many containing four parasites and a few five. They were mostly small, amoeboid, and non-pigmented, but a fair number of more advanced forms were found containing pigment. In a dry film which was taken at this time an imperfect sporocyte (rosette) was found. Leucocytosis was not noticed, but many of the polymorphonuclear leucocytes contained pigment. The red cells varied very much in size and shape. No crescent bodies and no parasites of the benign types were found. Hypodermic injections of 10 grs. of the acid hydrochlorate of quinine were administered every four hours. Periodic examinations of the blood were made, but the number of parasites in the peripheral circulation did not diminish appreciably. At noon on the day after admission they were fewer, but at 4 P.M. they had increased considerably in number, and at this time a very definite leucocytosis was observed. There was an increase of the small lymphocytes, and some of these had apparently become phagocytic, for they contained pigment. Some very large cells, having the characters of myelocytes, were also present; they contained enormous masses of pigment, and a few had taken up red cells which were infected with advanced forms of the parasite. The patient's temperature fell to normal on the morning after admission, November 16th, 1899, and remained normal until death. He gradually became more deeply unconscious, breathing stertorously, with the face congested and a little cyanosed. No definite localised paralysis was noticed. He passed urine under him; it was free from albumen. The quinine was continued, stimulants and ozone were tried, but the patient died at 12 midnight on November 16th. Blood was drawn from the spleen directly after death, but nothing but what had been already seen in blood from the finger was observed.

The post-mortem examination was unfortunately delayed for thirty-six hours. The liver was enlarged, weighing 5 lbs.; it had a blackish-lead appearance, and was soft on section. The spleen weighed 5½ ozs., was extremely soft, the central portion being almost diffuent, and was black on section. In the brain, the leaden hue characteristic of a chronic malarial subject was not present, the cortical vessels were somewhat congested, and the venous sinuses at the base of the brain were full of dark blood. It was firm in consistence. The heart muscle was a little pale and fatty. The kidneys appeared normal.

Microscopical Appearances.—Sections of the brain were made from the motor area, including Broca's convolution; the capillaries in every section contained red cells infected with parasites, mostly advanced and sporulating forms; large white cells were also present, containing masses of black pigment. The liver contained a considerable amount of black and yellow pigment; there was no cirrhosis. The spleen contained much black pigment in large masses, for the most part in the splenic cells; no parasites could be demonstrated. The blood vessels of the kidneys, including the Malpighian tufts, contained blood cells with much pigment.

It is noteworthy that the patient was only five days in a malarious country. We know, however, that probably the bite of a single infected *Anopheles* may be enough to induce an attack of fever in man. The date on which the patient was at Dakar was about the end of the rainy season, a time when pools suitable for breeding of *Anopheles* would exist, and consequently an unhealthy time. I have recently had an opportunity of examining a specimen of *Anopheles* which was caught at Dakar; it has the characters of the *Anopheles costalis* which is to be found all along the West African Coast. It can be readily distinguished from the *Anopheles claviger*, which is found in Italy by having four rod-like spots along the anterior margin of the wings, and not on the upper surface. The fatal result was no doubt due to the want of proper treatment early in the disease; there appears to have been no doctor on the ship, and the patient had had no experience of treating himself for fever. No doubt the enormous accumulation of parasites in the blood was due to the same cause. The failure of quinine in a case such as this is hardly to be wondered at; the patient came under treatment too late.

The importance of blood examination in such a case cannot be over-estimated; the patient was not sensible; no reliable history of the illness was forthcoming; he had practically no pyrexia, no rigors, and no sweating; without a blood examination a diagnosis of malaria would have been hardly justifiable.

In no case of malignant malaria that I have examined—either cases ending fatally or in those that recovered—have I seen such an enormous number of parasites in the peripheral circulation.

INFLUENZA IN ITALY.—Influenza is widely prevalent in Italy. In Turin half the population is suffering from the disease, and the public services are seriously interfered with in consequence. At Genoa it has been found necessary to open the lazaretto, and the elementary schools have been closed. The death-rate has risen to double the average. In the Riviera the scourge is rife. In Florence few households have escaped, but the disease is of a mild type. At Parma there have been some 14,000 cases. At Ferrara it is estimated that 20 per cent. of the inhabitants have suffered so far; all the schools are closed.

AN ACCOUNT

OF

SOME RESEARCHES INTO THE NATURE AND ACTION OF SNAKE VENOM.

BY CAPTAIN ROBERT HENRY ELLIOT,

M.B., B.S.Lond., F.R.C.S.Eng., D.P.H.Camb.,
Indian Medical Service, Madras.

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I.—PRELIMINARY REMARKS ON THE METHODS EMPLOYED.

Method of Collecting and Storing Venom, Bile, etc.

In order to collect and store venom, bile, etc., the snake is first chloroformed and nailed on to a deal table; the blood is then collected by manipulations to be described later on, and the gall bladder is removed by making a long median ventral incision over it, cutting out the bladder together with the surrounding fat, and then making an incision into the most dependent part of the sac with a sharp pair of scissors; the bile flows into an evaporating dish, which is at once removed to a water bath kept at a temperature of 100° F.; as soon as the contents of this dish have dried the vessel is placed under the receiver of an air-pump, over concentrated sulphuric acid, and the air is exhausted; after twelve hours in the receiver the dish is removed, and the now dry bile is easily separated from the bottom of the dish, with the aid of a spatula or knife; it is at once placed in a dry glass tube, and tightly corked till required for use.

After removing the gall bladder the poison sacs are next dissected out, and their contents squeezed into a dry watch-glass, which is placed in a cupboard for a few hours till the poison dries into scales; if the atmosphere is damp, as is the case in the monsoon, the venom is dried by floating the watch-glass on a water bath at 100° F. for a couple of hours. The ease with which the poison separates from the glass when dry is remarkable; tapping the bottom of the glass is enough to separate the whole amount of venom from it in a few seconds. The dry poison is removed without delay into glass tubes previously dried at a high temperature, and allowed to cool before use; the tube is tightly corked as soon as filled. When undertaking a series, or a number of series of experiments, the total stock of poison which it is intended to use is transferred to a glass mortar, finely pounded, and intimately mixed; it is then stored as before in a well-corked bottle and kept in the dark.

Every manipulation is carried on with the strictest attention to the prevention of the introduction of septic matter, all vessels being sterilised by heat beforehand, carbolic lotion 1-20 being used for such instruments as cannot be safely made hot; all corks used undergo a prolonged baking on a tin plate above the flame of a spirit lamp.

I have had frequent occasion to notice the correctness of a statement, made to me by Professor Fraser, that the poison of the Russell viper dries in long needle-shaped crystalline-looking masses unlike the shorter fracture of the dried poison of the cobra.

While working with live snakes a tourniquet of india-rubber tubing, a sharp knife, a cautery of some handy form, and a stock of crystals of potassium permanganate should always be kept handy. It is well, when possible, to have another medical man present; accidents occur when least expected, and the means to combat them should be ready at moment's notice. I should be wanting in gratitude if I failed here to acknowledge the debt I owe to Captain Samman, R.A.M.C., whose prompt action saved me from the very unpleasant consequences which might have followed a serious accident with which I met whilst handling a Russell viper. Captain Samman at once applied a firm ligature, and followed the fang puncture down to the bone with a knife; he then

sucked the wound dry, and finally filled it with crystals of potassium permanganate. The result was that I escaped with nothing more than a painful sloughing wound. In the future a stock of Calmette's antivenene will always be kept at hand.

Standardisation of Solution and Mode of Administration.

When it is intended to perform a series of experiments, a rough calculation is first made of the total quantity of poison likely to be required, and a quantity in excess of this is carefully weighed out in decimals of a gram, on a scale showing $\frac{1}{10}$ mg. In order to minimise any possible error in weighing the writer never weighs out less than 20 mg. of poison at a time; each milligramme of venom is then dissolved in 1 or in 10 c.cm. of freshly boiled and cooled water, according to the strength of solution required. It will be noticed that these two solutions are respectively of the strength of 0.001 gram and 0.0001 gram of venom per c.cm. of water; the weaker solution is only used when the doses to be given are so small as to render their calculation difficult otherwise.

While conducting a series of experiments the solution is frequently stirred with a glass rod in order to ensure the evenness of the strength of solution. For each dose some solution is drawn up into a 10 c.cm. syringe, and the air having been expelled, the exact amount which it is required to inject is marked off by the aid of the revolving button on the piston axis; the dose is then given, either subcutaneously, or otherwise as may be desired. The syringe is sterilised by filling it several times in succession before operation from a beaker of rapidly boiling water.

Parallel series of experiments were conducted to ascertain whether the degree of dilution of the venom in the above-named two strengths influenced the lethal properties of the dose. The length of this article forbids the publication of these tables here; but the result showed most clearly that the influence of the 10-fold dilution was inappreciable. It will be noticed, however, that in the various series of experiments one or other strength has been rigidly adhered to.

Preparation of Animal.

The animal is prepared for the injection by cutting off fur or feathers, and carefully washing the skin with 1-20 carbolic lotion.

Before undertaking any series of experiments it is necessary that all preliminaries should be carefully arranged beforehand in order to avoid confusion. Each animal of the series is therefore first weighed in pounds, ounces, and quarter-ounces; the result is converted into kilogrammes.

Means for subsequent identification are next taken; rabbits are branded in one ear with a serial number, care being taken to brand deep enough to destroy the fur and fur-bearing skin and no more; if less is done the mark wears out, while if more is done the result is sloughing, cicatrisation, and confusion; the animals scarcely seem to feel the branding. Fowls are marked by means of a wooden tally tied on under one wing. In all cases the colour, sex, etc., of the animal is noted.

The weight in kilos. being known, and the dose per kilo. having been decided on, a simple multiplication gives us the total dose the animal is to be given; and knowing the strength of our solution of venom, another easy calculation gives us the actual dose required in cubic centimetres and fractions of a centimetre.

The following columns in the experiment book can now be entered:

Serial No. of Experiment.	Date.	Hour.	Identifying Marks.	Weight in Kilos.	Dose per Kilo.	Actual Dose in c.cm.	Remarks.	Course of Events.
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The first seven columns should be entered before starting to work on the series, the others subsequently.

The preparation of the mongoose requires a separate paragraph. These animals are so vicious, so wonderfully agile in their movements, and so strong and active, that it is advisable to weigh them, calculate their dose of poison, and administer it at one and the same time; they were brought in cages by the men of a caste who spend their lives in such occupations; in order to catch them, a running noose was passed through a hole in an iron rod, and this was insinuated over the ani-

mal's neck through the slightly opened door of the cage, the noose was then quickly pulled tight, and the animal was dragged out, securely tied, weighed and dealt with at once. In spite of every precaution, both I and one of my assistants received severe bites; these were delivered down to the bone in the fraction of a second, and were extremely painful.

Calculation of Dose: Idiosyncrasy of Animals.

Before starting to work on any species of animal, a long series of experiments was first undertaken to ascertain the dose of the poison to be used which would be certainly fatal in a limited period of time. At first an effort was made to work with the minimum lethal dose per kilo., but it was soon found that this method introduced many difficulties. It was found, for example, that a dose of cobra venom corresponding to 0.0004 gram was the lowest dose per kilo. fatal to a rabbit; on the other hand, higher doses than this from time to time proved non-lethal, and rabbits occasionally recovered from doses as high as 0.0007 per kilo., though this was very rare.

If one fact stood out in bolder relief than any other it was this: that the personal element (if one may be excused the term applied to animals) is a factor never to be forgotten. Granted that the greatest care is taken to weigh the animals under the same conditions, that the poison is from the same stock, and most carefully weighed and apportioned, that every effort is made to inject the venom into the same tissues in all experiments, and to keep all known conditions as even as possible, granted all this, there still remains an element of uncertainty as to the fate of the subject which I can only attribute to "the personal factor." In order to eliminate this factor as far as possible, the dose chosen has always been one capable of certainly causing death, or at least of producing serious symptoms of snake poisoning.

In order to impose a further check on results, no series of experiments was undertaken without putting aside one or more animals as control snake-poison subjects. By this means the standardising of the lethal dose was kept as accurate as possible. This was the more necessary, because it was noticed that certain batches of animals presented a greater resistance than others, possibly due to the method of feeding, etc.

Lethal Dose for Various Animals.

Rabbits will often appear to get over the first effects of the venom, and will look as if on the way to recovery, but loss of weight continues, and after a longer or shorter period animals will succumb which at first sight one hoped would survive; their lower resistance to these secondary effects of venom poisoning renders them very inferior to fowls as subjects; the latter make a better fight to begin with, and do not suffer to anything like the same extent from remote sequelæ. Rabbits in the hills of India are also very susceptible to the influences of the frequent and trying changes of climate which prevail.

Rabbits.

All doses of cobra venom below, and including 0.0003 gram per kilo. of body weight proved non-lethal; doses of 0.0004, 0.0005, and 0.0006 gram per kilo. were lethal in most cases, but could not be certainly relied on; even 0.0007 gram per kilo. occasionally failed to kill, but it never failed to produce grave and well-marked signs of cobraism; doses of 0.0008 and 0.0009 were fatal in a very few hours. A dose of 0.0007 gram per kilo. killed in from six to eighteen hours as a rule, but life might be prolonged for days; it was accordingly selected as the dose for most of the experiments. The above conclusions appear to harmonise well with Professor Calmette's observations on dosage in his lecture delivered in the laboratories of the Royal Colleges on July 27th, 1896.

Daboia venom in doses of 0.0004 up to 0.0009 took a fortnight or more to kill; even so high a dose as 0.001 took twelve days to kill, and one of 0.002 took seven days; a dose of 0.003, however, killed with very fair uniformity in under twelve hours; 0.004 killed in four hours and a-half. The dose of 0.003 gram per kilo. was, therefore, chosen for daboia poison experiments.

Fowls.

Cobra venom in doses up to and under 0.001 proved non-lethal; 0.0015 gram per kilo. killed in fifty hours; 0.002 and 0.0025 killed in over twelve hours, and 0.003 in between six and twelve hours; these latter doses were therefore selected.

Daboia venom in doses of and above 0.003 gram per kilo. of body weight proved fatal; 0.003 gram killed in about twelve hours; all higher doses also proved lethal.

THE UNIVERSITY OF HEIDELBERG AND FEMALE MEDICAL STUDENTS.—The Medical Faculty of the University of Heidelberg has, after conference with the German Government, decided to admit to matriculation women provided with the necessary certificates of "maturity."