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THE HEALTH PROBLEM OF ARACHNIDISM

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SYNOPSIS

The authors give data on arachnidism (the systemic poisoning caused by the bite of the spider *Latrodectus*) in general, on its distribution in the world and in Yugoslavia in particular, on the *Latrodectus* spider, and on the characteristic clinical syndrome of arachnidism. The bite of the *Latrodectus* causes great pain, disables the bitten person for a certain time, and may even cause death in a few instances. The results of the authors' own observations in the clinic and on experimental animals are given. Of all forms of therapy tried by them, the simultaneous application of calcium, antivenom, and sometimes procaine infiltration for the relief of local pains gave the best results. In view of the apparently increasing importance of arachnidism, the authors recommend the international exchange of experience on the problem.

Arachnidism is the name given to the acute poisoning caused by the bite of the venomous spider *Latrodectus*; in some countries, arachnidism may be caused by other spiders as well. The genus *Latrodectus* is spread over all the continents, the species *Latrodectus tredecimguttatus* being found in southern Europe and North Africa. Its black variety, *L. erebus*, has been described in Spain and Egypt, and in the steppe regions of Southern Russia and Asia, where it is most commonly known under the folk-name " Karakurt " (the black wolf). This black variety has also been noted in Istria, Yugoslavia. According to Sampayo,[20] there are three subspecies of *L. tredecimguttatus* : *L. hasselti* in southern and south-eastern Asia, Africa, and Australia; *L. menavodi* in Madagascar; and *L. katipo* in New Zealand. The species *L. pallidus* is found in Asia, and *L. hystrix* in Arabia in particular. In the Americas, from Canada to Patagonia, the species *L. mactans* is common. *L. geometricus* is found in the tropical and subtropical areas of Asia, Africa, and America; *L. folliatus* in South America; and *L. concinnus* and *L. indistinctus* in South Africa.

The bite of all these spiders has approximately the same effect.

Arachnidism has been known since antiquity and has been described by various authors since the Middle Ages. There are, however, signs that arachnidism has recently become more common, both in Yugoslavia and elsewhere.[1] In the summer of 1953, the *Latrodectus* caused alarm among the population of Italy, appearing in great numbers in the vicinity of Rome. One casualty was recorded in a young and vigorous man, as reported by Bettini and by Biocca (personal communications—1953). Similar reports appeared in American newspapers, and in 1950 Gajardo-Tobar [6] reported two casualties that occurred in Chile.

The appearance of this spider is periodic; in some years it is found in enormous numbers and may afterwards be missed for years, sometimes for decennia. It is not an aggressive spider, biting only in self-defence when provoked, and its bite may therefore be considered a mere accident and of practical importance only when its numbers multiply excessively and such accidents become frequent. In several regions of Istria, for example, the *Latrodectus* is present in such numbers that specimens may be collected from almost every square yard.[15]

Almost all our patients were bitten when in the fields, the greater part of them during harvesting and threshing. It is interesting that 18% were bitten on the same part of the body—namely, on the volar side above the left radiocarpal articulation. That is the site harvesters place on sheaves when binding them.[15]

According to published data, a great number of bites by *L. mactans* and *L. geometricus* occur in the home, often in privies where the spider hides under the boards.[2] Bites on the penis are said to be frequent. So far we have seen no accidents of this nature, nor have we seen the *Latrodectus* in houses. Russian authors have recorded actual epidemics of arachnidism among cattle at the end of the past century and the beginning of this,[23] and accidents among cattle have also been observed in Indonesia.[19] In Istria, we have not seen this at all.[13]

The causative agent of arachnidism in Europe is *L. tredecimguttatus*. Only the female is venomous. Her body is up to 1.5 cm in length, she is of a velvet-black colour, and may have as many as 17 deep-red spots on her ball-shaped abdomen. The male is much smaller and harmless. According to our observations, the male's bite cannot harm even a white mouse, which is, however, killed by the bite of the female within 10 to 20 minutes.

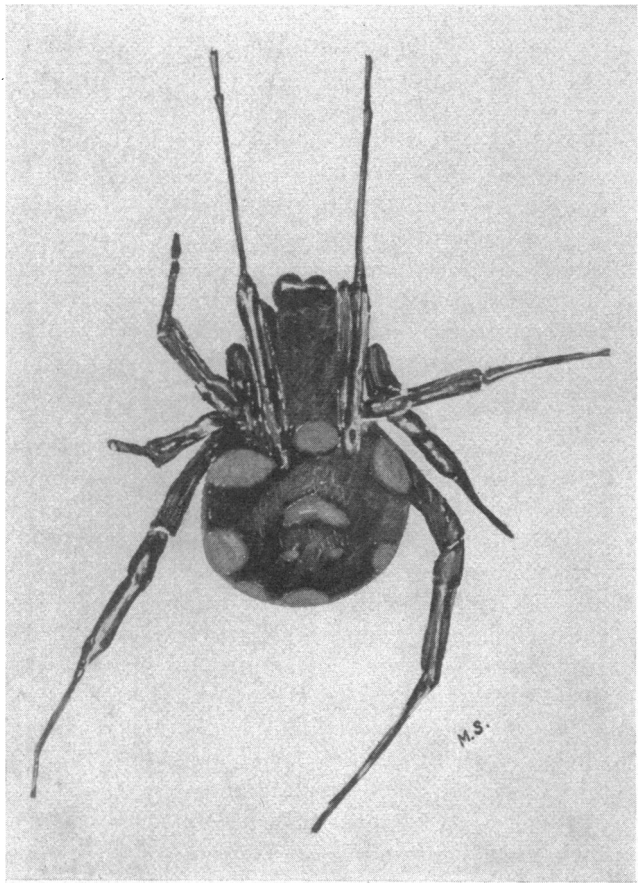
The *Latrodectus* nests in wheat, on the brink of ditches under stones, and in bushes, feeding on various insects which are caught in the web. The victim is first wrapped up in a viscous secretion from the web glands, then killed by the bite, and afterwards sucked.

The venom-producing mechanism of the *Latrodectus* consists of glands and hollow chelicerae which have both a cranial and a thornlike caudal process. When the spider plunges the chelicerae into the victim's body the venom is pressed out by the musculature in the wall of the gland.

So far as we know, few or no accidents due to the *Latrodectus* were recorded in Istria before 1948.[12] In the period 1948-53, more than 180 cases were observed in an area with not more than 30,000 inhabitants; most of those occurred in the District of Pula and some in the District of Poreč, while sporadic cases were reported from other regions of Istria. It is likely that arachnidism has increased not only in these regions of Istria, where it has been observed in recent years, but also in other regions—though to a far lesser extent.

At the General Hospital at Pula, 124 patients were treated for arachnidism, and one of us (Maretić) made clinical observations during the period 1948-53. If one considers that, according to Bogen & Loomis,[3] only 615

FIG. 1. LATRODECTUS TREDECIMGUTTATUS, ADULT FEMALE



Size: ×3 Drawn by M. Stanić

cases had been recorded in the whole of the USA by 1935, it is evident that our cases represent a very considerable number. In Yugoslavia, arachnidism has been seen in Dalmatia,[22] Montenegro,[18] and Macedonia as well as in Istria, although it is less frequent there.

Clinical Features

The poisoning caused by the bite of the *Latrodectus* has a serious and dramatic course. Bitten persons, although their lives are not generally in danger, suffer great pain and are disabled for a certain time owing to the long convalescence. The syndrome of arachnidism is very characteristic, but those who are faced with it for the first time meet with many difficulties of differential diagnosis. The bite itself is superficial, similar to a slight prick with a needle, and many persons do not even perceive it. Most of our patients had dramatic symptoms of arachnidism without knowing they had been bitten, a fact that increases the difficulties in establishing a diagnosis. The period from the moment of the bite to the appearance of the first symptoms is normally short—generally only 10-20 minutes, although it may extend up to one to two hours. Sometimes a burning is felt at the bitten site immediately after the bite, and this pain is followed by other symptoms. One characteristic symptom is an early pain in the regional lymphatic nodes (axillary or inguinal), where a swelling may often be palpated. Locally, a typical erythema with urtica, local perspiration, and excitation of the arrectores pilorum arises. Usually a reddish-blue ring with very sharp edges appears on the following day; this area is anaesthetic, and an anaesthesia dolorosa may occur.

The general condition becomes poor quite early. The patient feels a pressure in the chest, and the pains, which extend to the belly, the lumbar region, and the extremities (particularly the lower ones), gradually increase and become insupportable. The skin over the whole body becomes hyperaesthetic. In serious cases, patients are not able to stand upright, become stiff as if they had lumbago, or walk around heavily and awkwardly like tabetics. At the beginning of the illness, the pains prevail in the belly and the lumbar region, but on the second and third days they are greater in the lower extremities, mostly in the soles of the feet, where a sharp burning is felt. The patients are tachypnoeic and breathe superficially, sometimes stridulously. Loss of weight is also characteristic; some of our patients lost 5 kg within three days. The main symptom in man is the very intense pain, which compels the patient to seek medical help. Our patients described the pain as mostly felt in their muscles and bones, " as if somebody was tearing their flesh with a pair of tongs ". Some of them felt " as if they would burst ", as their flesh distended and swelled. Pavor mortis and

restlessness were rather pronounced. In a patient of ours these symptoms occurred suddenly and were so intense that his family wanted to take him to the psychiatric department as they thought he had become mad.[16] Psychotic states were observed in two cases.

The body temperature is normal or slightly above normal, and there may be profuse sweating and sometimes shedding of tears, troubled salivation, rhinitis, and bronchitis. This general state was observed to a greater or lesser extent in all bitten persons. Excessive salivation or, on the contrary, a dry mouth are frequently seen; one patient of ours excreted about 1,500 ml of saliva in 24 hours. Convulsions, together with the aforesaid restlessness, give a peculiar aspect to this disease. In some patients we saw trismus.

The rigidity of the abdominal musculature, together with disappearance of abdominal reflexes, vomiting, and sometimes more or less localized pains in various parts of the belly, lead on occasion to a wrong diagnosis of the abdominal condition, and cases are to be found in the literature in which a laparotomy was performed.

Increased tendon reflexes are a rather constant symptom.

An increase in the cerebrospinal-fluid pressure was observed in 12 of our patients while we were carrying out lumbar punctures.[12] This increase appeared to be very high when the pressure was measured by a manometer. In one of the patients, who showed premorbid values of 160-170 mm H_2O, the pressure increased to 460 mm H_2O in the course of arachnidism.[16]

Changes in the eye. A more or less pronounced conjunctivitis was observed in all our patients; most of them had an oedema of the eyelids, and in some cases changes in the fundus of the eye were observed as well. The hyperaemic oedema of the eyelids, together with conjunctivitis and hyperaemia of the skin in the region of the face and head, gives a characteristic appearance to the patient. Three out of 10 patients who, in 1951, were not treated with either calcium or antivenom showed considerable filling of the veins of the fundus of the eye, but this had completely disappeared when the control visit was made three weeks later. In some cases, mydriasis was observed.

Cardiovascular changes. An increase in blood-pressure was observed in almost all our patients; the systolic increase amounted to 100 mm Hg. According to our observations, this transitory hypertension is of a convergent type. Hypertension was also occasionally noted in the earliest phase of arachnidism, while in some other cases there were signs of slight shock where the blood-pressure even decreased.

At the onset of arachnidism there is some tachycardia, and bradycardia is frequently noted some hours later. We made electrocardiograms of seven patients, and in one case found changes in the S-T segment with a prolonga-

tion of the Q-T interval. These may be explained as signs of changes in the calcium and potassium plasma levels. The control electrocardiogram taken after recovery was quite normal.

Urinary changes. An oliguria and a high specific gravity of urine, usually above 1,040, often with albuminuria, are typical of this illness. In the first days, patients usually secrete 200-300 ml or less of urine, and when other symptoms disappear a normal diuresis sets in. The causes of oliguria may be manifold. It is beyond doubt that a decisive influence is exercised by the great loss of fluid, particularly by sweating and perhaps by salivation as well. Oliguria was also sometimes observed in patients with a full bladder; the effect of the toxin on the vegetative nervous system is probably the cause of this retention of urine, and in our opinion there may also be direct damage to the kidneys.

Chromocystoscopy was carried out on 13 patients; in four of these, a retardation of the colour was observed in the acute phase of poisoning. Albuminuria was very common in our patients. Leucocytes and erythrocytes were usually found in the urine, and in two cases there were also granular casts. These findings always became normal when the other signs of arachnidism had disappeared.

Symptoms of the digestive tract. We often observed that our patients complained of heartburn; however, on analysis of their gastric juice, we never found hyperacidity, but normal, even hypoacid, values. Vomiting was a very frequent symptom.

In some cases, a pronounced increase in the size of the liver occurred, and in two cases a subicterus was observed. Bilirubin was not found in the urine, but there was an increased urobilinogen value. Takata-Ara and formol-gel tests were always found to be negative. The values of the thymol test were often at the upper limit of normal, sometimes increased, and in one case the turbidity was 12. Anorexia and constipation were always part of the clinical picture.

Signs of alarm reaction are rather pronounced in arachnidism at the onset of the intoxication. Clinical signs of shock are sometimes manifest, but usually one notes a change in the blood picture in that there is a rapid fall in the count of eosonophils and lymphocytes, with a neutrophilic leucocytosis, a moderate increase in rest nitrogen, and typical changes in the sugar curve, the metabolism of electrolytes, and haemoconcentration. As regards blood-sugar, a slight hyperglycaemia or hypoglycaemia were found in some cases, and glycosuria in one case.

Blood-sugar changes were studied in animal experiments, as will be shown later. A decrease in sodium and chloride and an increase in phosphates and proteins were observed in the blood plasma. The haematocrit values were increased.

A rash, scarlatinoid, morbilliform, papular, even vesicular—generalized, or localized on the belly, the chest, or in the vicinity of the bitten site—commonly followed by pruritus, was observed in serious cases some days after the bite.

The duration of the illness in untreated persons is one week, sometimes even longer. The convalescence lasts a long time, about one month or even more.

Experimental Investigations and Toxicology

To analyse the symptomatology of the toxic effect of the poison, and for various other reasons, many experiments were performed on rats, mice, cats, guinea-pigs, rabbits, dogs, and cold-blooded animals.

In our experiments carried out to compare the effect of the venoms of *L. tredecimguttatus*, *L. hasselti*, and *L. mactans*, an equal response was shown by all experimental animals. The antivenom against the bite of *L. tredecimguttatus* also protected white rats against the bite of *L. mactans*; and a rat immunized against the venom of *L. tredecimguttatus* was resistant to the bite of *L. hasselti* as well.

H. L. Keegan, of the Army Medical School in Washington, D.C., to whom we sent our *L. tredecimguttatus* antivenom, tested it against the venom of *L. mactans* and *L. hasselti* and found that it gave full protection to laboratory animals. As we know that spider venoms, and consequently antivenoms, are highly specific, this is biological proof that the venoms of *L. tredecimguttatus*, *L. mactans*, and *L. hasselti* are practically identical.

Experimental animals showed a restlessness similar to that of bitten persons; this was particularly expressed by the jerks and odd attitudes of rats. At a further stage of the intoxication, restlessness was replaced by paralytic symptoms. Animals also lost weight, some bitten rats losing 20% within 24 hours. Hyperaemia of the skin in the region of the head and face could be observed in guinea-pigs, cats, rats, and other animals.

Salivation was most pronounced in kittens, and lacrimation in rats, mice, and guinea-pigs.

The changes in the blood-sugar curve observed in some of our patients were checked on a series of animals which were bled at various intervals after being deliberately exposed to the bite of the spider. One hour after the bite we observed hypoglycaemia and within two hours a slight hyperglycaemia, which reverted to a decrease below normal values at the final stage. Histological analysis of the organs of our animals showed oedema, parenchymal degeneration, necrosis or nephrosis of the kidney, degenerative liver changes, hyperaemia and oedema of the brain and lungs, and hyperaemia of other organs. In the adrenals and the lymphatic organs the changes typical of an alarm reaction were seen.[14] Ulcers were found on the mucous membranes in the stomach and intestines.

Not all animals are equally sensitive to the venom of the *Latrodectus*. According to information contained in the literature, the camel is very sensitive,[23] and we ourselves had an opportunity of observing great sensitiveness in the horse, as will be seen later. Of the small laboratory animals the most sensitive is the mouse, which is killed by a single *Latrodectus* bite within 10-20 minutes. Guinea-pigs weighing 250 g may be killed within one to two hours, and rats of 100 g and kittens of 400-800 g in about 24 hours. Rabbits are fairly resistant, and are killed by several bites only after some days. Dogs are also resistant; none of the four dogs weighing 7-12 kg and bitten by 4-6 spiders was killed. No response was observed in turtles and lizards which had been exposed to large doses of *Latrodectus* venom.

The venom of the *Latrodectus* is neurotropic but has a great effect on the whole organism. It is stated that this venom has a toxic effect 15 times greater than that of the rattlesnake. The sites of action are the nervous termina.

According to Vellard,[23] the pH of the venom changes according to temperature. At temperatures above 25°C it becomes alkaline and more toxic, and at lower temperatures acid and less toxic. This is perhaps the reason why bites are most toxic in summer. The venom coagulates at temperatures of 55°-60°C. It is limpid and of a lemon-yellow colour. Its chemical components are not known, but they are thought to be toxalbumins. The venom gland of a *Latrodectus* contains about 0.3 mg to 0.5 mg of venom. Once injected into the bite this spreads very quickly from the site of the bite by the lymph.

One of us (Maretić) made the following experiment :

In a series of 15 rats bitten in the tarsus by the *Latrodectus*, the legs were amputated after intervals of from 10 seconds to 10 minutes after the bite. Even those animals whose legs were amputated 15 seconds after the bite showed typical initial signs of restlessness and convulsions. However, in the further course of the illness a full picture of arachnidism developed only in those rats whose legs had been amputated not earlier than five minutes after the bite, i.e., the time necessary for a full absorption of the venom.

Immunology

It has long been known that spider toxins have antigenic properties and that antitoxins can be obtained by immunization of laboratory and bigger animals. That an intoxication with *Latrodectus* venom gives full immunity is proved by the results of the following experiments :

In the summer of 1951, 11 rats out of a number of 128 which had been exposed to the bite of the *Latrodectus* survived arachnidism with very marked symptoms and acquired a very solid immunity. After one to two

months, they were again exposed to the bite of the *Latrodectus*, the first animal being bitten by one spider, the second by two, the third by three, and so on. Those animals which had been exposed to the simultaneous bites of 3 spiders did not show any signs of arachnidism, whereas such signs were observed in animals which had been bitten by 4-6 spiders simultaneously; rats which had been exposed to 7-8 simultaneous bites were killed very suddenly.

Rats proved to be very sensitive to *Latrodectus* venom. Intact rats may live for 24 or 48 hours or even longer after being bitten, but only rarely do they survive; on the other hand, adrenalectomized rats are killed within half an hour. However, the acquired immunity of adrenalectomized rats having previously survived arachnidism was so great that they were protected.

Therapy

Methods of treatment of arachnidism are very old. Even Celsus, in the first century, recommended baths and some local drugs; Avicenna, in the tenth century, recommended opiates and baths.[11] Various methods of treatment have been preserved to our day in the folk-medicine of some peoples. Thus, in Greece, a person bitten by the spider is warmed in a baker's oven; on the Croatian littoral, according to Damin,[4] the patient is swung on stretched ropes; and it is said that in Abyssinia the bitten person has to dance to the point of exhaustion. In past centuries, the so-called " tarentism " was rife in Europe.[10] This was thought to be caused by the bite of the spider *Tarantula apuliae*, and as a cure the people danced to frenzied melodies in the streets and squares of European cities until they fell to the earth from exhaustion. These melodies have been conserved in the dance " tarantella ". In the world of that time, full of superstitions and unclear conceptions, these manifestations were widespread and became a veritable plague for some regions of Germany, Italy, and certain other countries. Some authors are of the opinion that these manifestations had a connexion with chorea, others that they were a form of hysteria. It is obvious that tarentism was in fact a manifestation of mass hysteria, but it is perhaps possible that it was originated by persons bitten by the spider *Latrodectus*, not by the *Tarantula*. It would not be surprising that the two were confused, since this occurs even nowadays. In the vicinity of Vodnjan, Istria, we had an opportunity of hearing that both spiders were called " tarantola " by peasants.

As we have seen, a patient bitten by the *Latrodectus* shows great restlessness; he is impelled to move and to walk, and is convulsed and writhes. We have further seen that in our patients and experimental animals such movements did, up to a point, help them to tolerate their pains. It is easily possible that such movements were the basis of hysterical tarentism.

Many methods have been described in recent literature for the treatment of arachnidism. We have tried some of them. In our experience, morphine, glucosides, aneurin, and some other remedies proved to have no substantial effect.

Procaine

After an intravenous injection of 10 ml of a 0.5% solution of procaine, we obtained transitory but considerable relief of pain in our patients. Far better results were obtained by local infiltration in cases with localized pains.

Cortisone, hydrocortisone, and ACTH

Seven of our patients were treated with cortisone (cortone acetate), six with hydrocortisone (hydrocortone tablets), and one with ACTH. Experiments were carried out on 18 rats with an equal number of control animals. The bite of the *Latrodectus* has an effect of great stress on the organism, and some of the symptoms may be considered to be those of an alarm reaction. Some patients were freed of their major symptoms within a few hours,[14] and the greater number of them within 24 hours. Similar positive effects were observed in animals. Rats treated with cortisone lived, on the average, 70 hours after being bitten, and the controls 34 hours. Two of eight rats treated with hydrocortisone survived, while all the controls were killed. In patients treated with these drugs a recurrence of symptoms was frequently seen.

Magnesium sulfate

Doses of from 10 ml to 20 ml of a 10% solution of magnesium sulfate given intravenously are recommended by many authors for the treatment of arachnidism.[5] We made use of this method on four patients. After intravenous injection of the drug, the patients experienced a feeling of warmth and the pains decreased, almost disappearing. A drawback of this method of treatment is that symptoms may recur within 20 minutes or less and the injections should not be repeated too frequently.

Calcium

The treatment of arachnidism with calcium salts was first recommended by Gilbert & Stewart.[8] In applying this therapy, we obtained results similar to those with magnesium sulfate—namely, an immediate and great relief of pain and disappearance of symptoms after intravenous injection—but to a far greater degree. Here too, recurrence of pain may be observed within 20 minutes or after some hours, but these relapses have a much

easier course. It is absolutely necessary to repeat the calcium injections several times. A good effect is also obtained by intramuscular injection of calcium gluconate—recommended by American authors [9]—though this works slower than the intravenous injection. We treated 27 patients in all with calcium salts, and we made use of calcium chlorate, bromate, and gluconate with the same effect. The observations that we made on the changes in calcium metabolism in the serum of our patients speak in favour of treatment with calcium.

Antivenom

In 1901, Kobert [11] recommended immunization with the whole body of *L. erebus*. In 1903, Ščerbina immunized camels, which are very sensitive to the venom of the Karakurt, directly by bites or with extract from the cephalothorax. With their serum he succeeded in curing camels to which thirteen-fold lethal doses had been given. Similar results were obtained by Konstansov in 1904. In 1919, Houssay & Negrette immunized rabbits directly by bite; in 1925, Brazil & Vellard produced antivenoms for various spiders; and in 1928, Troise, availing himself of the procedure of these authors, succeeded in preparing an antitoxin for the venom of *L. mactans*. In 1936, D'Amour made comparative tests of the value of convalescent sera and an antivenom obtained by an immunization of sheep; the latter showed much greater effect. In 1937, Finlayson prepared antivenoms for the bite of all three kinds of *Latrodectus* found in South Africa (*L. concinnus*, *L. indistinctus*, and *L. geometricus*). Up to 3,000 spiders were used by Smith, Dorn & D'Amour, for the immunization of sheep. A specific horse serum against the bite of the Karakurt was prepared by the Russian author Maksiyanovich in 1939. In 1941-42 Houssay, Pirosky & Sampayo of the Bacteriological Institute of the National Department of Hygiene in Buenos Aires, prepared a very good serum by immunizing horses, obtaining a very high titre by purification; 1 ml of the antivenom protects a guinea-pig from 3,000 lethal doses. They used 1,436 cephalothoraces for the immunization, and 820 more for hyperimmunization.[20] With 5 ml of this serum given intramuscularly they obtained excellent therapeutic results. A relief of pain set in after a few minutes, and some hours later the pains completely disappeared. The following day the patients felt well, as was the case with other antivenoms. The treatment of arachnidism by convalescent serum has been tried; Bogen [2] reported varying results, but we saw no results in our patients.

The practical requirements of Istria, where arachnidism has recently become a health problem, led us to try to prepare an antivenom for our spider, *L. tredecimguttatus*, particularly in view of the inadequacy of the usual symptomatic therapy.

In 1951, one of us (Maretić) immunized rabbits against the venom of the *Latrodectus* by applying a direct bite. At the end of these tests rabbits

weighing from 1,800 g to 2,300 g were able to resist up to 120 simultaneous bites. As little as 0.8 ml of the serum of the rabbit proved sufficient for neutralizing in vitro an emulsion of two pairs of venom glands in 1 ml of physiological saline, capable of killing a 300-g guinea-pig in 3½ hours. This antivenom showed good results in 12 patients of ours. With an intramuscular injection of 8-10 ml the state of the patients improved considerably after some hours, and after 24 hours and even earlier they were practically cured.

In 1952, one of us (Stanić [21]) prepared a specific serum at the Central Institute of Hygiene in Zagreb, using as antigen the macerated cephalothoraces of spiders. A certain number of spiders being required for studying the action of the *Latrodectus* venom and for determining the lethal dose and the immunization properties, we had to organize the collection of spiders, which were sent to Zagreb from Pula by parcel post, individually packed in pharmaceutical boxes. The spiders were thus able to live for some weeks during the season. About 350 spiders were despatched to Zagreb in this manner during the summers of 1952 and 1953.

Obtaining the venom by a preparation of the glands or by provoking the spiders being a rather tedious undertaking, we decided to make use of a simpler but satisfactory method. We stunned the spiders with ether and with a pair of fine scissors cut off the front part of the cephalothorax behind the first pair of legs, where the venom glands are situated. The macerate prepared from this was centrifuged in 1 ml of physiological saline. A white mouse injected intravenously with 0.1 ml, or even 0.05 ml, of this clear liquid was killed in a few minutes. We took as one DCL (dosis certe letalis) 0.025 ml, this being able to kill a mouse within half an hour. The macerate of one spider contains 40 DCL at least. In various specimens of the *Latrodectus* we noted considerable differences of toxicity, probably due to external conditions, and we therefore decided to use as a preliminary definition of one DCL the amount of venom by which a mouse is killed within half an hour after showing evident signs of arachnidism.

A wether with a body weight of about 40 kg was used for immunization. We injected subcutaneously into its throat region the macerate of one cephalothorax in 2 ml of physiological saline. The wether supported the injection without showing any symptoms. The next injection consisted of two macerated cephalothoraces and the wether lay down, refused food, and secreted much saliva. On the third day he recovered. Four days later the wether was given a third injection containing the macerates of three spiders to which he responded with similar symptoms, although somewhat less pronounced. A fourth injection given four days later was tolerated without any symptoms. Later, at intervals of four or five days, we repeatedly injected the macerates of six spiders, bled 20 ml of the wether's blood, and separated the serum by centrifugation. Four DCL were then added to 0.1 ml of serum, and after a neutralization of 20 minutes the mixture was

injected intravenously into a mouse. Five minutes later the mouse began to blink, and signs of salivation were noted which, however, soon disappeared; no other symptoms occurred. The same amount of venom mixed with 0.2 ml of serum had no toxic effect on the mouse.

Control mice were given the same quantity of venom with different amounts of the serum of a non-immunized wether; all died before long with typical symptoms of arachnidism. A trial of neutralization of the *Latrodectus* venom with the antitoxin against the venom of the *Vipera ammodytes* yielded no positive results.[21]

Eight days after the last injection of the macerates of six cephalothoraces 500 ml of blood were taken from the wether. We separated 330 ml of serum, added 33 mg of merthiolate, filtered the mixture sterilely through a Seitz filter, and stored ampoules of 5 ml of the filtrate. Immunization carried out with this serum proved that a mouse to which it was given in a dilution of 1 : 50, and even 1 : 150, was protected against one DCL. With 0.2 ml of this serum we succeeded within one hour in curing mice which had already shown marked symptoms of salivation.

We successfully treated 16 of our patients with this serum; within 10-20 minutes after being given 5 ml intravenously, they showed visible improvement, the symptoms disappeared, and 2-3 hours later they felt quite well. A few hours after that they recovered their appetites and were able to sleep. Similar results had been reported by Gajardo-Tobar.[7] None of our 28 patients treated with either rabbit or sheep serum showed any signs of serum reaction.

We also tried to immunize a horse, but he was unexpectedly killed by a single macerate within 24 hours. The horse seems to be as sensitive as the camel. Immediately after he had been given an injection in the neck region at 11 a.m., a big local oedema appeared and an increase in body temperature and a tremor were observed. Later these signs disappeared, but during the night symptoms of arachnidism emerged. The following morning the horse was found in a pool of its own saliva and could only forcibly be set on its feet. An immense salivation dominated the clinical picture. The horse was dyspnoeic and refused to take either food or water. When we arrived with the serum we found the animal dying of suffocation. Dissection showed that the voluminous lungs and the trachea were filled with a frothy, white, and haemorrhagic secretion. The histological findings agreed with those found in other animals. Another horse fell seriously ill after administration of only $^1/_5$ of a macerate, but was immediately cured with the antivenom. From that time we abandoned the immunization of horses, which we had approached with a view to obtaining larger quantities of serum. We are now preparing a refined serum by peptic digestion similar to the Argentinian antivenom, the good effects of which have been described by Gajardo-Tobar.

However, the quickest and best therapeutic effect is obtained by a

simultaneous application of antivenom and calcium, as has been recommended by Miller.[17] If first calcium, and later antivenom are injected intravenously into a patient showing the most marked symptoms of arachnidism, pains disappear immediately after the calcium injection and do not re-appear since the antivenom begins to act in the meantime. Some local pains may remain but they can be relieved by infiltration with procaine. By this combined treatment with calcium, antivenom, and sometimes procaine infiltration—which proved to be the most effective and by which the patient is practically relieved of his pain within a few minutes—the problem of arachnidism in our country may be considered practically solved.[a]

The Control of Spiders

The control of spiders may be carried out either by mechanical destruction of the spiders themselves and of their cocoons—although in our experience this has proved rather difficult—or by the application of insecticides. We did not apply insecticides in the field, but our experiments proved that DDT was not suitable. Specimens exposed to a very strong concentration of DDT, which cannot be obtained under natural conditions, lived 24 hours and longer. Better results were obtained with Gammexane (gamma-isomer benzene hexachloride), when the *Latrodectus* was killed under similar conditions within half an hour. In our opinion, however, the control of spiders by the insecticides known so far appears to be rather problematical and expensive.

Discussion

In this paper we have described the problem of arachnidism in Yugoslavia and the way in which we have approached the solution. In our opinion, arachnidism must have become a problem in other countries as well, since, according to our information, it has been increasing in recent years.

We suggest that there is definite need for an international exchange of experience on arachnidism; this would be desirable and would probably prove very useful.

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[a] Since the manuscript was submitted for publication, 12 new cases have been treated with calcium and antivenom with equally quick results (August 1954).

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RÉSUMÉ

L'arachnidisme est l'empoisonnement aigu causé par la piqûre des araignées du genre *Latrodectus*, ou, dans certains pays, par celle d'araignées d'autres genres. Ces araignées se rencontrent dans tous les continents et leurs piqûres ont à peu près le même effet partout. L'arachnidisme est connu depuis l'antiquité et a été décrit par divers auteurs depuis le Moyen-Age. Il semble qu'il se soit répandu en Yougoslavie ainsi que dans d'autres pays au cours des récentes années. En 1953, la pullulation de ces araignées a alarmé la population des environs de Rome. Quelques cas mortels ont été signalés en Italie et en Amérique.

En Europe, l'arachnidisme est causé par *L. tredecimguttatus*, dont seule la femelle est venimeuse. De couleur noire, veloutée, l'abdomen taché de points rouges, elle mesure 1,5 cm. Le mâle, plus petit, est inoffensif. Cette araignée niche dans les blés et les buissons. L'appareil à venin se compose des glandes et de chelicères creuses terminées par une épine. Des quantités de venin de 0,3-0,5 ml sont injectées et diffusent rapidement par la voie lymphatique. Cette araignée sévit périodiquement, en très grand nombre certaines années, pour disparaître ensuite pendant longtemps, dix ans parfois. Elle ne pique qu'en état de défense. Les morsures, considérées normalement comme accidentelles, n'ont d'importance pour la population que si elles se multiplient, lorsque l'araignée pullule. En Istrie, où l'étude résumée ici, a été effectuée, la plupart des piqûres survinrent dans les champs, au cours de la moisson ou du battage ; elles étaient le plus souvent localisées au-dessus du poignet, à l'endroit de la main qui soutient les gerbes que le moissonneur va lier. Il semble que l'arachnidisme n'ait guère été signalé en Istrie avant 1948. Mais de 1948 à 1953, plus de 180 cas sont survenus dans une région ne comprenant guère plus de 30.000 habitants. Ce nombre de cas est proportionnellement très élevé, comparé à celui d'autres pays. L'intoxication arachnidienne, sans généralement mettre en danger la vie du sujet piqué, provoque des troubles sérieux et entraîne une longue incapacité de travail. Le venin de *Latrodectus* est neurotrope, mais a un effet systémique. Les premiers symptômes apparaissent 10-12 minutes après la piqûre, qui peut, au moment même, passer inaperçue, étant superficielle et souvent quasi indolore. L'état général s'aggrave rapidement. La peau devient hypersensible. Les douleurs, particulièrement aiguës dans la région lombaire et l'abdomen, s'étendent aux extrémités et deviennent intolérables. Des convulsions peuvent survenir. La perte de poids est rapide ; elle peut atteindre 5 kg en 3 jours. La température reste normale ou ne s'élève que légèrement. De la salivation excessive, de la rhinite, de la bronchite peuvent accompagner ces symptômes. En l'absence de traitement, la maladie peut durer une semaine et la convalescence se prolonger au-delà d'un mois. Le venin de *Latrodectus* est quinze fois plus toxique que celui du serpent à sonnettes. Le chameau et le cheval sont parmi les animaux les plus sensibles.

Parmi les substances proposées et mises à l'épreuve pour soulager les malades, la cortisone, l'hydrocortisone et l'ACTH ont allégé les douleurs en quelques heures, sans cependant éviter toujours le retour des symptômes. Les sels de calcium, en injections intraveineuses répétées, ont donné des résultats favorables. On sait depuis longtemps que les toxines d'araignées ont un pouvoir antigénique, et que des sérums antitoxiques peuvent être préparés sur les animaux. Un sérum antitoxique contre *Latrodectus* a été préparé sur le mouton ou le lapin, et son inoculation à raison de 5 ml par voie intraveineuse a donné de bons résultats, qui ont pu être encore améliorés par une thérapeutique mixte : calcium et sérum antitoxique. Le calcium, injecté le premier, fait disparaître immédiatement les symptômes aigus. L'action subséquente du sérum inoculé peu après empêche leur réapparition. La procaïne peut être un appoint dans ce traitement. Cette thérapeutique semble avoir apporté la solution pratique du problème de l'arachnidisme en Yougoslavie. Les auteurs estiment que des échanges de vue sur cette question entre les divers pays seraient extrêmement utiles.

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