. 233. Case 68. Oblique section of a straight artery of the renal cortex. Intimal thickening with almost total loss of staining of fibrin (thick wavy layer). P.T.A.H. x 95.

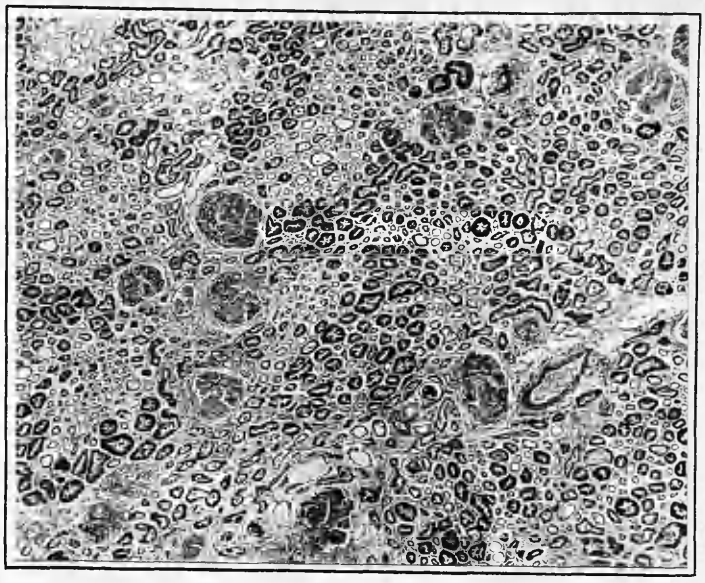


Fig. 234. Case 68. Acute, subacute and chronic renal glomerular damage. P.T.A.H. x 45.

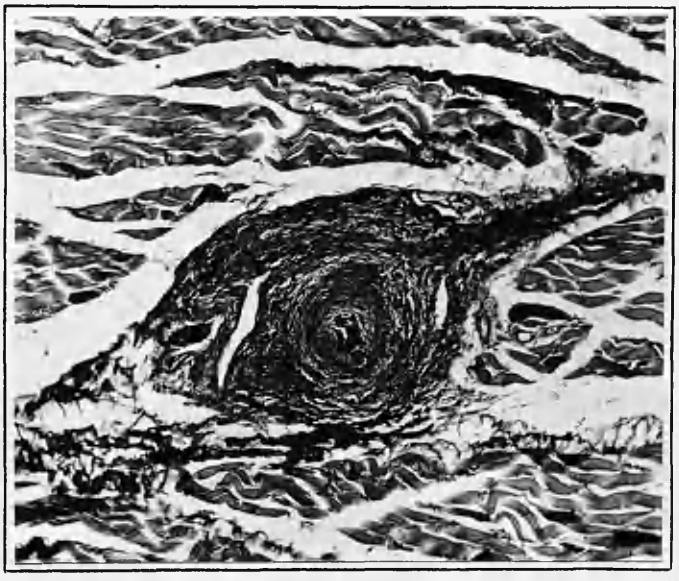


Fig. 235. Case 68. Polyarteritis in psoas muscle with well staining intimal fibrin, and widespread loss of staining of skeletal muscle fibres. P.T.A.H. x 95.

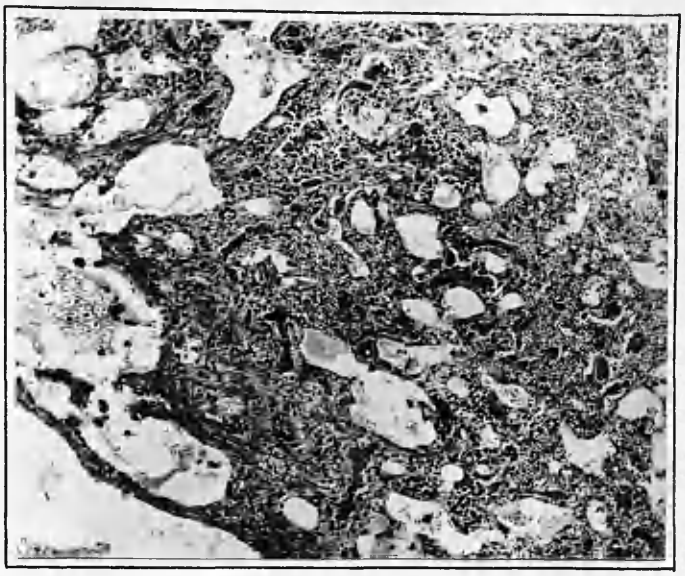


Fig. 236. Case 69. Cavernous sinusoidal channels with cords and clumps of liver cells (dark) in the surrounding rather fibrous stroma. P.T.A.H. x 95.

Fig. 237. Case 69. Necrotic zone in adenoma of liver with widespread sinusoidal thrombosis, and the fibrin strands show signs of retraction towards the side of the channels. P.T.A.H. x 95.

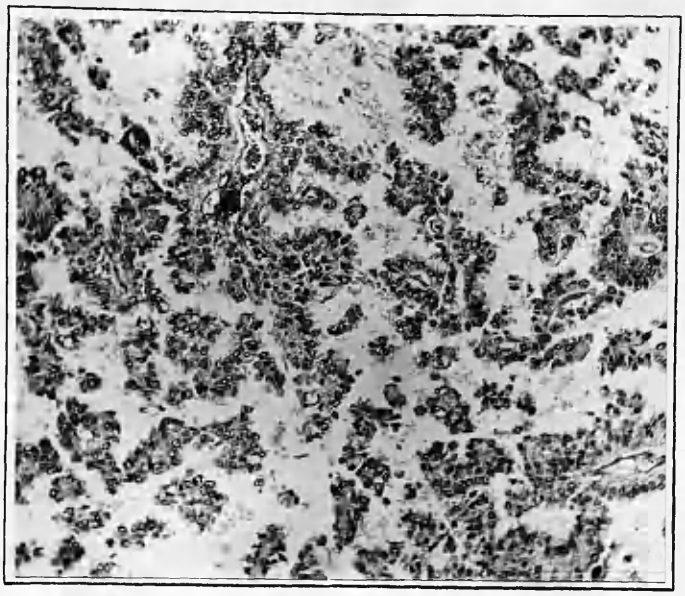


Fig. 238. Case 70. This shows the typical histological features of the tumour called a myxo-papillary sacro-coccygeal tumour. P.T.A.H. x 95.

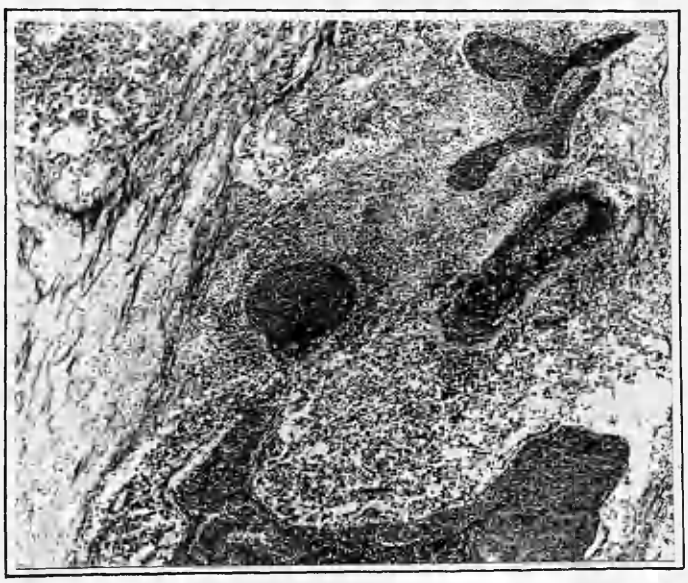


Fig. 239. Case 70. Section of the pelvic mass showing thrombosis in the vessels. P.T.A.H. x 45.

Fig. 240. Case 70. A small pulmonary nodule of secondary tumour showing moderately widespread capillary thrombosis. P.T.A.H. x 95.

Fig. 241. Case 70. Liver tissue compressed by a nodule of secondary tumour, and no evidence of sinusoidal thrombosis. P.T.A.H. x 95.

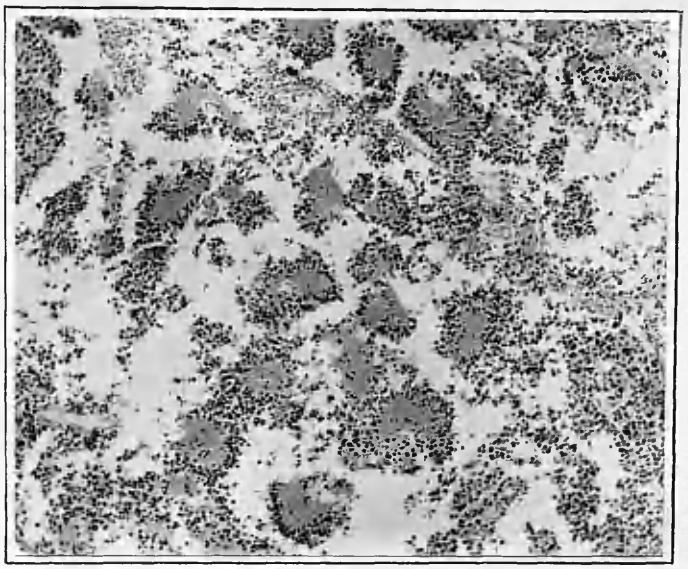


Fig. 242. Case 71. Metastatic neuroblastoma in para-aortic lymph node, showing rosette formations. P.T.A.H. x 95.

Fig. 243. Case 71. Section of the primary tumour showing widespread capillary thrombosis in relation to the tumour. P.T.A.H. x 95.

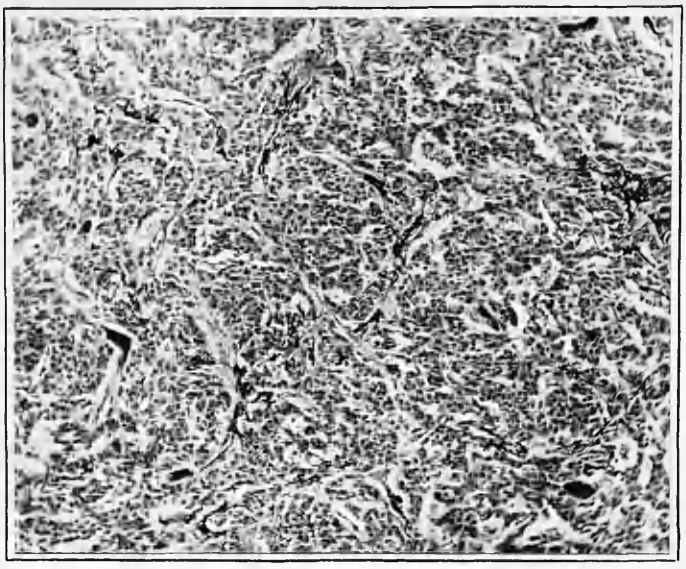


Fig. 244. Case 71. Hepatic metastasis showing widespread capillary thrombosis. P.T.A.H. x 95.

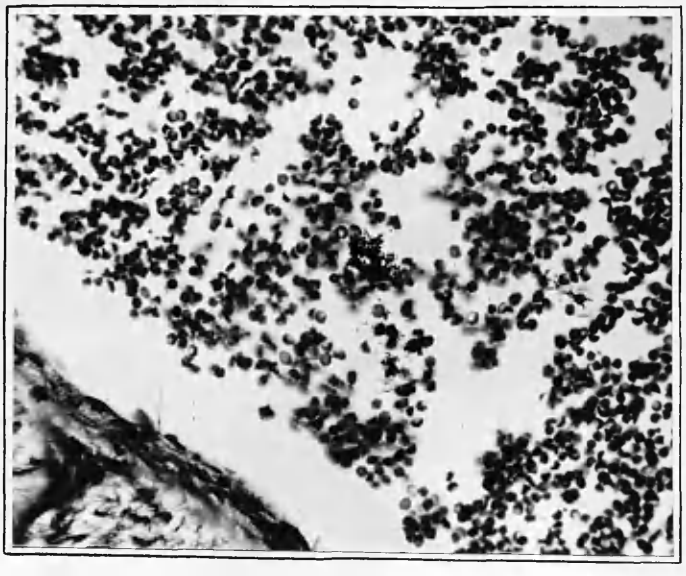


Fig. 245. A fine wisp of fibrin is present in the centre of the field. (1 point). P.T.A.H. x 310.

Fig. 246. A moderate sized wisp of fibrin. (3 points). P.T.A.H. x 170.

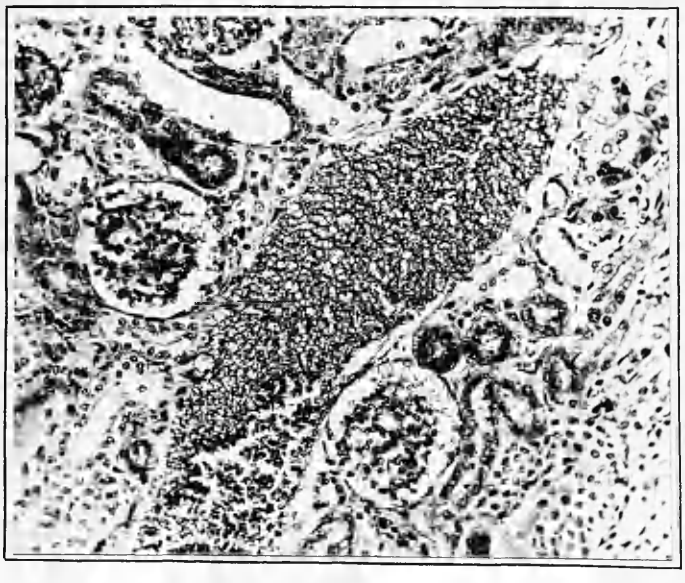


Fig. 247. A large fibrin clot. (6 points). P.T.A.H. x 170.

DATE: 5/4/58 Babies : Rapid Fibrinogen Method

*Means of 53 Results* : 0·124 ≡ 230 mg.%
σ : ± 0·062 ≡ ±79 mg.%
r : + 0·955
*Regression Equation* : $y = 1208x + 80$

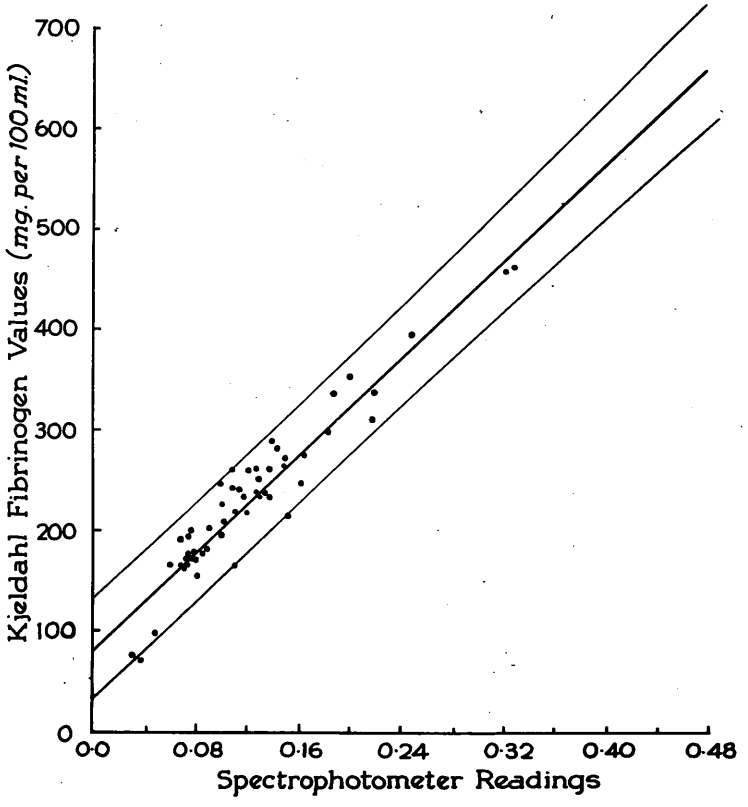



Fig. 248.

DATE : 5/4/58 Correlation of Kjeldahl Fibrinogen Values from Cord Blood and Heel Stab Sources

*Means of 39 Results* : *Cord* 237 mg.%. *Heel* 229 mg.%

$\sigma$ : ±76 mg.% ±88 mg.%

r : +0·846

*Regression Equation* : $y = 0{\cdot}981x - 3$.

—— *Actual graph*

----- *Expected graph*

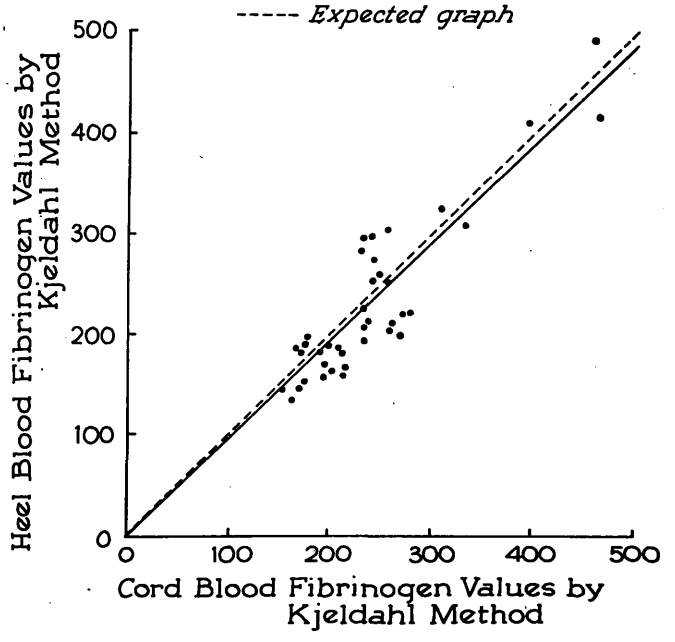



Fig. 249.

## TABLE I

### Blood Fibrinogen Levels of 13 Babies before Death.

| No. | Age | Cord | Fibrinogen Values (mg. per 100 ml.) Heel Blood Values (each column = one day) | Cause of Death |
|---|---|---|---|---|
| 72 | 9 days | 268 | 295 — — — — — — 80 — — ‖ | Prem: Early bro'pneumonia |
| 73 | ½ hour | 95 | ‖ | Cord round neck: Atelect. |
| 74 | 6 hours | — | 345 ‖ | Congenital heart disease |
| 75 | 1½hours | — | 350 190 ‖ | Congenital heart disease |
| ✓ 76 | 2 hours | 240 | ‖ — | Prem: Early bro'pneumonia |
| 77 | 3 hours | 70 | 195 ‖ | Atelectasis |
| 78 | 19hours | 260 | 140 ‖ | Prem: Atelect. Hyal. M. |
| 79 | 6 days | 125 | — 190 — — — — — ‖ | Intravent. Haem: Pneumon. |
| 80 | 2 days | 190 | — — ‖ | Atelectasis |
| 81 | 11hours | 135 | ‖ | Prem: Subepend. Haem. |
| ✓ 82 | 2½days | — | 335 — — ‖ — | Atelect. Marked H.M. |
| 83 | 14days | — | 250 — — — — — — — Died on 14th day ‖ | Arnold Chiari: Pneumonia |
| ✓ 84 | 1½hours | 410 | ‖ — | Blood loss: Vasa Praevia |

‖ = death.

TABLE II

Blood fibrinogen v. Histological Assessment of Intravascular Fibrin

| GROUPED ACCORDING TO LAST VALUE OBTAINED BEFORE DEATH | | | | |
|---|---|---|---|---|
| 0 - 99 mg.% | 100 - 199 mg.% | 200 - 299 mg.% | 300 - 399 mg.% | 400 - 499 mg.% |
| No.72 - 10 points | No.75 - 64 points | No.76 - 15 points + | No.74 - 134 points | No.84 - 15 points + |
| No.73 - 8 " | No.77 - 66 " | No.83 - 95 " | No.82 - 41 " + | |
| | No.78 - 47 " | | | |
| | No.79 - 56 " | | | |
| | No.80 - 38 " | | | |
| | No.81 - 50 " | | | |
| MEAN - 9 points | - 53 points | - 95 points | - 134 points | ?174 points |

+ See text concerning these three patients. (pp.196-197 )

## TABLE III

Mean Fibrinogen Values (mg. per 100 ml.). Rapid Method Only

| Fibrinogen | Premature (Sick) Babies | Mature (Normal) Babies | Mature (Sick) Babies |
|---|---|---|---|
| Cord Blood Values | 195 | 207 | 235 |
| S.D. | ±76 | ±69 | ±92 |
| No. of Observations | 42 | 101 | 81 |
| Heel Blood Values | 236 | 225 | 234 |
| S.D. | ±98 | ±78 | ±100 |
| No. of Observations | 70 | 100 | 166 |

TABLE IV

Incidence of All Thrombi (Antemortem, Agonal, Postmortem)

In 755 Stillbirths, Neonatal Deaths, Infants and Children

| ORGAN | STILLBIRTHS No. | STILLBIRTHS %+ | NEONATES living less than 48 hr. No. | NEONATES living less than 48 hr. %+ | NEONATES living more than 48 hr. No. | NEONATES living more than 48 hr. %+ | INFANTS and CHILDREN No. | INFANTS and CHILDREN %+ | TOTAL No. | TOTAL %+ |
|---|---|---|---|---|---|---|---|---|---|---|
| Thyroid | 2/17 | 12 | 2/21 | 10 | 5/42 | 12 | 7/13 | 54 | 16/93 | 17 |
| Lung | 13/282 | 5 | 22/121 | 18 | 30/85 | 35 | 14/75 | 19 | 79/563 | 14 |
| Adrenal | 18/201 | 9 | 17/114 | 15 | 9/80 | 11 | 9/70 | 13 | 53/465 | 11 |
| C.N.S. | 4/126 | 3 | 9/100 | 9 | 14/75 | 19 | 7/30 | 23 | 33/331 | 10 |
| Liver | 20/209 | 10 | 12/206 | 6 | 11/84 | 13 | 8/74 | 11 | 51/573 | 9 |
| Spleen | 3/78 | 4 | 0/52 | 0 | 9/77 | 12 | 10/54 | 19 | 22/261 | 8 |
| Pancreas | 0/110 | 0 | 10/91 | 11 | 10/81 | 12 | 6/67 | 4 | 23/348 | 7 |
| Intestine | 0/26 | 0 | 0/38 | 0 | 6/56 | 11 | 7/59 | 12 | 13/179 | 7 |
| Pituitary | 0/97 | 0 | 1/55 | 2 | 5/58 | 9 | 9/59 | 15 | 15/269 | 6 |
| Kidney | 7/185 | 4 | 5/102 | 5 | 9/84 | 11 | 6/48 | 13 | 27/419 | 6 |
| Coronary Vessels | 4/153 | 3 | 6/76 | 9 | 4/74 | 5 | 3/68 | 4 | 17/371 | 5 |
| Skin | 1/92 | 1 | 4/65 | 6 | 5/25 | 20 | 0/5 | 0 | 10/187 | 5 |

+ To the nearest whole number.

TABLE V

Varieties of Antemortem Thrombosis, and Cases Illustrating These

A. PURE FIBRIN

1. Origin in Utero and At Birth: Cases 1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14, 15, 16, 17, 18, 20, 21, 22, 23, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35+, 36, 37, 38+, 50.

2. Postnatal Origin: Cases 44, 53, 59, 62, 63, 64, 65.

B. MIXED THROMBI

1. Apparently Non-Infected Thrombi Related to Infection: Cases 39, 40, 42, 43+, 46+, 47, 54, 55, 56, 57, 60, 61, 66.

2. Infected Thrombi: Cases 19, 35+, 38+, 41, 43+, 45, 46+, 48.

3. Traumatic Thrombosis: Cases 10, 24, 49.

4. Thrombosis in Vessels of Tumours: Cases 69, 70, 71.

5. Thrombosis in Surgical Conditions: Cases 51, 52.

6. Thrombosis in Allergic Arteritis: Case 68.

7. Thrombosis of Unknown Aetiology: Cases 58, 67.

C. THROMBI OF OTHER BLOOD CONSTITUENTS

D. TUMOUR THROMBUS

Groups C and D are not considered in detail in this thesis.

+ Four Cases showing more than one variety of antemortem thrombus.

TABLE VI

Incidence of Antemortem Thrombosis

| CASES | No. WITH THROMBOSIS | TOTAL | PER CENT |
|---|---|---|---|
| A. Stillbirths | 10 | 331+ | 3.02 |
| B. Neonates dying in 48 hr. | 9 | 226 | 4.00 |
| C. Other Neonates | 33 | 119 | 27.73 |
| D. Infants and Children | 16 | 79+ | 20.25 |
| TOTAL | 68 | 755 | 9.01 |

+ 1 stillbirth showed thrombosis in an adenoma of liver, and 2 children showed thrombosis in relation to malignant tumours. (pp. 191-194 )

TABLE VII

Incidence of Antemortem Thrombi Among 68 Cases Showing These Thrombi

| ORGAN | STILLBIRTHS | | NEONATES living less than 48 hr. | | NEONATES living more than 48 hr. | | INFANTS and CHILDREN | | TOTAL | |
|---|---|---|---|---|---|---|---|---|---|---|
| | No. | %+ | No. | %+ | No. | %+ | No. | %+ | No. | %+ |
| Liver | 7/10 | 70 | 3/8 | 38 | 7/32 | 22 | 4/16 | 25 | 21/66 | 33 |
| Spleen | 1/6 | 17 | 0/6 | 0 | 8/26 | 31 | 5/15 | 33 | 14/53 | 26 |
| Lung | 0/9 | 0 | 3/9 | 33 | 10/33 | 30 | 3/15 | 20 | 16/63 | 25 |
| Adrenal | 1/7 | 14 | 4/7 | 57 | 5/30 | 17 | 3/14 | 21 | 13/58 | 22 |
| Kidney | 0/8 | 0 | 1/7 | 14 | 5/32 | 16 | 4/14 | 30 | 10/61 | 17 |
| Intestine | 0/3 | 0 | 0/3 | 0 | 3/19 | 15 | 3/11 | 27 | 6/36 | 17 |
| C.N.S. | 0/4 | 0 | 1/7 | 14 | 5/27 | 18 | 2/12 | 17 | 8/50 | 16 |
| Pancreas | 0/5 | 0 | 0/5 | 0 | 1/26 | 4 | 1/12 | 8 | 2/48 | 4 |
| Coronary Vessels | 0/6 | 0 | 1/5 | 20 | 0/24 | 0 | 1/15 | 7 | 2/50 | 4 |
| Thyroid | 0/1 | 0 | 1/3 | 33 | 0/14 | 0 | 0/12 | 0 | 1/30 | 3 |
| Pituitary | 0/4 | 0 | 0/2 | 0 | 1/21 | 5 | 0/13 | 0 | 1/30 | 3 |

+ To the nearest whole number.

TABLE VIII

Relationship of Antemortem Thrombosis to Death in 68 Cases

| | Causal | Partly Causal | Non-Causal | Total |
|---|---|---|---|---|
| STILLBIRTHS | Case 3 | Cases 1,2,4,7,8, | Cases 5,6,9,10, | |
| No. | 1 | 5 | 4 | 10 |
| EARLY NEONATAL DEATHS | Cases 11,12, 14,15,18, | Cases 13,16, | Cases 17,19, | |
| No. | 5 | 2 | 2 | 9 |
| LATE NEONATAL DEATHS | Cases 20,21, 22,23,27,32, 33,45,46, | Cases 24,26,28, 29,30,31,34,35, 50,51, | Cases 25,36,37, 38,39,40,41,42, 43,44,47,48,49,52, | |
| No. | 9 | 10 | 14 | 33 |
| INFANTS AND CHILDREN | | Cases 53,54,59, 63,64,65,66,68, | Cases 55,56,57, 58,60,61,62,67, | |
| No. | 0 | 8 | 8 | 16 |
| TOTAL | 15 | 25 | 28 | 68 |

TABLE IX

Incidence of Pure Fibrin Thrombi in 43 Cases* with This Feature

| ORGAN | STILLBIRTHS No. | STILLBIRTHS %+ | NEONATES living less than 48 hr. No. | NEONATES living less than 48 hr. %+ | NEONATES living more than 48 hr. No. | NEONATES living more than 48 hr. %+ | INFANTS and CHILDREN No. | INFANTS and CHILDREN %+ | TOTAL No. | TOTAL %+ |
|---|---|---|---|---|---|---|---|---|---|---|
| Liver | 7/9 | 78 | 2/7 | 29 | 5/19 | 26 | 2/5 | 40 | 16/40 | 40 |
| Adrenal | 1/6 | 17 | 4/6 | 67 | 4/18 | 22 | 1/4 | 25 | 10/34 | 30 |
| Lung | 0/8 | 0 | 3/8 | 38 | 7/20 | 35 | 1/5 | 20 | 11/41 | 28 |
| C.N.S. | 0/3 | 0 | 1/6 | 17 | 4/15 | 27 | 1/3 | 33 | 6/27 | 22 |
| Spleen | 1/4 | 25 | 0/6 | 0 | 6/14 | 43 | 0/5 | 0 | 7/29 | 21 |
| Intestine | 0/2 | 0 | 0/1 | 0 | 2/9 | 22 | 1/2 | 50 | 3/14 | 21 |
| Kidney | 0/7 | 0 | 1/6 | 17 | 1/19 | 5 | 3/4 | 75 | 5/36 | 14 |
| Thyroid | 0/1 | 0 | 1/3 | 33 | 0/8 | 0 | 0/4 | 0 | 1/16 | 6 |
| Pituitary | 0/3 | 0 | 0/2 | 0 | 1/11 | 9 | 0/4 | 0 | 1/20 | 5 |

\+ To the nearest whole number.

* Cases 1 - 9; 11 - 18; 20 - 23, 25 - 38, 44, 50; 53, 59, and 62 - 65 inclusive.

TABLE X

Time-table of the Organisation of Thrombi

1) Weeks 1 and 2 - thrombi remain unaltered in shape or position. Cases 1 - 2, 4 - 8, 11, 12, 14 - 18, 20 - 31, and 45.

2) Week 3 - retraction of thrombi towards vessel wall; early phase of "fibrinous vasculosis" of Lendrum; ? no vital response required (see text p. ) Cases 3, 13, 33 - 35, 46 and 50.

3) Week 4 - endothelial proliferation and re-canalisation of thrombus; late phase of "fibrinous vasculosis"; Cases 9, 32, 37 and 38.

4) - loss of staining properties of fibrin commences; some time after the fourth week since none of the above cases show this.

5) - loss of staining properties of fibrin is complete by the twelfth week at the latest. Case 68.

TABLE XI

Condition during Pregnancy of 43 Mothers Whose Infants showed Pure Fibrin Thrombi

| CONDITION | STILLBORN INFANTS Cases | NEONATES living less than 48 hr. Cases | NEONATES living more than 48 hr. Cases | INFANTS & CHILDREN Cases | TOTAL No. | TOTAL %+ |
|---|---|---|---|---|---|---|
| No abnormality | 3,6,9, | 17, | 22,29,30,34, 36,37,38,44, | 53,59,63,64, 65, | 17 | |
| | | | | | | 49 |
| No information | | | 25,26,28,32, | | 4 | |
| A.P.H. + Pl. Praevia | 4, | | 20, | | 2 | |
| A.P.H. | | 13, | 35, | | 2 | |
| Mixed Acc. Haemorrhage | | 14, | 31, | | 2 | 19 |
| Conc. Acc. Haemorrhage | 1, | | | | 1 | |
| P.P.H. | | 12, | | | 1 | |
| Tox. of Pregnancy | 2,8, | 11, | 23, | | 4 | |
| | | | | | | 12 |
| Eclampsia | 7, | | | | 1 | |
| Puerperal Sepsis | | 16, | | | 1 | |
| Hydramnios | 5, | | | | 1 | |
| Caeserean Section for Disproportion | | 18, | | | 1 | |
| Anaemia | | | 27,33, | | 2 | |
| Cardiac (M/S) | | | 21, | | 1 | |
| Chronic Bronchitis | | 15, | | | 1 | |
| Quiescent tuberculosis | | | 50, | | 1 | |
| Threat. Miscarriage (3/12) | | | | 62, | 1 | |

+To the nearest whole number.