

January rain fell in considerable quantities, and both the collectors were laid up for many days with fever and ague, which retarded collecting, but altogether about 450 skins of birds were obtained from a radius of about thirty miles inland from Port Moresby. In the immediate neighbourhood of Port Moresby birds were plentiful, but the beautiful Bird of Paradise (*P. raggiana*) is only found in the thick forests on the mountains of the interior. Parrakeets, parrots and cockatoos, pigeons and doves, were numerous among the jungle, and the belts of tall trees along the rivers Laroki and Vutura. The farthest point reached inland was Munikaira, situated about thirty miles to the north-east, the difficulty in procuring natives as carriers preventing Mr. Stone from proceeding further; at this point he made a camp for several days, but the wet season and consequent unhealthiness of the place precluded further exploration.

The following birds appear to be undescribed:—*Eluradus stonii*, Stone's Cat-bird, like *Æ. buscoides*, of N.W. New Guinea, but distinguished by a black head and unspotted abdomen. Hab. Laroki River.

*Dicaeum rubro-coronatum* (Red-crowned Flower-pecker). Although having a red spot on the breast, like *D. vulneratum*, *D. schistaceiceps*, &c., this species differs from them all in having the back purplish, with a scarlet crown and rump. I cannot find any species agreeing with it. Hab. Port Moresby.

*Fantheenas rawlinsoni*, closely allied to *F. hypanochrous*, but differing in its crown being of a ruddy violet, the under tail-coverts being black, and the under-surface also ruddy violet, without the strong chestnut appearance of *F. hypanochrous*. Hab. Laroki River.

R. BOWDLER SHARPE

#### ABSTRACT REPORT TO "NATURE" ON EXPERIMENTATION ON ANIMALS FOR THE ADVANCE OF PRACTICAL MEDICINE\*

##### VI.

##### Experimentation with Nitrite of Amyl.

IN the progress of scientific therapeutics no addition to the curative resources of medicine has of late attracted more attention than the nitrite of amyl. This agent is now one of the useful agents in the hands of the physician, and, what is most to the purpose, it is one of the most useful for relieving the cruellest and painfullest diseases. The discovery of the properties it possesses resulted in the purest way from experimental study, the record of which I am entitled to write as the one who introduced the agent into medicine, defined its mode of action, and thereby determined its place in the lists of curative chemical substances.

Nitrite of amyl was discovered by Balard thirty years ago. It was examined afterwards by Rieckher. It was made by the action of nitrous acid on amyl alcohol, and the vapour of it was said to produce headache when it was inhaled. Many years passed before any further observation was made upon the substance, and indeed, Gregory, in his edition of "Organic Chemistry," published in 1852, merely refers, and that incidentally, to the nitrate of amyl. He passes over the nitrite in silence.

The observation that the vapour of nitrite of amyl causes headache, or rather a sense of fulness of the head than headache, rested, I believe, on the observations of Rieckher, and was not improved upon until Prof. Guthrie, of Edinburgh, and now of the School of Mines, London, noticed, while distilling the nitrite, the further facts that the vapour, after being inhaled, induces flushing of the face, rapid action of the heart, a peculiar breathlessness such as occurs from fast running, and disturbance of cerebral action. These facts, published by the learned professor, became known to Mr. Morison, a dentist practising in

Edinburgh. Mr. Morison thought that the vapour of nitrite of amyl might be a powerful stimulant, and might be made use of in cases of syncope and exhaustion. He brought a specimen of the compound to London, and placed it before the College of Dentists, of which he was a member. The Council of that Institution thereupon submitted the specimen to me for investigation and report, with the request that I would fully inquire into its physiological and therapeutical properties by experiment.

The first public record of my researches, commenced in this manner, was read to the physiological section of the British Association for the Advancement of Science at the meeting of the Association held at Newcastle-on-Tyne in 1863. It is unfortunate that by some accident the original paper as it was read at the meeting was not included in the volume of Transactions of the Association. A short and fair abstract of it was, however, published in the *Medical Times and Gazette* (Sept. 26, 1863, pp. 334-5). The first remarkable effect I observed upon the living body from the vapour of the nitrite was the peculiar redness of the skin. On the face a deep blush was excited by inhalation of the vapour, which blush soon became a perfect crimson. With this there was a rapid increase in the motion of the heart, and following upon the same there was quickened respiration and panting. These observations, which resembled those noted by Prof. Guthrie, were taken in a systematic manner from symptoms produced on myself. A piece of paper was rolled into the form of a funnel, the nitrite was dropped into the open mouth of the funnel, and then I inhaled vapour from the funnel until distinct objective and subjective symptoms were recognised. Dr. Gibb, afterwards known as Sir George Duncan Gibb, took notes of these signs as they were developed in me, and then he himself inhaled while I recorded symptoms. Afterwards Mr. Kempton, a member of the Council of the College of Dentists, submitted himself to experiment. The result was the confirmation of certain very extraordinary phenomena induced by the nitrite, but what the nature of those phenomena could be was unknown. One thing was certain, that here was an agent of great potency in its action on the animal economy, and therefore of promise as an agent for cure. The question was what disease would it cure or alleviate? Towards the relief of what class of human maladies could it be applied?

I should have been well content if I could have pursued this inquiry solely by observation on man. But soon I found that the experimental pursuit on the human animal was far too dangerous a risk to be ventured upon. An enthusiastic adventurous experimentalist in my laboratory made a few inhalations too many, and well nigh paid the penalty with his life. The rapid action of his heart was followed by confusion of the senses and by sudden prostration, and extreme pallor and faintness from which there was not a safe recovery for two hours, nor a complete recovery for two days. The only lesson taught by this experience was that the original idea of using nitrite of amyl for the cure of syncope was false. All else was as dark as ever, and if I had had no other means of research at command, I should have laid this now valuable remedy aside as a dangerous substance, a substance not to be added to the armoury of practical medicine.

In this dilemma it seemed to be justifiable to test the action of the agent on animals inferior to man.

The first point to be ascertained was whether this substance acted after the manner of an anæsthetic. Animals therefore of different classes, frogs, guinea pigs, cats, and rabbits, were subjected to its vapour as I had been; but the inhalation in their case was carried further, and they were allowed to pass into insensibility. The insensibility appeared to be death, and in the warm-blooded animals was death. The consciousness of external impressions remained until the moment of collapse, then there was insensibility, but then also in the warm bloods the

\* Continued from p. 291.



life had ceased. Thus it was shown that nitrite of amyl was not an anæsthetic. It did not produce sleep.

After the life of the animals of warm blood was suddenly extinguished by the vapour,—and apparently the extinction was without pain,—I remarked that the internal organs of the body after the death were in some instances exceedingly congested with blood. The lungs and the brain were commonly in this state; but it struck me, though I could not explain the fact at the moment, that exceptionally these organs, when the death of the animal was instantaneous, were left quite bloodless, and actually white in their texture. Further, I observed that in the warm bloods the muscular irritability remained for a very long time after death, often for many hours. These phenomena were strange on the warm-blooded animals, but they were trifling in comparison with what was observed on cold-blooded animals. I discovered that in the frog the complete insensibility, and, as it seemed, absolute death, produced by the nitrite was not death really, but a suspended animation, a condition like that which has been called trance in the human subject. A condition of simulated death so perfect that no sign of life could be obtained, and yet from which, after so long an interval of time as nine days, the animal would wake up and enter again into life as if nothing had been done to derange its life. During all this time the limbs of the animal remained mobile; not a muscle was stiffened into the rigidity of death. There was induced, in fact, not only the trance of the human subject, but the corresponding cataleptic state of the muscular fibre. In addition I learned that during this state of suspense of life, the blood, though it was darkened and deprived of its capacity of becoming oxidised, and otherwise changed, was held in the fluid state. Like the muscles, it remained free of the change called pectous; it did not coagulate.

The next step in the investigation had relation to the action of the nitrite on the vessels which constitute the minute circulation. The change in the circulation in the web of the frog under its influence was carefully investigated; the condition of the circulation through the semi-transparent ear of the rabbit while the animal was breathing the vapour was also carefully investigated. The result of these inquiries was to discover that nitrite of amyl exerts a direct action on the nervous function, and that the action consists of a paralysing influence on the nervous mechanism by which the minute arterial system is controlled and governed. To repeat the words of the report I made to the meeting at Newcastle, "the action of the nitrite was directly on the nervous system, and that such action, transferred to the filaments of nerves surrounding the arteries, paralysed the vaso nerves, on which the heart immediately injected the vessels, causing the peculiar redness of the skin and the other phenomena that have been narrated."

In this preliminary inquiry I advanced the new propositions that we had in our possession a chemical substance which, being introduced into the body, overcomes the arterial tonicity, and causes phenomena analogous to those changes in the vascular current which follow upon division of the sympathetic nerve.

I further suggested that in cases of trance and catalepsy in the human subject, some substance analogous in its action to the nitrite is produced in the body by some error of secretion, some modification of the animal chemistry, and that the foreign substance so engendered is the cause of the disease. The first of these propositions is, I consider, proven; the second is not proven by any new research, but is still the most reasonable exposition of the phenomena to which it refers.

In continuation of experiment on the action of the nitrite of amyl on the nervous system, I studied next its local action, and came to the conclusion that its action on the nervous matter is not through the blood, but by direct impression through the nervous cords to the vas-

cular motor nervous supply. I compared other bodies of the nitrite order—such as nitrite of methyl, ethyl, and butyl—with it in their operation. I compared it in its action with emotional shocks, and correlated the blush on the cheek or the pallor of the cheek which it produces with the blush or pallor induced by the impressions creating shame, fear, or other similar passions. I traced, through the whole of the phenomena induced by the agent, the action of the base amyl, and the effect of the addition of the elements, nitrogen and oxygen; and I showed that when oxygen and nitrogen are brought into combination with the base, the physiological effect is modified and the specific influence of the substance on the vascular system is declared. I was led to compare the action of nitrite of amyl with other chemical bodies, and, using it as a key, was enabled to show the analogical action of many other compounds. Notably, I pointed out from the observations collected during this inquiry, that alcohol produces its influence on the extreme vascular system by the same paralysing process. By investigating the effect of the agent after its long-continued inhalation, I was able to show that it induces changes in the circulation of the lung which lead to congestions and even to hæmorrhages like those which occur in some forms of pulmonary consumption, and thus the nervous origin of consumption of the lungs was brought fairly under notice as a new element of study in the clinical history of that fatal disease. In yet another series of observations I learned that rabbits afflicted with a singularly loathsome skin disease—resembling *lepra* in man—recover rapidly in an atmosphere containing the nitrite vapour; that the dry and colourless and scaly skin of the animals become suffused with blood; that with this increased capillary circulation the scales fall off and healthy skin begins to appear; that the fur of the animals begins to grow; that the general nutrition of the animals is soon improved, and that within a month their cure is completed.

From my point of view the disclosure of these facts alone were a sufficient vindication of the line of research by experiment on living animals pursued with the nitrite of amyl. They were, however, very poor indeed, when they are compared with another disclosure of fact which came out of the same experimental research.

In 1863 I had learned that the influence of the nitrite of amyl was on the nervous vascular supply, that it paralysed temporarily the nervous action, and that the vascular redness it induces is due to this paralysis. In the succeeding year I followed up this subject more closely, and by an extension of observation I was led to the conclusion that in the nitrite of amyl we had found the most potent chemical agent that had ever been discovered for overcoming muscular spasm generally. The singular cataleptic and passive state of the voluntary muscles was an evidence of this fact, and it tallied with the earlier observation of the effect on the vascular tension. In addition, I saw that in this nitrite I held a substance which would not fix itself with the tissues of the animal and require to be eliminated by the slow process of fluid excretion through the kidney or skin, but that, owing to its insolubility and volatility, it would escape by the organs of respiration as well as by the other channels of elimination. I had learned, indeed, that in animals like frogs, from the bodies of which, owing to the thickness of the cutaneous tissue, the transpiration is easy, the spontaneous evaporation of the nitrite, extending over the long period of nine days, was sufficient of itself to lead to restoration of vital function. The study of the whole series of facts, when the facts were carefully collected and weighed, led to the demonstration that the original view as to the nitrite of amyl being a stimulant and an extreme excitant was wrong; it disclosed that the phenomena of excitation, as they at first seemed, were phenomena really of suppressed nervous function, that the vascular injec-



tion meant loss of vascular resistance, and that the supposed stimulant was indeed a paralyser of the most active kind.

In turn this reading of the true physiological action of the nitrite of amyl led me safely to its true therapeutical value, and the result was that its exact place in therapeutics was fixed correctly before ever it was used for the treatment and cure of disease. At the meeting of the British Association for the Advancement of Science held at Bath in 1864, I pointed out its therapeutical position. The application of nitrite of amyl as a new remedy for the use of the physician was clear: it was a remedy to be applied in controlling muscular spasm. It was, I said, selecting for my illustration the most terrible and typical of all the spasmodic diseases, it was the remedy even for tetanus or lockjaw, and this view I afterwards demonstrated by the direct experiment of neutralising strychnine tetanus in the frog by the application of the nitrite, of suspending the tetanic symptoms by the agent until the strychnine was eliminated, and of physiologically curing a disease which had been physiologically produced and which, but for the antidote, would have been irrevocably fatal.

So soon as the therapeutical position of nitrite of amyl had been discovered by experiment the practical adaptation of it was comparatively easy. I had only to learn how it had best be administered; how to administer it, by inhalation, by the mouth, by subcutaneous injection; how to make it combine with other medicinal substances, and how to select the most suitable substances with which to join it in combination. The researches in these directions were all conducted on human animals, or rather on one animal—the experimenter himself. The modes of administration were also recorded for the guidance of practitioners, and the remedy was in time fairly launched on a true scientific basis, its action explained, its use described, its effects predicated.

I spent three years in research on the physiological properties of nitrite of amyl in order to discover its place as a means of cure of human maladies. If I had spent thirty years instead of three the time and labour had not been badly repaid. The practical results of my work in the benefit conferred on mankind in mitigation of suffering and in cure of diseases of an intractable nature have been rapid in their course beyond expectation. Dr. Lauder Brunton first tried the application of the nitrite of amyl for the relief of one of the most acutely painful of the spasmodic diseases, the disease known as angina pectoris, and gained an immediate success. Dr. Anstie came to me for the remedy in a case where a man was in the pangs of death from acute spasmodic asthma, and after five minutes of the inhalation of the vapour found his patient breathing with the most perfect freedom, or, as he expressed it to me, "the man became conscious and natural in a few seconds so soon as the physiological action of the remedy took effect; it was like dragging a drowning man out of the water." Dr. Farquharson administered the vapour to a man in excruciating agony from colic, and witnessed the same relief so soon as the physiological effect was produced.

A little later came the application of the nitrite of amyl for the treatment of tetanus, the crucial trial of the agent which I had originally proposed. Mr. Foster, of Huntingdon, was the first surgeon to put it to the test in this disease. A man, after an injury, was seized with tetanus. In the spasmodic grasp of the malady he "was rolled up like a ball." Under the inhalation of the vapour of the nitrite of amyl his muscles relaxed, and whenever the spasm threatened to recur the administration of the vapour of the paralyzing agent relaxed the contraction. So for nine days, during which an ounce of the remedy was given by inhalation, the death from the spasm was prevented; by that holding on, the cause of the spasm became inactive, as I had anticipated, and the recovery was secured.

Two other equally successful instances of this same kind have been recorded, and recently Dr. Fowler, of New York, has published a fourth experience identical in character, but with a remarkable additional fact appended. The sufferer who was, as we should once have said, fatally stricken with tetanus, made a primary recovery under the administration of the nitrite of amyl. Unfortunately the supply of the remedy ran out, and before a new supply could be obtained the tetanic spasms returned and continued with increasing violence. At last the remedy was reobtained, and after a lapse of sixty hours was re-administered. The relaxation of the tetanus was again secured, the return of the spasm was controlled over a period of several days, and once more the art of the physiologist was rewarded in the recovery of that stricken patient from one of the most terribly excruciating forms of painful death.

I have put no word of my own experience on the use of nitrite of amyl, long and successful though it has been, on the present record. I have supplied but a few typical facts from the experiences of other observers, and if I could put in all it would be but the record of the uses of a remedy which is as yet but beginning to be applied for the cure of painful diseases not only of men, but of lower animals also, especially of dogs and horses. The point I want to keep in mind is that the results already obtained are the fruits of experimental inquiry. I stood at the gate of the place where this new remedy came from. I took it first as a physician, from the hand of the chemist. I determined its place in medicine. Then other men took it from me, and confirmed my estimate. Thus the history of this remedy is made clear from its beginning, and it is most just to say that if I or some one else, given to like method of research by experiment, had not tested the agent in the same way, the results that have already been obtained from it had been lost. Whether the results are worthy the method—whether, for instance, the experiment of producing and curing tetanus in a frog is warrantable in order to discover a plan by which tetanus induced in man by natural disease can be cured by art—these are the serious kind of questions on which opinion is now divided. It is my duty to show the practical arguments in favour of the experimentation.

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(To be continued.)

#### NOTES

ON Friday last, in the House of Commons, Mr. Reed asked whether the memorial, already printed in our columns, signed by many of the most eminent men of science in the kingdom in favour of the establishment of a permanent Museum of Science had been presented to the Lord President of the Council; if so, whether he had any objection to laying it upon the table of the House; and whether the Government propose to take any action in the matter.—Lord Sandon in reply stated that he was glad the hon. gentleman had called attention to the important memorial to the Lord President of the Council, which had been signed by, he might almost say, all the most eminent men of science in the kingdom, in favour of the establishment of a permanent Museum of Science at South Kensington. He added that it was one of the many gratifying results of the remarkable exhibition of scientific apparatus which we have had the satisfaction of getting together at South Kensington, with the assistance of the leading men of science both of this country and of almost every civilised State. Lord Sandon promised to at once lay the paper on the table of the House. He was not in a position to say what action will be taken respecting it, but assured the hon. gentleman that it was receiving the best consideration of Her Majesty's Government.