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OBSERVATIONS ON BILHARZIASIS OF DOMESTIC RUMINANTS IN SOUTH AFRICA

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ABSTRACT

McCULLY, R. M. & KRUGER, S. P. Observations on bilharziasis of domestic ruminants in South Africa. *Onderstepoort J. vet. Res.* 36 (1), 129–162

Bilharziasis of 100 sheep and 14 cattle caused by *Schistosoma mattheei* Veglia & Le Roux, 1929, was studied in detail from the histopathological aspect. The ovine cases included natural as well as experimentally infested animals. The most significant changes resulted from the presence of schistosome ova and the dead schistosomes in the branches of the intrahepatic portal vein. The host reaction to the ova is of a granulomatous nature which is interpreted as a type of delayed hypersensitivity reaction. In a few cases there was an even more marked sensitivity superimposed on this. It was characterized by concentrations of eosinophiles around miracidial-containing ova as well as shells of ova present in the centre of mature granulomas. This was accompanied by necrosis of adjacent liver cord cells and necrosis of masses of eosinophiles. This appears to be analogous to the toxaemic form of human bilharziasis.

In both sheep and cattle, particularly the latter, the host response to dead adult schistosomes in the intrahepatic branches of the portal vein was striking. The initial thrombosis was followed by a granulomatous response to remove the parasite, and a localized lymphoid proliferation which destroyed the wall of the vein and remained after the schistosome had been removed.

The Hoeppli phenomenon occurred in response to ova in both sheep and cattle, being more pronounced and more frequently present in cattle. The conclusion is drawn by the authors that cattle are less affected by bilharziasis than sheep and goats.

INTRODUCTION

One of the schistosomes which is pathogenic for man, *Schistosoma mattheei* Veglia & Le Roux, 1929, is the cause of bilharziasis of domestic ruminants in South Africa. The study of this disease in sheep and cattle was considered worthwhile not only because of its economic and zoonotic significance but also due to the fact that these are natural hosts to one species of a group of blood flukes which are of such current importance for humans in many parts of the world. Based on natural and experimental cases in sheep, Le Roux (1929) reported many of the clinical, parasitological and pathological features of the disease. The present report is an account of a comparative study with emphasis on the pathological changes observed in the detailed analysis of a large number of recent ovine necropsies, some of Le Roux's original ones, and a smaller number of bovine necropsies.

GENERAL ASPECTS CONCERNING MATERIALS AND EXPERIMENTAL METHODS USED

The materials forming the basis of this report were 100 cases of bilharziasis of sheep and 14 of cattle. Orienting details concerning the cases of each of these species follow in turn.

Sheep

For the convenience of referring to specific animals they were assigned case reference numbers (CRNs). The 100 cases were divided into four categories according to the source and/or circumstances of their inclusion in this study as follows:—

Category 1 consisted of 32 cases, (CRNs 1 to 32) from the files of the Pathology Section at Onderstepoort. They were some of the cases on which the

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original and most extensive study of bilharziasis caused by *S. mattheei*, to date, was based (Le Roux, 1929). Microscopic sections and/or paraffin blocks were still available. These cases were included because of their historical as well as their comparative value.

Category 2 contained 12 cases of bilharziasis (CRNs 33 to 43, and 47) in which the infestation was acquired by sheep raised under natural conditions on farms in Zululand and the Potgietersrus district of the Transvaal.

Category 3, the largest, consisted of 47 experimental cases (CRNs 44 to 93 excluding 47 and 64) produced at Onderstepoort for the specific purpose of studying the host-parasite relationship in the disease and for developing and perfecting techniques to facilitate future research. Parasitological data on this category are presented in Table 1.

Category 4 was composed of eight previously infested sheep (CRNs 64 and 94 to 100), which having shed *S. mattheei* ova in large numbers over a long period of time ceased to do so. They were then exposed to various numbers of cercariae of *S. mattheei* using one of several different routes of infestation. (See Table 2 for parasitological data.)

Infestation of experimental sheep

The source of the cercariae was the snail colony of *Bulinus* (*Physopsis*) *globosus* (Morelet, 1866) which was established from specimens collected in Zululand, and maintained at Onderstepoort for use in bilharziasis research. The infestation of the snails with *S. mattheei* was accomplished by exposing them to miracidia which were hatched from ova from faeces of naturally-infested cattle by using a miracidia-hatching-apparatus (Kruger & Heitmann, 1967). Cercariae were harvested under the influence of strong artificial light for three hours. They were counted by removing aliquots and the desired number were placed in a wide mouth glass jar of 500 ml capacity. Most of the experimental cases were produced by first thoroughly cleaning and then immersing one of the front legs up to the elbow for 30 minutes in a volume of water containing the cercariae. This was proven to be a satisfactory method of infesting sheep (Kruger & Reinecke, Onderstepoort, personal communication, 1965).

In order to have cercariae available in the winter an outside thermally controlled breeding colony for snails was established (Heitmann, 1968).

All experimental sheep were free from other helminths and throughout the course of the experiment they were maintained under worm-free conditions.

Necropsy

For most cases, the termination of the life of the sheep depended on the natural course of the disease. In the winter months this was frequently dependent on the extent to which secondary pulmonary infections developed. Sheep which developed secondary infections were not treated with antibiotics or any other medicinals. Very weak sheep and those in which death appeared imminent were killed by electrocution or exsanguination after which they were necropsied immediately and the adult schistosomes counted in most cases. A variety of techniques was used to collect the adult schistosomes for counting.

(*a*) *Counting worms* in situ *within veins:* Initial attempts to count the worms by observing them in the veins of the portal system proved to be rather unsatisfactory because it was not only very time-consuming, but also inaccurate. One of the reasons for this was that when the fat around the mesenteric vessels congealed, it was difficult to see all the adult parasites. For those animals which died overnight it was necessary to continue with this method, however, because post-mortem clots within the portal system hampered the recovery of the worms by perfusion.

(*b*) *Perfusion of the portal system:* In those animals that were killed and necropsied immediately, the worms were collected by using a perfusion technique (Kruger & McCully, 1967). The collection of live schistosomes was necessary for some of the parasitological studies. In such instances, the animal was heparinized by the intravenous injection of 10,000 units of heparin five minutes prior to death by either electrocution or exsanguination. The carcass was placed in a position of left lateral recumbency on a necropsy table. The thorax and abdomen were opened by removing the right thoracic and abdominal wall. After the viscera of these cavities were examined, the recovery of the parasites was accomplished as follows: Glass cannulas with 60 cm-lengths of 1 cm diameter latex tubing attached were inserted into and made fast—with the cannulas directed caudad—in the following vessels: posterior aorta, just craniad to the diaphragm; extrahepatic portal vein, just caudad to its entrance into the liver; thoracic portion of the posterior vena cava 3 cm craniad to the diaphragm. [The cannulation of the latter vein prevented a building up of pressure in the liver and was subsequently used in the further recovery of parasites (*vide infra*)]. Forceps were then placed on the abdominal aorta and posterior vena cava approximately at the level of the fourth lumbar vertebra and on the portal vein at the portal fissure between the liver and the cannulated portion. The tubing of the aortic cannula was then attached to the lower outlet of a carboy containing 5 gallons of normal saline. Air was pumped into the closed carboy by means of a small portable, electric, centrifugal pump, until a pressure of 5 lb/in.^{2} had been attained. This pressure was maintained during perfusion.

Before starting the pump a 20 gauge hypodermic needle was inserted into the latex tubing near the aortic cannula. This permitted the escape of air from the tube the moment pressure was applied. Its removal obviated air blocks and allowed the saline to flow evenly. Saline was thus forced through the vascular system of the gastro-intestinal tract and out the cannulated end of the extrahepatic portal vein. The open end of the tube was held over a 300 mesh to the linear inch sieve and the adult parasites were flushed out of the veins onto the sieve. The efficiency of this procedure was enhanced by using warm (45° C), rather than cold saline, and by gently manipulating the viscera, as if kneading dough, during the perfusion. When it was unnecessary to collect the schistosomes alive, the thoroughness and the speed of

recovery of the worms were increased by the injection of 10 ml of 40 per cent formalin into the lumen of the latex tubing through which the saline was flowing.

In order to recover any worms present in the intrahepatic portal vein, the veins were perfused by attaching the saline source to the thoracic portion of the posterior vena cava. Air was removed from the tubing by first inserting a hypodermic needle and then applying the pressure. A forceps was placed on the posterior vena cava at a point just caudad to the liver. The saline under pressure then passed through the liver from the posterior vena cava via the hepatic and other efferent veins thus out of the liver where the worms were collected on a sieve as they passed from a cannula placed in the intrahepatic portal vein. In heavily infested cases a considerable amount of haematin and numerous schistosome ova were flushed from the liver onto the sieve and because of fibrin and perhaps other material some were caught up in the meshes.

If it was unnecessary in the parasitological studies to collect living parasites, treatment of the sheep three hours prior to death with a schistosomacidal drug such as tartar emetic or one of the more recently developed ones caused most of the worms to release their hold on the vein wall, with the result that they were swept into the intrahepatic portion of the portal vein, an example of "liver shift". Then at necropsy by applying the opposite flow perfusion to the liver, as described, their collection was accomplished.

(*c*) *Perfusion of the pulmonary blood vessels:* In order to determine whether there were schistosomes in the pulmonary artery, it was also flushed out using an opposite flow method as follows:

With the thoracic viscera *in situ* the pericardial sac was removed, the left ventricle incised and a cannula inserted through the mitral valve into the left atrium and secured by a ligature tied around the base of the heart. A second cannula was placed in the pulmonary artery and ligated in position. The saline was forced through the left atrium, the pulmonary veins, the capillary bed of the lung and out through the cannula in the pulmonary artery on to a sieve which collected any worms which were present. The addition of formalin facilitated the recovery of adult parasites.

Worms were transferred to glass beakers, subsequently transferred to plastic (perspex) counting chambers and counted with the aid of a stereomicroscope.

(*d*) *Examination and collection of tissue for histopathology:* Tissue specimens of the majority of organs after their thorough macroscopic examination were taken and placed in 10 per cent buffered neutral formalin.

The liver from each case was examined for lesions, which, if present, were taken for subsequent histological examination. First the surfaces were carefully scrutinized. Thereafter with the aid of a sharp pointed knife the intrahepatic portal vein, its interlobar and then its interlobular branches, were opened from the largest portion at its inlet to the smaller lumens at the periphery of the lobes. The intima of these veins was examined. The peripheral sharp edges of all lobes were then incised at intervals of 8 to 10 mm to a depth of approximately 3·5 cm and examined. Following this the remainder of the liver was cut with a sharp knife into slices approximately 1 cm thick. Both cut surfaces of each slice were checked for lesions.

Processing of tissues for histopathology: Following fixation, representative blocks of the tissues were trimmed, processed through the usual solvents and embedded in paraffin wax. Sections of 6 micron thickness were cut with a sliding microtome and stained with haematoxylin and eosin. Perfusion did not markedly alter the histology of the tissues. Tissues from the unperfused animals were collected and handled in the same manner.

Cattle

With the exception of one ox which was experimentally infested at Onderstepoort, all of the bovine cases were natural infestations which originated from several farms in Zululand. Some were necropsied on the farms but others were taken to Onderstepoort where they were held for varying lengths of time before being killed, several remaining infested with *S. mattheei* for over three years. The cases were divided into three categories as follows:

Category 1: Seven naturally-infested bilharziasis animals (CRNs 1 to 6 and 9 in Table 6) which were treated with one or other schistosomacidal drug. All were killed and necropsied during a period of six months following the last treatment.

Category 2: Six naturally-acquired bilharziasis animals (CRNs 7 and 8, and 10 to 13 in Table 6) that were similarly treated but killed and necropsied only after at least eight months from the last treatment had expired. (The longest interval between treatment and necropsy was 42 months.)

Category 3: One experimentally-infested animal (CRN 14 in Table 6) that was never treated for the disease.

Tissues from the 14 cattle were collected during 10 complete necropsies performed either at the farm or at Onderstepoort and when the viscera was examined in the Onderstepoort abattoir at the time the others were slaughtered. Initially parasite counts were made with the worms *in situ* in the veins of the portal system at necropsy. Thereafter collection by perfusion of this system shortly after death proved to be the most efficient method for determining the number of parasites. A glass cannula was inserted into the cut end of the anterior mesenteric artery and ligated in position. Warm water or normal saline was then pumped through under pressure obtained by using a portable, hand-operated, orchard spray pump. The addition of formalin again facilitated the collection of the worms. The macroscopic examination, collection and processing of the tissues were carried out as described for the sheep.

RESULTS

Parasitology studies

Effect of the number of cercariae on longevity of sheep: One of the aims in the parasitological studies on the host-parasite relationship was to determine the effect of various numbers of the cercariae on sheep. It was found that with the heavier infestations sheep will succumb in a relatively short time and that with low infestations the sheep may live for much longer. This is illustrated in Fig. 1 using some of the experimental cases shown in Table 1 as well as some which were still alive at the time Fig. 1 was prepared. The calculation of Fig. 1 was done by means of transformation and the least square method of curve fitting. In the calculation, especially of the lower limit, it was necessary to use animals which were still alive. Further in the overall calculation animals were used which were not included in Table 1 and on which the pathology has not been done.

Effect of the host on egg production of the female parasite: As one would expect, a specific number of the parasites in a sheep has a more severe effect than the same number on a larger animal, the ox. It was also learned from the experimental case which received 20,000 cercariae, that an ox can be significantly affected by bilharziasis. It was observed however that an ox can after a period of time make a significant recovery. Clinical improvement closely paralleled a decline in the production of ova as determined by both counting of ova and hatching of miracidia from 5 gm samples of faeces. Table 3 illustrates the decline in egg productivity in the experimental oxen. This was in spite of the fact that an excess of 9,000 adults was present at this time as determined by a necropsy a few days later. A similar reduction occurred in sheep (Table 4).

TABLE 1.—*Data on sheep cases in Category* 3

Case Ref. No.	Total cercariae	Duration of infestation (days)	Number of adults counted	Case Ref. No.	Total cercariae	Duration of infestation (days)	Number of adults counted
44	700	61	21	70	9,400	45	5,877
45	2,000	183	300	71	9,400	61	3,648
46	500	189	68	72	8,700	63	2,809
48	2,000	115	154	73	10,000	53	4,676
49*	15,300	72	88	74	10,000	56	2,115
50	91,000	58	35,100	75	5,000	58	—
51	60,000	63	4,884	76	10,000	56	3,506
52*	15,300	85	54	77	1,000	80	—
53	31,000	67	4,430	78	5,000	80	—
54	—	1,460	—	79	5,000	90	—
55	12,670	75	4,108	80	5,000	79	2,145
56	7,478	80	1,906	81	8,700	84	2,841
57	10,000	68	—	82	1,000	121	318
58	4,500	51	2,874	83	7,500	185	—
59	8,794	128	3,867	84	1,000	115	291
60	500	171	36	85	5,000	135	2,486
61	9,440	155	381	86	1,000	161	—
62	7,800	267	597	87	1,000	176	136
63	6,400	130	1,086	88	1,000	181	673
65	1,850	246	54	90	1,000	178	408
66	4,000	254	189	91	1,000	184	388
67	7,500	101	848	92	1,000	189	271
68	10,000	105	—	93	2,000	281	642
69	6,000	101	—				

* Cercariae were injected subcutaneously. All other sheep were infested percutaneously.
"—" means not counted.

TABLE 2.—*Data on sheep cases in Category* 4

Case reference No.	Method of challenge infestation	Cercariae in challenge	Duration (days) after challenge	Number of adult worms
64	Cutaneous	8,300	25	2,779
94	"	2,000	99	94
95	*Per os*	11,150	71	46
96	Cutaneous	1,751	567	—
97	Subcutaneous inj.	11,725	83	2,188
98	Cutaneous	15,665	82	1,130
99	*Per os*	8,950	90	22
100	Subcutaneous inj.	11,725	89	62

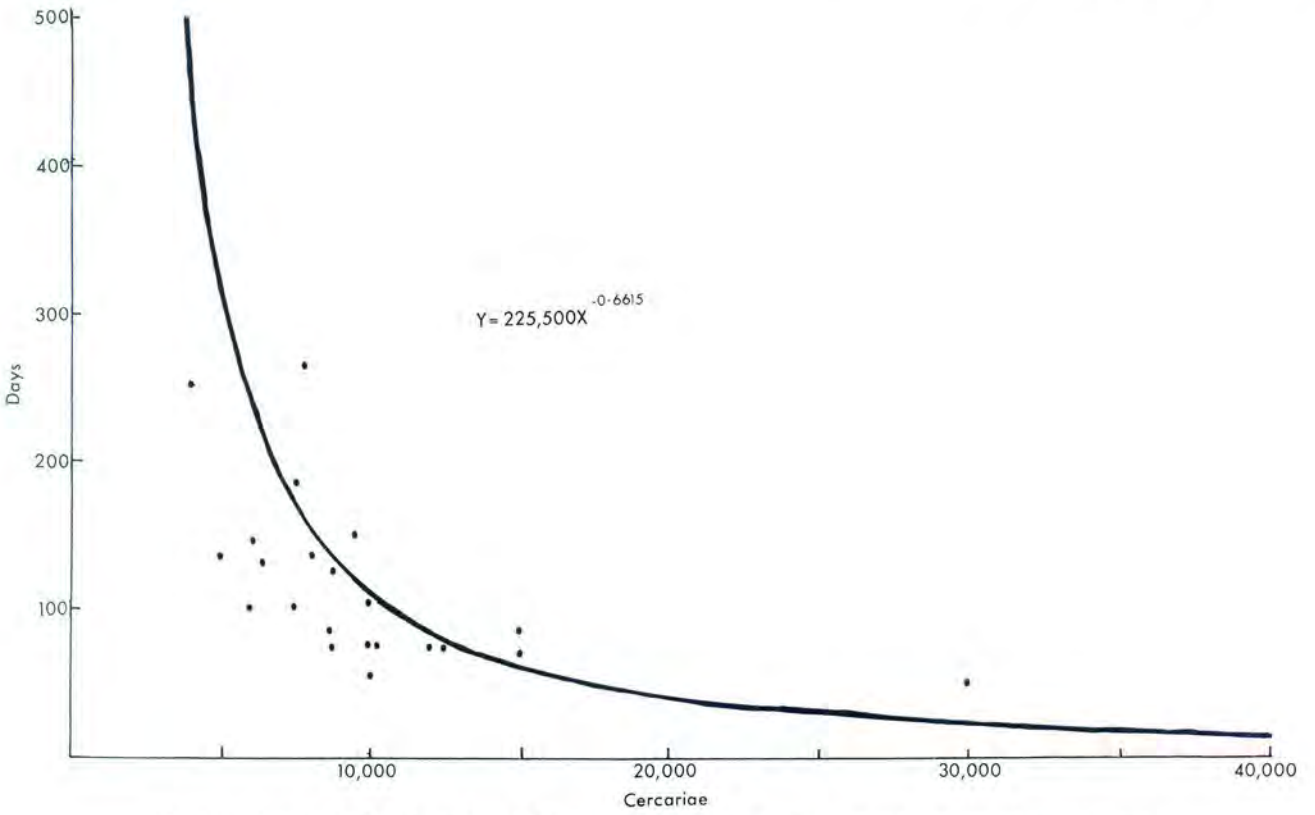


FIG. 1.—The effect of the number of *S. mattheei* cercariae on the longevity of experimental sheep as outlined in text

TABLE 3.—*The effect of the bovine host on egg production of the female schistosome as outlined in the text*

Days	52	58	60	73	82	117	120	163	164	198
*Miracidia	62	73	104	236	453	271	84	0	—	—
*Eggs	25	36	48	65	104	116	18	0	2	1

* From 5 gm samples of faeces

TABLE 4.—*The effect of the ovine host on egg production of the female schistosome as outlined in the text*

Sheep No.	*Days after infestation*	*Miracidia**
1	50	4
	58	11
2	127	512
	130	480
3	140	23
	208	19
	298	11
4	90	2
	495	4
	581	0
5	136	144
	202	14
	279	7
	553	1
6	309	33
	774	1

* From 5 gm samples of faeces

Pathology Studies—Sheep

The macroscopic finding on the first 32 cases of which the microscopic findings are shown in Table 5 were included in the original report in which these cases were used (Le Roux, 1929). The account which follows was based on the current experimental and natural cases of this study.

Ante-mortem examination: Depending upon the duration and severity of the infestation, there were various degrees of loss of condition and unsightliness of the sheep. It was noticed that in as short a period as two months after experimental infestation, heavily infested animals were markedly affected. They showed paleness of the mucous membranes due to anaemia, weakness, inappetence, progressive emaciation and a break in the wool. The wool was frequently matted with manure. Sometimes there was a stringy, mucoid, foetid faeces or haemorrhagic diarrhoea. Less heavily infested sheep which had survived the disease longer eventually showed similar signs with anaemia, emaciation, poor haircoat and general weakness but not a haemorrhagic diarrhoea although blood-flecked faeces were seen. Those with secondary pneumonia rapidly became exhausted after slight physical exertion. Sheep were more prone to contract pneumonia in the winter because they could acquire

secondary respiratory infections. This tendency appeared to be proportional to the severity of the parasitism but it was also observed that sheep having fewer parasites became more susceptible to pneumonia when the schistosomal infestations were of long duration.

Post-mortem examination: Subcutis and body fat: There was severe loss of condition as shown by depletion and serous atrophy of the subcutaneous and depot fat. Focal areas of fat necrosis were apparent in the mesentery and omentum but this was never as prominent a feature as was the serous atrophy.

Body cavities: Severely affected sheep frequently had 1 litre, or more, of ascitic fluid in the abdomen. Hydrothorax was even more extensive with resultant atelectasis of the apical and cardiac lobes of the lungs. There was hydropericardium, the pericardial sac quite often being greatly distended by fluid. The heart appeared normal but the heart blood appeared thin and watery.

Lungs: In the terminal cases severe pulmonary oedema was common. It often accompanied the extreme degree of hydrothorax and hydropericardium. Other secondary changes consisted of areas of atelectasis in the apical and cardiac lobes, these also being the usual sites of pneumonic areas when present. The most prominent feature, which was obvious to some degree in all the sheep lungs, was the pigmentation by haematin that gave the lung a grey colour [Plate 13 (81)].

Liver: The livers were characterized by a dark grey colour [Plate 13 (82)]. Some sheep had a very small liver. The decrease in size was the result of atrophy, the severity of which appeared to parallel the emaciation of the sheep. Because of this and a slight increase in connective tissues, they were firmer than normal and offered more resistance to incision. Small white to yellow foci of approximately 1 mm diameter were obvious in the parenchyma beneath the capsule and on the cut surface. Their number varied considerably but the size was fairly constant. In a relatively small number of the livers there were numerous, somewhat similar but slightly elongated, yellowish-green streaks in the portal canals. The linear streaks were accompanied by foci of the same size but their colour was yellowish-green instead of white to yellow. In most livers there were also some slightly larger, more sharply delineated, white foci between 2 and 3 mm in diameter. Larger nodules 7 to 8 mm in diameter were frequently seen in the interlobular branches of the portal vein located approximately 2 to 3 cm from the sharp borders of the liver. No consistent parenchymal changes occurred but fairly extensive fatty metamorphosis which gave the liver a finely mottled appearance was frequently present in those sheep which had been off feed for several days. When the intrahepatic portal vein and its branches were examined, various numbers of living adult schistosomes were discovered. The number was considerably influenced by the interval between death and the necropsy because of the tendency for the worms to move towards the liver in the portal vein after death. They were of course numerous in the ones which were treated a few hours before death. There were no thrombi in response to the live or the very recently killed schistosomes but thrombosis was extensive in response to parasites which had been dead for a few days. Many of these were found within the thrombi, sometimes in groups of six or more. The appearance of the thrombus depended on its age and the size of vessel. Some were of occlusive nature, either partially or completely; others were obturative thrombi.

On the cut surface of the liver, small white objects could be seen in the lumens of the smaller interlobular veins. When a blade was drawn over the surface, many of these objects, which proved to be dead schistosomes, were pulled out. Others were apparently bound fast by the host response of the vessel wall in which the worms were present. In a few sheep there were thin, shrunken areas along the sharp borders of the livers. They were up to 3 by 5 cm in their greatest dimensions and on cut surface it became even more apparent that they were old infarcts. Frequently, the main interlobular branch of the portal vein to the area was obstructed by an occlusive thrombus. The infarcted areas were darker than the remainder of the liver. Severe wrinkling of the capsule and hobnailed livers were not observed in the newly acquired cases but Le Roux (1929) illustrated and described such livers.

Gastro-intestinal tract: By simply holding the mesentery against a light, the single and conjoined pairs of adult schistosomes were easily seen in the veins. In heavily infested animals, veins of the forestomachs, abomasum—especially near the pylorus—and the duodenum contained many parasites. The veins of the initial part of the duodenum often appeared tortuous and severely congested. After very thorough perfusion even with the addition of formalin to the saline, adult schistosome pairs frequently remained in veins of the forestomachs and both small and large intestine. In unperfused viscera the mucosa of the abomasum, small intestine, caecum and rectum usually contained small red foci. Some of them had fresh blood on their surface. The mucosa was occasionally quite thickened, though unevenly so. In the most severe cases the rectum contained a mixture of discoloured blood and mucoid faeces.

Mesenteric lymph nodes: In heavily infested cases, and in mildly infested cases of long duration, the chain of mesenteric lymph nodes was considerably enlarged, being occasionally two or three times the normal size. On their cut surface the medulla was enlarged with no sharp line of distinction between it and the cortex, the colour throughout being pale grey because of mild pigmentation. In a number of the more severely infested animals, masses of adult schistosomes could be demonstrated within veins of the lymph nodes.

Other tissues: The pancreatico-intestinal lymph node was more enlarged and more darkly pigmented than other visceral lymph nodes. In some cases there was slight tumor splenis which was apparently due to lymphoid hyperplasia of the white pulp, judged by the size of the splenic corpuscles on the cut surface. In the heavily infested cases, adult schistosomes were present in the splenic veins. Lesions due to schistosome ova or adults were never observed macroscopically in the kidneys or urinary bladder of sheep. In emaciated animals there was extensive atrophy and depletion of the skeletal musculature.

Microscopic examination: Table 5 graphically shows the significant histopathologic changes in the sheep.

Liver: Host reactions to ova: Numerically, lesions in all cases were most often due to schistosome ova and the host response to them varied considerably. Based on the histopathological changes, six types of reactions were commonly recognized. They are designated in Table 5 by the numbers 1 to 6 in the first line. The characteristics of the individual types were determined to be as follows:

Type 1: Schistosome ova which were principally in the portal area, were quite often in the interlobular branch of the portal vein, and were surrounded by small round cells [Plate 1 (2)] in most instances but there were indications of granuloma formation around some ova.

Type 2: There was an exaggerated histiocytic response [Plate 1 (4)] to the relatively few ova that were present primarily in the portal canals. The histiocytes had confluent cytoplasm and both their cytoplasm and nuclei were vesicular in appearance [Plate 1 (5)]. These cells predominated the portal areas completely and were so numerous that they frequently obstructed the lumens of the interlobular branches of the portal vein [Plate 1 (6)].

Type 3: There was an exaggerated histiocytic response just as in Type 2. It was further characterized by the presence of many eosinophiles which were mingled with the histiocytes [Plate 2 (7)]. They were especially concentrated around ova resulting in "microabscesses" in the centres of the reactions [Plate 2 (9)]. In these sites some groups of eosinophiles had become necrotic with the result that there was only eosinophilic amorphous material remaining.

Type 4: This type was composed of numerous granulomas [Plate 2 (8)]. The ova were surrounded by epithelioid cells together with some multinucleated, foreign-body type giant cells [Plate 2 (10) and (12)]. On the outer perimeter of the granulomas there was a wide zone of small round cells [Plate 3 (14)].

Type 5: This was a stage intermediate between Types 4 and 6, with characteristic lesions of both about equally divided.

Type 6: The ova, which were very numerous, were frequently mineralized [Plate 3 (13)]. They were usually encompassed by healed granulomas [Plate 2 (11)] in which fibrocytes were the main component. There were few inflammatory cells remaining, the fibrosis being the outstanding feature. As a result of these lesions, many lumens of the small branches of the portal vein were either partially or totally obstructed and there was considerable fibrosis in the remainder of the portal area. In a few cases part of the obstruction of the veins was due to smooth muscle hypertrophy and apparently also hyperplasia.

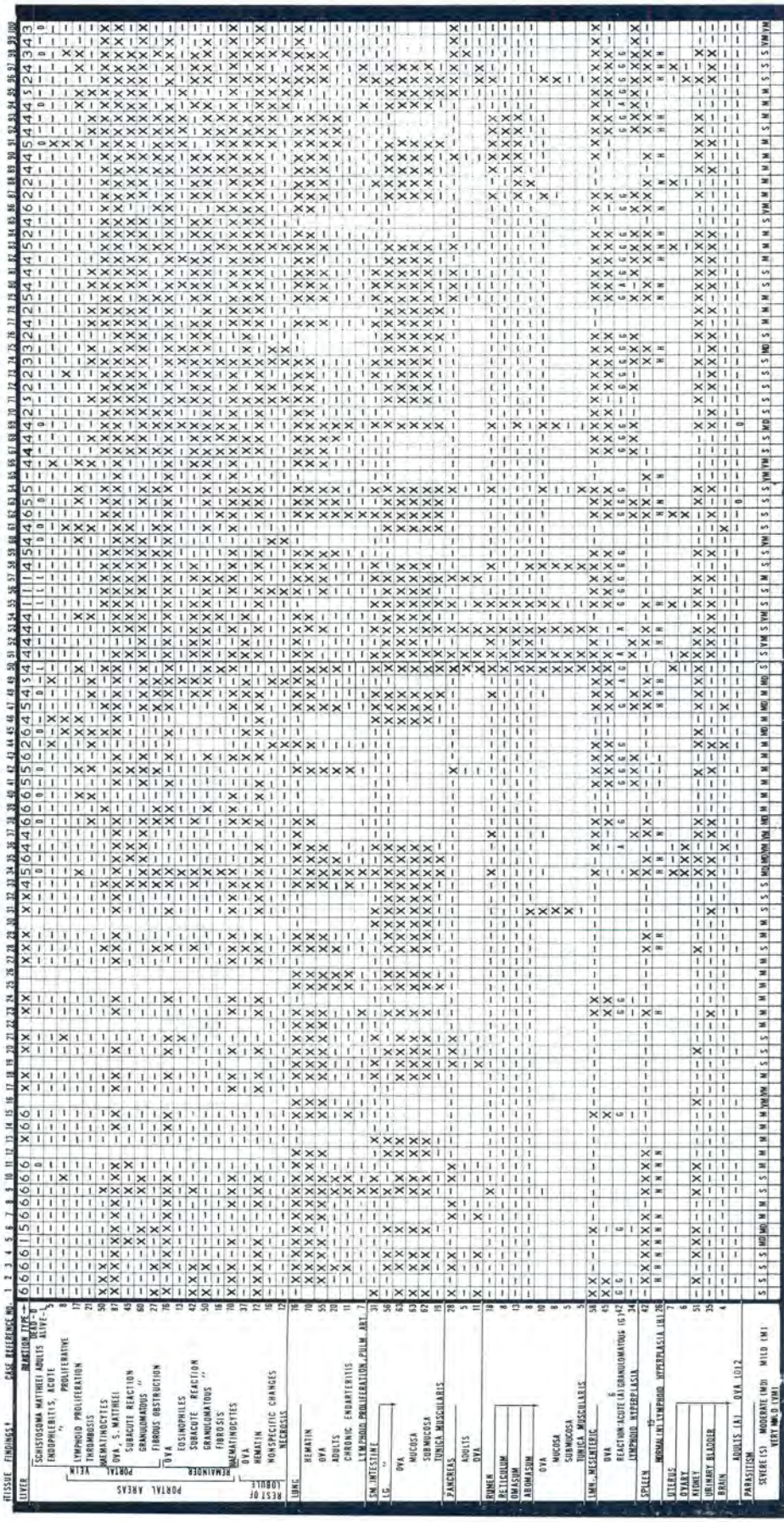
Type "S": The hepatic lesions of several sheep did not fit into the above classification. They did, however, resemble Type 3 more closely than any of the other types. These cases were classified as Type "S", a special type which differed from the other because of the enormous number of eosinophiles taking part in the reaction. Many groups of eosinophiles occurred in the veins and the remainder of the portal area either in the presence or absence of schistosome ova [Plate 3 (15)]. A zone of intensively eosinophilic stained necrotic cells [Plate 3 (16)], which were interpreted as having been eosinophiles, surrounded some ova. Just outside the necrotic zone, epithelioid cells were lined up in a row. It was apparent that the Type "S" reaction was superimposed on the others in some instances [Plate 4 (19)]. This was most apparent in one which had been a Type 4 previously. The central zone of epithelioid cells was surrounded by a thick band of eosinophiles and round cells. Some granulomas had acquired eosinophilic antigen-antibody material on the shell of the ova [Plate 3 (18)]. It appeared that eosinophiles had infiltrated to the centre of some of the old granulomas [Plate 4 (21)]. Epithelioid cells were sometimes arranged as spokes in a wheel [Plate 4 (22)] around an ovum. Many small round cells accompanied the eosinophiles in the veins of the portal canals and the surrounding portal areas. The periphery of some lobules was involved by the cellular elements [Plate 3 (17)]. Coagulation necrosis of cord cells occurred adjacent to eosinophilic reactions to ova and occasionally where there were only eosinophiles and no ova.

According to these criteria, it was possible to classify most of the 94 cases from which liver was examined but there were a few in which ova were so scanty that they were not classified. Several others were also unclassified because slides were no longer available by the time of such classification. If the liver had been previously studied on these cases, it is indicated by an "X" in the appropriate block in the first line on Table 5. In many of the cases there were acute, subacute and chronic lesions in response to ova. The classification into types was based on the most numerous kind of lesion.

Elaboration on other items in Table 5: From the things concerning the liver in Table 5 it can be seen that the significant hepatic changes occurred in the portal areas. Some of the small interlobular veins were usually involved, followed quite closely by the remainder of the portal area. The rest of the lobule was less often the site of ova and reactions thereto, but haematin was frequently present.

In the liver sections, *S. mattheei* adults, which were alive at the time of the post-mortem examination, were present within branches of the portal vein of four cases. They were free within the lumen with no visible reaction to most of them. Dead adult schistosomes were present in fifteen, four of which had been treated with effective schistosomacidal drugs. The initial response to, or result of their presence, was the formation of thrombi [Plate 5 (25)], some of which blocked the lumen of the veins. Thrombosis was followed by a further host response from the vessel wall consisting at first of an accumulation of histiocytes around the dead parasite [Plate 5 (26)]. Material from dead parasites was eventually phagocytosed by foreign-body type giant cells [Plate 5 (28)]. A rather diffuse proliferation of lymphoid cells in the intima often extended to the remainder of the wall and some were virtually destroyed [Plate 4 (24)]. In a few instances remnants of dead adult parasites were outside the veins in the liver parenchyma. These represented parasites

TABLE 5.—*The incidence and distribution of histopathological changes in the sheep cases*



which had been expelled from the veins through the mechanism of the vascular reaction. Remnants of schistosomes with haematin in the gut were sometimes present in veins completely obstructed by host reaction [Plate 5 (30)].

In cases of very long duration there were very chronic lesions attached to the intima of branches of the portal veins. They consisted of thick fibrous capsules surrounding fibrotic, often mineralized centres. This was apparently the end point of some of the granulomas, some of which resulted from dead parasites but others were possibly due to ova.

In five cases there was evidence of an acute endophlebitis due to the live schistosomes. The oedematous intima of some of the interlobular branches of the portal vein containing the worms was infiltrated with small round cells and eosinophiles [Plate 4 (20)]. There was also endothelial hyperplasia.

In eight cases, more advanced involvement of the intima was shown as a proliferative endophlebitis. Extensive endothelial hyperplasia, coupled with an increase in subendothelial connective tissue, resulted in intimal protrusions into the lumen.

Lymphoid proliferation was observed in the wall of some of the interlobular branches of the portal vein in 17 cases. The dead schistosomes were present in the lumen of some of the affected veins [Plate 4 (23)] but were absent from others with similar lymphoid involvement.

In 21 cases there was thrombosis in interlobular branches of the portal vein [Plate 5 (25)]. Dead adult schistosomes were associated with many of the thrombi but with others there were none. In still other branches, thrombi had formed at the site of schistosome ova [Plate 5 (27, 29)] and had partially blocked the lumens. Where it was in response to ova, the thrombosis was not extensive but of a very focal nature. Conversely, thrombi in response to the dead adults were extensive. Some were recently formed but others had been present much longer as indicated by various degrees of organization.

Host erythrocytes are ingested and subsequently digested in the digestive tract of adult schistosomes. Since their digestive tract has no posterior outlet, the contents must be periodically regurgitated. Haematin is one of the products which results from the destruction of erythrocytes and which is regurgitated. This pigment is readily phagocytosed by cells of the reticulo-endothelial system of the host. Such macrophages containing haematin will be referred to as "haematinocytes" by the same token that similar cells containing haemosiderin are called haemosiderocytes. Haematinocytes were quite numerous in the lumen of interlobular branches of the portal vein [Plate 1 (3)] of half of the cases and occasionally in hepatic veins [Plate 1 (1)] and heart blood.

Ova of *S. mattheei* were present in the lumen of some of the interlobular branches of the portal veins in 87 of the cases. The number of ova in a vein varied from one to many within a single vein. The number of vessels affected in a case differed widely from only a few to involvement of practically all of them in the sections examined. Reactions to the ova varied from an acute one characterized by the presence of a few polymorphonuclear leucocytes in the intima to a very chronic one in which an extensive amount of connective tissue filled much of the lumen of some veins. Between these extremes, subacute and granulomatous reactions were recognized. Those which were considered to be subacute were composed primarily of round cells that accumulated around ova along the intima. A diffuse proliferation of histiocytes surrounded some ova. The older granulomatous response in turn consisted of epithelioid and giant cells. Some of the granulomas had fibroblasts at their periphery. With the disappearance of the epithelioid cells and as a consequence of the maturation of the fibroblasts, the ova were encapsulated by connective tissue. The ova, usually located in the centre of the reaction, varied in appearance. Those most recently released by the female frequently contained viable-appearing miracidia. Many encapsulated ova were mineralized as well. There was a remarkable spectrum of host reaction to the ova within an individual case. Since it appears that this depends on both the duration of the ova in the liver and the experience of the host with the parasite, these factors will be dealt with further in the discussion.

Ova in the remaining portions of the portal areas were present in 76 cases. In response, there were eosinophiles in 13 cases. Just as in the veins there was a subacute reaction of round cells, a granulomatous response of epithelioid and giant cells or fibrous encapsulation. Haematinocytes were numerous in the portal areas of 70 cases. Along the hepatic sinusoids the haematin had been phagocytosed by the Kupffer cells, these being prominent in 72 cases.

An occasional ovum was present in other parts of some of the lobules of 37 cases. In 16 cases there were some non-specific changes. These included focal necrosis, fairly extensive fatty metamorphosis of either centrilobular or peripheral distribution, and atrophy of liver cord cells. Although necrosis was present in 12 cases, there was no specific pattern by which it could always be attributed to bilharziasis. In some of the 12 cases, however, there were areas of necrosis which were unequivocally due to bilharziasis. Those were areas of infarction [Plate 6 (31)] on the sharp edges of the liver lobes which resulted from the obstruction of the branch of the portal vein to the area by a dead schistosome and the thrombosis and other host response thereto. In the infarcted areas there was atrophy, fatty metamorphosis and necrosis of liver cord cells, an accumulation of macrophages containing lipofuscin and haematin, and extensive fibrosis.

In other areas of those which contained the infarcts as well as other livers, lipofuscin that had a smudgy, greyish-brown appearance was occasionally present in the vicinity of dead schistosomes and ova to which there had been severe host reactions. Giant cells frequently encircled the pigment.

Lung: In 70 of the 76 cases from which lung was examined, there were numerous haematinocytes in the alveolar capillaries or just outside in thickened alveolar septa [Plate 6 (32)], the number present varying from case to case. Ova were in the lung of 55 cases. They were usually located immediately adjacent to the small bronchioles and alveolar ducts

[Plate 6 (34)] where they had been arrested in the narrow lumen of the accompanying small branches of the pulmonary artery. Almost without exception, the ova were surrounded by granulomas [Plate 6 (35)]. The thin wall of some of the vessels was completely destroyed by the expanding granuloma. Though epithelioid and giant cells comprised the granulomas primarily [Plate 6 (33)], a few fibroblasts were present. In some instances there was encapsulation of mineralized ova by connective tissue which was organized in concentric layers. In those cases in which the Type "S" reaction occurred in the liver, there were similar reactions to ova in the lung with eosinophiles very numerous.

Adults of *S. mattheei* were observed in the branches of the pulmonary artery in the lung sections of 20 cases. Some were dead but others were alive when the tissue was collected post mortem. There were reactions presumably due to the presence of the live worms in some instances but frequently there were none. In some of these the intima was oedematous; there was endothelial hyperplasia accompanied by eosinophiles and small round cells. There was chronic endarteritis in 11 cases. In a few, apparently in response to the live worm, there was a villous proliferation from the intima bulging into the lumen. Most of the chronic changes, however, were due to the presence of dead parasites. The granulomas frequently contained foreign-body type giant cells with phagocytosed remnants of dead worms. Recognizable portions of dead schistosomes were occasionally incorporated into the arterial wall [Plate 6 (37)]. In seven cases the granulomatous response was accompanied by a marked proliferation of lymphocytes. Massive lymphoid proliferation had completely destroyed the wall of some arteries and the cells immediately surrounding the dead worms were lymphocytes [Plate 6 (36)].

There was secondary bacterial pneumonia in some cases which may have been influenced by the overall effect of the bilharziasis but pneumonia was not directly attributable to the presence of the adult worms or their ova in the vessels of the lungs in any case.

Intestines: Sections of the small and/or large intestine were examined from many of the sheep. Significant changes due to ova were present in the large and/or small intestine of 63 sheep. Ova were most numerous in the mucosa and submucosa and less prevalent in the muscularis mucosa [Plate 7 (45)] and between the circular and longitudinal layers of the tunica muscularis [Plate 7 (46)]. They were also found beneath the serosa on the surface of the outer longitudinal layer of muscle. Others were present within the crypts of Lieberkühn [Plate 7 (38)].

In the mucosa, the ova had sometimes elicited only a very mild response [Plate 7 (39)]. In other animals there was haemorrhage and many eosinophiles surrounding ova recently released from the parasite. Necrosis in the immediate vicinity of ova [Plate 7 (40)] was quite common and frequently there were polymorphonuclear leucocytes nearby. In other cases the response was mainly small round cells [Plate 7 (41)]. Small granulomas composed of epithelioid cells and fibroblasts surrounded the ova in some cases. Mineralized ova, either bare [Plate 7 (43)] or encapsulated by mature connective tissue [Plate 7 (44)], were present in the mucosa of some of the cases of long standing. In the submucosa and the tunica muscularis, the host response was most often of a granulomatous nature, with encapsulation of calcified ova by connective tissue [Plate 7 (42)] being the most chronic stage. Adults were occasionally seen within the lumen of the intestinal and mesenteric veins.

Other tissues: The pancreas was sectioned in 28 cases. Adult worms were present in veins of five and there were ova [Plate 8 (52)] in the parenchyma of 11 cases. The response to the ova varied from an essentially negative reaction to a granulomatous one with eventual encapsulation. Sections of the forestomachs were examined in a number of cases as follows: rumen (18), reticulum (8) and omasum (13). Adult schistosomes were sometimes observed within veins [Plate 8 (48)] and ova occurred in the wall of all of these structures at one place or another. They were most plentiful in the lamina propria of the mucosa where they evoked either a diffuse, subacute infiltration of round cells [Plate 7 (47)] or a granulomatous response. Ova were present in the mucosa [Plate 8 (49)], submucosa and tunica muscularis of the abomasum of one or other animal. The results of the examination of the abomasum are shown with the forestomachs in Tabel 5. Ova were present in the lamina propria at the muco-cutaneous junction [Plate 8 (50)] of the rectum and the anus of the only animal from which this juncture was sectioned. Ova were present immediately adjacent to some of the circumanal glands [Plate 8 (51)]. Mesenteric lymph nodes of 58 sheep were examined and there were ova in 45 of these. Though present in both cortex and medulla, they were most frequent in the latter [Plate 8 (53)]. Many ova were distinct in the lumen [Plate 8 (54)] of small veins of the medulla and adult schistosomes were occasionally in some of the larger veins. The reaction in the nodes was acute in six cases and granulomatous in 42 cases. Ova were absent from a few exhibiting a reaction. Fibrosis or encapsulation of the ova sometimes resulted in extensive sclerosis of the medulla. Lymphoid hyperplasia was prominent in 34 cases. There was some haematin in the mesenteric lymph nodes but there was far more in the hepatic nodes [Plate 8 (55)].

The spleens of 42 sheep were sectioned. Ova were not found in any of them in spite of the fact that adult schistosomes were occasionally present in the splenic vein when it was examined at necropsy. Twenty-six of the spleens showed lymphoid hyperplasia.

None of the sections of uterus and ovaries which were examined contained schistosomes or their ova. Kidney sections of 51 sheep were examined histologically. Schistosome ova were present in the kidney of only a single animal [Plate 9 (56)]. They were located in the cortex quite near the medulla and there was practically no host response to them. Ova were present in one of the 35 urinary bladders examined [Plate 9 (57)]. In this case numerous ova were limited to a relatively small area of the lamina propria. Most of them were calcified and the only remaining evidence of host response was an increase in the amount of connective tissue in the lamina propria.

There were numerous eosinophiles in the adrenal medulla of the cases showing the Type "S" reaction in the liver.

In the few sections of brain and spinal cord which were examined, neither adult schistosomes nor ova were found.

Pathological Studies—Cattle

Ante-mortem examination: Some of the cattle which carried a low burden of parasites showed few clinical signs of disease. The heavier the burden the more indication there was that bilharziasis was significantly affecting the animal. This was best observed in the experimental case. When infested percutaneously with 20,000 cercariae the ox was in good flesh. After approximately two months there was a rapid decline in condition. This was preceded by a period during which there was severe watery diarrhoea which contained a considerable amount of fresh blood. The ox had a hollow appearance to the abdomen, which was also slightly tucked up, and an anxious, pinched expression on its face. There was tenesmus during which watery faeces dribbled from the anus. As a result of combined loss of blood through ingestion of erythrocytes by the parasites and haemorrhage into the gut the animal became quite anaemic. The condition of the animal steadily deteriorated for a time but began to recover without any treatment other than continual access to water and a good high protein ration with adequate roughage. Some of the other cattle showed similar signs before treatment. Mild haematuria was also observed. Following treatment with one of several schistosomacidal drugs of apparently varying efficacy, there was a period during which the outward appearance of the animals seemed to deteriorate as manifested by rough haircoat and lassitude, but in several weeks this was followed by considerable improvement in the overall appearance of some of them. There was a significant change in the haircoat, the appetite improved and normal bowel movements occurred. Some of the cattle, however, showed little improvement. It was subsequently found that the treatment had been less effective than in those showing improvement.

Post-mortem examination: Liver: The findings in the cattle of Category 1 that were necropsied between one and three weeks after having been treated with an effective schistosomacidal drug were largely dependent upon the changes resulting from the presence of the dead worms. This was particularly manifested in the liver. Most of the dead worms passed through the large portion of the intrahepatic portal vein and its interlobular branches and became arrested in the interlobular branches. Some of the veins first designated as interlobulars had quite large lumens compared to the small interlobular branches which were present in the portal canals. In these larger branches the dead worms caused thrombosis but due to the size the parasite completely filled the lumens of those of the portal canals leaving no room for thrombi to form. Thrombi were most often present in those branches of the portal vein which were approximately 3 cm from the sharp borders of the lobes. In one animal which was necropsied only 10 days after treatment, most of the dead worms were lodged in the veins of the portal canals. On the cut surfaces of slices of liver, numerous small, white objects were spread rather unevenly throughout. When the surfaces were gently scraped with a blade, the dead worms were pulled from the veins. In another animal which had been treated two weeks previously, areas of focal necrosis and larger areas of fatty change occurred in addition to the thrombi resulting from the dead schistosomes. The intravenous lesions had obstructed the flow of blood through the portal system to such an extent that severe ascites occurred. These changes were all superimposed on those already in the liver, *viz.* small granulomas in response to the ova which had accumulated over a period of time. The livers were slightly darker than normal, but never as heavily pigmented as those of the sheep. Neither were the lungs ever pigmented to such an extent that they were grey as quite often with the sheep. Similar vascular changes but with alterations, i.e. organization of the thrombi, and more host reaction to the dead worms were found in those necropsied after longer periods following treatment.

In the cattle necropsied beyond the six month period following treatment (Category 2), the most significant findings in the liver were firm, white nodules in the larger interlobular veins. Found about 3 cm from the sharp borders of the lobes, the nodules were in positions identical to those where so many dead parasites and thrombi were found in the livers of cattle slaughtered shortly after having been treated. If the animal was in poor condition, the liver was usually atrophic and cut with a slightly-increased resistance.

The liver of the one experimental bovine case (Category 3) was not remarkable other than the numerous white foci scattered throughout the parenchyma.

Other tissues: At various sites in the intestinal tract of all the cattle the mucosa was flecked with slightly elevated, red, 1 to 3 mm sized foci, some of which proved to be accompanied by fresh petechiae. These were due to schistosome ova and resulting granulomas. The mucosa of the rectum was thickened in the chronic cases. The mesenteric lymph nodes were slightly enlarged in the mild cases and considerably more so in the severe ones. Lesions in the urinary bladder of cattle [Plate 9 (58)] commonly occurred. They consisted of nodular, slightly elevated, thickened areas of the mucosa, some of which had a necrotic surface. In some, the surface was yellowish-green and slightly ulcerated. Some nodules contained mineralized material.

Microscopic examination: Liver: Although some of the microscopic features regarding the host response to ova were the same as for sheep, they were not similar enough for the same groups of criteria, *viz.* Types 1 to 6, to be applied. Many changes were attributed specifically to ova, others to live schistosomes and many to dead ones but there were also lesions which could not be attributed exclusively to any one of these. After careful study, three types of host response were defined and in order to avoid confusion with the types of reaction to ova in sheep livers were designated A, B and C. This classification took into consideration the changes resulting from both the ova and the worm itself.

Type A: One of the significant features of this type was the role played by reticulo-endothelial cells at the periphery of the hepatic lobules and similar cells in the intima of the veins of the portal canals, the smaller interlobular branches of the portal. Mononuclear type cells and elongated endothelioid cells were present in a diffuse array along the periphery of the lobules [Plate 10 (63)] and in the hepatic sinusoids where they extended far centrad. Small round cells were as equally numerous and multinucleated giant cells were quite common in the veins and sinusoids. Many of the giant cells contained haematin in their cytoplasm [Plate 10 (65)].

Adult schistosomes, some dead and some alive, their ova and the haematin granules were present in varying numbers from one case to another. The adults occurred in the interlobular branches of the portal vein where in response, the wall and the surrounding area were infiltrated by many small cells. The most marked alterations were caused by the dead schistosomes. These changes varied according to the duration of the worm in the lumen and possibly also to immunological factors. The findings were also affected by the size of the veins containing the embolic dead worms. Some were within veins so small that the lumens were completely filled by the mass of the parasite alone [Plate 10 (68)]. As there was no room left for blood, there were no thrombi. From the intima arose an intense reaction, which eventually became a granulomatous one. Epithelioid and/or endothelioid cells arranged themselves along the cuticle of the parasite. As the autodigestion of the dead worm proceeded, remains of the parasite stained poorly with eosin and its histologic features became less and less distinct. It was concurrently invaded by host cells which phagocytosed the more durable remnants such as cuticle and haematin. Lymphoid proliferations filled the lumen, infiltrated the wall and extended beyond until they became the predominant reaction following the disappearance of the recognizable parasite and the destruction of the wall of the vein. Eventually a relatively large lymphoid mass, with only slightly recognizable signs of the worms remaining, marked the site of the affected vein. The pattern in which some of the cells of the mass were arranged was influenced by the cuticle of the parasite because it persisted longer than any of the other portions. "Ghost" lines which indicated the former outline of the worm were the result.

In the veins with lumens having greater diameters there were thrombi [Plate 10 (67)] in addition to the extensive host response to the embolic dead worms. The combinations partially or completely occluded the lumens. Thrombosis apparently occurred relatively soon after the verminous emboli arrived at the site. Some thrombi were concentrically laminated. There was usually a marked intimal reaction at the level of the lodged worm. These reactions were essentially the same as those in the small veins described above. The situation was frequently found where dead schistosomes were surrounded by epithelioid cells [Plate 11 (69)] in the centre of a lymphoid cell mass which filled the lumen and displaced the wall of the vein.

There was also a prominent intimal response to some live schistosomes which became lodged in veins. The response to these was as follows: the intima was usually oedematous; a piling up of endothelial cells indicated hyperplasia; projections from the intima extended into the lumen; and there were many eosinophiles on the surface as well as in the depth of these projections [Plate 10 (64)]. In some veins this was carried to such an extreme that the lumens were almost filled with villous projections, covered by hyperplastic epithelium and eosinophiles. Schistosome specimens were not always present in veins showing these intimal changes, however.

Schistosome ova were most frequently present in the small interlobular veins located in the portal canals. They provoked a granulomatous reaction primarily. Single or groups of several ova were surrounded by granulomas which were attached to the intima and were continuous with other inflammatory changes of the intima. Veins containing only ova, with and without a granulomatous response, occasionally exhibited a proliferative, villous endophlebitis. It thus appeared that ova alone could possibly provoke this type of response though one could not exclude the possibility that there had previously been adult schistosomes in that part of the vein.

In the transverse section of a fairly large vein the following could occasionally be observed: a viable schistosome with no reaction on its surface, dead schistosomes with a closely associated granulomatous reaction, ova with granulomatous reactions, a dead schistosome surrounded by necrotic debris, and a thrombus which was considerably organized.

In the cattle, more frequently than in sheep, the ova were not entrapped in the veins but had passed into the portal areas. The host reaction to them was sometimes ill-defined, being of a rather indefinite nature. The ova were located in the vicinity of the portal areas in the midst of small round cells and the diffuse reticulo-endothelial reaction which extended into the sinusoids. Other ova in the portal areas or further in the lobules were well-circumscribed by small granulomas. This diffuse reaction was observed in the absence of ova in many of the lobules, haematin being the only evidence of infestation. In a few of the lobules there was centrilobular coagulation necrosis. Necrosis adjacent to occluded interlobular veins was present to a limited extent in two heavily infested animals which were autopsied within a few weeks after treatment with an effective schistosomacidal drug.

Type B: Scant evidence of bilharzial infestation was present in the liver. The relatively rare ova regardless of their location, were encircled by small granulomas. Some of the ova in the veins were surrounded by an amorphous eosinophilic antigen-antibody type of reaction with a granulomatous reaction surrounding it, the whole process occupying much of the lumen [Plate 11 (73)]. Other giant cells with pieces of ovum in their cytoplasm were encircled by small round cells [Plate 11 (74)]. In the portal areas a number of eosinophiles and round cells [Plate 11 (72)] were sometimes present and the ova were occasionally also surrounded by an eosinophilic antigen-antibody deposit. Most of the veins

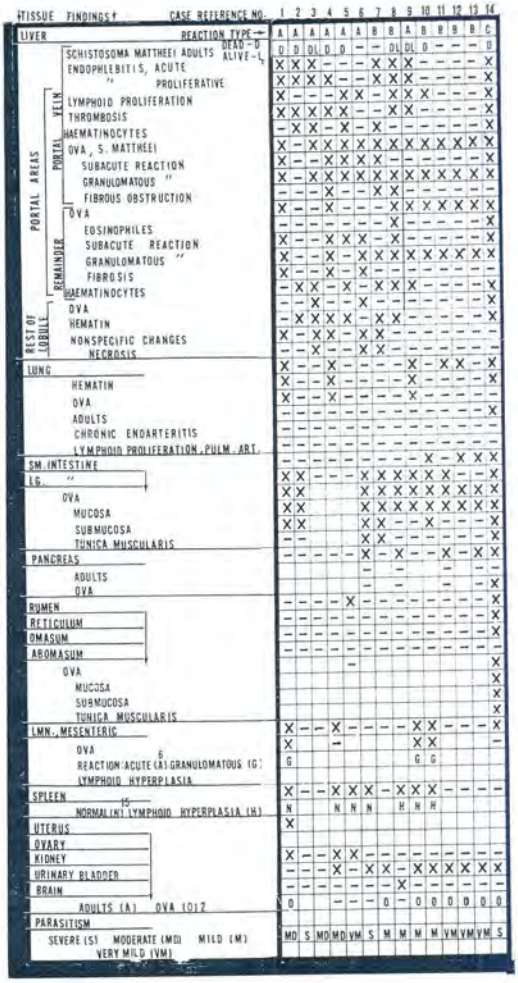
of the portal canal, the portal areas and the remaining portions of the liver lobules were completely free of signs of previous infestation. Some of the larger branches of the portal vein exhibited severe proliferative endophlebitis [Plate 11 (71)] with many eosinophiles on the surface of and within the depth of the villous projections. More complicated intimal formations of longer duration were occasionally seen in other veins, some of which had adult worms in the meshwork of the lacelike proliferations [Plate 10 (66)]. In the sections from the periphery of the lobes near the sharp edge, lymphoid masses [Plate 11 (70)] occupied positions which were previously the locations of the medium-sized interlobular branches of the portal vein. Vague lines, "ghost" lines as explained in Type A, indicated the former positions of the worms.

Type C: Extensive host reaction affected virtually every interlobular branch and larger branches of the portal vein. The reaction was a diffuse granulomatous proliferation from the intima [Plate 12 (75)] with many eosinophiles and some giant cells admixed. Ova were plentiful in these veins but few had passed through to the portal areas. An as equally severe host response greeted those which did [Plate 12 (76)]. Myriads of eosinophiles enveloped dead schistosomes in these veins [Plate 12 (77)], and around some there was an eosinophilic zone of necrosis. The lumens, the walls and the immediate surroundings of some of the larger veins had been replaced by masses of lymphoid cells as in the other types of reactions. Marked hypertrophy and hyperplasia of the smooth muscle of the media was a prominent finding in the wall of the veins having the diffuse host response in the lumen. Small thrombi accompanied some of the reactions. Though not a prominent feature of this type, several of the larger veins exhibited a proliferative villous endophlebitis. In some of the veins fortuitously sectioned so that they could be studied in longitudinal plane, the diffuse granulomatous response was present all along the intima on both sides of the lumens for the entire length of the portions visible.

The foregoing descriptions of the liver reactions, Types A, B and C, included elaboration on the hepatic changes which are shown in Table 6 and further detail is not necessary.

Other tissues: Sections of lung from six of the fourteen cattle were examined. Haematin was prominent in four of the six and in lesser quantities in the other two. Adult schistosomes were present in the pulmonary artery of one. There was no evidence of chronic endarteritis or lymphoid proliferation in any of them. Either small and/or large intestine were studied from 11 of 14 cattle. Ova were present somewhere in all of them, being consistently present in the mucosa, quite common in the submucosa but rarely in the tunica muscularis. Adult schistosomes were occasionally present in intestinal veins, some of which showed a proliferative, villous endophlebitis [Plate 12 (78)]. In other veins having a similar intimal response there were only ova, these occasionally contained within the intimal extensions protruding into the lumens [Plate 12 (79)]. Fibrous granulomatous masses surrounding ova filled some of the lumens [Plate 12 (80)]. The reaction to the

TABLE 6.—*The incidence and distribution of histopathological changes in the cattle cases*



dead parasite often resulted in the destruction of the wall of the mesenteric vein. In the experimental, untreated case the forestomachs were found to have ova in all layers of the wall. The reaction was of a granulomatous nature. In one of the five cattle from which pancreas was studied there were many ova. In response to them there were myriads of eosinophiles. Ova were present in three out of the five cattle from which mesenteric lymph nodes were examined. In each case there was a granulomatous response. Spleen was examined from seven cattle. Neither adults nor ova were ever observed in this tissue. Schistosome ova were present in the myometrium [Plate 9 (62)] of the only uterus that was sectioned. They were surrounded by granulomas. Ova were present in the lamina propria of seven of the nine urinary bladders examined from cattle. The host response varied from one animal to another. One type amounted to a somewhat nodular, yet fairly diffusely distributed, lymphoid proliferation in the lamina propria. Scattered here and there amidst the lymphoid cells, there were schistosome ova surrounded by granulomas. In the second type a more severe reaction to relatively few ova was present, the lamina propria being diffusely infiltrated by eosinophiles and small round cells [Plate 9 (59)].

The eosinophiles were apparently attracted to the ova and even to their empty shells [Plate 9 (61)]. Over such areas, the epithelium was either eroded or ulcerated. In response to adult schistosomes in the vesicular veins of one case, there was a rather mild endophlebitis. In the adventitia of veins containing the worms there was an intense infiltrate of eosinophiles [Plate 9 (60)]. The same was true in regard to some small veins which had lumens too small to accommodate the adult forms.

Discussion

The histopathology of the various types of bilharziasis which are due to *Schistosoma haematobium* (Bilharz, 1952) Weinland, 1858, *Schistosoma mansoni* Sambon, 1907 and *Schistosoma japonicum* Katsurada, 1904 has been covered in detail in a voluminous literature as emphasized in a recently published book edited by Mostofi (1967). There are reports concerning *Schistosoma bovis* (Sonsino, 1876) but few on *S. mattheei* in either sheep or cattle. Reports about the above-mentioned schistosomes in both man and experimental laboratory animals have therefore been relied on for making various comparisons with some of the things so far observed in this study.

Bilharziasis of sheep

The currently collected natural cases came from two areas of South Africa where they occurred under remarkable extremes of environmental conditions. In Zululand the conditions on the involved farms were similar to those described in a previous outbreak of bilharziasis (Strydom, 1962). Those from the Potgietersrus district occurred under conditions of such severe drought that supplementary feeding of livestock was absolutely essential to maintain them in the area. This outbreak was reported by Hurter & Potgieter (1967). The present authors were invited to visit the farm involved in order to make additional observations and collect material.

With a limited amount of water available a situation had developed with a concentration of snails which were heavily infested and a concentration of small ruminants which were becoming heavily infested as they drank. It resulted in a level of infestation in these animals which can only, realistically, be considered superinfestation. The predicament which developed on this farm emphasized the importance of taking the precautions necessary to insure protection of what water there is available in a drought area. It is also essential from the standpoint of human health. The control and prevention of bilharziasis in both of these areas clearly fell within the bounds of good management and husbandry practices.

Le Roux (1929) quite thoroughly described the macroscopic changes caused by this disease in sheep but the histopathology of it was not so convincingly dealt with. All of the cases from his original study were not preserved but fortunately enough were still available to permit comparisons of cases of forty years ago with present day material. The majority of his cases which were restudied were quite obviously of much longer duration than current cases with perhaps one exception. The cases with hobnailed livers which he described, however, were not among them.

Le Roux (1929) called attention to the roles of the ova, the pigment and the dead schistosomes in producing lesions. Further study has shown that the number of ova in the liver is a good indication of the severity of the investation if the duration of the disease can be determined. Ova in the liver vary in number according to several obvious factors. A few ova may indicate mild infestation, parasitism of short duration, a paucity of the female schistosome or poor ova production by those present. Numerous ova may mean severe parasitism, a marked level of ovigenesis or a relatively mild infestation of long duration. The amount of haematin in a liver is also a useful indication of the degree of infestation and its duration. Except for the relatively small amount entering the lymphatics and phagocytosed in the mesenteric lymph nodes, most haematin regurgitated from the gut of the schistosomes enters the liver with the portal blood. Haematinocytes in the intrahepatic branches of the portal vein indicate that some of the haematin has been phagocytosed prior to its arrival in the liver lobule. Cells of the reticuloendothelial system, including those of Kupffer, continue the phagocytosis of haematin in the liver lobules. It was apparent that, once filled with haematin, many of the cells, including Kupffer cells, pass out of the liver by two possible routes. Kupffer cells, which become detached, and possibly other phagocytes from the portal areas which reach the hepatic sinusoids probably leave by the efferent veins of the lobule passing eventually into the hepatic veins and on to the heart in the venous blood. Haematinocytes also appear to pass from the portal areas into the lymphatics and hence to the lymph nodes draining the liver [Plate 13 (83)]. Unphagocytosed haematin which passes through the liver to be phagocytosed in the lungs as well as haematinocytes reaching the capillaries of these organs contribute to the grey colour of them in heavily infested cases or those of long duration.

Certain conclusions can be drawn from the distribution of the haematin within the liver lobule. Though never identical, the distribution within the lobules was often similar in an individual case. A general scattering of pigment with all the aforementioned sites involved meant an active production by a large number of schistosomes. Haematin concentrated in haematinocytes of the portal areas meant relatively low parasitism of long duration. Where the haematinocytes were even more densely concentrated it meant that there had been a low number of parasites over a long period of time after which the parasites died, this being followed by another long period of time. An aid to making these deductions was the number of ova present and the age of the reaction surrounding them. This could easily be estimated in terms of chronicity by the quality of the reaction. Fairley (1920) emphasized that the pigments of bilharziasis and malaria are identical. Johnson, Hamilton & Gridley (1954) were also of the opinion that they cannot be distinguished, both being haemoglobin derivatives. They characterized the pigment as anisotropic, non-fluorescent and negative for iron by the Prussian blue methods but positive by microincineration.

After studying Manson's schistosomiasis, Von Lichtenberg (1955) classified lesions resulting from schistosome ova in intrahepatic portal radicles.

He found three types, namely, substitution of the lumen and wall of the vessel by granulomas with the result that it was no longer possible to recognize the vessels except by inference, secondly, sclerosis and narrowing of the vessels and thirdly, intrahepatic thrombophlebitis associated with the ova and resultant granulomatous reaction.

Coelho (1955) also found lesions due to eggs of *S. mansoni* to be primarily endovascular. He divided the reactions, which he thinks are due to the release of substances by miracidia, into three stages, *viz.* local tissue necrosis with exudative inflammation which occurs while the miracidia are alive, secondly, histiocytic reaction around ova in which miracidia are dead, the histiocytes being interpreted as evidence of antigen-antibody reaction, and the third stage consisting of giant-cell formation, fibrous regression, formation of collagenous nodules and recanalization. The result of the third stage was that the reactional tissue disappeared and the functional reintegration of the vessel was partially or completely restored.

Cheever (1961) using *S. mansoni* infested mice, observed that the granulomata in response to ova were also primarily endovascular.

Our observations in regard to sheep also support this as there were far more ova granulomas in the small interlobular veins of the portal canals than elsewhere. Applying the criteria which Von Lichtenberg (1955) and Coelho (1955) used in classifying reactions into types and stages respectively, it is obvious that the course of the reactions in the sheep is essentially similar to what they observed. There is some question, however, in regard to the restoration of the patency of the vessels in the more severely involved segments.

For many years various host reactions to schistosome ova have been alluded to as being hypersensitive in origin, as allergic manifestations, indicators of antigen-antibody reactions and many other similar designations have been applied. Andrade (according to De Paola & Winslow, 1967) believes that a "delayed type of hypersensitivity" occurs in some cases of Manson's schistosomiasis and that it is represented by an active hepatitis with no correlation between the intensity of the reaction and the number of parasitic elements. It has now been shown by Warren, Domingo & Cowan (1967) that in mice sensitized with *S. mansoni* eggs that the sensitization fulfils the basic criteria for an immunologic reaction of the delayed hypersensitivity type. They demonstrated significant increases in the size of the ova, granulomas in the sensitized over those of the unsensitized mouse. They showed that this sensitivity was transferred to other mice by cells and not by serum. In view of this work it appears that the prediction of Shaw & Ghareeb (1938) has been proven, in part if not in whole. On histological evidence they were inclined to the view that size of the dose, reinfestation, immunity and allergy determine the type of reaction to the ova "in a manner comparable to what Rich & McCordock (1929) have found in tuberculosis". With this added evidence that there are definite similarities between the granulomas in response to schistosome ova and the tubercles in response to tubercle bacilli, perhaps the use of the term pseudotubercle to designate the granuloma due to the schistosome ovum is vindicated. From the histopathological study of the host response of sheep to *S. mattheei* ova there is little doubt that there is a delayed hypersensitivity reaction in these animals as well. It will, however, be necessary to demonstrate the specificity of the sensitization by cells and to determine whether or not it is transferred by serum. In the sheep Types 2, 3 and "S" are interpreted as indicating highly reactive host responses. The presence of numerous eosinophiles in Type 3 and even more so in Type "S" further suggests a strong degree of hypersensitivity. The sudden appearance of eosinophiles, and their subsequent necrosis, in the centres of obviously old granulomas, some containing only remnants of ova shells, and the manifestation of the attraction of the eosinophiles to recently released ova is convincing evidence that some substance closely associated with the ova is responsible for this action. Using a complicated system and immuno-fluorescent staining, Von Lichtenberg (1964) demonstrated stainable schistosome antigen (SSA) within schistosome eggs in tissue as well as finding haloes of tiny dust-like granules on flecks near the eggs in the centres of granulomas. A similar material must be present in association with the ova of *S. mattheei* in these sheep. Von Lichtenberg (1964) postulated that the pseudotubercle contains antigen "sequestered" by phagocytes which would eventually be ingested and metabolized mostly within the granuloma. He indicated that, because of this antigen, the host would be sensitized and become capable of accelerated antigen-sequestration and destruction. The attraction of the eosinophiles to the "sequestered" antigen in the centres of the granulomas in the type "S" reaction is interpreted as meaning that the sheep has indeed become sensitized or possibly hypersensitized. While it is accepted that "sequestered" antigen also had an effect in sensitizing these sheep, the question can be asked why do not all of them show the Type "S" reaction. This exaggerated reaction involving the eosinophiles was obviously brought about rather suddenly by a change in the host-parasite relationship. There were three sheep which showed the Type "S" response to ova in the liver. One of these had been previously infested naturally but eventually became negative for ova shedding as determined by the miracidial hatching apparatus. It was given *per os* a total of 11,150 cercariae in three divided doses at five and seven day intervals. Only 46 adult worms were recovered at necropsy 71 days after the first challenge dose of cercariae was given. The other two had not been previously infested. One of them received a total of 15,300 cercariae given subcutaneously in two doses with a two day interval. A necropsy was performed on Day 72 at which 88 adult worms were recovered. The second was given percutaneously 9,400 cercariae in two doses separated by an eight day interval. At necropsy 61 days later 3648 worms were recovered. Similar experiments on other sheep did not result in Type "S" reactions and the reason for its occurrence in these cases cannot be satisfactorily explained. Von Lichtenberg (1964) pointed out that although differing in their response to diagnostic tests, the antigens of schistosomes and eggs share reactivity with the immunofluorescent antibody. It was thought that possibly the cercariae were responsible but since it occurred in only these three

sheep this was not a suitable explanation. Though the specific cause was undetermined this was interpreted as an increased sensitivity superimposed on a state of delayed hypersensitivity. The resulting attraction of eosinophiles to newly released ova, remnants of ova in the centres of large and very old granulomas and the accumulation of eosinophiles in the reaction around the portal canals were quite striking. Meleney, Sandground, Moore, Most & Carney (1953) interpreted the early cellular infiltrates in the periportal areas as an allergic phenomenon resulting from schistosomes in the mesenteric veins. Similar infiltrations were frequent in sheep even in the absence of ova in the immediate vicinity.

The acute or toxaemic form recognized in the human appears to be caused by a heavy initial exposure and is seldom seen in persons living in an endemic area (Andrade & Cheever, 1967). In such cases the periovular granulomas which were noted to be in the same evolutionary phase frequently showed central necrosis and numerous eosinophiles (Andrade & Cheever, 1967).

Bogliolo (1967) reports that in some individuals a hypersensitivity reaction occurs in the initial infestation and occasionally in individuals already hypersensitive because of previous infestation. One of the cases cited as showing the toxaemic form of the disease was an individual infested many years previously and showed Symmer's fibrosis (Bogliolo, 1967). In other words the acute toxaemic state may develop in a chronically infested patient with hepatosplenic schistosomiasis. Bogliolo (1967) attributed this to a change or modification of the already existing sensitivity or reactivity.

Andrade (according to Bogliolo, 1967) had the concept that some of the reactions to schistosome eggs could be considered hypoergic, normergic and hyperergic granulomas and this could not be solely explained by the stage of the eggs. Bogliolo (1967) indicated that in the acute toxaemic forms the granulomas are frequently exaggerated and that the necrotic and exudative features corresponding to the hyperergic reaction of Andrade are present.

In an analysis of 100 cases of schistosomiasis mansoni, De Paola & Winslow (1967) found that 15 per cent contained severe inflammatory infiltration in the portal tracts with destruction of liver cells in the periphery of the lobules without correlation with the parasitic elements. They referred to this as "piece-meal necrosis". Such necrosis was frequently observed in the Type "S" reaction in the sheep and less often in Type 3.

From the foregoing paragraphs and the previous descriptions and discussions of the Type "S" reactions in sheep, it would appear that the acute or toxaemic form occasionally seen in man also occurs in sheep, *viz.* the Type "S" reaction of the chronic cases. If it occurs in the initial stage of the disease in sheep sometimes, and the authors suspect that it might, it has not been studied histologically.

With few exceptions the reactions to ova in the liver of the sheep could be classified in the broad spectrum of granulomatous reactions. The exceptions were reactions to those recently arrived ova because insufficient time had elapsed for a granuloma to form. A study of the complete pathogenesis of the granuloma was not initiated as that was not intended from the start. Except for the occasional eosinophile or neutrophile present, the first cells observed around ova were small round ones but there were invariably well-developed granulomas elsewhere in the liver. Faust & Meleney (1924) in regard to *S. haematobium* infestation in human necropsies pointed out that persons dying from the disease have been repeatedly infested with the result that the stage of egg production is still present at death. As a result of this, all stages of reaction to the eggs as well as the end result of eggs deposited in the past, scar formation, are seen. So it is in the sheep. Some granulomas possibly terminate in resolution rather than sclerosis but once the fibrotic changes occur they remain as signs of the encounter for a long time.

Before considering the question of whether there is cirrhosis of the liver in sheep with bilharziasis, a brief review of pertinent points on this in regard to man and experimental animals is indicated. The name of Symmers has long been associated with a marked increase in connective tissue in the liver of humans suffering from the hepatic involvement of bilharziasis. Symmers (1904) gave a detailed description of the changes in the appearance of the liver resulting from bilharziasis and likened the macroscopic appearance of the cut surface of the organ to what it would look like "if a number of white clay-pipe stems had been thrust at various angles through the organ". Since then the term "Symmers' clay-pipe stem cirrhosis" has been closely associated with hepatic involvement in bilharziasis. Many of the conditions which are characterized by fibrosis and which were once called one or other type of cirrhosis are not now considered by some pathologists to fulfil criteria presently prescribed for a true cirrhosis. Hamilton, Hutchison, Jamison & Jones (1959) placed cases which had "clay-pipe stem cirrhosis" of Symmers in a group which they designated "'pipe stem' portal fibrosis". A second group of cases showed coarse nodular cirrhosis and evidence was presented to support the author's contention that dead adult schistosomes may be capable of causing this histologic alteration in the liver of humans. Their third group was characterized by diffuse involvement of the majority of the fine portal areas by some degree of fairly regular fibrosis and was designated as diffuse fibrosis cases. Hashem (according to Hamilton *et al.*, 1959) described coarse periportal fibrosis in the endemic form of the hepatosplenomegaly due to bilharziasis. Bogliolo (1957) considered Hashem's diffuse portal fibrosis to be synonymous with Symmer's clay-pipe stem cirrhosis. Hamilton *et al.* (1959) were of the opinion that the changes described by Hashem fail to fulfil the criteria for true portal cirrhosis.

From these and other references it is evident that there is non-unanimity of opinion. There are at least three groups of distinct reactions (Hamilton *et al.*, 1959). Using these as a guideline for sorting out the types of fibrosis present in the sheep cases, the one called "pipe stem" portal fibrosis was most frequently present. Rather than being uniform it appeared to be associated with fibrosis of the ova granulomas. It is apparent from Le Roux's illustration

and descriptions (1929) that he saw diffuse portal fibrosis and probably coarse nodular cirrhosis as well but the currently collected cases did not show these changes.

Gillman (1957) was of the opinion that venous obstruction by dead adults was important in the pathogenesis of hepatic bilharziasis. Menenzes (1963) considers the dead worm of importance in production of Symmers' fibrosis.

From their schistosomiasis studies in the mouse, Cameron & Gangulay (1964) considered the chronic hepatic lesions not to be a true cirrhosis and "more correctly labelled as a confluent, progressive, schistosomal fibrosis which is the outcome of many egg granulomas". They considered that infarcts play a small part in the subsequent fibrosis but that schistosomal pigment is a potent fibrogenic agent. They found the hepatic fibrosis to be a reversible process. Gear (1967) has made the same observation in monkeys following successful therapy with schistosomacidal drugs. The present authors feel that the dense collagenous deposits observed in very chronic cases of sheep will probably remain for a very long time but cases with long time intervals between treatment and necropsy have not been studied by them.

Macroscopically the grey lungs due to the accumulation of haematin are the best indication of bilharziasis in the thorax. Hydro-thorax, hydro-pericardium, the secondary atelectasis and the pneumonic areas of the apical and cardiac lobes were most severe in sheep which one must regard as having a massive infestation, or in other words, as being superinfested. Varying numbers of adults were recovered from the lungs of a few heavily infested sheep and none in others when the pulmonary vasculature was perfused. Those which were recovered were frequently very small and stunted in appearance. Their original source was not definitely determined. The impression was gained, however, that they represented adults which had matured in, and continued to remain in the pulmonary arterial tree but the possibility that they somehow bypassed the liver was not ruled out.

With the exception of the mouth, pharynx and the oesophagus, all segments of the digestive tract were affected by adult schistosomes and ova deposition. Our observations on the additional sheep only confirm the astute observation of Le Roux (1929) on this system. Also as observed by Le Roux, the ova in the mesenteric lymph nodes were due to the fact that adult schistosomes depositing the ova were in veins of the nodes. A smaller number may possibly pass into the lymphatics.

The demonstration of single cases in each of the urinary organs, the kidney and urinary bladder, is interpreted as an indication of the rarity of their involvement in ovine bilharziasis.

Accurate counts were not made on the number of schistosomes causing mortality in natural infestations of sheep. Those observed were not simple cases of bilharziasis but mostly dual and frequently multiparasitic infestations. The impression was gained, however, that bilharziasis may predispose to heavier parasitism by other helminths. In the experimental cases, even those which were lightly infested, it was observed that the animals eventually became very weak, emaciated and apparently quite anaemic. Anaemia occurs in the human with schistosomiasis complicated by splenomegaly (Woodruff, Shafei, Awwad, Pellitt & Abaza, 1966). The anaemia which was apparent clinically and at the time of necropsy in many of the sheep in this study was studied in detail on a limited number of them. These findings along with other clinical pathology of the disease in both experimental and natural cases will be reported in a separate paper (Malherbe, W. D., Vet. Faculty, Univ. Pretoria, personal communication, 1968). Lengy (1962) found severe anaemia in a lamb infested with between 20,000 and 30,000 cercariae of *S. bovis*, the haemaglobin value dropping to 2·5 gm per 100 ml of blood and the total erythrocytes to 1·49 million per cubic mm in 16 weeks. We consider that this level of infestation is a superinfestation far exceeding what will result from natural infestations even under, parasitologically speaking, "ideal conditions". Elsdon-Dew & Bhagwandeen (1967) called attention to the differences in the individual parasite load as being a factor determining the degree of pathogenesis in man. It also appears to be a very important one in sheep.

Bilharziasis of cattle

The total number of cattle cases which were studied was not included, but even had they been, they were still too few to feel confident that there were enough on which to base a complete description of the spectrum of this disease in cattle. There is, however, such a dearth of reports concerning the pathology that perhaps this account will, if for no other useful purpose, serve as a stimulus for a more thorough study by someone in a position to deal with more cattle, especially naturally occurring cases.

There were obvious differences between the disease in cattle and sheep. The corresponding difference in the size of animal, however, stifles comparison because level of parasitism for comparative purposes as regard to severity of effect on two hosts must of necessity start on an even basis. Should this be based on the overall body weights, length of the intestinal tracts or the weight of the livers? In areas where natural cases were occurring the sheep were dying from massive infestations of schistosomes and other parasites whereas cattle though considerably affected were not dying except following schistosomacidal therapy.

Pigmentation of the lungs and liver of sheep is striking but of little or no prominence macroscopically in cattle. In correspondingly heavy infestation, the adults are found readily in the mesenteric veins of either species. Urinary bladder involvement of sheep as previously pointed out is very rare but common in cattle. The impression was gained that more ova reach the liver of sheep than ova do in cattle. There are two thoughts about why this is so in addition to the aforementioned considerations of size of animal, size of liver, levels of parasitisms, etc. The first is that perhaps *S. mattheei* in cattle produce fewer eggs than those of sheep over a long period of time and the second thought is that perhaps the ova produced, more easily gain the lumen of the intestinal tract of cattle than in sheep. Should it prove to be the latter

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it would support the thought that the schistosome *S. mattheei* and cattle have a better adapted host-parasite relationship than exists between *S. mattheei* and sheep.

The eosinophilic antigen-antibody deposits around many of the schistosome ova in some of the bovine livers [Plate 13 (84)] are interpreted as indications of a strong hypersensitivity to antigen associated with the ova. This reaction is histologically typical of those observed by others and it is spoken of as the " Hoeppli " phenomenon (Von Lichtenberg, Sadun & Bruce, 1962). They observed it in the liver of a woodchuck which was infested with *S. mansoni* describing it as "precipitation of highly refringent eosinophilic material around the intact egg shell". Meleney *et al.* (1953) described a similar reaction around the ova of *S. japonicum* as a flame-like, red-staining material extending outward from the egg shell. They also mentioned the fact that this had been first depicted by Hoeppli (1932). They further called attention to the term "eosinophilic fringe" as applied to this reaction around ova of *S. mansoni*, it having been used by Koppisch (1941). Von Lichtenberg (1964) thought that immuno-fluorescent staining of eggs was probably related to precipitin antibodies responsible for, among other things, the Hoeppli phenomenon. Though present less often than in cattle, it was also observed around some of the ova of sheep livers in this study. The presence of an ovum with the Hoeppli phenomenon surrounded by a large multinucleated foreign-body type giant cell which is in turn surrounded by a zone of small round cells within the lumen of an intrahepatic branch of the portal vein of an ox is believed to be a unique finding and, as far as can be determined, without precedent in the literature. If the Hoeppli phenomenon is interpreted as an indication of a strong hypersensitivity to antigen associated with the ova (Von Lichtenberg, *et al.*, 1962) then this must surely be interpreted as a strong host hypersensitivity to the Hoeppli phenomenon.

The thrombophlebitis associated with the dead adult schistosome has been dealt with by many authors, having been observed in man, experimental and domestic animals [Shaw *et al.*, 1938; Coelho (according to Hamilton *et al.*, 1959); Menenzes, 1963; McCully, 1966]. In many of these cattle and sheep the final result was removal of the dead worm and the thrombus from the vein with the accompanying destruction of the wall, a large lymphoid nodule frequently marking the site of the lesion. These lymphoid nodules of some of the cattle were previously described (McCully, 1966) and somewhat similar ones were observed in the hippopotamus (McCully, van Niekerk & Kruger, 1967). In the latter species there was no specific correlation made in regard to their being a response to dead adults as in cattle. There was actually a much closer resemblance to a true lymph node in the hippopotamus than in cattle or sheep. The authors believe that such nodules occur in the hippopotamus in response to the living adult *Schistosoma hippopotami* Thurston, 1963.

Letulle (according to Dew, 1923) described in humans an endophlebitis of veins containing bilharzial adults and regarded it as being due to the local action of a toxin. McCully (1966) described a similar endophlebitis of the intrahepatic branches of the portal vein of ruminants. It was attributed to the live adult *S. mattheei.* McCully *et al.* (1967) described extensive cardiovascular changes in the hippopotamus. The changes were characterized by the formation of either single or multilayered structures in the heart, pulmonary arteries and various veins, the new linings being called pseudo-endocardium and pseudo-intima respectively. They were attributed to the presence of live adult *S. hippopotami* with a suspected state of sensitivity existing in the host.

The role of haematin in the liver of the cattle deserves further consideration. Perhaps a better designation would be haematin and closely associated substances. By this it is wished to infer that there are thought to be other substances from the gut of the schistosomes, more specifically enzymes which being present in the gut would have ample opportunity to adhere to the granules of haematin pigment. Aside from being a potent fibrogenic agent (Cameron *et al.*, 1964) there was evidence to suggest that it was either irritating or acted by some other means to stimulate phagocytosis by macrophages and multinucleated giant cells. While some of the latter might be classified as foreign-body type, others were more like the Langhans type.

The presence of schistosome ova in seven of the nine urinary bladders examined indicates a high incidence of involvement. In a survey of 2,509 cattle in abattoirs in Southern Rhodesia, Condy (1960) found adult schistosomes of *S. bovis* in the mesenteric veins of 1,735 (69·15 per cent). The main lesions observed were in the urinary bladder where some could invariably be seen in the trigone. He was, however, able to demonstrate ova in only 3 per cent of the 1,000 urinary bladders examined. He found schistosome ova in a small number of ovaries and Fallopian tubes and, in one case only, in the uterus. Ova were found in the only uterus which was sectioned from the present group of cattle. It was sectioned because there were macroscopic indications of lesions.

Pitchford (1959) mentioned the possibility that there may be more than one schistosome parasitising cattle in South Africa. All of the schistosomes in the currently collected sheep cases and those in cattle were considered to be *S. mattheei.*

Regions of South Africa which are presently those farming areas in which low level bilharzial infestations are fairly constant in cattle having access to natural water are predominantly cattle-raising locales. Were they sheep-raising areas instead, the disease would undoubtedly be of more economic importance to the country. Based on experience recovering *S. mattheei* from cattle sent from the Lowveld to the Pretoria and Johannesburg abattoirs, it is known that most of them have a few schistosomes in the mesenteric veins.

Bilharziasis of domestic ruminants thus appears to be a problem only under certain changes in the environment. Sudden changes in the ecological state have been associated with unusually wet weather

over a period which is normally dry or in instances of concentrations of animals and snails around a limited water supply, an example of which was given.

Summary

This report primarily concerns the macroscopic and microscopic pathology in sheep and cattle with either natural or experimental bilharziasis due to *S. mattheei*. It is based on the study of 100 cases in sheep and 14 in cattle. The macroscopic findings were essentially the same as those previously reported for the sheep. Histopathologically the most significant changes result from the ova and dead schistosomes. The liver reflects the effect of ova which reach the small interlobular branches of the portal vein. It is suspected from the granulomatous response to the ova, this by the way being primarily endovascular, that the lesions are a type of delayed hypersensitivity reaction. There was evidence in a few cases that there was an even more sensitive reaction superimposed on this. Correlations between these and the toxaemic form of the disease in humans were made. The Hoeppli phenomenon was observed in response to ova in both sheep and cattle, being more pronounced in the latter.

Examples of conditions which can lead significantly to increased levels of parasitism in enzootic areas are given. The conclusion is drawn that cattle are less affected than sheep and goats.

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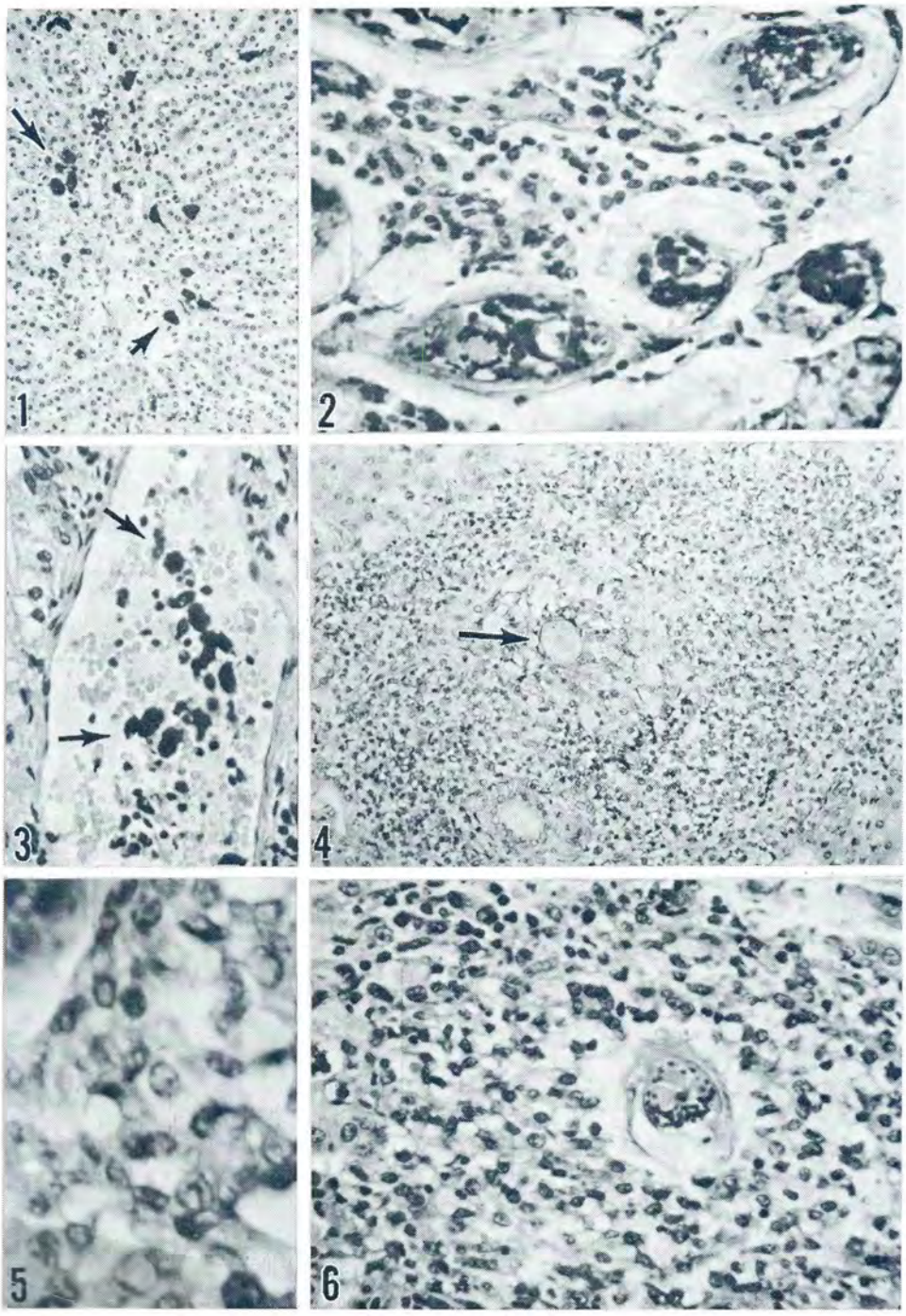

PLATE 1.—Photomicrographs** from microscopic sections of ovine liver. 1. Haematinocytes (arrows) in the central vein and the hepatic sinusoids. ×150. 2. Type 1 reaction to schistosome ova within an interlobular branch of the portal vein. ×150. 3. Haematinocytes (arrows) in a small branch of the portal vein. ×300. 4. Type 2 reaction to schistosome ovum (arrow) in a portal area. ×150. 5. Higher magnification of the histiocytic cells of Type 2 reaction. ×750. 6. Typical Type 2 reaction with the exaggerated histiocytic response to an ovum in the lumen of a small branch of the portal vein. ×150

** These and all other photomicrographs on the plates which follow were photographed from microscopic sections stained with haematoxylin and eosin (H & E)

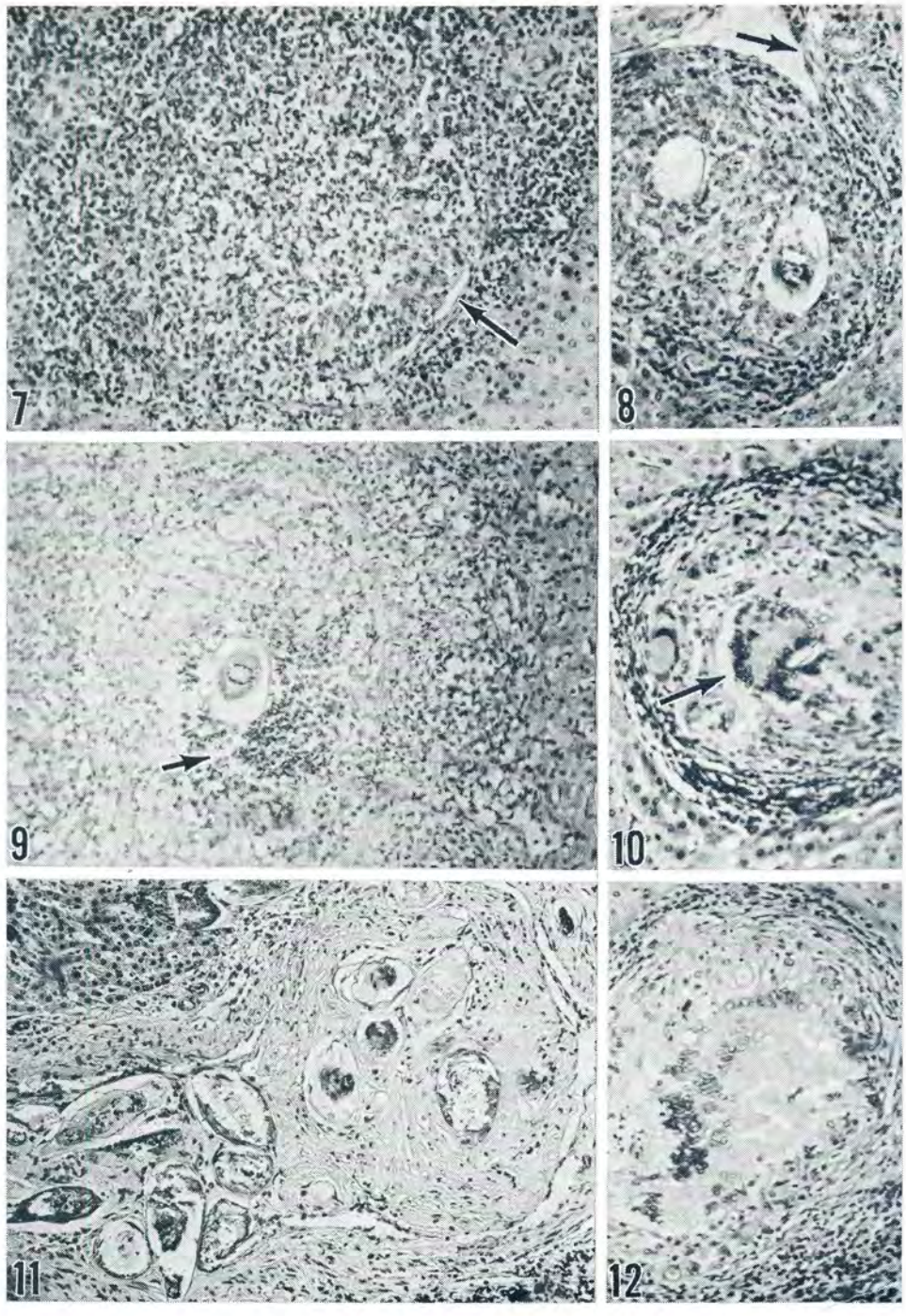

PLATE 2.—Photomicrographs from microscopic sections of ovine livers. 7. Type 3 reaction within an interlobular branch of the portal vein of a portal canal. Notice that the reaction consisting of histiocytes and eosinophiles almost fills the lumen (arrow). ×150. 8. Type 4 reaction within an interlobular branch of the portal vein. Notice bile ducts (arrow). ×150. 9. Type 3 reaction in an interlobular branch of the portal vein. Notice the concentration of necrotic eosinophiles (arrow) near the ovum as well as elsewhere among the histiocytes. ×300. 10. A slightly more mature Type 4 reaction. Notice the large multinucleated foreign-body type giant cell (arrow) in the centre. ×150. 11. Type 6 reaction showing fibrotic encapsulation of ova within a small branch of the portal vein. ×150. 12. Advanced stage of Type 4 reaction. Notice the capsule which is forming around the epithelioid and giant cells. ×150

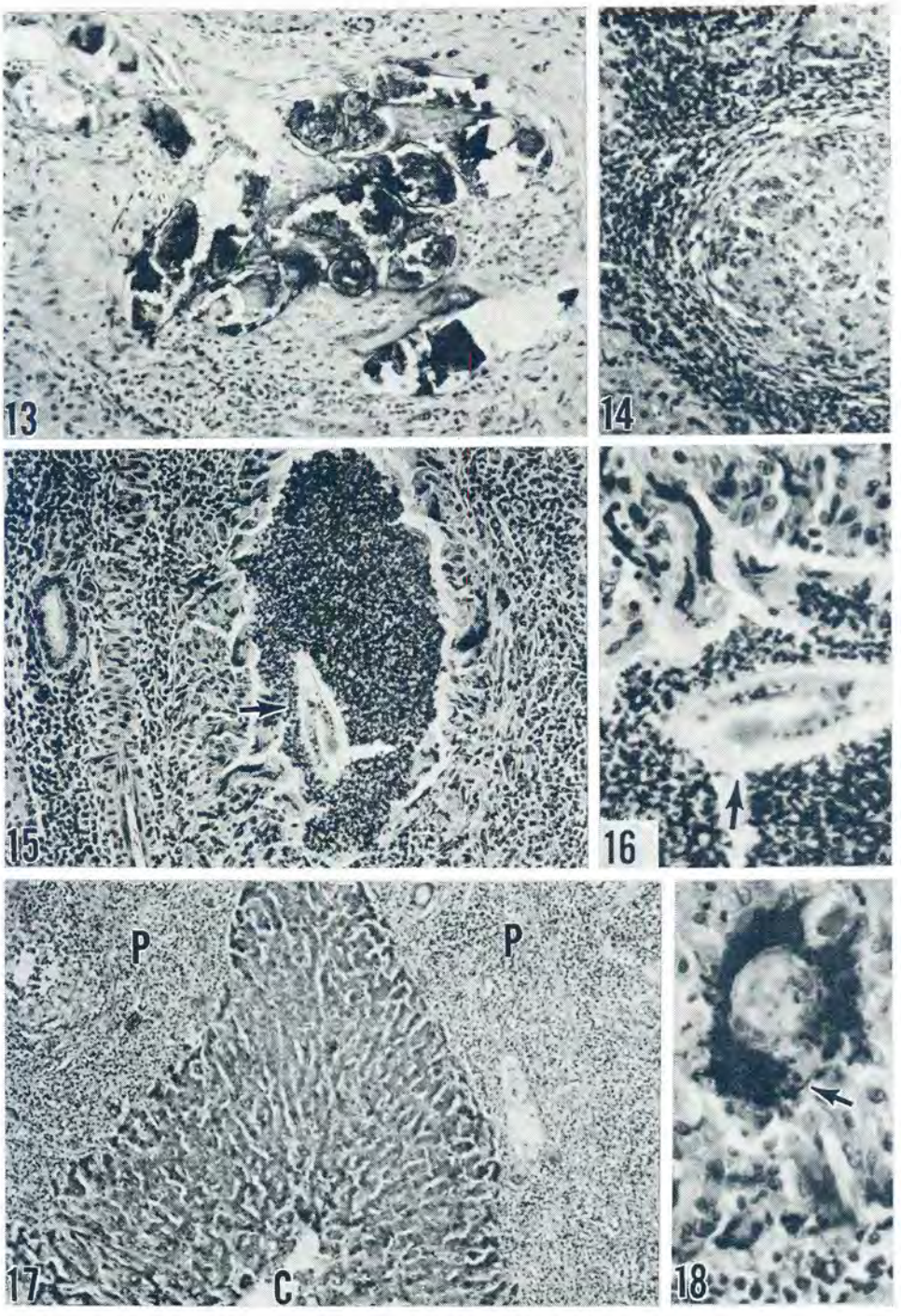

PLATE 3.—Photomicrographs from microscopic sections of ovine livers. 13. Calcified ova in Type 6 reaction of an interlobular branch of the portal vein. ×150. 14. Outer zone of small round cells surrounding the inner zone of the Type 4 reaction. ×150. 15. Type "S" reaction to ovum in an interlobular branch of the portal vein. Notice ovum (arrow) surrounded by necrotic eosinophiles which are in turn encircled by epithelioid and giant cells. ×150. 16. Higher magnification of the ovum (arrow), the zone of necrotic eosinophiles and epithelioid cells of (15). ×300. 17. Type "S" reaction in the portal areas of a lobule. Central vein (C) and portal areas (P). 18. Antigen-antibody type of substance (arrow) around an ovum in Type " S " reaction. ×300

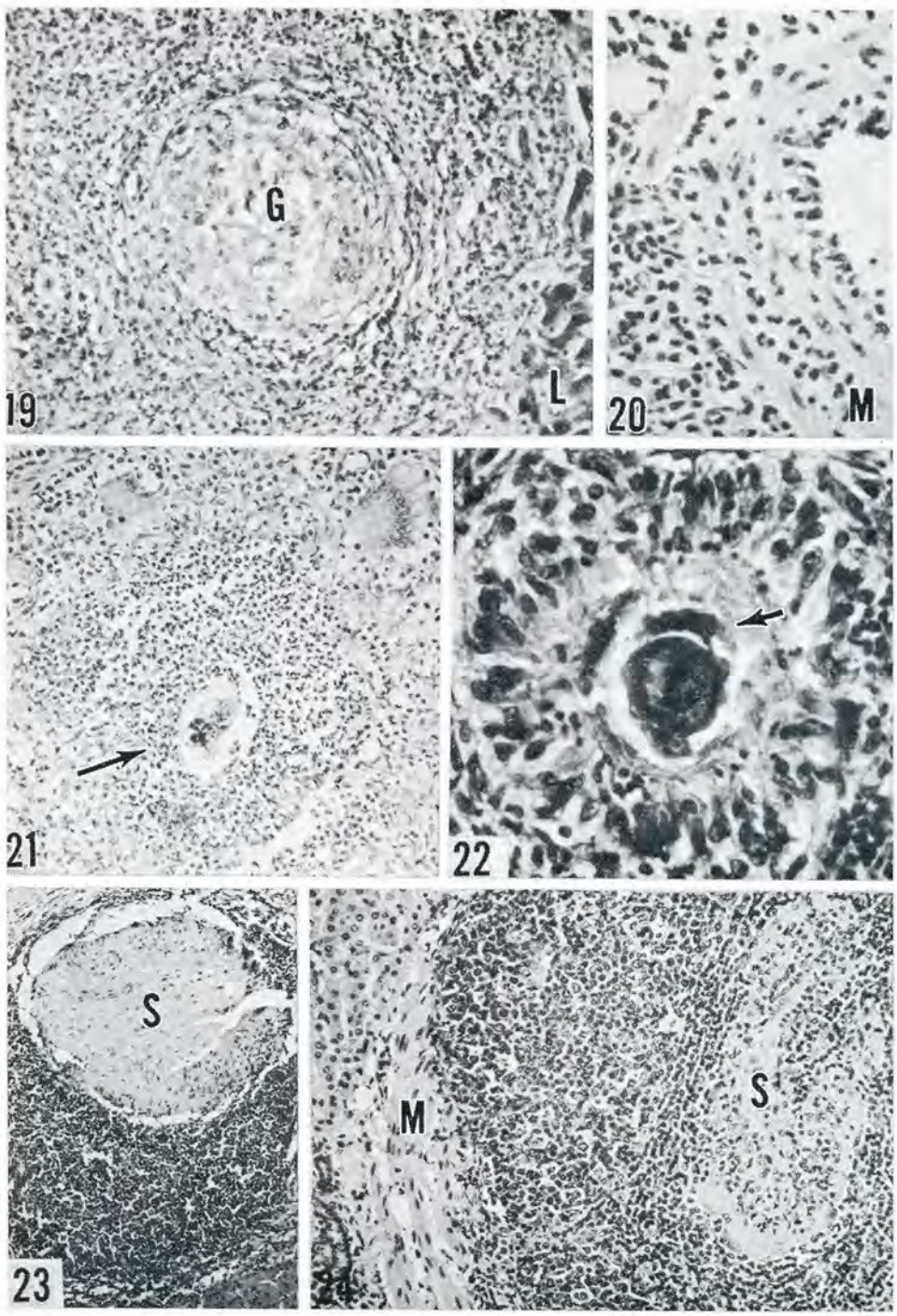

PLATE 4.—Photomicrographs from microscopic sections of ovine livers. 19. Type " S " reaction which is superimposed on a Type 4 granulomatous one. Notice the wide outer zone of inflammation composed of eosinophiles and small round cells surrounding a granuloma (G). Liver cord cells (L). ×150. 20. Small branch of the portal vein showing panphlebitis. Notice the eosinophiles in the media (M). ×300. 21. Type "S" reaction superimposed on Type 4. Notice the necrosis of eosinophiles centrally around the ovum (arrow) and the multinucleated giant and epithelioid cells peripherally. ×150. 22. Ovum granuloma from a case showing Type "S" reaction. Notice the material around the ovum (arrow) and the spokewheel arrangement of the epithelioid cells. ×300. 23. Lymphoid reaction to a dead schistosome (S) in a small branch of the portal vein. ×75. 24. Lymphoid reaction to a dead schistosome (S) in a larger branch of the portal vein. Notice that the wall of the vein has been destroyed with only remnants of smooth muscle remaining (M). ×150

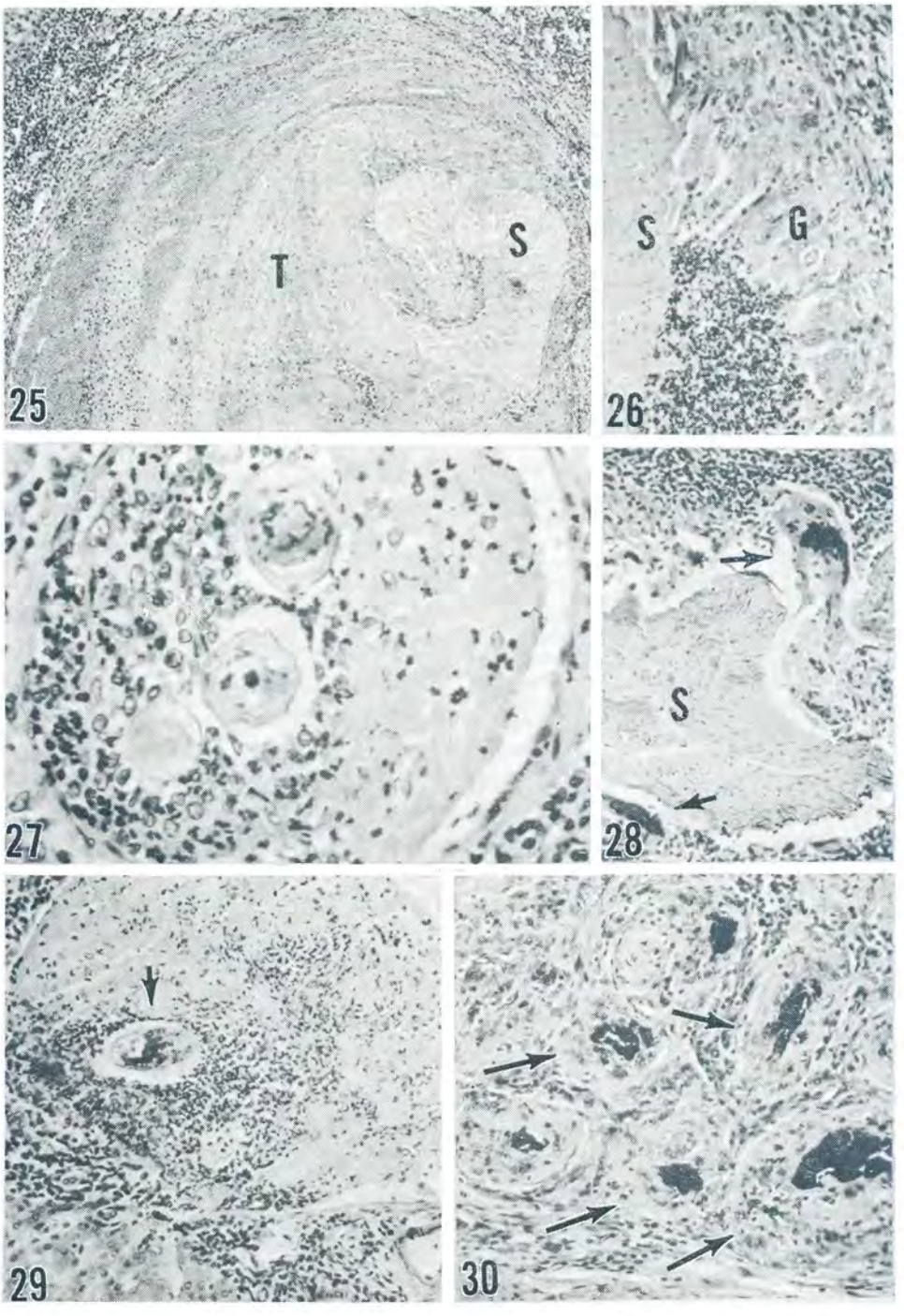

PLATE 5.—Photomicrographs from microscopic sections of ovine livers. 25. Dead schistosome (S) within a thrombus (T) in a branch of the portal vein. ×75. 26. Granulomatous response (G) to dead schistosome (S) within a branch of the portal vein. ×150. 27. Cellular response from the intima and thrombosis of an interlobular branch of the portal vein because of schistosome ova. ×303. 28. Phagocytosis of parasitic material by foreign-body type giant cells (arrows). Dead parasite (S). ×150. 29. Inflammatory response from the intima and thrombosis of the vein in a portal canal as a result of an ovum (arrow). ×150. 30. Multiple cross sections of schistosomes (arrows) with host response in a branch of the portal vein. Notice the haematin in the gut of the parasite. ×150

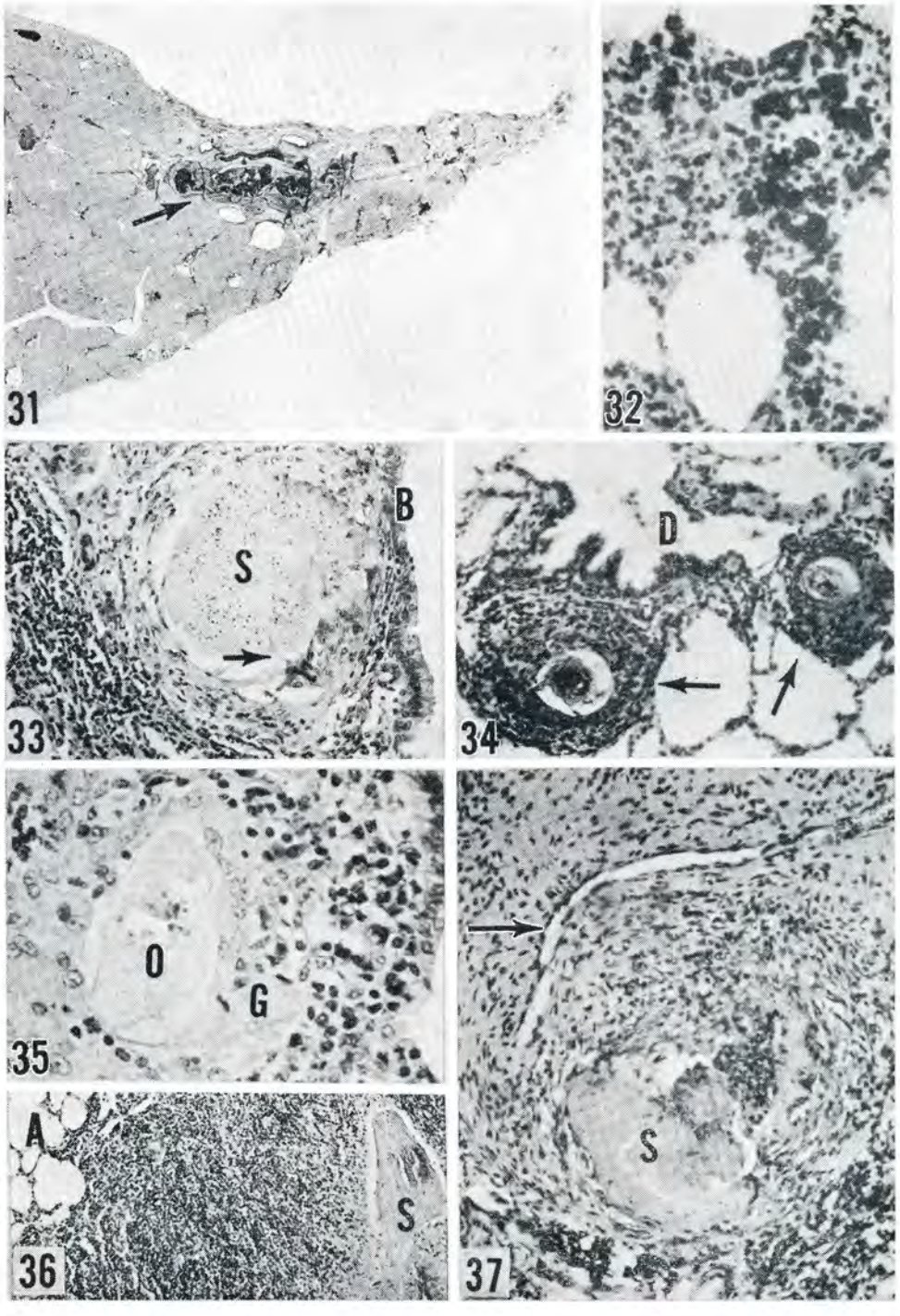

PLATE 6.—Photomicrographs from microscopic sections of an ovine liver and lungs. 31. Liver. An area of old infarction near the sharp edge of a lobe. Notice the obstruction of the branches of the portal vein (arrow). ×5. 32. Lung. Alveolar septa containing many haematinocytes. ×300. 33. Lung. Dead schistosome (S) in small artery adjacent to a bronchiole (B). Notice epithelioid cells and giant cells (arrow). ×150. 34. Two ova in arterioles (arrows) next to the alveolar duct (D). ×150. 35. Granulomatous reaction (G) surrounding ovum (O) within a small artery next to a bronchiole. ×300. 36. Extensive lymphoid proliferation within a branch of the pulmonary artery in response to a dead schistosome (S). Notice that the wall is no longer recognizable. Alveoli (A). ×75. 37. Dead schistosome (S) incorporated into the wall of a branch of the pulmonary artery. Lumen (arrow). ×150

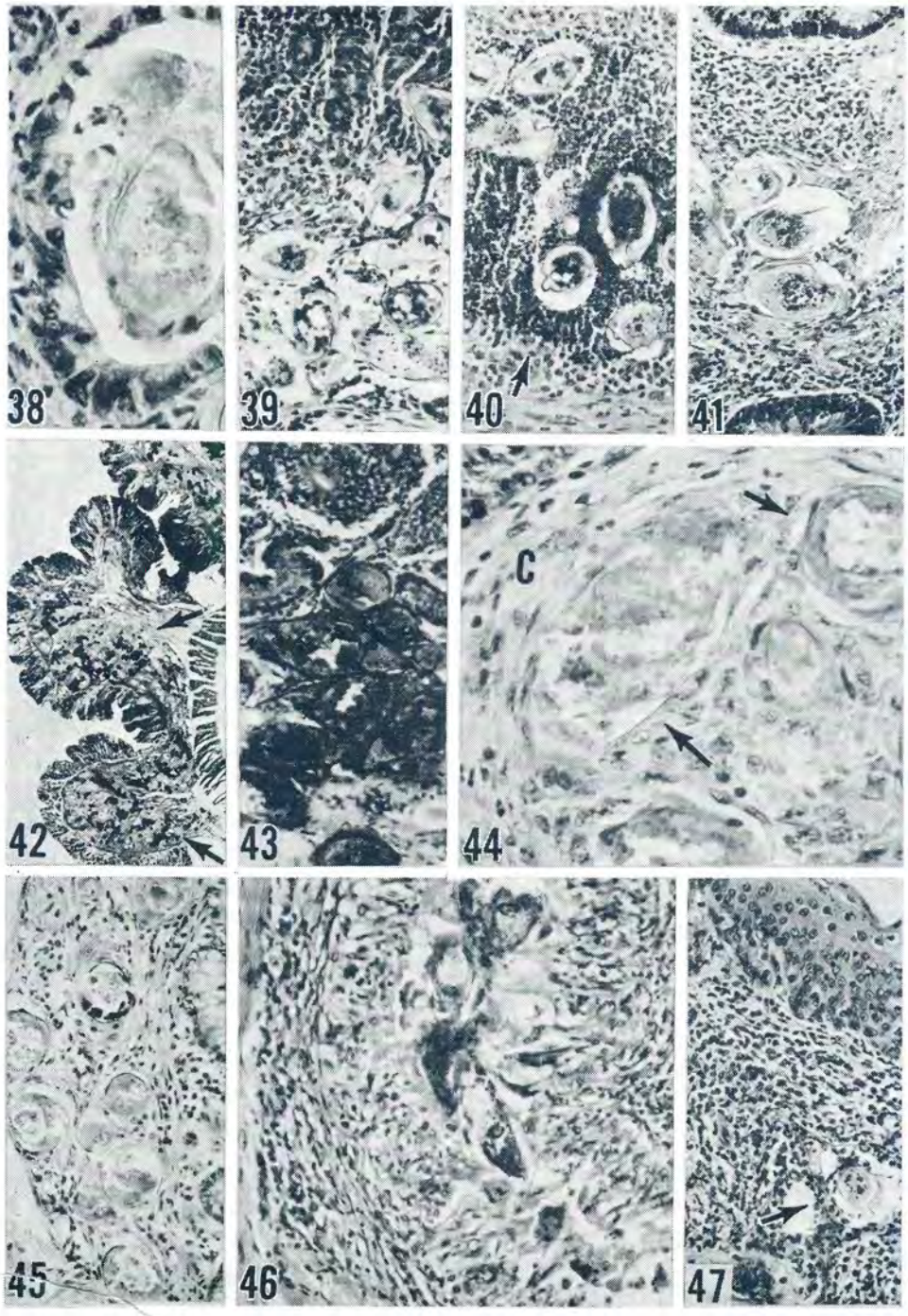

PLATE 7.—Photomicrographs from microscopic sections of ovine gastro-intestinal tract. 38. Small intestine. Ova in a crypt of Lieberkuhn. ×300. 39. Small intestine. Clutch of ova in the mucosa with little host reaction. ×150. 40. Small intestine. Intensely eosinophilic necrotic area (arrow) around ova in mucosa. ×150. 41. Small intestine. Host reaction around ova in mucosa. ×150. 42. Large intestine. Greatly thickened submucosa containing numerous mineralized ova (arrrows). ×10. 43. Large intestine. Mineralized ova in the mucosa. ×150. 44. Small intestine. Encapsulated ova (arrows) in the mucosa. Notice the mature appearance of the capsule (C). ×300. 45. Large intestine. Ova actually within the muscularis mucosae. ×150. 46. Small intestine. Granulomata in response to ova between the inner and outer layers of the tunica muscularis. ×150. 47. Reticulum. Diffuse infiltrate in the lamina propria in response to ovum (arrow). ×150

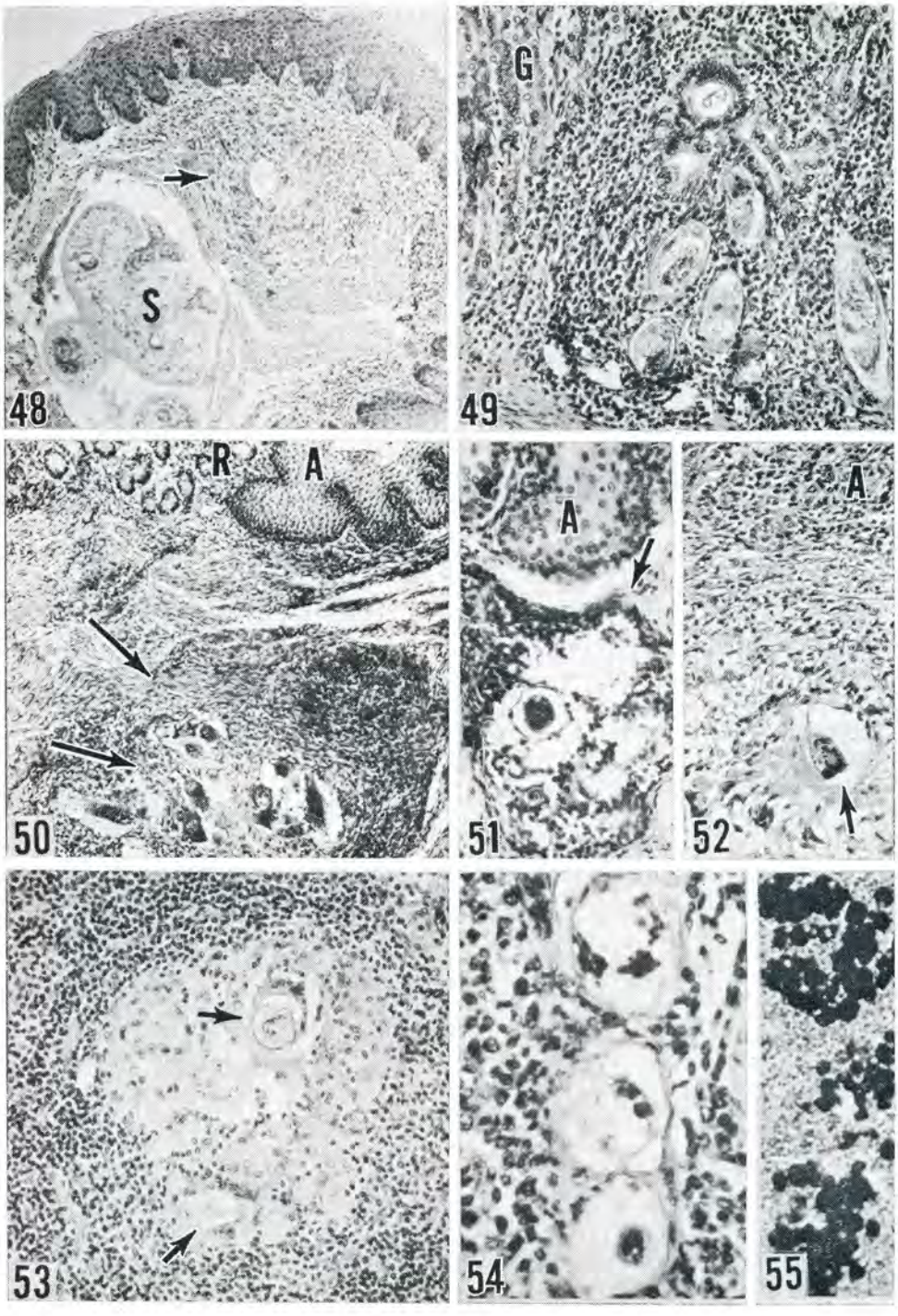

PLATE 8.—Photomicrographs from microscopic sections of the abdominal viscera. 48. Omasum. Schistosome (S) in a vein and an ovum granuloma (arrow) in the lamina propria. ×75. 49. Abomasum. Notice glands (G) and ova with surrounding inflammation in lamina propria. ×150. 50. Mucocutaneous junction of the anus. Glandular epithelium of the rectum (R). Stratified squamous epithelium of the anus (A). Notice the granulomata caused by schistosome ova (arrows) in the underlying tissues. ×75. 51. Anus. Ovum granuloma (arrow) adjacent to circumanal gland (A). ×150. 52. Pancreas. Ovum (arrow) within a granuloma. Notice the acini (A). ×150. 53. Mesenteric lymph node. Granuloma due to schistosome ova (arrows) in the medulla. ×150. 54. Mesenteric lymph node. Schistosome ova which were frequent in small veins were readily seen. Notice here that three are lined up in the lumen of a small vein. ×300. 55. Portal lymph node. Haematinocytes within the medulla. ×75

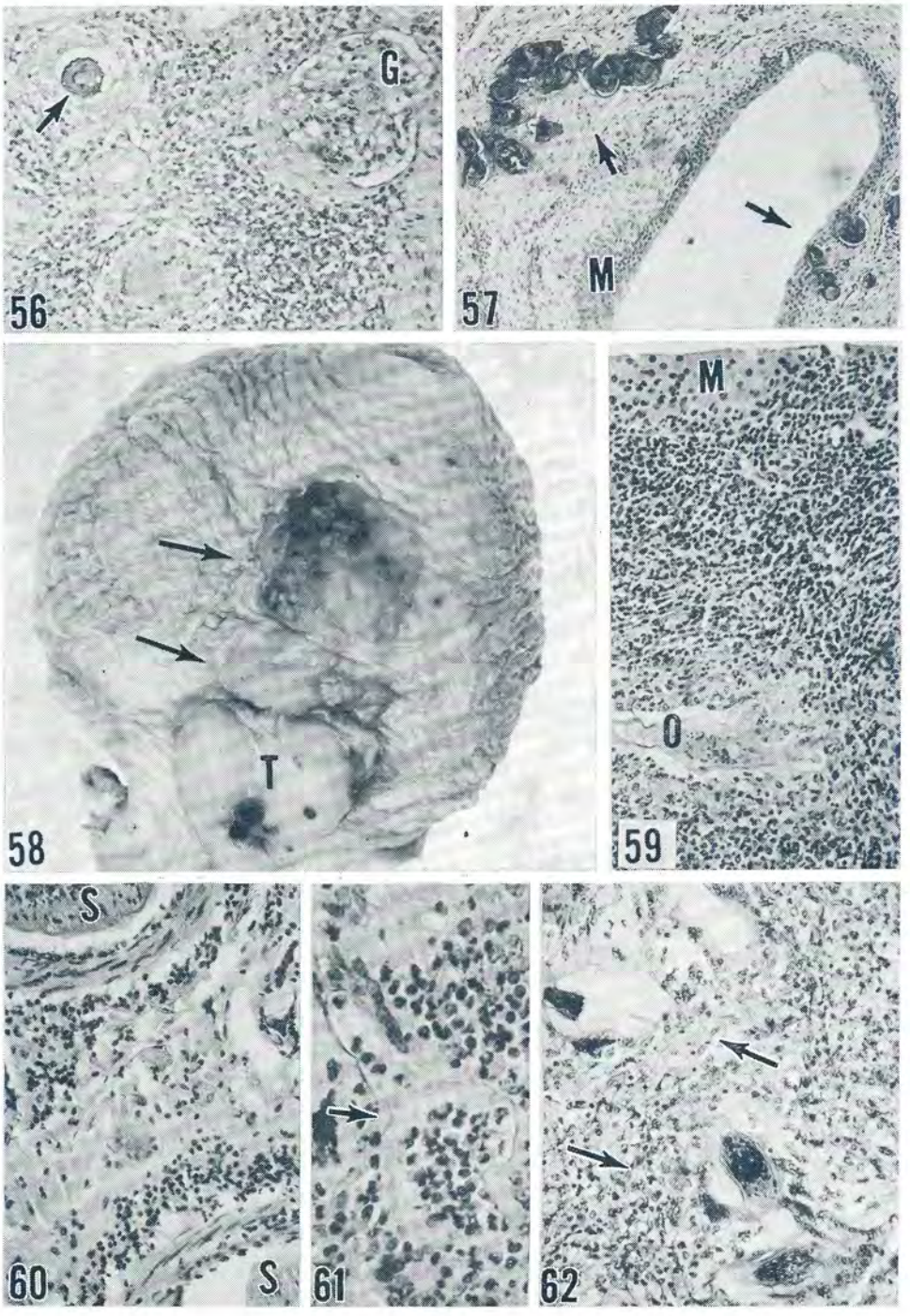

PLATE 9.—Macroscopic photograph of urinary bladder of an ox and photomicrographs from microscopic sections of the genito-urinary tract of sheep and cattle. 56. Skeep kidney. An extremely rare finding, a schistosome ovum (arrow) and granulomas near a glomerulus (G). ×150. 57. Urinary bladder of a sheep. Schistosome ova (arrows) in the lamina propria, another rare finding. Transitional epithelium of the mucosa (M.) ×75. 58. Macroscopic photograph of the urinary bladder of an ox. Notice the multiple raised areas of the mucosa (arrows) near the trigone (T) and haemorrhages on the trigone and elsewhere on the mucosa. 59. Urinary bladder of an ox. Schistosome ovum (O). Transitional epithelium of the mucosa (M) overlying an intense reaction consisting predominantly of eosinophiles and small round cells. ×150. 60. Urinary bladder of an ox. Perivenous infiltration by eosinophiles and small round cells. Notice schistosomes (S) in the veins. ×150. 61. Urinary bladder of an ox. Eosinophiles surrounding and within the lumen of the shell of a schistosome ovum (arrow). ×300. 62. Bovine uterus. Ova granulomas (arrows) within myometrium. ×150

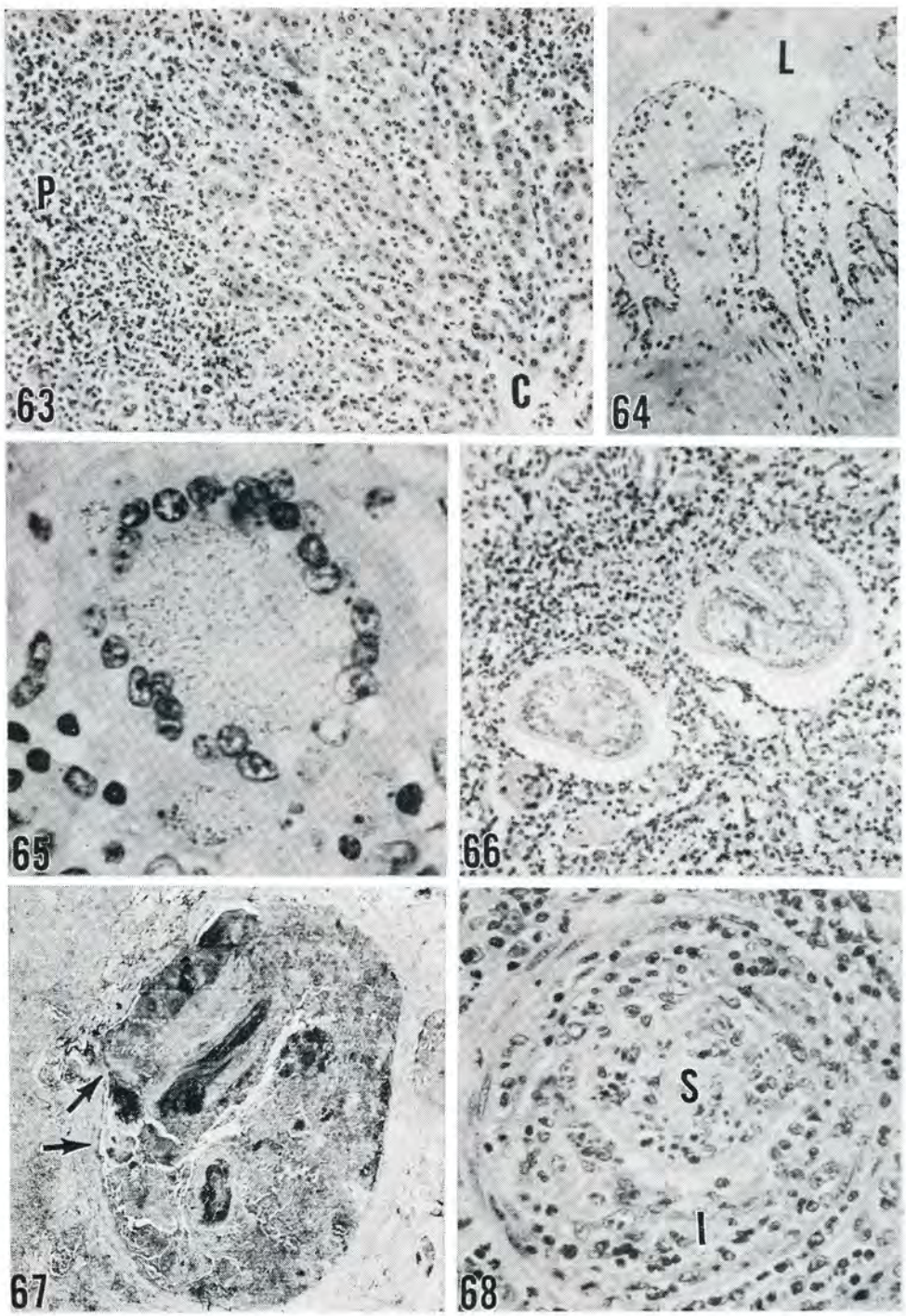

PLATE 10.—Photomicrographs from microscopic sections of bovine liver. 63. Diffuse mononuclear infiltrate in the portal areas and extending into the sinusoids. Central vein (C) and portal areas (P). ×150. 64. Branch of portal vein. Proliferative endophlebitis with many eosinophiles within the intimal projections. Lumen (L). ×150. 65. Haematin in the cytoplasm of a multinucleated foreign-body type cell within the hepatic sinusoids. ×300. 66. Branch of portal vein. Viable-appearing adult schistosomes enmeshed in the proliferative reaction from the intima. ×150. 67. Branch of the portal vein. Thrombus due to the presence of dead schistosomes (arrows). ×10. 68. Small interlobular branch of the portal vein. Extensive cellular reaction (I) from the intima in response to dead schistosome (S). ×300

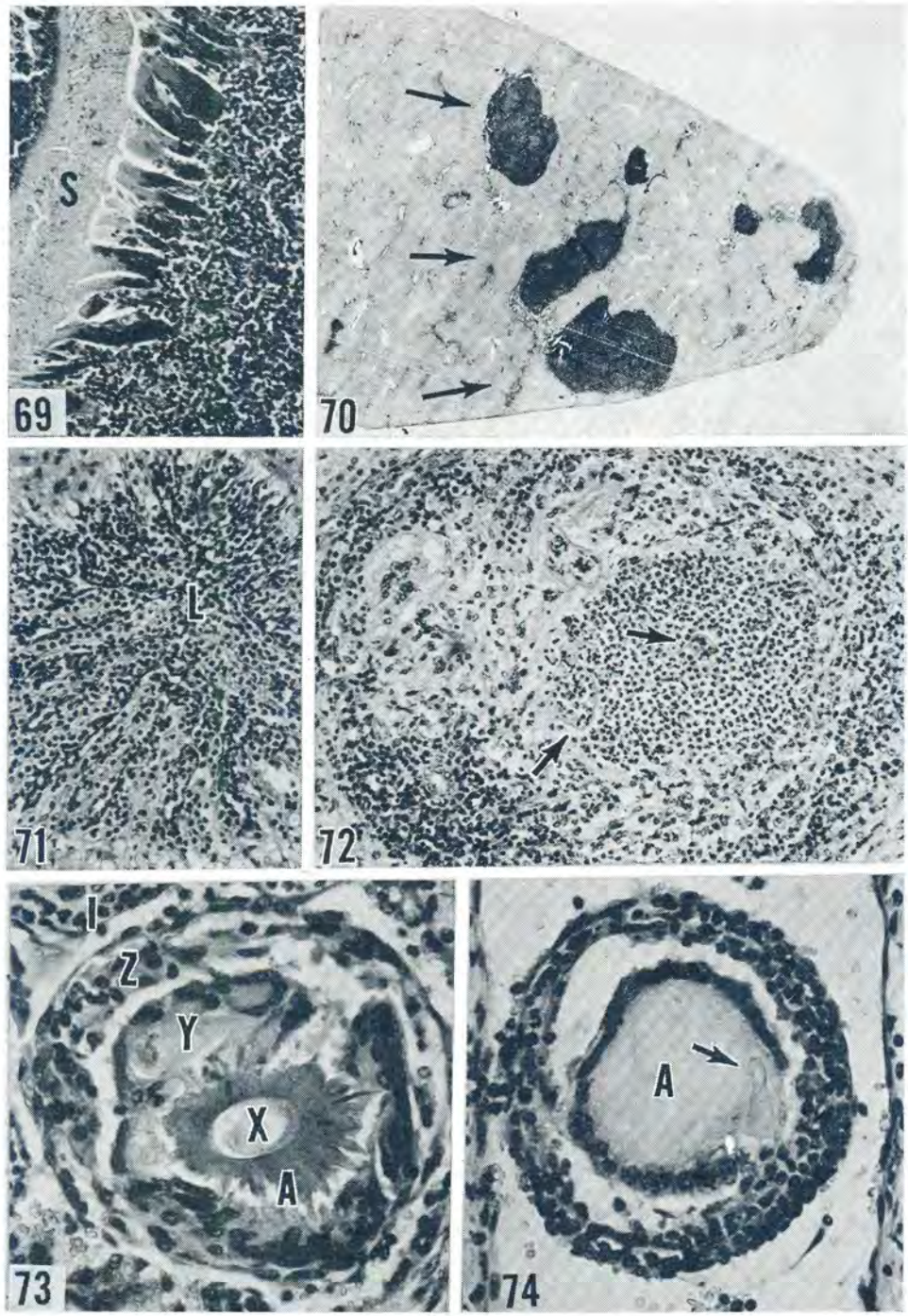

PLATE 11.—Photomicrographs from microscopic sections of bovine liver. 69. Granulomatous reaction to dead schistosome (S) in the centre of a lymphoid nodule within a branch of the portal vein. Notice the elongated cells immediately around the parasite. × 150. 70. Lymphoid nodules in small branches of the portal vein (arrows) near the sharp border of the lobe. × 5. 71. Lumen of a small branch of the portal vein which is completely filled by the villous intimal projections that are infiltrated with eosinophiles. Centre of lumen (L). × 150. 72. Pocket of eosinophiles around remnants of ova (arrows) within a granuloma. × 150. 73. Lumen of small interlobular branch of the portal vein. Ovum (X) surrounded by stellate-shaped accumulation of eosinophilic, antigen-antibody material (A), the Hoeppli phenomenon, within a large multinucleated giant cell (Y) which is in turn encircled by another group of cells (Z) within the vein. Intima (I). × 300. 74. "Bull's eye". Multinucleated giant cell (A) containing remnant of ovum shell (arrow) encircled by several rows of small round cells, all within the lumen of a small branch of the portal vein. × 300

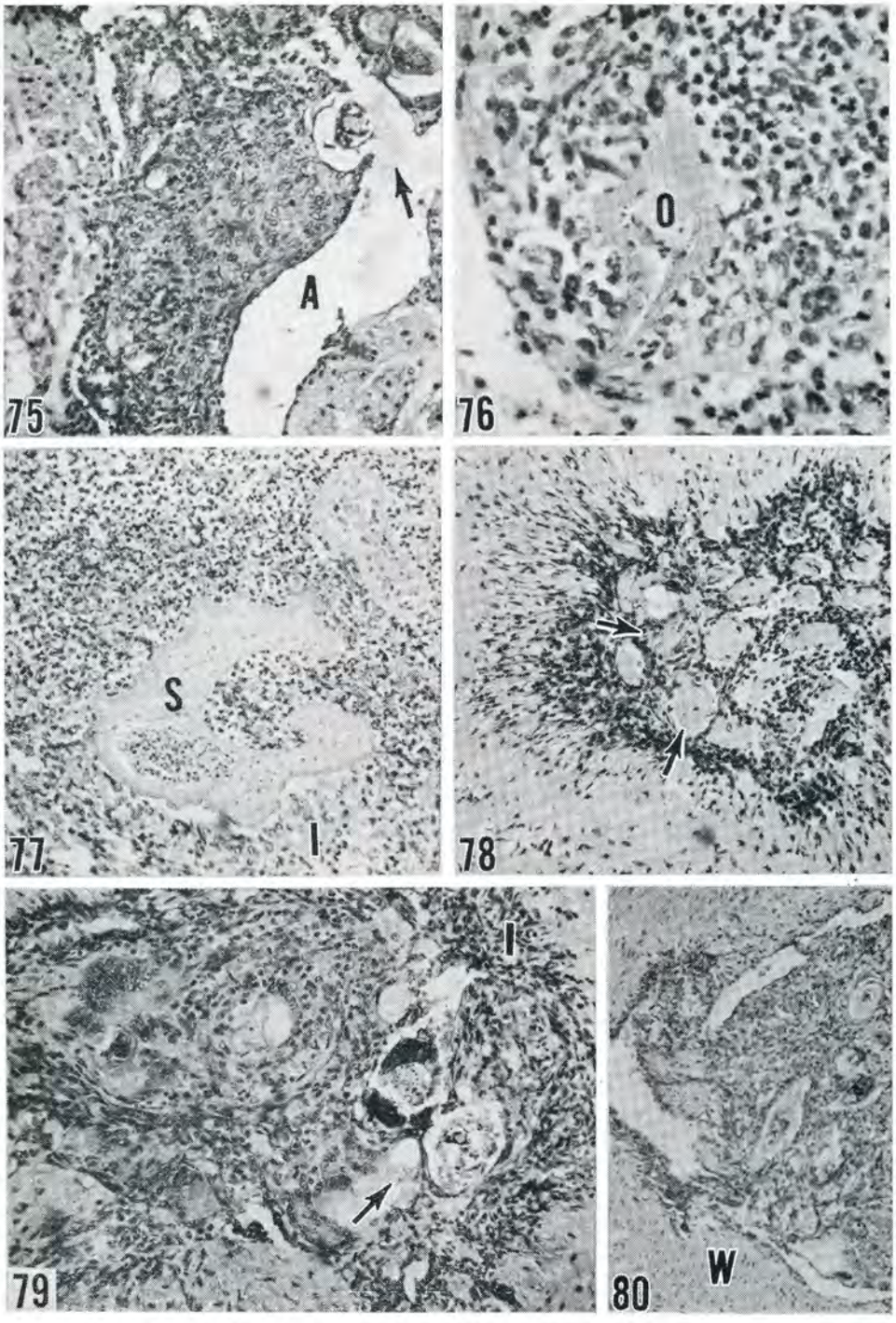

PLATE 12.—Photomicrographs from microscopic sections of branches of the portal vein and tributaries of the mesenteric veins. 75. Small interlobular branch of the portal vein in a portal canal. Notice the diffuse epithelioid proliferation surrounding the ova (arrow) and filling the lumen during life. Artefactural space (A). × 150. 76. Small interlobular branch of the portal vein. Ovum (O) encrusted with eosinophilic, antigen-antibody material, the Hoeppli phenomenon, surrounded by eosinophiles within a granuloma in the lumen. × 300. 77. Branch of the portal vein. Reaction to dead schistosome (S). Intimal proliferation (I). × 150. 78. Tributary of mesenteric vein. Severe proliferative, villous endophlebitis. Notice the collagenous piths (arrows) of the larger projections which have been sectioned transversely. × 150. 79. Mesenteric vein. Proliferative and granulomatous endophlebitis in reaction to ova (arrow). Intima (I). × 150. 80. Mesenteric vein. Fibrosis of an ovum granuloma within the lumen. Wall of vein (W). × 75

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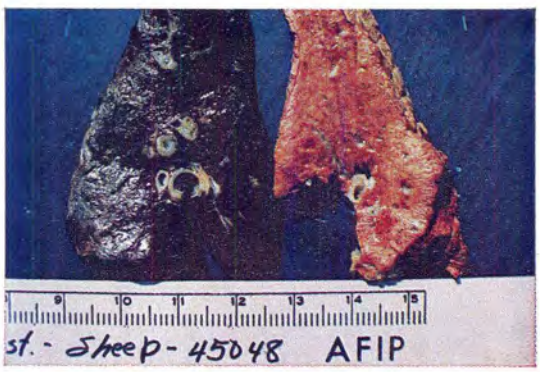

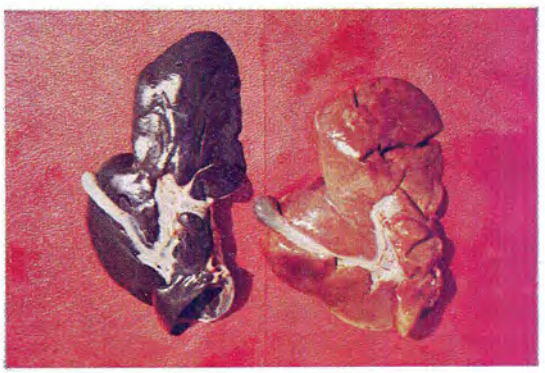

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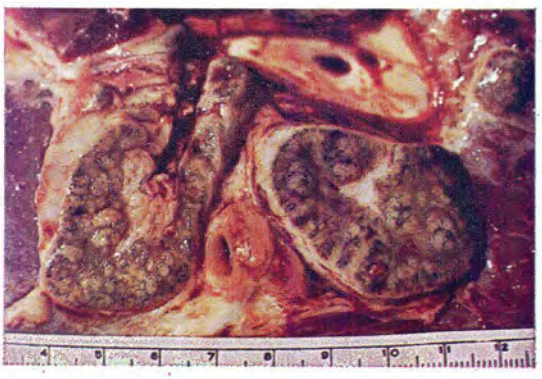

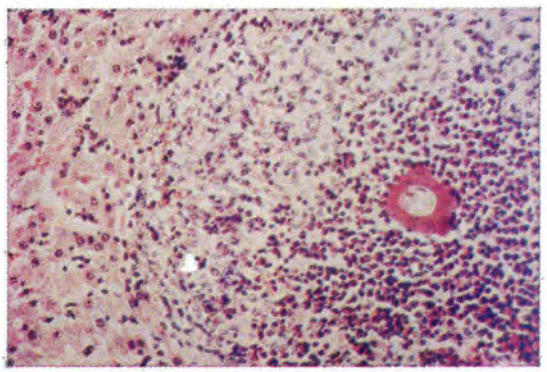

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PLATE 13.—Colour plate of changes seen in ovine and bovine bilharziasis. 81. Left: cut surface of grey lung of a sheep with bilharziasis compared to a normal on the right. 82. Right: Normal liver from a slaughtered sheep compared to a grey liver of a sheep heavily infested with *S. mattheei*. 83. Heavily pigmented periportal lymph nodes of an ox with bilharziasis. 84. Photomicrograph. Hoeppli reaction around a schistosome ovum in the liver of an ox. Notice the concentration of eosinophiles in the centre of the granuloma. × 150 H.E.