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CLINICAL AND PATHOLOGICAL OBSERVATIONS ON SIXTY-FIVE CASES OF VIPER BITE IN ISRAEL

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The present article consists of a clinical study of 61 cases of viper bite in Upper Galilee and the Jordan Valley as well as an anatomical and histological examination of four additional cases which were observed at different hospitals in the Tel-Aviv region.

According to the opinion of the zoologists, all the poisonous snakes of this country belong to the family Viperidae. Cases of snake bite by the family Colubridae are unknown. There is still a difference of opinion as to whether poisonous snakes of the latter family exist in Israel. The most common types of snakes and their distribution are as follows:

1. *Vipera palestinae* in the center of the country and in the north.
2. *Echis coloratus* in the Judean Desert.
3. *Cerastes cerastes* in the south.

Considering the geographical regions in which the cases occurred and the snakes which were identified (33 in number) it appears that our material applies only to bites by the Palestinian viper. In Table 1 the statistical data of all of our cases are assembled.

VIPER VENOM AND ITS ABSORPTION

According to the literature, snake venom contains proteins (albumin and globulin), proteoses and peptones, enzymes, salts, etc. Previously it was thought that the actual poison was linked to the protein and peptone fractions, but lately it has become possible to isolate two specific toxins—ophiotoxin ($C_{17}H_{26}O_{10}$) from cobra venom and crotalotoxin ($C_{24}H_{54}O_{21}$) from viper venom. These substances belong to the nitrogen free glucosides of the saponines.

According to our clinical observations we have been of the opinion that snake venom is absorbed and spreads via the lymph channels. This is proved, among other things, by its slow absorption, the toxic lymphangitis and the lymphadenitis which developed in 11 cases only a few hours after the bite, and the widespread hemorrhages which spread along the lymph channels. Cases coming to postmortem also showed, at times, this distribution of hemorrhages along the lymph channels and around the regional lymph nodes.

In the literature we also found experimental support for this assumption. According to G. Duran-Reynals (1939), snake venom, especially of the viperae, contains a factor which promotes its penetration into the tissues, in particular the connective tissue and the capillaries. This factor is not necessarily identical

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with the toxic element of the venom. Intravenous injection of snake venom into rabbits intensifies the spread of India ink introduced under the skin. It appears that this spreading factor, which is also found in the toxins of various bacilli, is none other than the enzyme hyaluronidase. It is well known that the fluid in the interstitial spaces of animal tissues combines with hyaluronic acid which belongs

TABLE 1

Statistical data

Distribution of cases according to:

1. *Sex.* Male—44; female—17

2. *Age in years*

0– 9	4
10–19	17
20–29	18
30–39	13
40–49	6
50–59	2
Over 60	1

3. *Month of occurrence*

January	1
February	1
March	1
April	2
May	5
June	9
July	12
August	10
September	12
October	7
November	0
December	1

4. *Degree of seriousness*

Light	26
Medium	14
Severe	4
Critical	13
Fatal	4 (all between 1940–1944)

5. *Interval in hours between bite and hospital admission*

	Cases	Died		Cases	Died
Less than ½ hrs.	1	0	3 to 6 hrs.	5	0
½ to 1 hrs.	6	1	6 to 12 hrs.	5	2
1 to 3 hrs.	40	1	Over 12 hrs.	4	0

6. *Location of bite.* Upper limbs—35; lower limbs—26

7. *Circumstances attending the bite*

The majority of bites (31 cases) occurred during accidental treading on the snake. The next most frequent cause (21 cases) was that of putting the hand into a place which was concealed from sight. Three cases occurred during sleep and two during an attempt to grasp the snake with the hand.

to the mucopolysaccharide acids. This substance unites the cells of the connective tissue with the aid of a jellylike matrix and is itself broken up under the influence of hyaluronidase, thereby increasing the permeability of the tissues. The venom passes from the interstitial tissues to the lymph channels and thence, indirectly, into the circulation of the blood. Experimental proof for this view is also found in the works of Barness and Trueta (1941). These authors have again

confirmed that substances of low molecular weight are absorbed through the lymph vessels. They have shown that viper venom, whose molecular weight is greater than 20,000, is not absorbed from the tip of the toe of a rabbit if the lymph vessels are cut. However, if these vessels remain intact but the blood vessels between the upper and lower leg are cut, then the venom is absorbed with ease. Cobra venom, whose molecular weight is less than 5,000, is absorbed through the blood vessels even though the lymph vessels are cut. These facts

TABLE 2

Clinical manifestations of viper bite in their order of frequency in 61 cases

Local swelling	58
Local pains	56
Vomiting	36
Discoloration (skin)	33
Shock	26
Fever	26
Diarrhea (bloody stools in 6)	20
Anemia	20
Abdominal pains	19
Sanguinolent blebs	17
Serous blebs	13
Quincke's edema	15
Toxic lymphangitis	11
Nausea	11
Weakness	11
Cold perspiration	7
Retention of urine	5
Skin hemorrhages (except the region of bite)	5
Restlessness	4
Bradycardia	3
Hemorrhages in the mucous membranes	3
Disturbances in swallowing	2
Hematuria	1
Late sequelae	
Lymphedema	3
Contracture (of Dupuytren's type)	2
Neuritis, peripheral	1
Gangrene of foot	1

gain special importance in treatment, for the flow of lymph (and of course the absorption of venom) is dependant on the movements of the muscles of the limbs. Active movements increase the flow of lymph, wheras complete rest of the muscles stops the flow of the lymph entirely.

THE CLINICAL PICTURE

Table 2 summarizes the clinical signs of snake bite in their order of frequency; 61 cases were investigated from this aspect. Table 3 shows their patho-physiological relations. Four typical cases of snake bite are described below.

Case No. 25 (Chart I, Fig. 1)

A. K., male, aged 24, was admitted to hospital on May 10, 1945. About ½ hour before this he was out walking, dressed in sandals, and was bitten by a snake. The snake itself he did not see. He was immediately taken to the local clinic. There his leg was bandaged above the knee and after the bites had been somewhat enlarged by a scalpel, crystals of potassium permanganate were rubbed in. He was also given an injection of Serum Antivenimeux prepared in South Africa. Several minutes after the bite he became pale, began to vomit and to have diarrhea which was accompanied by abdominal pain. Immediately after this he felt his tongue swelling and he was covered with a cold sweat.

On admission it was noticed that his tongue was swollen to two or three times its normal size. His lips were also considerably swollen. The pulse was impalpable. Blood pressure was 60/45 mm. Local findings: on the outer and anterior part of the dorsum of the right foot were small scratches stained violet, with swelling around them. There was severe hemoconcen-

TABLE 3

Clinical manifestations according to their patho-physiological relations

I. *Anaphylactoid syndrome (association of vomiting, diarrhea, shock, etc.)*

	Cases		Cases
a) Anaphylactoid shock: mild	5	d) Eosinophilia early	9
moderate	8	late	8
severe	12	after administration of serum	12
b) Quincke's edema	15	e) Disturbances in swallowing (edema?)	2
c) Urticaria	2	f) Thrombocytopenia	2

II. *Local signs*		III. *Hemorrhages*	
Swelling	58	Skin, local	26
Discoloration	33	Skin, distant	5
Cutaneous blebs	30	Melena	2
Sanguinolent	17	Hematemesis	2
Serous	13	Hemorrhages in mucous membrane	3
Traces of the snake's denture	34	Epistaxis	2
Typical	8	Hematuria	1
Non-typical	26	Anemia	20
Toxic lymphangitis	11		

tration: r.b.c. 5,6 million, w.b.c. 17,000, Hb. 17 gm %. Urine: albumen +, urobilinogen +, sugar −, deposit −.

12 midnight. The diarrhea had ceased, the patient was still vomiting and the tongue was still swollen. The pulse was now palpable, soft. Patient very dry. A drip transfusion of physiological saline was started. B.P. 90/60. Respirations slow and deep.

1.30 a.m. Still vomiting. B.P. 100/65. Transfusion continued and supplemented with blood. The dorsum of the right foot near the ankle was swollen and the skin in this area was bluish and tender to pressure.

8.30 a.m. Feels well. B.P. 125/80. The drip has been continued all night and during this time he has received, in addition to a solution of salt and glucose, a liter of fresh, citrated blood. The tongue is now only slightly swollen. The right calf swollen to above the knee-joint. The foot now blue. Transfusion stopped. Urine: albumen +, urobilinogen−, sugar−, deposit nil.

5 p.m. General condition good. Complains of pain in the right arm and leg. The thigh swollen to the inguinal region. Extensive subcutaneous hemorrhages in the medial part of

the right thigh. Further hemorrhages noticed in the groins. The skin of the right forearm swollen and shows purpuric spots. The tongue now normal in size.

Restless and vomiting during the evening. B. P. 100/70-130/30.

May 12. 9 a.m. The swelling has now risen above the groins and the difference in the circumferences of the thighs is 14.5 cm. Extensive hemorrhages in the skin, and on both sides of the calf there have appeared large blisters filled with serum (see Fig. 1).

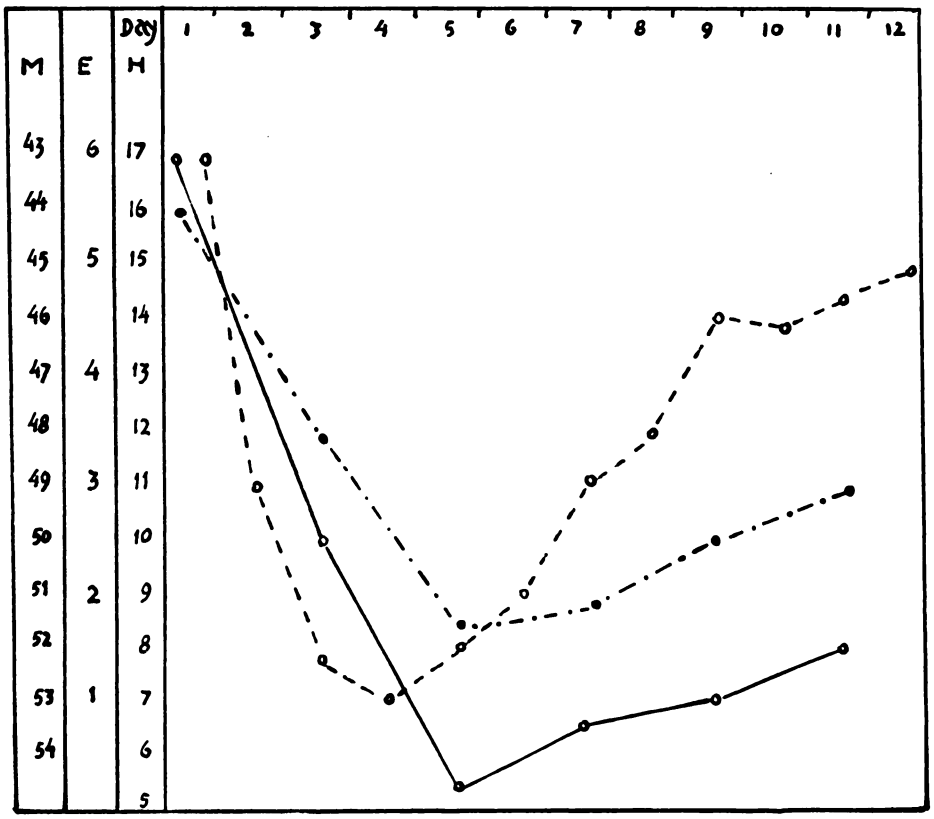

CHART I. *Case No. 25*

Legends

M— — — — — — — — Average of Combined Measures

E—. —. —. —. —. —. —. Red Blood Corpuscles

H———————— Hemoglobin

5 p.m. Nausea and vomiting several times. Progressive swelling in the right lumbar region with extensive areas of hemorrhages under the skin.

May 14. Progressive pallor. Blood count shows severe anemia: r.b.c. 1.8 million, Hb. 5.5 gm %, w.b.c. 6,000, icterus index 4, platelets and reticulocytes normal. Swelling is now up to the lower border of the ribs together with widespread hemorrhages. In the mucous membrane of the palate numerous hemorrhagic spots and small white areas. Swelling of the thigh diminishing. Several of the blisters have now burst and are oozing serum. The hemorrhagic areas are turning yellow. A further blood transfusion is given: 250 cc. packed red cells and ½ liter fresh, citrated blood. Circulation normal.

May 16. Still pale. Blood count: r.b.c. 1,8 million, w.b.c. 6,500, reticulocytes 6%, eosino-

philes 15%. Examination of the fluid from one of the blisters showed: color yellowish, albumen 4.2%, red and white corpuscles in the same proportions as in the blood. Van den Bergh, direct and indirect, negative. Nothing abnormal detected in the urine. Complains of headache. B.P. 120/70. During the last two days has been excreting between 2 and 3 liters of urine in the 24 hours.

May 20. General condition excellent. Rapid diminution of the swelling. Blood count: r.b.c. 2,8 million, w.b.c. 7,000 (eos. 5%), reticulocytes 6.6%. Got up. No abnormal findings in the urine. Specific gravity 1018.

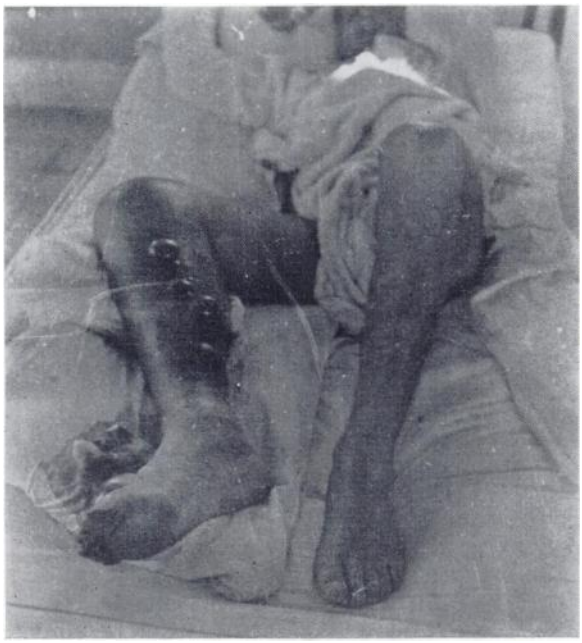

FIG. 1

May 28. Discharged. Condition good. The very extensive swelling has almost completely disappeared. Only the skin is stained bluish-yellow. Blood count: r.b.c. 4,3 million, Hb. 11 gm %.

Case No. 44 (Chart II)

R. B., female, aged 46, was admitted to hospital on July 26, 1946, at 11.15 p.m. At 9.30 p.m., while walking in the grounds of the settlement, saw something shining on her legs and suddenly felt a stabbing sensation on the dorsum of the right foot. She proceeded a little further and then a doctor was brought to her. He put her foot in a splint and put ice on it. She was then sent to hospital on a lorry. The ride was a very rough one and each bump gave her a pain in her abdomen. About ½ hour after the bite she started to vomit and to have diarrhea. The diarrhea was continuous and accompanied by severe abdominal pains. Passed urine together with feces. Arrived in hospital at 11.15 p.m.

On admission was fully conscious, the skin was covered with a cold sweat, the pulse was impalpable and blood pressure could not be read. Continual diarrhea. At midnight a drip was started. Locally the right leg was swollen. In the middle of the dorsum, close to the internal border, were visible bluish spots on the skin, two of which were much larger and separated from each other by 1 cm. Round these spots there was a blue discoloration.

Examination of the blood showed hemoconcentration: r.b.c. 5.73 million, Hb. 19 gm, w.b.c. 17,000 (polymorphs 78%, stab 14%, lymphos 4%, eos 1%). In testing for the coagulation time the blood clotted in a dry test tube after four minutes but after an hour became fluid once again (fibrinolysis?).

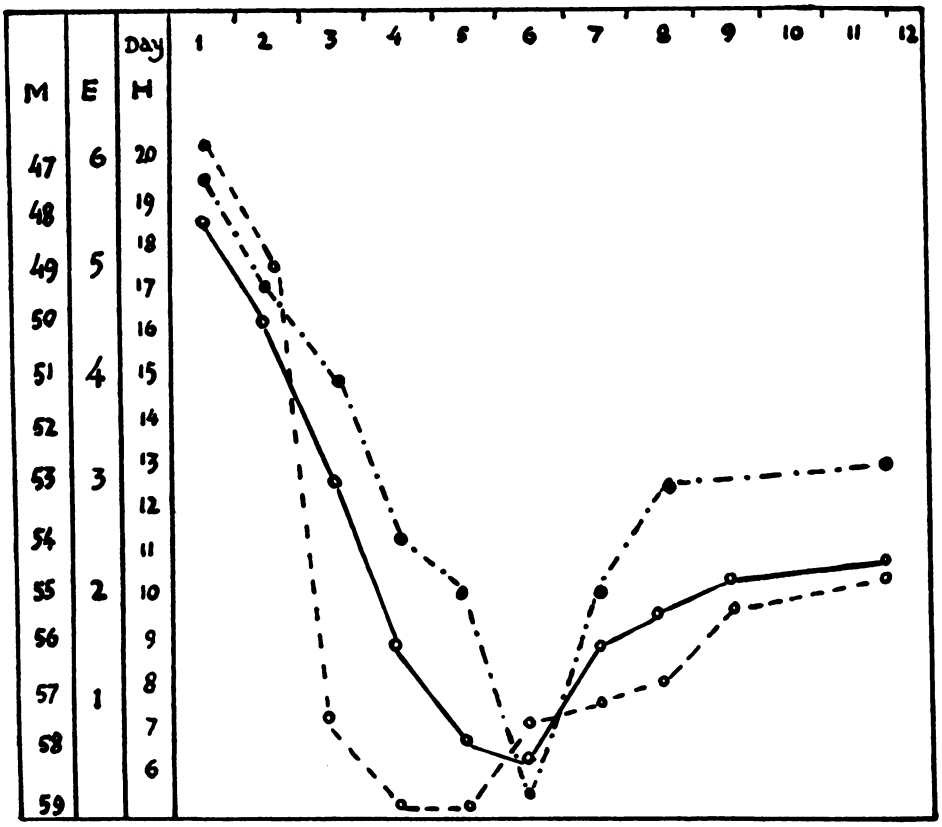

CHART II. *Case No. 44*
Legends as in Chart 1

Progress of the illness (see also Chart II)

July 27. 1.45 a.m. B.P. 80/60. Feeling much better but continues to have diarrhea and to vomit. Thirsty.

9 a.m. Diarrhea and vomiting. B.P. 75/50. Pulse rate 120 per minute. Bladder catheterized and 600 cc. of urine removed. Urine showed albumen +, sugar and urobilinogen absent, and in the deposit, hyaline and granular casts.

12 noon. B.P. 75/50. Extensive urticaria on both sides of the abdomen. Taking fluids freely. Drowsy.

5 p.m. Slight collapse. The B.P. fell to 60 mm. Hg. systolic despite the continuing drip transfusion. Given a transfusion of 250 cc. of blood and a further liter during the course of the day. Several ampoules of ephedrine were added to the solution of glucose and saline which was being given by the drip.

8 p.m. Weak and drowsy. Temperature rise to 38°C.

12 midnight. Vomiting, diarrhea, profuse sweating. The swelling of the foot increased

during the day and spread to above the knee. Numerous widespread hemorrhages on the foot.

July 28. The B.P. during the day varied between 95/65 and 105/70. The patient continued to vomit and to have diarrhea but less than the day before. The drip was continued and a further transfusion of 250 cc. of blood was given. The temperature still up and reached 39°C. Passed 850 cc. of urine in the 24 hours. The swelling now above the pelvis. Widespread hemorrhages on the dorsum of the foot, the posterior part of the calf and on the inside of the thigh. During the day the skin showed a bluish marbling.

July 29. Feels much better. Drinking freely and passing urine in large quantities. Specific gravity of urine 1010. The swelling reaches to the abdomen and lumbar regions and spreads over to the vulva and the left groin. The labia majora very swollen and distended with blood. Large hemorrhages in the region of the groins. Blisters on the leg and the calf. The transfusion continued. The patient has become pale. Blood examination showed severe anemia: r.b.c. 2.75 million, Hb. 8 gm %, w.b.c. 14,000, the differential count showing a shift to the left.

July 30. The improvement continues. The drip discontinued. Hemorrhages in the skin of the pelvic region and the lower legs, especially in areas subject to pressure. The B.P. rose to 120/80. Urine: albumen +, and in the deposit granular casts and leucocytes; glucose and urobilinogen absent.

July 31. Pallor still more marked. The blood picture showed r.b.c. 1.2 million, Hb. 6 gm %, w.b.c. 7,200, occasional reticulocytes only. The differential count showed polymorphs 64%, stabs 2%, lymphos 30%, monos 3%, eos 1%. Plasma bilirubin 1.1 mg %. Given 600 cc. blood and 800 cc. of blood cells freed from plasma. During the transfusion complained of difficulty in breathing. The blisters on the swollen leg became so big that they had to be emptied by puncture.

Aug. 1. Spread of swelling halted. The swollen leg shows numerous yellowish and bluish blisters. The sound leg shows thrombophlebitis where the transfusion was given. Still complaining of difficulty in breathing. Dullness over the lower part of the back of the right lung and diminished breath sounds. B.P. 125/70.

Aug. 3. Feels well but weak. Breathing free. The swelling diminishing. The hemorrhage has spread over nearly the whole of the lower body. Numerous blisters on the back of the foot and the calf, some closed and some with a serous discharge. B.P. 130/70. After some improvement in the diarrhea during the last two days, started once again to pass numerous motions. No parasites were found in the stools. Urine: albumen +, urobilinogen +, and in the deposit, leucocytes. Temperature during the last few days has kept in the region of 38°C.

Aug. 4. Blood: r.b.c. 2.3 million, Hb. 8.5 gm %. w.b.c. 16,500, reticulocytes 16.5% (!) Polychromatophilia. Anisocytosis. Bilirubin 1.5 mg %.

Aug. 8. General condition good. Decrease in the swelling maintained. The hemorrhagic areas becoming yellow. The blood still shows reticulocytosis. The looseness of the bowels improved. Anesthesia of the toes and the foot that has been bitten, but normal sensation in the lower calf.

Aug. 19. Feels well. Diarrhea stopped completely. Passing urine freely. The specific gravity has risen to 1020. Sensation in the skin of the toes still absent. An ulcer covered with a black crust has appeared on the dorsum of the bitten foot. Under the crust there is a purulent discharge. Blood picture improved. r.b.c. 3 million, Hb. 12 gm %, w.b.c. 7,600. Reticulocytes have fallen to normal. The swelling of the bitten extremity almost completely disappeared.

Sep. 1. General condition very good indeed. On the back of the bitten foot an ulcer 3 x 5 cm. with good granulations at its base.

Sep. 25. Up and about. No abnormal findings in the urine.

Follow up on Jan. 2, 1947.

The wound on the right leg completely healed. Feeling of tension in the toes as if the foot was "in a vise". Tires on walking and the right foot "drags". The skin still bluish.

The pulse in the dorsalis pedis easily felt. Scars on the dorsum of the foot. Toes turned upwards except for the big toe. Absence of sensation in the skin of the toes.

Case No. 26 (Chart III)

M. M., aged 17, female. Arrived at the hospital at 6 in the evening on May 26, 1945. She had slept on the seashore of the Sea of Galilee and at dawn felt cold. Put her hand into the rucksack to extract a blanket. In the rucksack there was a snake which bit her on the tip

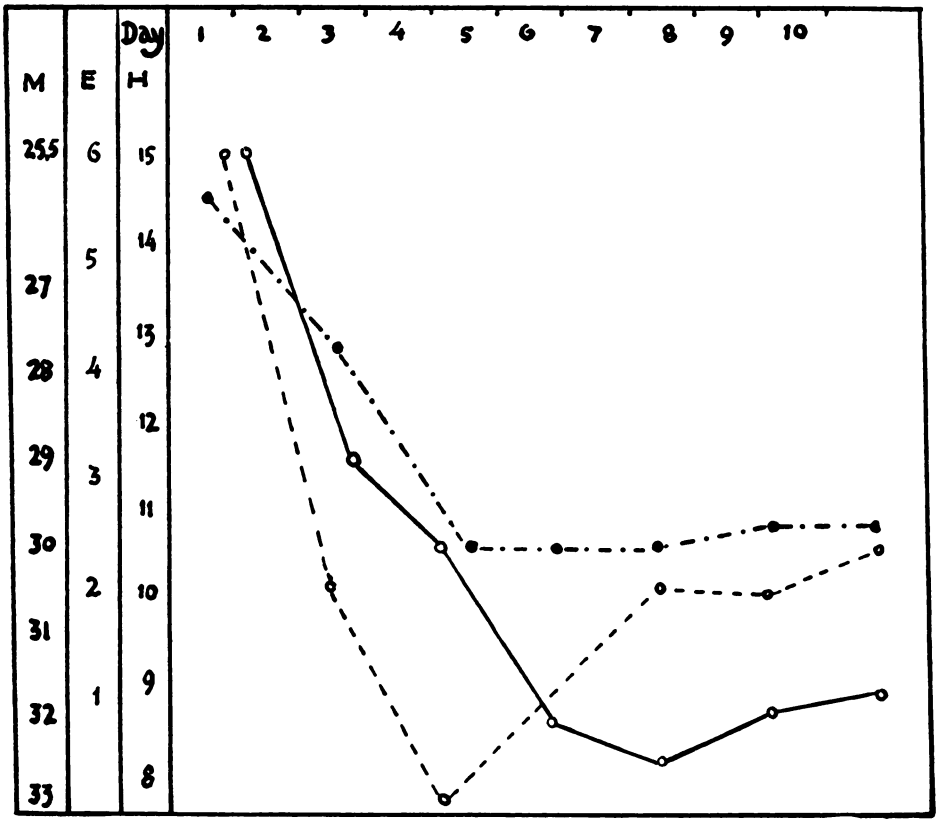

CHART III. *Case No. 26*
Legends as in Chart 1

of the middle finger of the right hand. Several minutes later her tongue swelled up and she found it difficult to speak. Ten minutes later she received first aid treatment, and was given an injection of Serum Antivenimeux. Her companions bound up her hand immediately after the bite but later removed the bandage. About ½ hour after the bite she started to vomit and to have diarrhea. On admission complained of abdominal pain. She was menstruating and in the second day of her period.

Condition on admission. Fully conscious, restless and throwing herself from side to side. Diarrhea. Vomiting from time to time. Pulse not palpable. The B.P. could not be measured. Hemoconcentration (r.b.c. 6.4 million, Hb. 15 gm %, w.b.c. 33,800). Incised wound on tip of right middle finger and the whole of the tip blue. Tongue very swollen and about 2 to 3 times its normal size. Lips also swollen. Tachycardia—116 per minute—regular.

7.30 a.m. Covered with a cold sweat.

9.30 a.m. Marked acrocyanosis. Vomited at times. Deep sighing respirations. Covered with a cold sweat. Veins collapsed. Entry into a vein in order to give a drip transfusion was successful only two hours after admission.

10.30 a.m. Right hand swelling. Hemorrhages on the inner side of right upper arm.

2 p.m. Pulse now felt. So far has not passed urine. Receiving transfusion of blood and plasma.

4 p.m. Feels more comfortable. Drinking freely. Vomiting ceased. Only one attack of diarrhea. Pulse very rapid indeed.

10 p.m. Diarrhea with bloody stools. Tongue now back to its normal size.

Midnight. Feels well. Continues to pass bloody stools.

May 27. Hematuria. Right arm swollen.

May 28. Feels well. Blue spots on tongue. Good urinary output. Urine concentration normal. Transfusion stopped.

May 29. Pale. Blood count: r.b.c. 2.8 million, Hb. 8.5 gm %. w.b.c. 7,500, occasional reticulocytes. Urobilinogen not detectable in the urine. Ecchymosis on the hard palate. Tongue still blue. Numerous hemorrhages in the right armpit.

June 4. Feels well. Still anemic. Diarrhea started afresh.

June 9. Loose motions continue. Free *E. histolytica* in the stools. Course of emetine injections commenced. Swelling of right arm less.

June 13. Received 6 injections of emetine, 0.05 gm. Diarrhea stopped after the second injection. Up and about.

June 17. Feels well. Urine: no abnormalities. Blood count: r.b.c. 2.9 million Hb. 10 gm %, w.b.c. 5000. Discharged.

Case No. 58 (Chart IV)

M. A., male, aged 10. Admitted on Oct. 28, 1947, at 8.30 p.m. About two hours previously was bitten by a snake on the top of his right foot. His friends saw a large snake slide away. Following the bite he played around for about 3 minutes. Fifteen minutes later he started to vomit, went pale and became pulseless. He was bandaged above the knee and the bandage was removed about 20 minutes later. The leg was put in a splint and ice was packed around it. While being conveyed to the hospital was restless but did not vomit or have diarrhea. Complained of thirst and abdominal pain.

Condition on admission. Vomited in the receiving room. Pulse soft but not very fast. B.P. (systolic) 60–65 mm. Hg. Tongue and upper lip swollen. Immediately on admission a drip transfusion was started. Hemoconcentration: r.b.c. 5.8 million, Hb. 19 gm %, w.b.c. 40,000. Differential count normal.

10 p.m. Drowsy. B.P. 85/60. So far has not passed urine.

Oct. 29. Slept fitfully during the night and passed urine. The urine contained albumen. The whole leg swollen and the swelling extended to the right lower abdomen. Small blood-blisters appeared on the side of the bite. Large subcutaneous hemorrhages on the upper part of the foot, the inside of the calf and thigh and the groins. Vomited in the forenoon. The vomitus contained blood clots. Platelets 25,000 per cmm. B.P. 110–120/80.

Oct. 30. The swelling extending over the abdominal wall up to the umbilicus. Patient markedly pale. Blood picture: r.b.c. 3.23 million, Hb. 12.7 gm %, w.b.c. 16,000.

Oct. 31. Further drop in r.b.c. (2.8 m) and Hb. (8 gm %). Given transfusion of 1 liter blood. The swelling has reached the right rib border and the left groin. Large subcutaneous hemorrhages in the swollen areas.

Nov. 2. The blisters have opened and ooze serum. The swelling on the right side is up to axilla.

Nov. 4. No further increase in the swelling. The hemorrhagic areas turning yellow. Hemorrhages in the mucous membrane of the eyelids. Platelets 28,000 per cmm. Blood values rising. Feels well. Albumen constantly present in the urine.

Nov. 6. Made a good recovery and left the hospital in good condition. On discharge the blood count showed: r.b.c. 3.8 million, Hb. 13 gm %, w.b.c. 7,000. Albumen absent from urine. On the skin of the dorsum of the foot close to the site of the bite a healing ulcer.

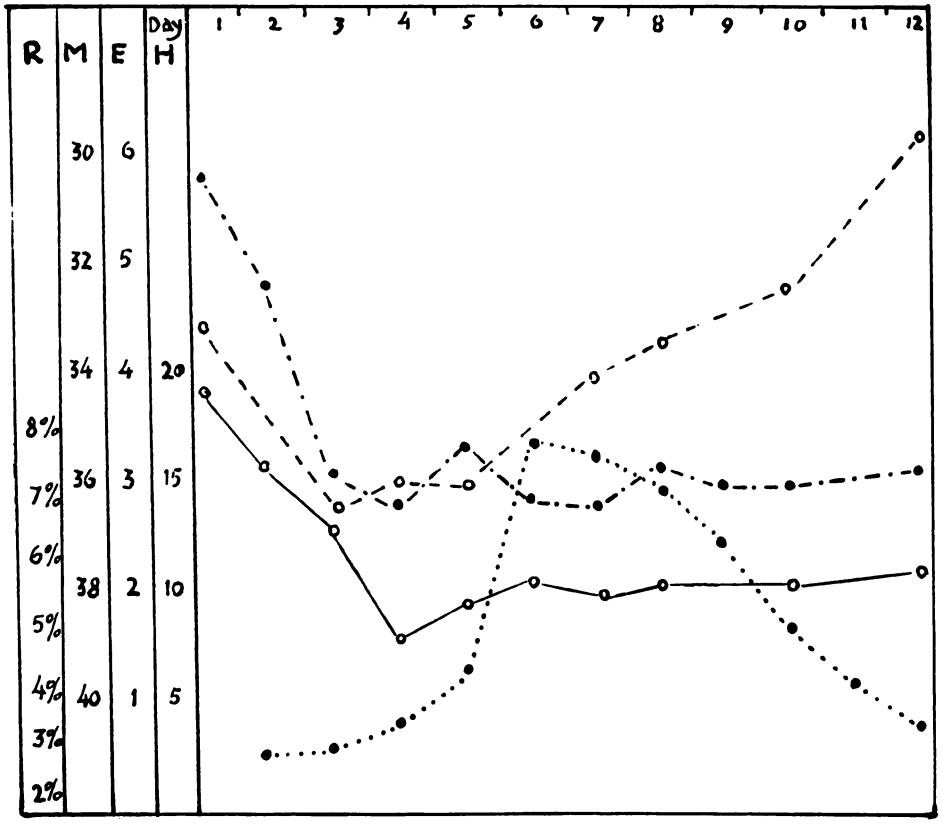

CHART IV
Legends as in Chart 1, plus "R"
R..... Reticulocytes

PATHOLOGICAL CHANGES

There are few references in the recent medical literature to the pathological changes following snake bite, especially in man, whereas there are a number of articles dealing with the changes in experimental animals. Taube and his co-workers published (1937) their findings on the pathological changes following the injection of rattlesnake venom into dogs, and Fiedler *et al.* (1940) on the resultant changes following the subcutaneous injection of rattlesnake venom into the *Macaca mulatta* monkey.

We have had the opportunity of carrying out examinations in four cases of snake bite.

Case 1. Woman, age 40. Bitten at 9.30 p.m. in two places in the lower lip. Severe collapse occurred very quickly, about 20 minutes later. A doctor extended the wounds and placed

some potassium permanganate crystals into them and gave an injection of Serum Antivenimeux. The patient was expiring by the time she reached hospital some two hours later and despite intensive antishock treatment died shortly afterwards.

Case 2. Male, age 33, bitten by a snake at 2 in the morning on his left thumb. His arm was immediately bandaged above the bite, but the doctor who examined him removed the bandage because he failed to find any evidence of a bite. Two hours later he began to have diarrhea with bloody stools and collapsed. He died about 10 hours after the bite.

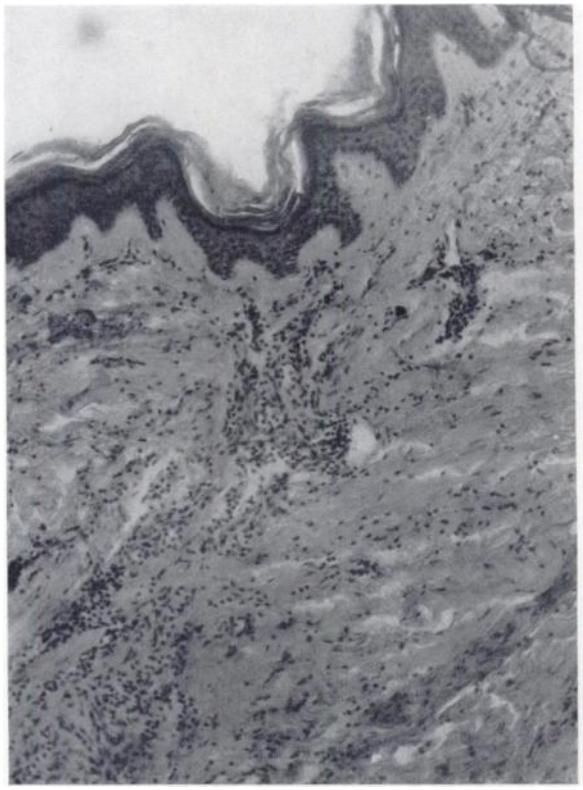

FIG. 2

Case 3. Male, age 60. Bitten on the foot during the evening and shortly afterwards received Serum Antivenimeux. Developed bloody stools and died about 18 hours after the bite.

Case 4. Girl, age 15. While out walking felt a prick on her leg. (This occurred about 6 hours before her admission to hospital.) Continued walking but 20 minutes later became unconscious. The doctor who examined her suspected a fracture because of the blue and swollen state of her leg. Several hours later there was hemorrhage from the bowel and the patient was admitted to hospital. There the swelling spread and reached to above the groin. The patient died 48 hours later in a state of shock.

As the anatomical and histological changes in all 4 cases were similar, it is possible to describe the findings in all of them together. Outstanding were the swelling and the hemorrhages. The skin, subcutaneous tissue and the muscles

were infiltrated with sanguineous fluid. These changes were also found in areas proximal to the bites as well as in areas distant from them. The regional lymph nodes were swollen and hemorrhagic; e.g., in bites of the leg the inguinal group of lymph nodes were chiefly affected.

Extensive hemorrhages were noted in the internal organs. In all the cases extensive hemorrhages were found under the endocardium of the left ventricle, in

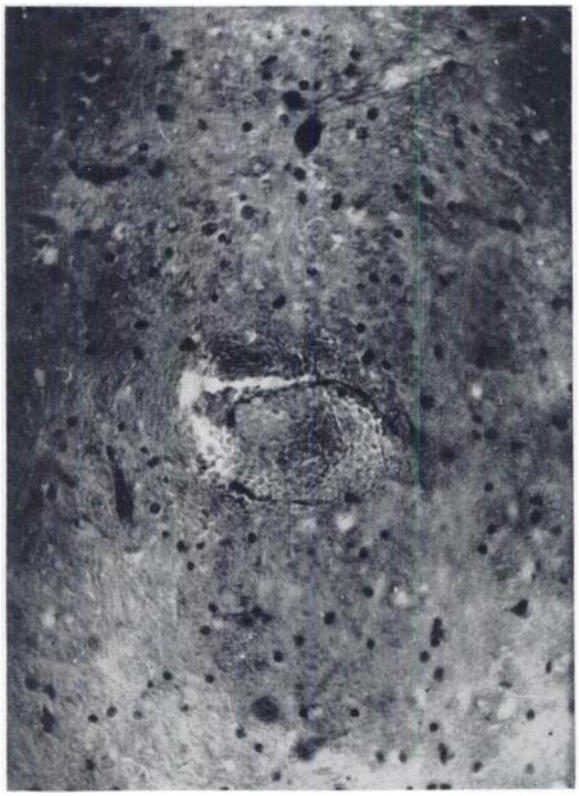

FIG. 3

the septum and papillary muscles. Petechiae were also found in the pleura, peritoneum and in the mucous membrane of the pelvis of the kidney and of the urinary bladder. In two cases hemorrhage into the mucous lining of the stomach and intestine were noted. At times the blood remained fluid in the vessels many hours after death and only clotted while postmortem was performed.

As would be expected from the macroscopic findings the outstanding histologic changes were the hemorrhages and acute stasis. Around the site of the bite was found a transudate of serous blood-stained fluid into the skin, subcutaneous tissue and the muscle. In the area immediately surrounding the bite there was an obvious leucocytic reaction (Fig. 2) as well as marked changes in the walls of the arterioles and capillaries. At times the wall was blurred and the endothelial

cells were swollen. Occasionally there was a tear in the wall with hemorrhage around it. Similar changes were also found in other organs distant from the site of the bite. Fig. 3 shows a small vessel in the pons with a tear and hemorrhage in the perivascular space.

Lymph nodes: great distention of the vessels with hemorrhages (Fig. 4). The endothelial cells of the sinuses are separated and show signs of phagocytosis.

FIG. 4

Kidneys: the blood vessels are distended both in the cortex and medulla. The capillaries of the glomeruli are stuffed with red blood cells (Fig. 5). At times there is an interruption in the wall of the capillaries accompanied by hemorrhage into the lumen of Bowman's capsule.

Intestines: the changes may be very severe. The capillaries of the mucous lining are greatly enlarged and distended with blood (Fig. 6 and 6a).

Lungs: distended and hemorrhagic.

The changes in the parenchymatous organs, except for those in the blood vessels, are few. Only the liver showed a slight proliferation of cells infiltrating into the sinuses which were distended. Fig. 7 shows the separation of the basal

membrane from the cells of the parenchyma (Seröse Entzündung, Eppinger).

Adrenal cortex: in one case fairly heavy lymphocytic infiltration was noted (Fig. 8).

Table 4 gives the laboratory findings in the cases examined.

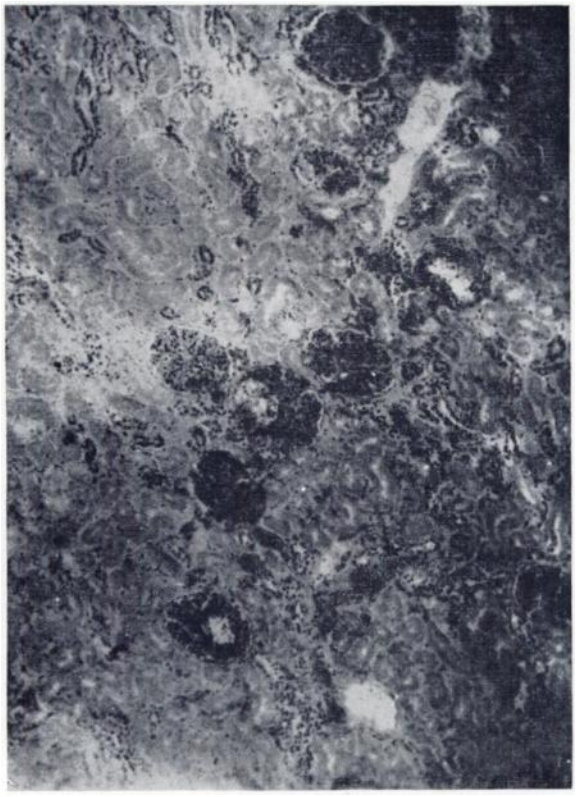

FIG. 5

PATHOGENESIS

Viper venom, as we have seen, causes first and foremost damage to the blood vessels and especially to the arterioles and capillaries. In them it leads to the escape through the damaged walls of fluid and solid contents of the blood. (Hemorrhage by diapedesis). At times, however, whole portions of the wall disintegrate and this leads to hemorrhage by rhexis.

These changes are found also in animal experiments. As far back as 1886, Reichert and Mitchell expressed the opinion that snake venom has a direct influence on the wall of the vessels. According to Fiedler there is a disintegration of the vessel walls and the connective tissue at the site of the bite which causes an outflow of fluid. At the same time the lymph vessels open up and the venom is carried to the regional lymph nodes. Here very severe changes occur and, as the

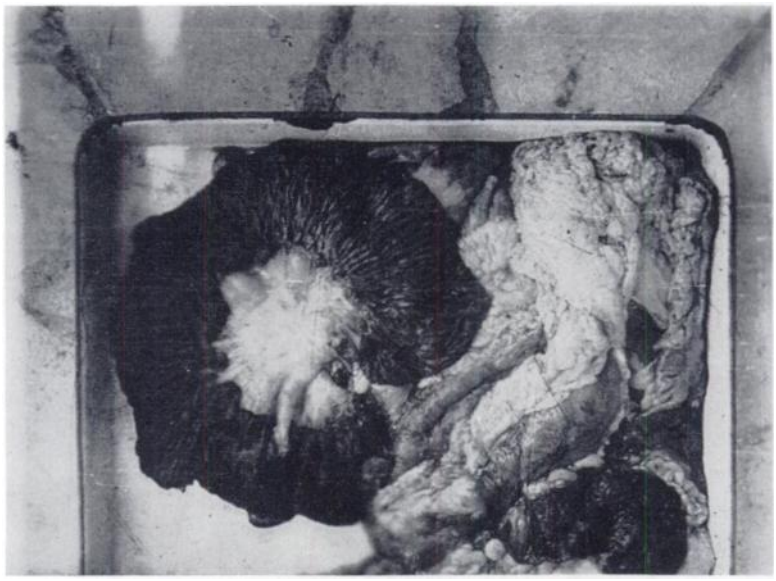

FIG. 6

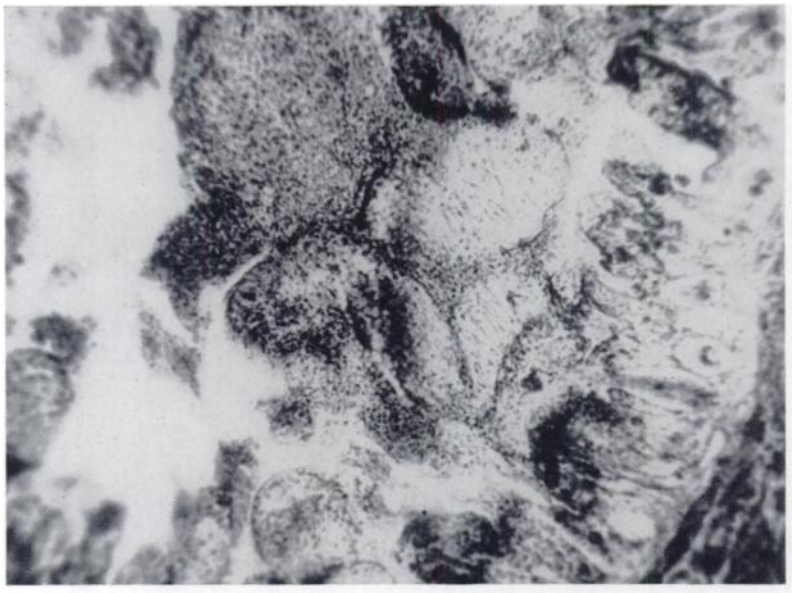

FIG. 6a

venom passes out of these nodes, fresh lymph vessels open up and so the cycle of events is repeated. In the interstitial spaces the venom further damages the arterioles and capillaries.

As has been pointed out above, the hemorrhages extend along the length of

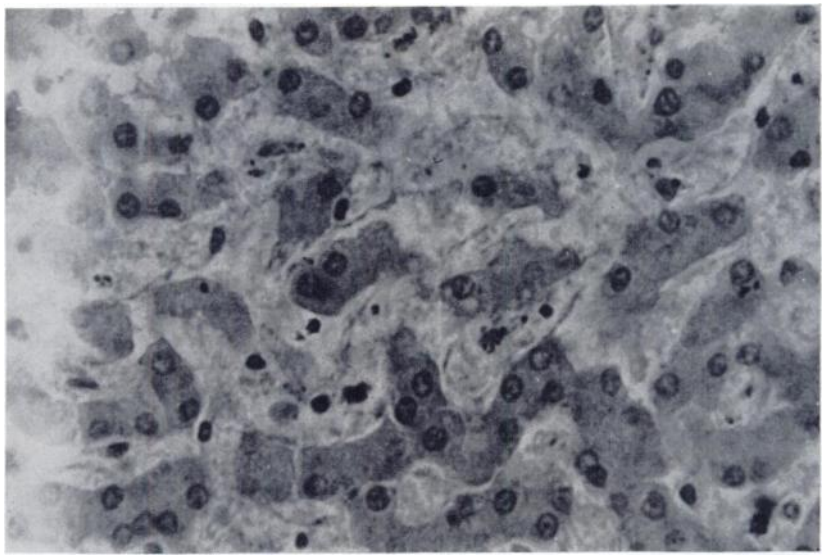

FIG. 7

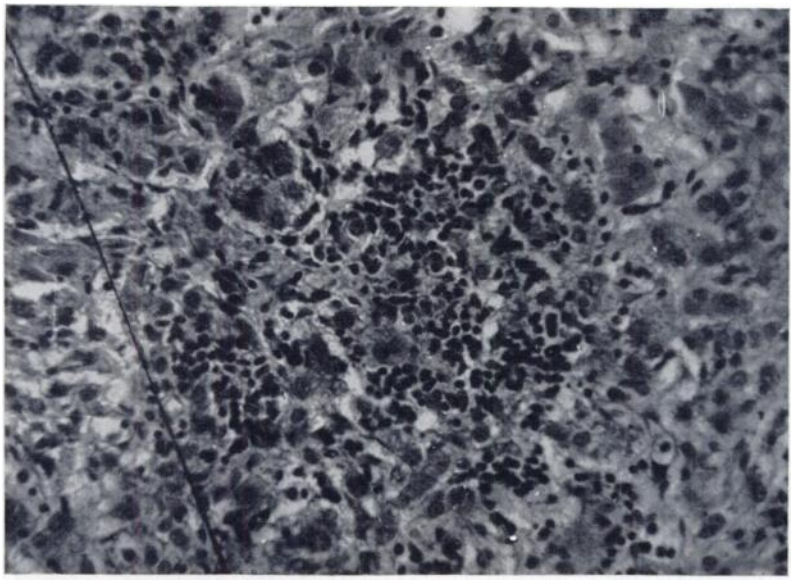

FIG. 8

the lymph channels in affected limbs. In two cases (one only is included in the present series) it was noted that there were hemorrhages in the region of the ramification of the lymph vessels in the serosa of the uterus, and in the second, of the bladder and retroperitoneal tissue. It is noteworthy that these hemorrhages were confined to one side only and did not pass over the midline.

The clinical picture is made up 1) of local signs such as: swelling, subcutaneous hemorrhages, blood and serous blisters, hemorrhage into the soft tissues, and 2) of general signs. The local signs are caused, as has been pointed out above, by the damaging effect of the venom on the capillaries of the blood and lymphatic systems. The venom is absorbed and gives rise to hemorrhages both local and at

TABLE 4

Laboratory findings in cases of snake bite in Israel

I. Hematology

1. *Hemoconcentration on admission*

Number Examined	Present	Absent	Max. Hb.	Max. r.b.c.
39	28	11	22.5 gm%	6.6 m.

2. *Leucocytes on admission*

	Cases
a) Leucocytosis, 10,000–20,000	20
20,000–30,000	8
30,000–40,000	5
40,000	1
b) Leucocytosis in cases without hemoconcentration	11 (range: 12,200 to 24,000)
c) Leucopenia	2

3. *Platelets*

On admission		One week later	
Normal	Decreased	Normal	Decreased
4	2	5	1

	No. exam.	Slow	Normal	Increased
4. Sedimentation rate of r.b.c	18	14	3	1
5. Coagulation time	13	0	13	0

		Present	Absent
6. Fibrinolysis*	12	5*	7

7. Prothrombin time. Prolonged only in cases in a state of shock

II. Urinalysis

	On admission	Subsequently
1. Normal findings		22
2. Albuminuria	16	23
3. Urobilinogenuria	6	24
4. Red blood corpuscles	4	6
5. Leucocytes	8	9
6. Granulated casts	9	10

* All in shock.

a distance and brings into operation a chain of generalized reactions which take on the form, in the first instance, of anaphylactoid shock. It is manifested in the gastro-intestinal system by nausea, vomiting, abdominal pain and incessant diarrhea, in the cardio-vascular system by severe peripheral shock (drop in blood pressure, disappearance of pulse, palpitation, hemoconcentration) and by allergic signs (urticaria, Quinke's edema in 15 cases, and eosinophilia).

This symptom complex at the onset has a remarkable resemblance to the

picture of anaphylactoid shock in man as described by Urbach and Gottlieb: "The clinical picture is striking; vomiting and violent colonic spasms appear, causing unbearable abdominal pain and uncontrollable diarrhea. There is an abrupt fall in the blood pressure, accompanied by a drop in temperature (although in occasional cases the temperature will rise). The patient becomes strikingly pale and finally cyanotic. Tachycardia is very commonly observed: this can be so severe that the pulse becomes imperceptible and the heart sounds barely audible. Acute pulmonary emphysema may ensue. The general condition becomes progressively worse and the patient loses consciousness."

We found no signs which referred to the respiratory system in our cases. In experimental medicine we also find support for the anaphylactoid factor in cases of snake poisoning. P. Boquet quotes Arthus who compared the symptoms following poisoning by snake venom to "Choc sero-anaphylactique". Rocha and Silva (1939–40) also compare the effects of snake poison with that of trypsin, both of which give rise to signs of anaphylactic shock.

Feldberg (1939) and Kellaway and Trethewie (1939) showed that perfusion of animal tissues with venom of various snakes give rise to the production of histamine in the perfusion fluid and protein substances which have the property of clotting (according to Esses, 1945).

This anaphylactoid shock passes readily over to the usual peripheral shock, apparently as a result of the increased outpouring of blood and plasma into the tissues. The typical picture of shock appears—low blood pressure which at times cannot even be measured, soft rapid pulse which sometimes can hardly be felt, and hemoconcentration. We consider the fibrinolysis, which we noted as occurring in a state of shock only, and also the lengthening of the prothrombin time, as due entirely to the shock itself.

The mechanism which brings about the state of shock leads also to its perpetuation. The increased permeability of the blood vessels, and the transudation of blood and plasma resulting from it, bring about the severe anemia which appears in the subsequent days. In all our cases which suffered from shock and severe anemia, we noticed extensive swelling in the form of massive edema which spread centripetally from the limb which was bitten to the body, half of which at times was affected. According to Noble and Gregersen (1946), accumulation of a liter of blood in the thigh increases its diameter by one cm. In several cases we obtained figures very much greater than this as is shown below.

Case no. 21: died of shock in less than 24 hours. The difference in circumference between the thighs was 8.5 cm., i.e. a difference in the diameter of 2.7 cm. In other words 2.7 liters of fluid passed out into the tissues in less than 24 hours.

Case no. 25: peripheral shock lasting 24 hours. Anemia developed over 7 days. On admission the Hb. was 17 gm % and the red blood cells 5.5 m. per cmm. In the course of a week the Hb. fell to 6.5 gm % and the r.b.c. to 1.84 million. The difference in the circumference of thighs was 13 cm. The increase in the diameter was therefore 4 cm in a week.

Case no. 44: shock and anemia. On admission, Hb. 19 gm % which fell to 6 gm % and r.b.c. 5.7 m. which fell to 1.2 m. per cmm. Difference in diameter of thighs was 4.4 cm. (in circumference 14 cm.).

Case no. 27: shock and anemia. On admission Hb. 17 gm % which fell to 10 gm % and

r.b.c. 6.95 m. and later 3.2 m. per cmm. The difference in circumference of thighs was 17 cm., i.e. 5.4 cm. in diameter.

Case no. 58: shock and anemia. On admission Hb. 19 gm % which fell to 10 gm %. r.b.c. 5.8 m. fell to 2.8 m. per cmm. Difference in circumference of thighs 8 cm. and in diameter, 2.5 cm.

These measurements are naturally only possible in the lower limbs because in the upper limbs the swelling very quickly reaches the back and chest, and the calculation is therefore very much more complicated. Two facts must also be taken into consideration: 1) all severe cases received intravenous saline and plasma. 2) The capillaries in the bitten limb are more permeable and there is a greater than normal transudation of fluid through them. Nevertheless we can give credit for a substantial part of the increase of thigh diameter to transudation of the blood. This "exsanguination" also explains the perpetuation of peripheral shock and the severe anemia. In the graphs accompanying the description of the cases we have attempted to show this relation by charting the increase of the circumference of the bitten limb and the variation in the Hb. and r.b.c. In none of our cases did we find signs of hemolysis. The qualitative examination of urobilinogen in the urine was normal; there was no reticulocytosis and the bilirubin in the blood was not increased. Signs of hemolysis appeared only at the end of the week due, apparently, to the breakdown of the Hb. of the blood which had collected in the tissues.

The extent of the anemia is shown by the observations that follow. On admission, 28 cases showed signs of hemoconcentration due to shock. The highest figures we obtained were 7.6 million red blood corpuscles per cmm. and for Hb., 22.5 gm%. As for the state of shock, in 17 cases it was impossible to measure the blood pressure and in a further 9 cases the systolic pressure was less than 80 mm. Hg. The pulse was not palpable in 13 cases and in a further 11 cases it was more than 120 per minute. In the subsequent days, up to the end of the first week, anemia developed in 20 cases; lowest values of r.b.c. were 1.2 million per cmm. and Hb. 3.0 gm%. Despite repeated transfusions which were given in 17 cases in the first 24 hours and which consisted at times of more than a liter of fresh citrated blood, severe anemia developed as we have pointed out above. Spontaneous regeneration, which quickly increased in rate, started in the second week and was associated with a rise in reticulocytes.

TREATMENT OF SNAKE BITE

Recent findings on the absorption of snake venom and the pathogenesis of the symptomatology of the intoxication has had its effect on treatment. The traditional treatment seemed to us outdated and lacking a logical basis. In 1947 we started on a new system of treatment which was subsequently used in the Jordan Valley and in the Galilee. The results of the treatment by the old methods are shown in Table 5.

Before passing on to the consideration of our new system of treatment we will consider the bases of the previous treatment which we have now given up entirely.

1. *Compression of arteries by tourniquet.* As far back as 1938 the Russian authors Schreiber and Maljugina pointed out that the application of a tourniquet does not prevent the absorption of the venom, for the local signs appear above the tourniquet. It also does not prevent the onset of generalized signs. Allen (1939) was also doubtful of the value of arterial compression in preventing the absorption of the venom. He was of the opinion that the venom spreads with great rapidity over a large area simultaneously, apparently via the lymph vessels. It is therefore unlikely to expect any effect from a tourniquet. Moreover,

TABLE 5

Evaluation of methods of treatment of snake bite in Israel

METHOD	COURSE OF THE CASES						
	Total	Mild	Moderate	Severe	Fatal	Shock developed	Swelling advanced
With tourniquet	34	13	9	11	1	14	27
Without tourniquet	23	12	4	6	1	6	14
With serum "Antivenimeux"						Serum sickness	
For prophylaxis	24	8	7	7	2	4	
For treatment	20	8	2	6	3		
Without serum	22	13	3	6	0		
Summary							
"Old line" treatment (tourniquet, serum, transfusions)	49	19	11	15	4		
"New line" treatment (splint, rest, transsions)	14	8	3	3	0		

in addition to the damage caused by the venom itself, this is likely to interfere with the vitality of the bitten limb. Our experience has also shown that the application of a tourniquet which has been in place for some time, leads occasionally to a worsening of the clinical condition, possibly because of the sudden release of a large quantity of venom into the circulation. In view of the slow absorption and of the successful preventive methods, we have entirely done away with the compression of the vessels and we do not even recommend it as a first aid measure.

2. *Excision.* There is no question that early excision of the part bitten could prevent the absorption of the poison. Practically speaking, however, even under the most favorable conditions, the doctor does not see the victim until 15–30 minutes have elapsed and in the meanwhile the venom has succeeded in passing into the interstitial spaces and into the abundant lymph capillaries. The quantity thus absorbed suffices to bring about the local and general effects of poisoning.

3. *Incision and suction.* Some advise that the skin around the bite be deeply

incised and the wound sucked by the mouth or some mechanical apparatus so as to extract the blood and the venom before it is absorbed. There is little doubt that this treatment can help to remove a certain amount of the venom from the area of the bite, but here also we cannot expect any great effect unless it is done within a very few minutes of the event.

4. *Introduction of various substances into the wound and incision.* We have given up this type of treatment because of the lack of efficacy and because of the local damaging effects of some of the substances used, e.g. potassium permanganate. The only acceptable local treatment which we would take into consideration is the injection of a substantial dose of a specific "serum antivenimeux" into the tissues around the actual site of the bite. It is possible that a specific serum has the ability to neutralize the enzyme hyaluronidase and so to interfere with the absorption of the poison.

The principles of treatment which we have laid down for ourselves are divided into 1) first aid measures and 2) medical treatment.

1. First aid measures

a) First and foremost, in our opinion, should be absolute immobilization of the bitten limb by a splint as would be done in the case of an open fracture. Following the animal experiments of Barness and Trueta (1941) we think that this step diminishes to a very large extent the absorption of the poison. The above authors are too far-reaching in demanding a closed plaster which in their opinion is likely to prevent the onset of extensive swelling. We tried their method in two of our cases which had been bitten on the toes without, however, incising the wounds as they recommend. In the first case we succeeded in preventing the onset of secondary shock but we were compelled to split the plaster lengthwise after several hours because of severe pain. The leg, as usual, swelled up during the next few hours but shock did not develop. In the second case the pain was not so severe, due apparently to the exhibition of analgesics, but here again severe interference of the circulation in the limb developed after a few hours. Although in this latter case we split the plaster cast lengthwise we could not prevent the onset of gangrene and a midcalf amputation had to be performed. Shock did not develop. After this sad experience we gave up using plaster casts and instead used plaster "longettes" moulded to the shape of the affected limb.

b) With respect to injection of specific snake venom anti-serum, we did not have any specific antiserum for the snakes of this country. The ones we used were produced by the Pasteur Institute of Algiers, Fitz-Simon in South Africa and by the Pasteur Institute of Paris, but were without effect whatsoever on the progress of the case when given either before the signs of poisoning appeared or subsequently. Table 5 shows this very clearly. In point of fact all the four fatal cases had received serum, whereas those cases which did not receive serum survived. (These four cases are not included in the anatomo-pathologic study but are included in the clinical study. The cause of death in the above four cases was peripheral shock.) In view of the small number of cases it is obvious that no conclusions can be drawn against the use of specific serum. We would be inter-

ested in trying out a specific serum if it should become available. Large doses would be injected subcutaneously in and around the bite, and in severe cases intravenously. However, as long as no specific sera for the snakes of this country are available, we do not intend to use serum for our cases.

c) In view of the fact that during the first stages of the syndrome there are signs of anaphylactoid shock it is reasonable to give antihistamines. These can also be given prophylactically even before the appearance of signs of poisoning. Our own experience in this field is as yet very small but in the few cases where we used these drugs, signs of generalized poisoning did not develop. However, at the moment, no firm conclusions can be drawn from our results. A further point in support of our recommendation is that in the literature it has been shown that the antihistamines neutralize the action of hyaluronidase. Trethewie and Day (1948) tried out Neo-antergan in mice experimentally poisoned by the venom of *Pseudoechesis porphyriacus* and in their opinion this drug is able to prevent the effects of the poisoning. The above snake belongs to the family of Colubridae and one cannot transfer the conclusions reached to cases of viper bite without further confirmation.

d) Speedy removal to hospital, which should be alerted beforehand, and the provision of blood donors are all important. We have insisted on carrying out the above instructions strictly, and despite the primitive state of transportation in this region we have managed to cut down delays to a minimum. To this we ascribe, in great part, our success in treatment; in the last few years there has not been one death in our institution from snake bite although the cases we received were not less serious than those admitted in previous years.

e) As can be seen from the foregoing statements, we have given up all local treatment except for the immobilization of the limb in a splint.

2. *Treatment in hospital*

a) We advise the injection of *specific* anti-serum in sufficient quantities and by various routes.

b) Antihistamines are given and continued as long as the patient is in the anaphylactoid stage. In one of our last cases (not included in the present series) we gave 5 mg. of Bezantine intravenously (a local product similar to Benadryl) because the patient vomited several times soon after the bite and we were unable to give the drug by mouth. Soon after the injection the patient stopped vomiting and further signs of generalized poisoning did not develop. The local signs were also very mild; the bite was on the hand and, apart from swelling which in the days following reached the shoulder, there were no other local signs.

c) No local treatment is given except that of keeping the affected limb in absolute rest by splinting, plaster "longettes" or sand-bags. We did, indeed, in a few cases place ice on the bitten area but we saw no advantage in the progress of the case.

d) The most important part of the treatment in hospital is *combating the shock* by transfusions of physiologic saline, plasma and blood. We also give blood transfusions in hemoconcentration due to shock, because later on, at times

within several hours, there is exsanguination into the tissues. There is no difference whatsoever between the treatment of shock due to snake bite and that of hemorrhage. Table 5 summarizes the results of the treatment and shows the comparison between the old and new systems.

e) There are certain theoretical reasons for the experimental trial of drugs like ACTH and cortisone in viper bites. These substances increase the retention of fluids in the tissues and can therefore be useful in the oligemia which is found in shock. They also dampen the action of hyaluronidase and there is, moveover, some effect of capillary permeability. It is worth-while emphasizing the effect of these hormones in allergic-anaphylactic conditions. Despite these advantages we have so far had no opportunity of trying out treatment on these lines.

SUMMARY

A study of 65 cases of viper bite in Israel is presented; 61 cases from the north of the country were given full clinical investigation and 4 cases from the center of the country were investigated anatomo-pathologically only. The clinical appearances are summarized according to frequency and classified patho-physiologically. Four cases are described in detail. Anatomo-histologic investigations are described and accompanied by photographs. New observations are made on the pathogenesis of the signs and symptoms of the poisoning. Principles of first aid and medical treatment are laid down on the basis of 10 years of clinical experience and a critical study of traditional methods is made. New methods of treatment are suggested for clinical trial.

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