A LECTURE ON ARSENIC AS A DRUG.

Delivered as part of the London Post-Graduate Course.

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GENTLEMEN,--There are certain forms of skin disease against which arsenic appears to possess specific power. They yield immediately to its influence, and with the most astonishing certainty. Of these, the condition known as pemphigus diutinus or persisting pemphigus stands foremost. As a rule, no fresh bullæ are produced after the administration of the arsenic has been commenced, and the patient quickly regains health, with perfect soundness of skin. There are, I am aware, a few exceptional cases, especially those which occur in elderly subjects and those which are complicated by disease of the mucous membrane of the mouth.

I fear that we learn but little by the observation, which is now generally admitted, that arsenic is an almost universal specific against pemphigus. As to the cause of what pemphigus is, we are quite ignorant, and equally so as to how arsenic acts in preventing its development. There are a few other rare affections of the skin concerning which one can speak with the utmost positiveness as regards the prompt efficiency of arsenic in their cure. I possess a portrait of a very typical case of the rare malady known as dermatitis herpetiformis. The woman who was its subject had the skin of her trunk and limbs covered with a vesicular eruption which resembled herpes zoster in its corymbiform arrangement. I had this woman under observation for six or seven years on account of repeated relapses of her disease. She was always cured in the most definite manner and very quickly by the use of arsenic. A boy who was the subject of one of the plates in the New Sydenham Society's Atlas suffered severely from an erythematous eruption of a peculiar type, which developed on his limbs and trunk, and which never yielded until arsenic was given, when it disappeared with the utmost promptitude. His mother finally got into the habit of giving him the mixture whenever she noticed that his temper was irritable, as this symptom was a sure precursor of his eruption. I believe that he finally got quite rid of his liability.

A man whom I have recently had under observation had suffered for many years, and in spite of much treatment, from an intensely pruriginous and vesicating eruption possibly allied to pemphigus. When he came to me he had, singularly enough, never had arsenic given. Its effect was magical. The little bullæ ceased to appear, the itching ceased, and, as he could now sleep well, he rapidly improved in health. Contrary, however, to what is generally observed in common pemphigus, we have been quite unable to leave off the drug. If it is suspended, the invariable result is that in a few days the skin begins to itch again, and some fresh vesicles are produced. We have been obliged also, in order to maintain the cure, to increase the dose, and to give it in quantities larger than the patient can suitably bear. In connection with this liberal administration of it, I have had repeated opportunities of observing its effects upon the palms and soles. It makes these burn and itch again, and perspire. In the instance of the soles, the profuse perspiration has on several occasions caused the epidermis to become sodden and to peel.

In the treatment of common psoriasis, although the effect of arsenic is quite as definite and certain as in pemphigus, it is not nearly so immediately curative. Sometimes its effects are first manifested by the patches taking on a congested condition and becoming very irritable. In a large majority of cases it will in the end, if well pushed, cause the eruption almost wholly to disappear. It seldom or never, however, brings about a complete cure, and of late years we have been

so much accustomed to reinforce it by efficient local measures that it is not always easy to estimate the proportion of our indebtedness to it. I believe that both its efficiency and its safety are in ratio with the youth of the patient. My own experience as regards the effect of arsenic in lichen planus has not been by any means uniform. In some cases it has seemed to do a great deal of good, whilst in others the eruption got worse while it was continued, and disappeared satisfactorily when tartar emetic was substituted for it. I have never seen this eruption yield to arsenic in a definite and rapid manner.

If you ask me as regards the value of arsenic in eruptions of the eczematous type, I must speak with great caution. My impression is that, if given in anything like full doses, it usually irritates and makes the eruption worse. If given in minute doses it certainly does not always hinder the cure by local measures, but it is very doubtful if it materially helps it. The late Mr. Startin and Dr. Hunt—both of whom made the cure of the disease their special aim in practice—were both in the habit of prescribing arsenic in eczema; but they used also local means at the same time, and it was impossible to say which was the means of cure. In cases of common acne, sycosis (non-parasitic), and various other chronic affections of the skin we are, I expect, most of us in the habit more or less frequently of adding small doses of arsenic to the rest of the remedies used. Even in the cryptogamic affections, more especially in chronic ringworm, some are inclined to put a certain amount of confidence in it. There is a general impression abroad that under all morbid conditions of the skin arsenic has a tendency to improve its nutrition. Thus, it is supposed to brighten the complexion, make the skin more transparent, and give glossiness to the hair. If it does really effect these objects—concerning which point I may confess to some doubt—they are to be brought about, I feel sure, only by using it very sparingly.

The observations just made may suitably lead us to discuss the question as to whether arsenic is a tonic. In certain morbid conditions—those, for instance, in which pemphigus and herpes are prone to occur—it certainly has a tonic influence, and the general health improves wonderfully under its use. It may, however, easily be the fact that this does not prove that it is a direct tonic, but only that by removing a troublesome and irritating disease it favours general improvement of health. Of this, however, I think we may feel quite sure, that if arsenic is to act as a tonic, everything depends on the smallness of the dose. It has been my almost invariable experience in patients in whom we had pushed it for the cure of any special disease, that they were very willing to leave it off, having usually felt languid and out of health during its continuance.

I have formed an unfavourable opinion as to the influence of arsenic upon elderly persons, and, unless the disease imperatively demands it, I never prescribe it for them. More especially is caution, I think, necessary if any symptoms of nerve degeneration are present. An old gentleman who suffered from paralysis agitans was, as I have good cause to remember, invariably made worse by the very smallest doses of arsenic. A physician whom we consulted insisted, although warned, in prescribing it, and the fact that we had done so was concealed from our patient. Although very small doses were given its effect was at once recognised, and so much annoyance was caused that we had difficulty in retaining our patient's confidence. I have met with other similar instances of susceptibility, but always in the aged. It is remarkable how very seldom in the young or middle-aged we encounter anything of the nature of idiosyncrasy in reference to arsenic. Opium, quinine, the iodides, mercury, and many other drugs are each in turn in not a few persons productive, even in the smallest doses, of symptoms of urgent disagreement, but very rarely indeed do we encounter anyone who shows special susceptibility to arsenic. At any rate this is, I think, true as regards its first use; there are a certain class in whom long continued use instead of producing tolerance appears to have the opposite effect. With the young arsenic appears usually to agree well, and even very young children, although they but seldom need it, will bear full doses without any ill effects.

Amongst the facts which have been thoroughly established as regards the possible effects of arsenic, we may, I think, now claim that it is an undoubted cause of peripheral neur-

itis.¹ Its influence in inducing herpes zoster when given for the cure of other skin diseases affords us the most common example of this. It is, however, by no means the only one. It has been observed by those studying cases of poisoning by arsenic, and is especially noted by Christison, that local and unsymmetrical forms of paralysis not very infrequently result. During its medicinal use patients not infrequently complain of local numbness, more especially of portions of the skin of the lower extremities. Numbness and tingling of the soles of the feet are by no means infrequent symptoms.

When in 1864 I first published cases of herpes zoster produced during the administration of arsenic, the observation was received with some scepticism, and it was thought that it might concern what was merely a coincidence. The observation has, however, been since confirmed by many others, and quite recently hospital statistics have been published by Dr. L. Neilsen, of Copenhagen, showing that herpes occurs far more frequently in those who are taking arsenic than in others. Dr. Neilsen found that in 520 cases of psoriasis for which arsenic was prescribed shingles followed in 10, while of 220 in which iodide of potassium was given there was not a single instance of it. I regard the establishment of the connection between arsenic and zoster as of great importance on account of the definiteness of the light which it is calculated to throw upon other questions. It is certain that the zoster does not usually occur in the beginning of the treatment but only after the drug has been used some time, and it also appears probable that the arsenic may be resumed after a time without material risk of reproducing the herpes.

It is a very important question, especially in reference to chronic skin diseases requiring its use during long periods, whether arsenic is prejudicial or otherwise to the general health. I have had under observation many patients suffering from psoriasis or lupus erythematosus, who have taken it more or less continuously for several years. My impression is that if given in small doses, with the exception of the risk that it may cause shingles, its effects are usually inappreciable, and that there is no danger of its cumulative influence. I have already, in speaking of its effect as a tonic, expressed some doubt as to whether, in a general way, patients are better for its use. My belief is that they are usually glad to leave it off. I am quite sure that this is the case if it has been pushed in anything like full doses. In cases of lupus erythematosus, for instance, in which it produces no effect unless it is pushed, the usual result is that patients feel languid and depressed, and experience a certain degree of emaciation. Almost without exception in these cases the disuse of the remedy is attended by a sense of general improvement of the health. In this respect arsenic appears to me to contrast strongly with the true tonics, such as quinine and nuxvomica, more especially with the latter. It does not seem to matter how long a patient may have taken nuxvomica, he will miss it, as he would a glass of bitter beer, when it is suspended. It is wholly otherwise in the case of arsenic. If arsenic be given in full doses for long periods, although it may be doubted whether there is any reason for styling it a cumulative drug, yet I am sure that its employment is not without danger. There are certain symptoms which ought to lead us to take alarm. If the patient has numbness and tingling in the palms and soles, or if there is numbness of any particular part of the skin, or if there is decided loss of flesh, then it ought to be suspended. Irritation of the conjunctiva is, of course, a well-known symptom of disagreement; but, in my experience, it has not been observed so frequently as some of the others just mentioned; and to them I must add liability to diarrhoea, and, in a certain number of cases, extreme irritability of the bladder. I cannot conceive of a patient receiving any general injury to health from arsenic whilst remaining under regular medical supervision, for the symptoms never set in suddenly. If, however, a patient who has experienced great relief for his skin affection has obtained a prescription which he uses on his own responsibility, and with, perhaps, considerable increase of the dose ordered, it is then possible that

serious, or even fatal, results may ensue. One case of this kind has occurred to myself. A gentleman who suffered from a most severe form of psoriasis, and who had found the greatest possible benefit from arsenic, whereas nothing else relieved him, increased the doses at his own discretion, and did not come to see me for more than a year. When, at length, he returned to me, he was emaciated, staggered in his gait, and was partially paraplegic. His nervous symptoms rapidly developed, and, after violent convulsive seizures, he passed into coma and died. In connection with this case I may remark that I have seen several others in which the use of arsenic appeared to cause or to increase the liability to epileptic attacks, and one or two others in which a form of partial paraplegia seemed to be definitely connected with its use. That it exerts a peculiar influence over the nutrition of the nervous system, which may display itself in different parts, and in very different ways, is, I think, unquestionable.

A few words must be said as regards the influence of arsenic on the skin in persons previously in health. When it is given for the cure of skin diseases it is sometimes difficult to tell whether the results are due to it or are parts of the original malady. Now and then, however, we have opportunities, when it is prescribed for maladies quite apart from the skin itself, of observing results concerning which there can be no fallacy. Such, for instance, occur when it is prescribed in order to delay the growth of cancer, or for the cure of chronic disease of the nails. Its effects upon the nutrition of the skin in such cases (supposing the doses to be large) are usually, I think, that the skin becomes brown and muddy-looking; it is also dry and harsh on the trunk and limbs generally, although there may be perspiration in the palms and soles. The discoloration may be attended with actual pigmentation, and may increase until it almost resembles the tint of Addison's disease. In extreme cases not only is there dryness and discoloration, but scaly patches may form on the knuckles, elbows, and knees, much resembling common psoriasis, but less well circumscribed. A much commoner result than this is, however, disturbance of the nutrition of the skin, not over the body generally, but over the palms and soles only. On these parts, in addition to dryness, corns may form, and in certain very rare cases these corns pass on into epithelial cancer. A peculiarly dry condition of the palms and soles, with tendency to the formation of corns, is by no means an infrequent result of long-continued courses of arsenic, and should, I think, always lead to its discontinuance.

Certainly one of the most remarkable facts as regards the influence of arsenic is that it appears to prevent certain affections which are very similar in nature to those which it causes. There are certain rare cases in which herpes recurs over and over again in the same locality; and respecting these I can speak with the greatest positiveness that the liability to recurrence is usually suspended during the continuance of arsenic. I am speaking of cases in which the herpes occurs on the skin, and is grouped exactly like zoster, although usually more limited in extent. The far more common forms of recurrent herpes which we see on the genitals, on the lips, and sometimes inside the mouth, are, I believe, just as definitely under the control of the drug. The latter must, however, be steadily continued. One of the most convincing proofs that the arsenic is really the means of arresting it is that the eruption recurs when it is suspended. I have had some most remarkable cases of liability to herpes in the mouth recurring every month for one or more years, in which the liability ceased immediately the drug was given. A portrait of one such, showing the severity of the herpes, is in the collection of the Royal College of Surgeons. In these cases, after the arsenic has been continued for a considerable time, the usual result is that it may be left off without any risk of recurrence of the disease. This cannot be done in the early stages, for scarcely less remarkable than the promptness of the disappearance when it is prescribed is the promptitude of the recurrence when it is suspended.

[Mr. Hutchinson quoted many cases in illustration of the statements made at different parts of his lecture. He concluded with the following summary]:

Thus, then, whilst I think that we may hold that our clinical knowledge respecting this powerful and most important drug has much advanced during the last quarter of

¹In the remarks made above, I have restricted myself to my own experience. Dr. Imbert Gourbeyre has in several articles, and finally in a monograph on the consequences of arsenical poisoning, collected a very considerable bibliography on the subject. His facts have been well recapitulated with important additions in a paper by Dr. Dana, of New York, published in *Brain*, January, 1887.

century, we cannot claim to have made any discovery as to its mode of action. We know for certain that it will cure psoriasis, pemphigus, and their allies, and that it will prevent the recurrence of recurrent herpes and many other relapsing maladies. We never cease to wonder at the extreme rapidity and certainty with which, in some of these, its effects become manifest. How those effects are brought about, however, we cannot even guess. We know also that it may, whilst curing some diseases, produce others, and that herpes zoster is one amongst several different type-forms of peripheral neuritis which may result directly from it. That it has some peculiar affinity for nerve tissue, and some peculiar influence upon nerve function, we may safely believe, but further than this we can scarcely go. As regards its general employment as a remedy for skin diseases, whilst recent observations have strengthened our faith in certain directions, they have limited it in others, and they have impressed upon us the great need of caution. They leave us with the practical creed that we may, as heretofore, freely avail ourselves of its services, but that we must, perhaps rather more than has heretofore been felt necessary, watch its effects, and be prepared, if need be, to forbid its further use.

ON THE PHYSIOLOGICAL ACTION OF CARBON MONOXIDE OF NICKEL.

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By the kindness of Mr. Ludwig Mond, we have had the opportunity of examining the physiological action of carbon monoxide of nickel, a substance of unique chemical composition represented by the formula $\text{Ni}(\text{CO})_4$. This substance was discovered by Mr. Mond co-operating with Dr. Carl Langer and Dr. Friedrich Quinke, and its chemical properties have been described by them.¹ It is a clear liquid of high refractive power, boiling at 43°C . at 751 millimetres, and having a specific gravity of 1.3185 at 17°C . The fluid is soluble in alcohol, benzene, chloroform, and pure olive oil. It readily evaporates on exposure to the air, the remainder, even in a well-stoppered bottle, undergoing decomposition. For this reason, it must be kept in sealed glass tubes, and we found it difficult to preserve it when the point of the tube was broken off and a small quantity removed for purposes of experiment, however quickly we sealed up the point in a blowpipe flame.²

The method of administration adopted was by subcutaneous injection. The following experiments were in the first instance made upon frogs:—

EXPERIMENT I.—At 11.3 A.M., 1.14 cubic centimetre injected under skin of the back. The substance evidently acted as an irritant, as the animal contorted its body and rubbed the skin over the seat of the injection with its hind limbs. At 11.30, there was paralysis of fore and hind limbs. At 11.50, respiration was very slow. At 12.20, the animal was dead. The blood was of a bright red colour, and when examined with the spectroscopic showed two absorption bands in the position characteristic of carbonic oxide hæmoglobin. The two bands persisted after the addition of sulphide of ammonium.

EXPERIMENT II.—At 2.48 P.M., 0.54 cubic centimetre injected under skin of back. At 2.51, the frog croaked repeatedly, and rubbed irritated spot with its hind limbs. At 2.53, we observed that the eyes were remarkably prominent. At 2.56, it rubbed its head with its fore limbs. At 3.12, the eyes were much retracted. The web of the foot, examined under the microscope, showed a very slow blood stream in the vessels. At 4.20, there was slow respiration, and 4.22 the animal was

dead. A spectroscopic examination showed two absorption bands, irreducible by sulphide of ammonium.

EXPERIMENT III.—At 3.25 P.M., 0.3 cubic centimetres injected under skin of the back. At 3.31, the frog rubbed its back with its hind limbs and its head with its fore limbs. At 3.32, the eyes were retracted. At 3.46, the circulation in the web was very slow. At 3.58, there was gasping respiration. At 4.2, there was almost complete stoppage of circulation in the web. At 4.8, the animal was killed. The heart was beating feebly, and a drop of bright red blood taken from it showed the double absorption band irreducible by sulphide of ammonium.

These experiments all pointed to the poisonous action being similar to that of carbonic oxide.

EXPERIMENT IV.—At 10.33 A.M., 0.3 cubic centimetres injected under the skin of the back of a white mouse. At 10.36, there was slow, prolonged breathing; 10.38, convulsive twitchings of limbs, especially of hind legs; 10.39, a general spasm; 10.39½, fibrillar twitchings of muscles; 10.40, gasping breathing, lying on back paralysed; and at 10.48 the animal was dead. On opening the body, the tissues were seen to be of a bright red colour, and the vessels were full of bright red blood. The blood from the heart showed a double absorption band in the spectrum, not changed by addition of sulphide of ammonium. The animal died in fifteen minutes.

EXPERIMENT V.—At 10.43, a small rabbit, weighing 330 grammes, had 1 cubic centimetre injected under skin of back. It died in twenty minutes. There was marked paralysis of the limbs, appearing first in the hind limbs. The respirations became extremely rapid and gasping towards the close of life. This was the first case in which the temperature of the rectum was taken at intervals. The first reading, immediately before receiving the injection, was 35.5°C ; the temperature steadily fell, and at the moment of death it was 32°C . This observation directed us to the remarkable reduction of temperature caused by $\text{Ni}(\text{CO})_4$. The next experiments illustrate this point.

EXPERIMENT VI.—A larger rabbit than the subject of Experiment V was taken, but the weighing was unfortunately overlooked. The animal was wrapped in a towel, and a thermometer was kept in the rectum during the greater part of the experiment. Great care was taken to keep the thermometer always at the same distance in the bowel, as it was found that pushing it a little further in or drawing it a little further out caused considerable variations. The following are the readings:—

12 noon, 37.3°C ; 12.5, 39.1; 12.10, 38.9; 12.12, 38.8 (0.13 cubic centimetre of $\text{Ni}(\text{CO})_4$ injected under skin of back); 12.13, 38.5; 12.14, 38.5; 12.16, 38.4; 12.17, 38.4; 12.18, 38.35; 12.20, 38.2; 12.21, 38.2; 12.22, 38.1; 12.23, 38.0 (no convulsions, respirations slower); 12.24, 37.85; 12.25, 37.7; 12.26, 37.68; 12.27, 37.6; 12.28, 37.5; 12.28.5, — (twitching of right hind leg); 12.29.5, 37.4; 12.30, 37.35; 12.31, 37.28; 12.32, 37.19 (twitching of right hind leg); 12.33, 37.1; 12.34, 37.0; 12.35, 36.91; 12.37, 36.8 (slight twitching); 12.38, 36.8; 12.39, 36.7; 12.40, 36.6; 12.41, 36.5; 12.42, 36.47; 12.43, 36.39; 12.44, 36.31; 12.45, 36.25; 12.46, 36.18; 12.47, 36.1; 12.48, 36.01; 12.49, 35.94; 12.50, 35.95 (thermometer pushed slightly farther in); 12.51, 35.95; 12.52, 35.9; 12.53, 35.89 (micratures on instrument); 12.54, —; 12.55, —; 12.55.5, 35.72; 12.56, 35.7; 12.57, 35.51; 12.58, 35.49 (twitching of right hind leg resumed); 12.59, 35.4; 1 P.M., 35.38; 1.1, 35.3; 1.2, 35.27; 1.3, 35.26; 1.4, 35.2; 1.5, 35.11 (marked twitching); 1.6, 35.09; 1.7, 35.06; 1.8, 35.02; 1.9, 35.00; 1.10, 34.91; 1.11, 34.9; 1.12, 34.88; 1.13, 34.9 (micratures on thermometer); 1.14, 34.9; 1.15, 34.82; 1.16, 34.72 (animal allowed to run about a little; shows weakness of hind limbs; vessels in ear full of bright red blood); 1.29, 33.3 (animal lies quiet on table without being held; slight tremor in right hind leg; twitching of right upper eyelid); 1.31, 32.5; 1.47, 31.93; 1.51, 31.6; 1.55, 31.4; 2.0, 31.0; 2.5, 30.47; 2.12, 30.0; 2.15, 29.5; 2.17, — (severe convulsive seizure, gasping); 2.20, 29.3; 2.25, 28.6; 2.34, 28.1 (rabbit placed in a large jar of pure oxygen); 2.47, 26.3; 3.0, 26; 3.5, — (respirations 52 per minute); 3.13, — (respirations 40 per minute; taken out of jar of oxygen and placed in a box before the fire to warm the body, which had become perceptibly cold; the temperature rose up to 28.5°); 4.30, — (animal died after a severe convulsive spasm).

This experiment shows that, after a subcutaneous injection of 0.13 cubic centimetres of $\text{Ni}(\text{CO})_4$, the temperature steadily fell from 38.8°C . to 26°C ., and that the animal died in four hours eighteen minutes. There was a fall of temperature of 12.8° .

EXPERIMENT VII.—A rabbit, weighing 572 grammes, was wrapped in a towel and the temperature of the rectum was taken at intervals.

12.10 noon, 38.9°C . (thermometer in rectum); 2.15, 37.0; 2.20, 37.0; 2.25, — (thermometer accidentally came out); 2.30, 36.5; 2.35, 35.8; 2.36, 35.5 (thermometer removed); 2.38, 35.6; 2.45, 35.6; 2.50, 36.0; 2.55, 35.9 (animal released and allowed to run about); 3.5 to 3.20, 36.6 (temperature remained fairly constant).

As already stated, we found that a slight variation in the

¹ *Journal of the Chemical Society*, August, 1890, vol. lvii.

² A notice of a communication on $\text{Ni}(\text{CO})_4$ by M. Hanriot appears in *Nature*, of April 9th, 1891, as having been communicated by him to the Société Chimique on February 27th. In this notice it is stated that M. Hanriot found the substance to be more poisonous than carbonic oxide, and that the blood gave the characteristic spectrum of CO-Hæmoglobin. Our work was carried on independently at intervals during last winter.