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A LECTURE ON THE ACCUMULATIVE ACTION OF MEDICINES, WITH SOME REMARKS ON SLOW POISONING.

By JAMES JOHNSTONE, M.D.,

Fellow of the Royal College of Physicians, Professor of
Materia Medica and Therapeutics at the Queen's Col-
lege, and Senior Physician to the General Hospital,
Birmingham.

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In the lectures on therapeutics which, during the last fifteen years, I have delivered at this Institution, I have frequently spoken of the *accumulative action* of medicines, or that power which they exercise over the animal economy by their continued operation when administered at short intervals, even in portions so small that no effect whatever would be produced by a single dose. To this subject, which has received less notice than it deserves from medical authors, I beg to call your attention.

The difference in character, as well as intensity, between the effect of a single dose of a medicine, and that of the same quantity of it when divided into several doses, and given at short intervals, is in many cases as striking as if two different substances had been employed. Thus, ten grains of calomel in one dose is a cathartic too powerful for most disorders that occur in this country; while a single grain of calomel, administered every night and morning for several successive days, till even more than ten grains have been taken, is very often prescribed as an alterative without much affecting the bowels. Again, two grains of tartarized antimony seldom fail to excite vomiting, but if a quarter of a grain be given at intervals of three or four hours, the medicine soon ceases even to nauseate, and becomes a powerful sedative and expectorant, which is advantageously given for the relief of inflammatory affections of the lungs and other viscera. In these instances the larger doses do not usually act accumulatively, because they irritate the intestinal canal, and therefore are not retained a sufficient time for that purpose. There are, however, other medicines of which the effect is increased, but not altered by their protracted operation: such are digitalis and iodine; the former being always sedative and diuretic, the latter a stimulant to the glandular and absorbent system, and an alterative.

Nothing in the treatment of disease is of more

importance than this accumulative action of medicine, for while many disorders which do not soon or ever yield to the most active measures, may be cured by the gradual influence of remedies far more gentle in their first action, the physician is sometimes rather disconcerted at finding that his patient has been salivated by a few doses of mercury, which were intended to act upon the digestion only, or that the heart has almost ceased to beat, owing to the depression which digitalis, prescribed as a diuretic, may have caused. Indeed, the benefits which are now derived from the foxglove, were purchased at a cost of life by no means inconsiderable, before it was introduced into the "*Materia Medica*," and its power was properly estimated.

The facts which I have stated are well known; and though the physiological explanation of them may admit of doubt, I believe that the accumulative action of a medicine is always dependent, *either upon the chemical changes in the animal fluids which it may occasion when the system is loaded with it, or upon diminution of the nervous power, consequent on long continued depression of the nervous system.*

This classification might perhaps, with very little modification be applied to general therapeutics, for it is probable that most, if not all, of those medicines, which are not purely chemical agents, act primarily upon the nervous system; and I am inclined to think that the operation of some upon one organ especially, and others upon another, is owing to the peculiar sensibility of various sets of ganglionic and spinal nerves to appropriate stimulants—both natural and artificial,—such as we know to exist in the cerebral system; so that in the same manner as the optic nerves are affected by the light alone, and the auditory nerves by sound, the nerves of the kidneys are excited by diuretics, those of the uterus by emmenagogues, and those of the intestines by cathartics, as well as by the ordinary secretions. Upon the same principle, the action of these organs is impaired when any substance which can stupefy their nerves may happen to come in contact with them. A medicine may enter an organ, and circulate through its vessels, but unless it either effect some chemical alteration, or be fitted to act upon its nerves, the functions of the part are not disturbed. Hence we find the colour and smell of rhubarb and other substances in secretions, which are neither thereby increased, nor otherwise materially changed; although other functions may be at that very time under the influence of these medicines.

I.—CHEMICAL CHANGES EFFECTED IN THE ANIMAL FLUIDS, BY THE ACCUMULATIVE ACTION OF MEDICINES.

That certain medicinal substances are conveyed into the circulating system by absorption is an undoubted fact; for many of them, including salts of mercury, iron, silver, potassium, &c., have been detected in the blood itself, as well as in the secretions from it. The taste of iodine in the saliva, when it has been rubbed into the skin, a fact which I have often observed; the blue tint of the internal membranes, and the dark colour of the skin, of those who have taken nitrate of silver for a long period; the red bones of animals which have been fed upon madder, and numerous other instances of a similar nature, likewise evince the presence of mineral and vegetable medicines in the fluids and tissues. It does not, however, necessarily happen that medicines which are absorbed, act chemically; for some of them when once deposited, either exert no apparent influence on the animal economy, or only on the nervous system, having during their passage through the alimentary canal, lacteals, and blood-vessels, undergone changes which rendered them ultimately inert; whereas, many others retaining the power which they previously possessed, prove beneficial or prejudicial to health, as the case may be. Thus the continued use of alkalis in minute quantities, more effectually counteracts the disposition to form lithic acid than the largest doses occasionally administered; and upon the same principle, the invalid often derives more relief from habitually drinking the natural mineral waters, which hold in solution very small portions of various salts, than from any other medicine. By the accumulative action of such remedies, the constitution of the animal solids, as well as of the fluids, becomes gradually modified; and the morbid tendencies which may have previously existed, either remain for a time in abeyance, or are permanently removed.

Of these changes in the animal fluids, the cure of those diseases which affect the functions of nutrition and secretion on the one hand, and on the other hand the tendency of some medicines, such as iodide of potassium, turpentine and copaiba, to induce cutaneous eruptions, are evidence; and this is corroborated by the experiments of several eminent physiologists, who have shown, that when saline and other medicaments are mixed with blood, its colour and consistency undergo considerable alterations. But as Hewson very justly remarks, we must not conclude that the effects within the body, would be the same as out of it, and it must be admitted, that though we may be inclined to believe in the power of some preparations of iron to increase the quantity of globules in the blood, and to give credit to other instances of vital chemistry, equally interesting, yet such phenomena require further elucidation before we can claim an exact knowledge of them. Nevertheless enough has been done to prove that the efficacy of many medicines is dependent upon their chemical action, and that though in former times the practice of the humoral

pathologists was often bad, their theories were not so far wrong as Hoffman and Cullen imagined.

II.—DIMINUTION OF THE NERVOUS POWER BY THE ACCUMULATIVE ACTION OF MEDICINE.

While the accumulative action of some medicines depends upon the chemical changes which they effect, it seems equally certain that the agency of others is entirely attributable to their diminishing the nervous power. The rapidity with which strychnine, and some of the other narcotic poisons, affect other animals, as well as man, can only be explained by the supposition that these substances possess a peculiar influence over the nervous matter, when brought into contact with it, and thus impair its functions. Changes in the structure of other parts of the body may, and often do, subsequently occur; but these I should, under such circumstances, regard as the result, and not the cause, of diminished nervous power. Indeed, the accumulative action of such medicines somewhat resembles the influence of long continued grief and anxiety of mind, which, by diminishing the energy of the nervous system, slowly, but surely, impede or pervert the organs of nutrition.

In cases of this class, the loss of nervous power is the first and leading characteristic, whether the agent, being absorbed, come in contact with the nervous system through the medium of the circulation, or by a more direct application to the nerves; and there can scarcely be a better proof of the mode in which this kind of accumulative action is produced, than the tendency of some medicinal substances, to cause paralysis and convulsions, with which, in many instances, the sufferer is afflicted for a considerable period afterwards. In a case related by Dr. Blackall, and mentioned by Dr. Christison, a person, while taking daily two drachms of an infusion of digitalis, was attacked with pain over the eyes and confusion, followed in twenty-four hours by diarrhoea, delirium, convulsions, and insensibility, with extreme depression of the pulse. The convulsions continued to recur for three weeks, with intervals of delirium, and at length he died in a convulsive fit.

The accumulative action of opium, of hyoscyamus, and of narcotics in general, may be explained upon the same principle. In shaking palsy, which, though excited by the fumes of mercury, often continues long after the individual has been removed from their influence, the ordinary symptoms indicate disturbance of the nervous system; while in most cases there is no salivation, nor are there any of those signs of disordered secretion and nutrition, which the salts of mercury commonly occasion. So likewise in paralysis from lead, the general symptoms show derangement of the nervous system, the black line along the gums merely proving that the metallic salt has been absorbed. These examples are, perhaps, sufficient for my present purpose, for, though they exhibit the *poisonous* effects of mercury and of lead, the principle of their accumulative action is the same as of medicines.

III.—OF SLOW POISONING.

Besides these which I have mentioned, there is

another mode of accumulative action, by which medicinal substances have acted as most deadly poisons. Amidst the various means which have been devised to take away life, it was some centuries ago discovered, that by irritating the alimentary canal, and thus disordering the digestive function, the habitual use of certain drugs, many of which are now very commonly employed in a different manner, and for a far different purpose, even in very minute doses, proved fatal. This, however, is the action of poisons, not of medicines, and therefore does not properly form a part of our present subject; but since nothing can more strikingly illustrate the power which medicinal substances may gradually acquire, I shall mention some of the most remarkable examples of slow poisoning, for reference to the greater number of which, as well as for several of the circumstances themselves, I am much indebted to the kindness of a very able and accomplished friend.

From the works of Theophrastus and of Plutarch, it would appear that slow poisoning was practised both by the Greeks and by the Romans long before the Christian æra. In some cases the nervous power was destroyed by narcotics; in others the digestion was impaired by irritating or corrosive drugs. Theophrastus, who died 288 years before Christ, says, it is asserted that a poison can be prepared from aconite so as to cause death within a few months, or even after a longer period; and that Thrasyas, of Mantinea, who seems to have been his contemporary, was acquainted with a mode of preparing other plants, so that small doses of them occasioned an easy death, though they induced no weakness for a long time after they had been taken. We are told by Plutarch, that Philip, the son of Demetrius, and king of Macedonia, wishing to put to death Aratus, of Sicyon, who was a distinguished general, desired one of his friends to administer poison, of a kind which caused lingering heat or fever, with a slight cough and spitting of blood, followed by gradual decay. This occurred about 213 years before Christ, and a few years afterwards, according to Livy, poisoning became very common at Rome. Among others, so says Tacitus, the Emperor Claudius, and his son Britannicus, were destroyed by this means. In both cases a slow poison, prepared by the infamous Locusta, and intended gradually to destroy the mental as well as physical powers, was administered, but as the patience of the murderers was exhausted before it took effect, a stronger dose was given to each of the victims, and they speedily perished. To Claudius the poison was at first given in a dish of mushrooms, but he was at last killed by a poisoned feather, which was put down his throat under pretence of making him vomit. Since the slow poison was not allowed time thoroughly to operate on these persons, it is doubtful what its effects might have been; and many of the symptoms which are described by the Greek and Roman historians, so much resemble those of some ordinary diseases, that in the absence of corroborative evidence, it might have been questioned whether the animal and vegetable substances that were used for this purpose really possessed the properties attributed to them. The fact, however, that the doctrine of slow poisoning was generally

received, not merely by the vulgar, but by men of the highest literary attainments in the Roman empire, affords proof that such a mode of destroying life was known and practised nearly two thousand years ago.

The deleterious properties of aconite, hemlock, and the poppy, which were the poisons most commonly employed, are well known at this day; and the ingenuity of more recent times, while adding to the catalogue of poisons as well as of crimes, has sanctioned the belief of the ancients in their fatal and imperceptible influence.

The instances of slow poisoning which are on record from the fifteenth to the nineteenth century, are indeed so numerous, that I can only attempt a passing allusion to some of the most remarkable of them. Of all the adepts in this horrid science, none excelled Cæsar Borgia, who was born in the latter half of the fifteenth century, and died in 1507. Endowed with talents of the highest order, which he entirely devoted to the promotion of his own selfish views, Borgia unscrupulously removed all who might be obstacles to his ambition, or even to his slightest gratifications. For this purpose he sometimes had recourse to poison which was so insidious in its operation, and so indiscriminately employed, that he became an object of terror to those whom he called his friends, as well as to his open enemies. It is said that the poisons thus used were of two kinds,—the one being a solid, white, mealy substance, of which the composition is unknown; the other a solution of arsenic. It was believed, in the time of the Borgias, that the latter was the saliva collected during the dying agonies of a bear, which had been poisoned with arsenic; though this is not very probable, since that poison does not require such preparation to fit it for the destruction of man. At last Cæsar Borgia himself nearly fell a sacrifice to his own machinations, and his father, Alexander VI., actually died in consequence of having drunk some poisoned wine which was intended for three Cardinals who were their guests. The convulsions with which they were almost instantly seized, must, however, have been caused by a very active agent; though the subsequent painful illness of Cæsar, who swallowed an antidote, might have been the effect of a small dose of arsenic, for those who have taken it, and do not die within a few days, seldom fail to suffer from irritation of the stomach during months and even years afterwards, and may never entirely recover.

The Borgias being too powerful to fear punishment, frequently had recourse to more speedy means of removing their victims than by slow poisoning; and the most remarkable examples of this secret murder occurred at a later period. In the seventeenth century, slow poisoning was carried on to such an extent in Italy, that the public attention was attracted to the subject; and two women, of the names of Spara and Tofania, have acquired especial notoriety by their skill. It is generally supposed that they made use of a solution of arsenic, but the Abbé Gagliani asserts that Aqua Toffana was a mixture of cantharides and opium, which he adds is the surest of all slow poisons, and one which no one would avoid through suspicion,

because the liquor has no taste, and is as limpid as rock water. At first the patients did not suffer from it, but after some repetitions of the poison, they gradually lost the appetite, and became subject to gnawing pains in the stomach, followed by debility, disease of the lungs, hectic fever, and death.

The use of slow poisons was not, however, confined to the Continent; for a remarkable instance of it happened in this country during the reign of James I., in the murder of Sir Thomas Overbury, which was perpetrated in the Tower of London, by the orders of Viscount Rochester, and is mentioned by several of our historians. The unfortunate prisoner is said to have taken poison, in very minute quantities, with almost every article of his food. Cantharides and arsenic were mixed with the pepper and the salt; lunar caustic was rubbed over his meat; and when his health failed, poisoned jellies and preserves ministered to his fastidious appetite. His strength was obviously declining, but after this treatment had been continued for six months, Rochester became impatient; and his fears being excited lest Overbury should yet live long enough to divulge some unpleasant secrets of which he was in possession, the prisoner's existence was at length terminated, either by corrosive sublimate, or by suffocation, but by which of these means it is not quite certain.

In the year 1676, the Marquise de Brinvilliers was found guilty of several murders, and was executed at Paris. Having formed a criminal attachment to a man of the name of Sainte-Croix, who was afterwards suffocated by the fumes of some deleterious compounds which he was preparing, they resolved to relieve themselves from the power and remonstrances of the Marchioness's relations by poison; and her father was without hesitation sacrificed. The first dose of poison was given to him in soup, and M. d'Aubray suffered so much pain after it, that he sent for a physician, who considered the illness to be an attack of indigestion, and under that impression prescribed for him. M. d'Aubray continued, however, in great pain, and in the space of a few days he expired. Her father being thus disposed of, two brothers and a sister still lived to censure the conduct of Madame de Brinvilliers, and to share the wealth which had been left by their parent. These obstacles could not be endured; and the Marchioness, with "her accomplice, Sainte-Croix, decided that they should be removed." "But this time," says Dumas, "to avoid suspicion, it was necessary to employ a poison less rapid in its action, than that which had killed M. d'Aubray. They recommended their experiments, not upon animals, lest the difference of organization might defeat their views, but in *anima vili*. The Marchioness was known as a pious and charitable woman, ever ready to relieve the distressed, and sharing with the Sisters of Mercy the attendance upon the sick, to whom she sent wine and medicine at the hospitals. Thus it caused no surprise to see her at the Hotel Dieu, distributing biscuits and preserved fruits to the convalescent; and her kindness was gratefully acknowledged. One month subsequent to this, she revisited the hospital, to enquire after some

patients, in whose welfare she was much interested, and she was told that they had suffered a relapse, that fresh symptoms had supervened, that a deadly languor overcame them, beneath whose wasting influence they gradually declined. Of its cause she could learn nothing. The physicians told her that the disease was unknown, and defied their utmost skill. She again enquired at the expiration of a fortnight; some of the patients were dead, others still lingered in hopeless agony—animated skeletons, whose only signs of life were the voice, sight, and breath. Within two months all were dead, and medical skill was as completely foiled upon their examination after death, as it had been in their treatment."

Encouraged by this success, Madame de Brinvilliers commenced operations upon her brothers and sister. The sister escaped by leaving Paris, but one of the brothers expired in two months, and the other about five months after they had been subject to the influence of poison; the pain of the stomach, sickness, burning in the chest, anxiety of mind and exhaustion, as well as the disorganization of the stomach, intestines, and liver, observed on examination of the bodies after death, indicating corrosive action of the substances which they had been taking. There can indeed be no doubt respecting the nature of the poisons, for on the death of Sainte-Croix, corrosive sublimate, vitriol, antimony, lunar caustic, and opium, together with an acrid preparation, of which the chemical composition could not be detected, were found in his cabinet; while a paper, written by the Marchioness, and detailing many of her crimes was likewise discovered in his house.

Besides those just enumerated, Professor Baldinger, whose authority is quoted by Beckmann, states that sugar of lead was an ingredient in one of the most subtle poisons. "There is no doubt," he says, "that the slow poison of the French and Italians, commonly called *succession powder*, (*poudre de la succession*,) owes its origin to sugar of lead. I know a chemist, who superintends the laboratory of a certain prince on the confines of Bohemia, and who, by the orders (perhaps not very laudable,) of his patron, has spent much time and labour in strengthening and moderating poisons. He has often declared, that of sugar of lead, with the addition of some more volatile corrosive, a very slow poison could be prepared, which, if swallowed by a dog or other animal, would insensibly destroy it in the course of some weeks or months," without any violent symptoms.

In relating the foregoing cases, the limits of a lecture would not permit of my entering further into details, than was necessary to show what substances were used as slow poisons, and what symptoms ensued. These are the facts which illustrate the accumulative action of poisons, in contrast to that of medicines; and for fuller information, I beg to refer those who may be curious in such matters, especially to Beckmann's "History of Inventions;" to Mackay, on "Popular Delusions;" and to the "Crimes Célèbres," of A. Dumas.

It is much to be feared that the crime of slow poisoning is by no means extinct. In the last century

it was certainly practised; for early in the reign of George the third, Mary Blandy was tried and hanged at Oxford for poisoning her father, by repeated doses of arsenic, and many still more recent instances are reported.

In most of the cases which I have mentioned, death took place in consequence of the destruction of the digestive powers, by the operation of corrosive poisons upon the alimentary canal, the symptoms of which I have several times witnessed, though in a very slight degree, when arsenic and nitrate of silver have been prescribed as medicines; and of the action of narcotics and sedatives upon the nervous system. Farther examples can scarcely be necessary. The formidable influence which medicines exert when administered so as to act accumulatively, ought to make us very seriously consider, not only the primary, but likewise the secondary and subsequent effects of whatever we may be about to prescribe; for although the frequent repetition of a small dose is acknowledged to be in many cases highly beneficial, it is equally true that some medicines may in this manner induce chronic inflammation of the nervous membrane of the stomach and intestines; that others may gradually impair the nervous power; and that a third kind may so change the composition of the animal fluids, as to substitute morbid deposits in the various tissues for those which are naturally formed by the process of healthy nutrition. Thus, while by judicious management, the accumulative action of medicines may be employed as a most efficacious mode of relieving many constitutional disorders, and especially those of a more chronic description, without proper caution we may lay the foundation of diseases, more mortal than those which it was our object to cure.

ON THE PATHOLOGY OF HOOPING-COUGH.

By T. OGIER WARD, M.D., Oxon.

TO THE EDITOR OF THE PROVINCIAL MEDICAL AND SURGICAL JOURNAL.

SIR,

In the number of the *Provincial Journal* for June 16th, there is a paper by Dr. Fife, of Newcastle, "On the Pathology and Treatment of Pertussis," to which my attention has been more particularly directed, by that disease having been rather prevalent lately in this place, and by my desire to ascertain whether any new light had been thrown upon its nature. In this expectation, I must say, I have been disappointed and it is because I agree with Dr. Fife in the importance of our having settled notions respecting its pathology, that I cannot adopt the view he has taken of its exclusively nervous character, an experience of nearly twenty years having convinced me that such a view is too narrow to be a safeguard for practice. I therefore venture to send you this letter as a kind of commentary and appendix to the theory, to which Dr. Fife has given the sanction of his name.

Dr. Fife sets out by stating his belief, that "the doctrine of the inflammatory nature of whooping-cough is advocated by the majority of the profession." I

cannot coincide with him in such an opinion, if he means that the disease is considered as inflammatory in all its stages; and I believe that the opinions of the majority of practical men, besides those of a great host of authors, are opposed to its being *absolutely* of an inflammatory nature, or hyperæmic. Of thirty-eight authors, whose opinions are quoted by Dr. Copland, in his Dictionary, Art. "Whooping-Cough," eighteen considered it as an irritative disease, eight as purely nervous, and only twelve as inflammatory. It may be asked why, with such a number of the ideas of the learned recorded on this subject, I should presume to propound another hypothesis? My reply is, that not one of them, even including that (the best,) of the accomplished lexicographer himself, appears to me as being perfectly satisfactory in embracing and explaining all the phenomena of pertussis; for although some of them admit its specific nature, they do not trace the influence of the specific element through all the phases of the disease.

The gist of Dr. Fife's argument is to show that pertussis is distinct from bronchitis, and the major portion of his paper is occupied by the proofs; but while he shows pretty clearly what it is not, he does not define as evidently what it is, inasmuch as its pathology, as far at least as I can ascertain, is comprised by him in the following propositions:—

1st. The larynx is mainly implicated in the production of the paroxysm of cough, the chest being comparatively passive, and the violence and convulsive nature of the cough resembling that which arises from the pressure of foreign bodies in the larynx.

2nd. The hoop or whoop is physiologically requisite to compensate for the interruption which respiration sustains during a paroxysm.

3rd. The vomiting which terminates the cough, in all probability, has its origin in the participation of the stomach in the morbid condition of the larynx.

4th. Hence the actual seat and nature of pertussis are essentially referrible to some morbid condition of the pneumogastric nerve, which influences the secretion of the mucus so frequently discharged from the stomach.

Now, admitting the truth of the first proposition, the second is by no means a corollary to it; for, although a deep inspiration always follows the expulsive efforts of a cough, yet it is by no means "*physiologically requisite*" that this inspiration should be attended by a whoop; *pathologically*, however, it is requisite that the whoop should occur, as this is the characteristic of the disease. Again, as Dr. Fife has omitted to state in what consists the morbid state of the larynx, we are not much enlightened by the third proposition,—that the stomach participates in this condition, whatever it may be; nor is the conclusion respecting the pneumogastric nerve at all borne out by the premises that the stomach and larynx are equally affected. It may be so, but there is no proof given, physiological or pathological, that it is so. Even if we take it for granted that the pneumogastric nerve is the point *départ* of the symptoms, Dr. Fife ought to have informed us how this morbid condition of the nerve has been produced.

But with the intention of contrasting pertussis with bronchitis, Dr. Fife has laid down six other propositions bearing on the pathology of the complaint, to which,