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REMARKS

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BY

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Remarks on Snake Venom and its Antidotes.

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THE mode of action of snake venom, and the possibility of finding an antidote which will prevent it from producing its ordinary lethal effect, are subjects of great importance at all times, but at present they have acquired an added interest from the curious relationship which the serpent virus appears to have with those products of disease germs which either destroy or preserve life, according to the mode in which they are applied. The active principle of the poison of the viper was said by Prince L. Bonaparte to be a substance which he called echidnine or viperine, and Professor Busk suggested that the poison may be due to a substance analogous to ptyaline, though differing from it.

In 1860 Dr. Weir Mitchell made a most elaborate and admirable study, both physiological and chemical, of the venom of the rattlesnake, and drew attention to "the singular likeness between the symptoms and lesions of crotalus poisoning and those of certain maladies, such as yellow fever."[1] This analogy, he tells us, had been observed by S. L. Mitchell, by Magendie, and by Gaspard, who also called attention to the resemblance between poisoning by putrefying substances and by serpent venom. In this research Weir Mitchell found that rattlesnake venom contained two albuminoid substances, one of which was coagulated by boiling and the other not. The coagulum formed by boiling was innocuous, but the portion which remained fluid was poisonous. Admixture with alcohol caused coagulation, but did not destroy the power of the

[1] Weir Mitchell, *Researches on the Venom of the Rattlesnake.* Smithsonian Contributions, p. 97.

venom, and the coagulum, when redissolved in water, was found to behave like diluted fresh venom. The next experiments of this kind were, I believe, some of my own, which I have not hitherto published. These were made in 1870 in Professor Burdon Sanderson's laboratory with the poison glands of the fer-de-lance from Santa Lucia in the West Indies. Dr. Burdon Sanderson kindly placed a whole kegful of these heads at my disposal, and some of them were very large, measuring about three inches in length by 2 or 2½ across the broadest part; they had been preserved in spirit, which had coagulated the albuminous constituents of the poison glands themselves and of the contents of the ducts. I dissected out the poison glands with their ducts, and tried to extract a poison from them by various solvents, but none of the extracts thus obtained, nor the residue which remained after evaporating the spirit in which the heads had been preserved, proved sufficiently poisonous to kill even a guinea-pig. The utmost result that I could obtain was a slight increase of excitability in the nervous system, with a tendency to spontaneous twitching, which never, however, amounted to convulsions. These experiments seemed to show that the poison of this snake was either albuminous or so closely connected with albuminous substances as to be destroyed by coagulation by spirit. My failure to obtain any lethal action from the extracts led me to discontinue the research. In 1873 Sir Joseph Fayrer and I made some experiments on the venom of the cobra, which gave different results, and seemed to show that the venom of the cobra differed from that of the rattlesnake and fer-de-lance in its active constituent being soluble in alcohol. Thus we found that the precipitate thrown down from cobra poison by alcohol caused tremor in a guinea-pig but did not kill it, and a similar result was obtained by the injection of cobra poison which arrived from India in a coagulated cheese-like condition, and had probably been coagulated by alcohol, although we had no note to this effect. An alcoholic extract of the poison, when injected into an animal, produced symptoms like those produced by the fresh poison. Cobra venom, when coagulated by boiling, still remained active, though when heated for half an hour under pressure corresponding with 102 C., its activity was destroyed.

In his experiments published in 1883 Wall[2] found that an

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[2] Wall, *Indian Snake Poisons*, London, W. H. Allen, 1883, p. 121.

aqueous solution of cobra venom retained its lethal power after exposure to a temperature of 107° C. (224.6°F.) for half an hour, was somewhat weakened by exposure for an hour, and was rendered inert by an exposure of two hours. Weir Mitchell[3] made the interesting observation that boiling altered the action of rattlesnake poison to a certain extent, inasmuch as the boiled venom produced almost no local action, although it caused death, and Wall[4] found that daboia poison heated to 80° or 100 C. lost its convulsant, though it still retained its paralysing, action.

Weir Mitchell again took up the subject of the composition of rattlesnake venom in 1883, and, along with Reichert, arrived at the conclusion that it contained three proteid substances, namely, an albumin which was inert, and a globulin and peptone which were poisonous. In cobra venom Wolfenden found serum albumin, globulin, and syntonin, with occasionally traces of peptone.[5] He considers the substance which Weir Mitchell and Reichert call a peptone to be an albumose; and, indeed, according to the newer nomenclature, it is so, for it gave a precipitate with acetic acid and ferrocyanide of potassium, which true peptones do not. In speaking of it we may therefore use the term albumose instead of peptone. According to Weir Mitchell and Reichert, the globulins have a greater action on the blood, circulation, and respiration than the albumoses, and tend to destroy the blood corpuscles, prevent coagulation, produce ecchymoses, lower the blood pressure, and paralyse the respiration. The albumoses act more on the tissues, and tend to cause œdema, putrefaction, and sloughing. The venom of the crotalidæ contains a comparatively large amount of globulins, and produces local swelling and blackening of the parts, while that of the cobra contains comparatively little globulin, and has little local action. The globulins and albumoses in different venoms are probably not altogether identical, for the albumose of the cobra seems to have a greater power to produce convulsions than that of the rattlesnake.[6]

Both cobra and crotalus venoms kill by paralysing the respiration, although they also weaken the circulation; and, when much has been injected, the patient becomes weak and collapsed, vomits, and dies with or without convulsions.

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[3] Weir Mitchell, *op. cit.*, p. 45. [4] Wall, *op. cit.*, p. 125.

[5] Wolfenden, *Jour. of Physiol.*, 1886, p. 327.

[6] Weir Mitchell and Reichert, *Researches on the Venoms of Poisonous Serpents.* Smithsonian Contributions, 1886, p. 156.

If the poison has been less in quantity, the local symptoms in the case of poisoning by the crotalidæ increase, the swelling extends, symptoms of blood poisoning appear, and the face becomes swollen and puffy, the pulse very feeble, and the respiration laboured.

In still slighter cases the symptoms may disappear very suddenly and the patient recover. Hæmoptysis and hæmaturia have been noticed even in cases of recovery. In order to prevent death from snake venom, besides using the common methods of ligature and excision of the bitten part, we may try to find antidotes which will render the poison innocuous, or we may endeavour to maintain life until the venom has either been excreted from the body or undergone destruction within it. Of the chemical antidotes, the most efficient appears to be permanganate of potash, first recommended by Winter Blyth.[7] This was tested by Sir Joseph Fayrer and myself.[8] This substance completely destroys the poisonous power of cobra venom when mixed directly with it, but we were not successful in preventing death by applying it to the wounded spot after the injection of cobra poison. Lacerda,[9] in 1881, stated that he had succeeded in saving the lives of animals by injecting a 1 per cent. solution of the permanganate into the cellular tissue in from one to two minutes after injection of the poison, and Vincent Richards[10] also succeeded in destroying the effect of cobra poison by permanganate injected as long as four minutes after the venom.

Weir Mitchell found that the beats of the heart in cases of crotalus poisoning could be maintained for some time by artificial respiration, and the resemblance which Fayrer and I found between the action of cobra venom and of curare or of conine led us to try whether an animal might not be kept alive until the cobra venom had been excreted and recovery ensured, as it can readily be in the case of curare. We succeeded in keeping an animal's heart beating for ten hours by artificial respiration, and a commission appointed in India to repeat our experiments almost succeeded in bringing an animal round after apparent death by snake bite; but, after recovering sensation and motion

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[7] Winter Blyth, *The Analyist*, February 28th, 1877, p. 204.

[8] Brunton and Fayrer, *Roy. Soc. Proc.*, 1878, vol. xxvii., p. 465.

[9] Lacerda, *O Veneno Ophidico e seus Antidotos*, p. 29. Rio de Janeiro, Lombaerts & Co., 1881.

[10] Vincent Richards, *Landmarks of Snake Poison Literature*, p. 149.

to some extent, it died a second time in reality twenty-four hours after its first apparent death. There has been a case since in Ceylon, where a man was brought round from apparent death by snake bite by artificial respiration continued for nine hours, but only to die a few days afterwards from pneumonia.[11]

Artificial respiration is very troublesome to maintain for a long time, and even if it were successful one would gladly welcome any easier way of saving life. According to the Allahabad *Pioneer*, strychnine has lately been proposed by Dr. Mueller, of Victoria, for the purpose of stimulating the nerve centres, which serpent venom paralyses, and thus preventing its deadly action. He applies it "by subcutaneous injections of 10 to 20 minims of the liquor strychninæ, and continued every fifteen minutes until the paralysing effect of the snake venom on the motor and vasomotor nerve cell are removed, and slight strychnine symptoms supervene. The quantity of the drug required for this purpose depends on the amount of venom imparted by the snake, and may, after the bite of a vigorous cobra, amount to a grain or more, since more than half a grain has been found necessary to neutralise the effects of the bite of the tiger snake, a reptile much resembling the cobra in appearance, but not imparting nearly as much venom."

The researches of P. Rokitansky have shown that strychnine is a most extraordinary stimulant of the respiratory centre, and Cash and I found it to have a no less remarkable power to stimulate the heart.[12] Nor is it only in the laboratory that strychnine manifests these extraordinary powers, for clinical experience shows its utility, and by its free use in one very extraordinary case I restored a man whose respiratory centre had so far failed that his breathing ceased when he fell asleep, and he could only keep himself alive by voluntary gasps. Strychnine is thus very likely to prove a physiological antidote to the depressing action of snake venom on the circulation and respiration, and we may very reasonably hope for benefit from its use in snake bite. But Dr. Mueller's directions seem rather dangerous and, if followed exactly, might lead rather to the death than the recovery of the patient. A whole grain of strychnine is a very large dose, and in two experiments by Sir

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[11] *Med. Press and Circular*, March 16, 1887.

[12] Brunton and Cash, *St. Bartholomew's Hospital Reports*, vol. xvi., p. 229.

Joseph Fayrer, two pariah dogs which had been bitten by cobras died in tetanic spasms after the injection of one-third and one-fourth of a grain of strychnine respectively. With care to give the strychnine in divided doses, and to watch the result it might be very useful and is well worthy of a trial, for it might perhaps maintain the respiration and circulation until the patient recovered.

But the depression of the respiration and heart are not the only effects of the poison, and violent vomiting is sometimes a very marked symptom, to say nothing of the hæmoptysis, hæmaturia, and discharge of blood by the motions which occasionally occur. Strychnine will not counteract these effects of the poison, and in order to prevent their occurrence we must try to aid its elimination. In thinking over what channels were most likely to serve this purpose, it has seemed to me that the salivary glands and the mucous membrane of the stomach and intestines are the most likely. Fayrer[13] found that venomous snakes appear to resist the action of large doses of venom injected into them, while non-venomous succumb, and this might be explained by supposing that the poison glands of the former excrete the injected venom just as the liver will excrete foreign bile injected into the duodenum. The non-venomous snakes, having no poison glands, would be unable to excrete the poison, and would therefore die. My friend Dr. Abeles presented me with two fine specimens of the cerastes, in order that I might test this hypothesis by excising the poison gland in one and seeing whether its resistant power to venom disappeared with the gland, but unfortunately they both died before the experiment could be performed.

Fayrer and I found that the cobra venom had an extraordinary irritant action on mucous membranes, and when it was introduced into the stomach of a frog it caused most violent vomiting, very unusual in that animal. This experiment suggests that the vomiting which forms such a prominent symptom in many cases may be due to the poison being excreted by the mucous membrane of the stomach, in much the same way as tartar emetic or apomorphine would be. If this hypothesis is correct we can readily understand why recovery may occur to a great extent as in the case of the animal treated with artificial

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[13] Fayrer, *Thanatophidia of India*, p. 75.

respiration by the Indian Commission, and yet may ultimately die. For if the poison were eliminated into the stomach and intestines by the mucous membrane, recovery would occur; but if the venom, instead of being removed from the stomach as quickly as it was excreted, were to remain there and undergo absorption, the condition would get worse, and death would ensue. It therefore seemed to me that one should try, if possible, to remove any poison that might have been eliminated, and this one might do by washing out the stomach with alcohol in some shape, for example, whisky or brandy. The want of means has prevented me from trying this method, but the hypothesis seems to me to explain the good results obtained by the free use of whisky or brandy internally. It is not the action of these substances on the nerve centres that prevents death from the venom, for men bitten while drunk have died from the bite, although it is usually stated that if a man can be made drunk after he has been bitten his life will be saved. This would seem to indicate that the whisky or brandy acts locally in the stomach, coagulating any venom which may have been excreted, and preventing reabsorption. The plan I therefore wished to test, had circumstances allowed, was to keep up artificial respiration, and wash out the stomach with whisky or brandy. It is obvious that this plan might be combined with the subcutaneous injection of strychnine, and that, while the circulation and respiration were maintained by strychnine, alcohol might be freely given, and after it had been removed by vomiting or the stomach tube, it could be given again and again, so as to wash the stomach out with it. This plan is itself not without danger; it should be tried in a laboratory, for large quantities of brandy or whisky might, by their strongly irritant action in the stomach, lead to reflex depression of the circulation and fatal shock, to say nothing of gastritis in case of recovery.

In some most interesting experiments, Sewall[14] has shown that the system may gradually become resistant to the action of snake venom, just as it may to that of infective diseases such as anthrax, and by injecting small quantities of venom he has rendered animals immune from the effects of larger doses, which rapidly killed other animals not protected by previous inoculation.

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[11] Sewall, *Journ. of Physiol.*, 1887, vol. viii., p. 203.

Several points of resemblance appear to exist between snake venom and the albuminoid products of anthrax. Thus Martin[15] has found that when the anthrax bacillus is grown in alkali albumen, and the bacilli themselves afterwards separated by filtration through porcelain, the filtrate contains a mixture of proto and deutero-albumose, and a trace of peptone formed by the action of the bacilli on the albumen. The albumoses produce, like those of snake poison, much local œdema, sluggishness, coma, and death. Like the venom-albumose, its activity is lessened, but not destroyed, by boiling. But, in addition to these substances he has obtained an alkaloid which has the same action as the albumose, but much more powerful, and this alkaloid, he thinks, is present in a nascent condition in the albumose, and is separated from it by the tissues of the living animal into which it has been introduced. Whether something of the same sort exists in serpent venom or not one cannot say, but the analogies between it and the products of disease germs are becoming every day more apparent, and it seems highly probable that while studies of serpent venom may throw light on the products of disease, a study of the latter may lead to the discovery of an efficient antidote to the former.

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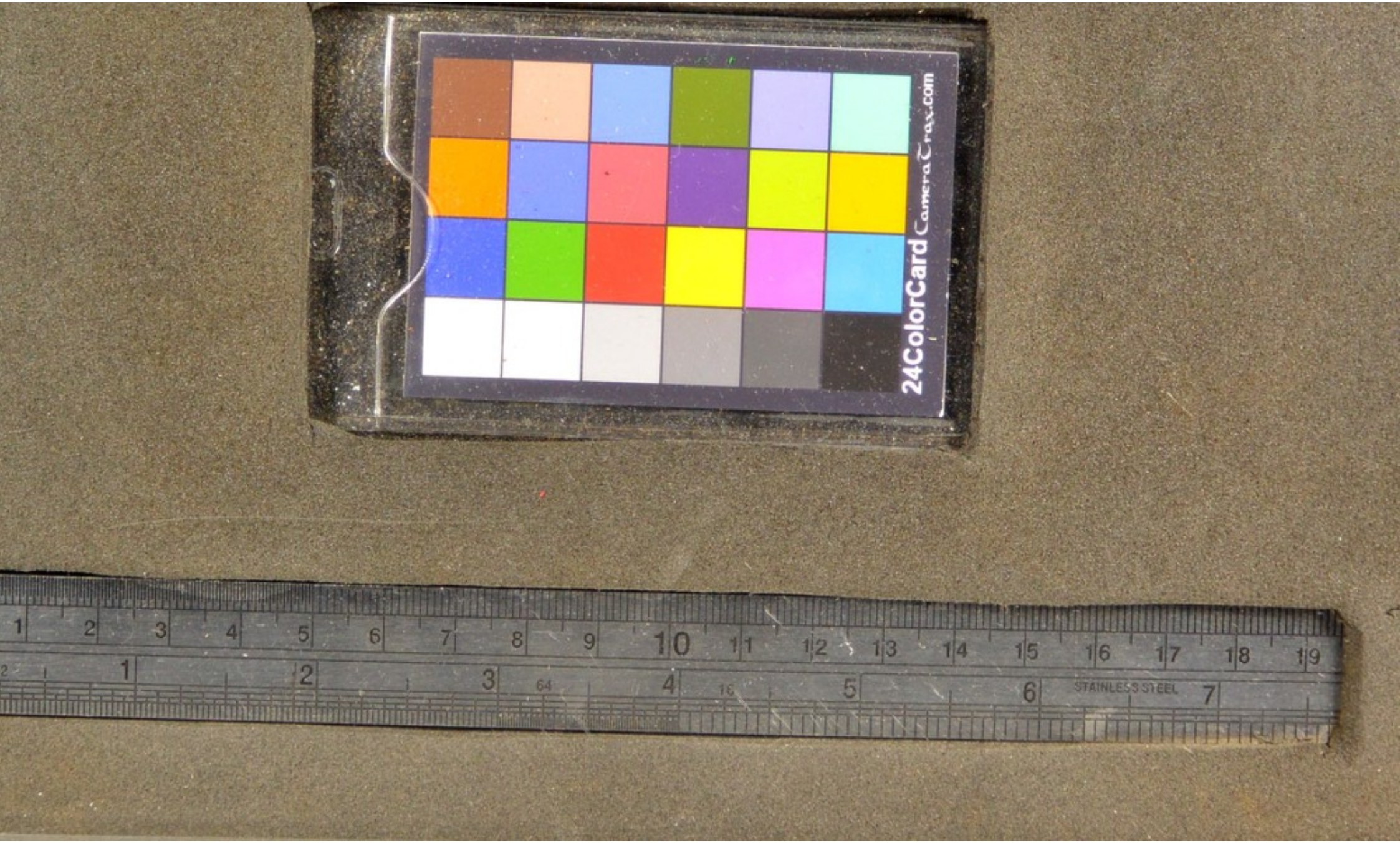
[15] Martin, *Roy. Soc. Proc.*, vol. xlviii., p. 78.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