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30. COMMENTS OF THE MODERATOR

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It is a role of the moderator to comment and to make a summary of papers presented to the Symposium. I will not withdraw from this obligation, all the more so that I and the collaborators of the Department of Physiopathology and the Hospital Vital Brazil from Instituto Butantan were not active participants in this session, in view of the high number of foreign specialists who had kindly accepted to take part in this Symposium. It is obvious that with 13 foreign participants registered, each of them having 30 minutes for presentation and discussion of his paper, there would be a 6 hours and 30 minutes long session. Thus, there was material impossibility to register papers of our group, and we did not do it in order to leave the time for our foreign colleagues who had a long journey to attend this Symposium.

In 1954, Dr. Afrânio do Amaral, at that time Director of the Instituto Butantan, gave me the attribution to direct and reorganize the Hospital Vital Brazil, function which I carried out until March, this year. In this service and in the Department of Physiopathology, I and my collaborators have had the opportunity of raising some experience in the subjects discussed in this session. During this period, 15,709 patients bitten by poisonous animals came to our service to look for medical assistance. I, therefore, profit this opportunity to address the house as a Moderator of one of this Symposium's sessions. Let us then start to comment the different papers presented today.

The paper of Dr. Parrish was presented by Dr. McCollough and it gave us the opportunity to become aware of many of the epidemiologic aspects of poisonous snake bites in the United States. Here in the southern hemisphere, and with different climate, our data are, obviously, different. These aspects of accidents by poisonous animals are very interesting and are useful, not only for the evaluation of the problem, but for the informations which may guide to improve prevention of these accidents as well.

Dr. McCollough showed a series of cases bitten by snakes from the genera *Crotalus* and *Agkistrodon* from the United States. The frequency, intensity, and extension of necroses are impressing. In our opinion they are typical consequences of deficient treatment by antivenin. Deficiency of serumtherapy may be due to three factors: unspecific antivenin, delayed treatment, and unsufficient doses. The first and the second factor cannot be blamed in those cases, only the deficiency of antivenins' doses. What may have contributed to this fact is that the authors referred to the number of vials as a criterion for dosage evaluation. This is a mistake we all made at the beginning; it is why, at those times, we had similar cases to those we have seen now. It is a nonsense to say that a patient was treated by such or such number of antivenin vials. Antivenin's potency vary from one producing laboratory to another and, unfortunately, there are many of them which do not indicate on the label the neutralizing capacity of venom in miligrams. Even the Instituto Butantan fell into the same error with some antivenins up to a short time ago, and it still does it with arachnidic antivenins. It is essential that all laboratories producing antivenins should indicate on the label the number of "units" contained for the venom. "Units", as we propose, is the ability of neutralizing 1 mg of venom. We use this designation and definition in our works since some time ago, because we consider it of great practical importance, either to the physician or to the researcher. The reason is that, once the anti-

venin is an agent neutralizing the venom, it is necessary to inject, the earlier the better, such a number of "units" which will be able to neutralize all of the venom that eventually has been inoculated by the animal. By knowing from the specialists of each country or region the quantity of venom in mg contained in the different species' glands, the physician will be able to evaluate the amount of "units" to be injected in order to neutralize actually the whole venom which may have been inoculated. It is an elemental and a simple arithmetic question without any difficulty for anyone. This criterion is as obvious as in medicine's other fields, where nobody would give a drug unless its quantity could be referred to in relation to weight or unit. For instance, nobody prescribes a corticoid without indicating its number in mg of "units". Thus, we do not understand how one may have the courage to indicate serumtherapy measured in mililiters or vials without knowing how many mg of venom the antivenin is able to neutralize. We insist that this tradition is wrong and it should be corrected. It is interesting that I have already found, in a publication of Vital Brazil of about 1910, the statement about the necessity of indicating antivenins' potency in mg of venom which they are able to neutralize; unfortunately, this was forgotten.

From this reasoning comes our opinion that the results we have seen are only a consequence of insufficient serumtherapy and not of antivenin's ineffectiveness, as it may have seemed like. Obviously, the specific treatment is useless after the necrosis occurrence. There is only the symptomatic, clinical, and surgical treatment left, which, infering from Dr. McCollough's words, has been well conducted.

About this point, we would still like to present an information: on about 1,600 cases of *Bothrops* bitten patients treated in the Hospital Vital Brazil in the last 11 years, there was, practically, no need for amputations excepting those cases which came to the Hospital late after the bite, when dry necrosis had already occurred.

Another treatment presented by Dr. McCollough, deserving some comments, is the one of incisions done for elimination of venom. To us it lacks physiological basis. These incisions intersect blood vessels and through these intersections is going to flow the circulating blood which does not carry any venom. The venom is in the tissue and it penetrates by lymphatic way. Circulation stops, as a consequence of the solution of continuity and the venom will stay at the site, aggravating necrosis. Besides, it will not be in contact with the antivenin coming through the blood circulation. In envenomations with proteolytic venoms, which provoke necrosis, incisions will enhance this effect. Something that has physiological basis is, withdrawal of the venom from the site of the bite by suction of the site attained by the fangs, if it is bleeding. Otherwise, to prick with a needle around the site is an aid to the outflow of serosity. If this procedure is carried out within the first half hour after the accident, part of the venom will be eliminated; later it is useless.

One more comment about the ligature which has been advised. Dr. Deoras has already asked a rather "venomous" question during discussion, and we agree with him. In fact, ligature is of no reason. If the venom is proteolytic, the circulation retention keeps the venom at the site, helping to provoke necrosis. If the venom is neurotoxic, it penetrates with or without ligature, since it contains an appreciable amount of hyaluronidase which helps venom's dissemination. And still, if the ligature is perfectly done as to really prevent the venom from penetrating the circulation, there will not be any blood circulation. Then, depending on how long the ligature was kept, loosening it will provoke shock which may be fatal, since the general condition is aggravated by the envenomation. Here, at the Hospital Vital Brazil, nurses are afraid, by experience, when a patient arrives with a good ligature; they will not open it, leaving it to the physician, because at this very moment many patients have had a peripheric shock. By the way, in experiments we made with Dr. Schenberg, present at this session, we provoked many shocks in dogs using only ligature. A well done ligature is enough to provoke a fatal shock even in normals, there is no need for venom. As a matter of fact, this mechanism of shock was discovered by Trueta in the II World War, during the bombings of London.

Dr. Kornalik presented very interesting data on the problem of fibrinolysis and blood incoagulability as provoked by snake venom. The demonstrated facts are valuable but their interpretation may be another. In order to make it clear

to the audience, it would perhaps be better to explain (in our point of view) what happens with coagulant and proteolytic venoms. *In vitro,* a small amount of venom clots the blood due to its coagulant fraction, which is active even in very small concentrations. This is not so with the proteolytic fraction. In higher amounts the venom provokes clotting by its coagulant fraction, then the fibrin formed is lysed by the proteolytic fraction and its high concentration permits its action before coagulation would occur. *In vivo,* small amounts of venom provoke hypercoagulability at the first minutes, fibrinogen clotting, and then blood incoagulability, due to a gradual and massive defibrination. In the phase of hypercoagulability, a fugacious fibrinolytic activity appears which disappears when the blood becomes incoagulable by defibrination. *In vivo,* there is no fibrinolysis or fibrinogenolysis by the direct action of venom because such high amounts would be necessary for provoking these effects which are, practically, impossible to obtain. Besides, they would almost instantly provoke death.

The presentation of Dr. Efrati's paper was very clear and synthetic. The clinical picture presented is exactly the same as the one observed in accidents by *Bothrops* snakes and all snakes with coagulant and proteolytic venoms. His definition of some symptoms as being an "anaphylactoid picture" is very appropriate, since they are due to the proteins' decomposition by the venom and the consequent liberation of resulting substances in the circulation. Thus, it provokes the same kind of shock obtained by injecting proteins or their degradation products. Dr. Efrati pointed out that he did not observe hemolysis, in spite of the venom being hemolytic *in vitro.* The reason is that through the bite, the venom is inoculated in tissues and it penetrates slowly the circulation. It is very diluted in the blood, never reaching a high concentration. But, if the venom is injected intravenously, the hemolysis will appear. Dr. Efrati refered to a case in which neurological symptoms appeared. I would like very much to discuss this with him and to find out what kind of symptoms they were, for two reasons: first, that I did not know that snakes from the genus *Vipera* had neurotoxins; second, that I would like to know if these neurological symptoms manifest the presence of modifications which produce what we call "neurotoxic facies", and which exist in all cases of envenomation through snakes containing neurotoxins. Unfortunately, I am not able to show a demonstrative slide. I will do it in other opportunity. Dr. Efrati's recommendation about the antivenin intravenous injection, the earlier the better, is very exact and we have here the same principle. However, we do not agree with his reference to the number of vials for the serumtherapy, for reasons we have already mentioned. I would still like to utter my personal point of view: I consider as very peculiar the fear of the physicians to inject greater amounts of antivenin while not fearing to leave the patient exposed to the risk of death and necrosis as a consequence of insufficient treatment.

The work of Dr. Ohsaka is extremely good and of an edifying experimental perfection. The way of evaluating *in vivo* the hemorrhagic action of venoms, giving way to compare different venoms, is very nice and based on a well imagined experiment technic. Dr. Ohsaka presented an important fact which is, the separation of two hemorrhagic fractions which are not bound to the proteolytic factor. This is a new fact to us, since the general idea is that the proteolytic factor is responsible for hemorrhage by causing the rupture of capillary walls. During the discussion of Dr. Ohsaka's paper, Dr. Purananda asked about the time the active venom substances may stay in the circulation. Since there was not a clear answer, I may inform about what happens with bothropic venom which is of the same kind as the Habu. In a severe envenomation, while the blood is incoagulable, the venom's active substances are present in the circulation even 48 hours after the bite. They are rapidly neutralized when antivenin is injected intravenously.

Dr. Schenone's paper was very well presented and we already knew part of it. He advises antihistaminics administration and we agree with that for a long time ago. About the indication of corticoids, however, we disagree. We do not have any proof that it is useful. It seems more likely to be some kind of a crutch in case there is no antivenin. One has to do something, so one gives corticoid. It is a rest to the doctor's conscience to give the patient some medical treatment. What should be done in the countries facing the problem of loxoscelism is to produce a *Loxosceles* antivenin which really neutralizes the spider venom, as it was done by the Instituto Butantan, here in Brazil. We have experience with this antivenin which presented some interesting peculiarities for the physician. At

the beginning, even when serumtherapy was given in time, some cases showed, after the treatment, a hemolytic syndrome. At that time, 2 to 5 vials were injected. Later, in other patients we started to inject 10 antivenin vials and, after that, no more cases of hemolysis were observed after the treatment. We do not mention "units" but vials because we did not succeed when we suggested that this antivenin should also indicate the quantity of mg or *gama* which it is able to neutralize. In the discussion of Dr. Schenone's paper he was asked about the cardiotoxic activity of *Latrodectus* venom which is apparent by the arterial hypertension he has observed in these envenomations. We would also like to comment this topic. We have, with much frequency, accidents by the spider *Phoneutria fera* which, like the *Latrodectus*, has a neurotoxic venom (different from the ophidic one, since it acts on the peripheric nervous system). In these cases the symptoms are identical to those refered to by Dr. Schenone, including the arterial hypertension. However, we do not consider the hypertension as due to a direct or indirect cardiotoxic activity on the neuro-vegetative nervous system, because as long as the pain is suppressed by means of an hypnotic or an anesthetic, the arterial pressure gets normal, and the hypertension reappears when the pain returns. We consider it, by this clinical evidence, as a secondary symptoms to the pain and not a direct venom activity.

The paper of Dr. Chapmann is extremely interesting to us because we have very few literature and data on ophidic accidents occurring in Africa. It has been a great lesson the way he presented the well tabulated data, including symptomatology. Dr. Chapmann is against incision as therapeutics, since he thinks, like we do, that necrosis provoked by the venom is already sufficient damage. Dr. Chapmann is also against ligature for the same reasons we already discussed before. He referred to the use of ligatures as a psychological effect but it seems to me that even this should not be tolerated. In the medical and physiopathological point of view, it may only be unfavourable to the patient.

Dr. Lieske brought an interesting contribution to the problem of snake bites, showing that even in Germany accidents of this kind may occur, provoked by snakes imported with merchandise. It is a hard problem and it can only be solved, as said Dr. Deoras, providing these countries with antivenins suitable for the snakes of the countries with which they have trading. We had the opportunity to know one case in quite a peculiar way. Once, when I was in Valparaiso, Chile, talking about poisonous animals, a physician from the Chilean navy said that this was no problem to them because there were no poisonous snakes in his country. Some days after being back in Brazil, a radio appeal came to Butantan, asking urgently for Elapidic antivenin. A dock worker in Valparaiso had been bitten by a poisonous coral snake while unloading some banana bunches arrived from Equador. The antivenin was sent in a few hours and, fortunately, the patient was saved. Dr. Lieske advised the use of corticoid in the treatment of snake bites. We disagree of this point of view based on an experiment made in collaboration with Dr. Langlada, published in Memórias do Instituto Butantan, 1964. Neither Dexamethasone nor ACTH in small, medium, and high doses showed any usefulness. On the contrary, they increased mortality with some venoms in experimented animals. All the same, we use corticoid in ophidic envenomation, but only for treatment of shock when it occurs. Dr. Lieske related some fatal cases, in spite of serumtherapy given in time. But, as admitted by himself, the antivenin doses were not sufficient. So we will not discuss this point.

Thanks for all collaborators to this Symposium.

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