A CLINICAL LECTURE ON THE ANALGESIC ACTION OF METHYL- ACETANILIDE OR EXALGINE.

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GENTLEMEN,—I intend to-day to depart a little from the kind of subject-matter which supplies the main topics for discussion in this lecture room. At the same time, the subject I propose to deal with is one that is obviously and intimately related to our studies in clinical medicine. We cannot, I think, too frequently be reminded that the chief object of these studies is to increase our therapeutic resources; and I do not know that there is any result of disease that more imperatively demands the attention of the physician than the relief or removal of pain. The success with which this can be accomplished may, on the whole, be regarded with complacency, for that success has proved one of the most powerful causes in establishing confidence in the art of medicine, and it has been associated with some of the greatest triumphs in the history of that art.

Restricting attention to pharmacological agents, you are aware that the most important of them are opium and several of its alkaloidal principles, belladonna, stramonium, and other plants yielding atropine-like bodies—aconite, cocaine, bromides, and volatile oils; as well as chloroform, ether, chloral, and other general anæsthetics and hypnotics of artificial production. Your pharmacological studies, however, have placed you in a position to appreciate the statement that the success obtainable by the use of these agents is not an altogether unqualified one. In the case of many of them, as of opium and belladonna, the relief of pain, produced by their general action or by their localised action is accompanied with other effects that are neither desired nor desirable. In the case of others, this relief can be obtained only when they are applied to or near the seat of pain, and this application is often impossible, and is generally attended with some inconvenience. Pain, further, is a sensation which, for its appreciation, does not require that all parts of the cerebro-spinal nervous system, nor even that all the sensory ganglia in the brain, nor all the fibres of a sensory nerve, should be involved. It is equally unnecessary for its removal that change should be produced in more than one or a few of the nerve structures concerned in its manifestation. Restricting attention to that part of its possible appreciation which is brought about by conduction along a sensory nerve, the distinction I am attempting to explain may be rendered more apparent if I remind you that in certain diseases of the nervous system, common or general sensibility may be retained, while in the same region the appreciation of excitations that usually cause pain may be absent; that, in fact, analgesia may be present, while tactile or thermal sensibility is retained. Whether this analgesia be due to a central or a peripheral change, its independent occurrence is significant, for it suggests that a pharmacological modification of a physiological condition, equally with a pathological modification, may remove pain by acting only on the special nerve fibres or on the special centres (hippocampal region of Ferrier) by which painful impressions are conducted or appreciated.

A pharmacological analgesia of this kind, indeed, appears now to be recognised as an effect producible especially by several bodies recently constructed by the chemist, and recently applied to the treatment of disease, and more particularly by many of the bodies included in the aromatic series of the carbon compounds. The salicyl compounds are probably those in which it has first been recognised, although, in all probability, the previously known pain-removing influence of quinine—a natural product in the same chemical series—is of the same kind. The analgesic power of most of the aromatic bodies is, however, only a subsidiary effect, generally overborne by such other effects as the antipyretic, diaphoretic, and antiseptic, and producible only by large doses. When used merely as analgesics, they accordingly, like opium and the older pain removers, have inconveniences, and they, also, are not to be

regarded as free from danger in their analgesic applications. The requirements of therapeutics have not been entirely satisfied by them; for, while they may remove neuralgic pain by any action on pain-conducting or pain-perceiving structures, they cause, when used in the doses required for this purpose, other actions which have nothing to do with the relief of pain, and, besides, are often injurious to the patient. We recognise these disadvantages in antipyrin and antifebrin, probably the most efficient analgesics in this series, for analgesia can rarely be produced by them except with large doses, and, therefore, with the inconveniences and dangers of gastric disturbance, deafness, profuse sweating, disturbance of the circulation, and changes in the blood.

The study of the members of this aromatic series has shown that even slight changes in their chemical constitution may be followed by marked changes in their pharmacological action. Antifebrin illustrates this. It is acetanilide, and when it is combined with methyl, the new body, methyl-acetanilide, is found to be a more powerful analgesic than the acetanilide from which it is derived, and the doses by which pain may be removed by it, are, according to the statements that have been made, too small to produce any of the inconvenient or dangerous effects which may be caused by larger doses.

Methyl-acetanilide or exalgine is one of the four methyl derivatives of acetanilide discovered by Hoffman in 1874—the other three being ortho-, meta-, and para-acetoluid. Its formula is C_9H_9NO . It is characterised by its complete solubility in benzole, boiling between 80° and 85° C.; by its melting point being between 99° and 100° C.; and by its forming a nearly colourless solution with strong nitric acid, which, when heated, becomes bright yellow, but does not evolve irritating fumes. It occurs in the form of colourless needle-shaped crystals of considerable length, which have a faintly aromatic odour and a slightly pungent taste. It is nearly insoluble in water, but is freely soluble in rectified spirit, and even in dilute alcohol. I find that from 16 to 20 grains may be dissolved in half a drachm of rectified spirit, and that this solution may be diluted with 3 or 4 ounces of water and still remain perfectly clear. As a solution so made, and containing half a grain or 1 grain in a teaspoonful, has but little taste, I have generally used it without the addition of any flavouring agent.

Some of the pharmacological properties of methyl-acetanilide or exalgine were determined by Hepp and Kahn in 1877; but what promises to prove its most valuable action has been made known only within the last few months by Bardet, Gaudineau, Binet, Dujardin-Beaumetz, and Desnos. I shall refer to the results of these observers only so far as to say that methyl-acetanilide or exalgine is not an aromatic body whose antithermic action is likely to prove valuable, as it is producible only by doses which verge on the toxic; but that the analgesic action of exalgine, on the other hand, and in remarkable contrast with the analgesia producible by acetanilide, is manifested by relatively small doses. As the observations I shall bring under your notice have shown, this analgesic action further may be decidedly produced without any other observable effect, unless it be a doubtful tendency to induce sleep, and, therefore, by doses which apparently are absolutely free from danger, and even from inconvenience.

For the opportunity of making the observations I am indebted to MM. Brignonnet and Naville, of Paris, who have paid much attention to the manufacture of methyl-acetanilide, and, judging from the beautiful crystalline specimens they have sent me, have succeeded in producing it in an extremely pure form. My observations have as yet been restricted to the influence it produces on pain.

I have administered it in essential neuralgias, and in pain produced by a number of diseases. Having had no previous personal knowledge of its properties, I have generally given it in the small dose of half a grain; but 1, 2, and 4-grain doses were also administered. The largest quantity given in twenty-four hours was 14 grains, and no disagreeable, much less dangerous, effect was produced by this quantity.

I shall now give a few details of the observations that have been made, commencing with cases of neuralgia:

T. D., aged 30, under treatment for bronchitis, has recently begun to suffer from neuralgia of the right inferior and superior trochlear nerves. The pain is described as "gnawing" and "toothache-like" in character, constant, but with exacerbations of a severe stabbing sensation during coughing. There is also pain in the right eyeball, and tenderness on pressure over the right supra-orbital foramen.

January 23rd. At 11.30 A.M., gave half a grain of exalgine. Pain

soon became less severe, and in one hour it had disappeared, and it remained completely absent for two hours.

January 24th. At 9.30 A.M., while pain was very severe, he received half a grain of exalgine. Within an hour great reduction in pain, but relief not so complete as with the first dose.

January 25th. Severe pain from 9.30 A.M. At 11.17 1 grain of exalgine was given. In one hour and ten minutes pain almost completely gone, and relief continued for nine hours.

January 26th. Severe pain from 9.20 A.M. At 11.43 1 grain of exalgine was given. In one hour almost no pain, though tenderness on pressure continued. Soon after the latter also disappeared, and there was no return of pain until the following morning.

January 27th. Severe pain began at 8.30 A.M. At 10.30 1 grain of exalgine was administered. In half an hour pain, and even tenderness on pressure, had completely disappeared, and they remained absent for twenty hours.

January 28th. Pain began at 7 A.M., and had become very severe at 8 A.M., when 1 grain of exalgine was given. The pain became much less in one hour, only slight tenderness was present in two hours, and there was neither pain nor tenderness in three hours.

On the 29th, 1 grain produced similar results, but within a shorter period.

On the 30th the pain commenced at 7 A.M. It was very severe at 8.20, when a grain of exalgine was given. In thirty minutes the pain had almost completely disappeared; in a few minutes afterwards the patient was asleep, and, when he awoke an hour afterwards, there was no pain nor tenderness. Since this date the patient has remained perfectly free from pain.

In the next case, that of A. T., aged 36, sciatica had been continuously present in the right leg for five months. During eleven weeks of this time he had been under treatment in Stirling Infirmary, where blisters, acupuncture, and several internal remedies had been employed, and had apparently lessened, without removing, the pain. He was admitted into the Edinburgh Royal Infirmary on January 4th, 1890. During the first few days following his admission no treatment for sciatica was adopted, and the pain increased in severity from day to day, so that immediately before using exalgine it was continuous, and of a dull "gnawing" character, but frequent severe paroxysms occurred, with tearing and stabbing sensations; and during the paroxysms, which generally lasted for from one to two hours, the patient moaned and perspired profusely. Exalgine was given on ten occasions during a week, and it is impossible to do more than briefly summarise the results. On each occasion the exalgine was given at the beginning of a severe paroxysm. Half a grain greatly reduced the pain in fifteen minutes, and it remained very slight for one hour and fifteen minutes; half a grain again greatly reduced the pain in fifteen minutes, and it remained very slight for three hours; 1 grain produced only slight relief; 1 grain almost completely removed the pain in forty minutes, and the relief continued for three hours and a half; 1 grain caused great relief in ten minutes, and almost complete removal of pain in thirty-five minutes; 1 grain caused great relief in fifteen minutes, and the pain was almost absent for one hour and ten minutes; 1 grain caused great relief in twenty minutes, after which the patient slept for six hours, and no paroxysm occurred during the three following days; 1 grain caused great relief in thirty minutes, and pain remained absent for eight hours; 1 grain caused great relief in thirty minutes, and pain remained absent for fifteen hours; and on January 21st, 1 grain caused great relief in twenty minutes, and no further paroxysm of pain has since occurred, although some uneasy sensations, not amounting to pain, have at times been felt in the right knee and leg.

In a case of herpes cervico-brachialis ten administrations of exalgine were made during five days. The patient, J. C., aged 35, suffered from continuous neuralgic pain, with exacerbations in severity, in the right interscapular and supra- and infrascapular regions, and extending down the whole of the right arm to the wrist. The pain began seven days before the eruption appeared, and it continued unabated after the appearance of the eruption. Exalgine was usually administered at the beginning of severe exacerbations of pain. Half a grain caused complete relief in ten minutes, which continued for an hour and twenty minutes; half a grain caused complete relief in a few minutes, when the patient fell asleep and slept for three hours; half a grain almost entirely removed the pain in twenty minutes, but the patient slept for only thirty minutes; three-quarters of a grain relieved the pain in a few minutes sufficiently to allow the patient to sleep, and

sleep continued for two hours; three-quarters of a grain gave sufficient relief to allow sleep in thirty minutes, and the sleep continued for two hours and a half; half a grain produced only slight relief; half a grain was followed in five minutes by sleep, and the patient awoke one hour afterwards without pain, and no further pain occurred for nine hours; 1 grain caused entire relief in ten minutes, and the pain remained altogether absent for four hours; 1 grain caused entire relief in twenty minutes, and the patient then slept for five hours. On awaking slight pain gradually returned, but it was now felt only in the wrist and back of the hand, and the pain did not again anywhere become sufficiently severe to require further administration of exalgine, although the herpetic eruption still continued.

In another case of neuralgic suffering the patient, C. B., aged 45, was recovering from hemiplegia of the right side. The pain affected the right arm, which had only partially recovered its motor power, and especially the neighbourhood of the shoulder, elbow, and wrist joints, and the whole hand. The pain had been present for a month; it was dull and aching in character, and nearly constantly present, though most severe during the afternoon and evening, and sleep was frequently prevented by it. Eleven administrations of exalgine were made during a period of three weeks. In ten of the administrations the dose was half a grain, and in the eleventh 1 grain. Marked success followed each administration; the pain was removed in from five to twenty-five minutes, and it always remained absent for several hours after each dose, and sometimes for several days. On one occasion, early in the treatment, three doses of half a grain were given at intervals during twelve hours, and, for the first time since the pain began, the patient remained entirely free from pain for twenty-four hours. On another occasion, at about the middle of the period of treatment, no exalgine was given in a day when pain had occurred, and the patient suffered severely in the afternoon, slept only for a short time at night, and had severe pain also during the following morning and forenoon. Since the last administration (January 17th) there has been no return of pain.

I have been anxious to test the analgesic action in the pain of locomotor ataxy, but it has happened that no case of this disease has recently been admitted into my wards. Professor Grainger Stewart has, however, kindly allowed me to make observations on two of his cases. One, A. D., aged 28, has suffered from ataxy for three years. She has frequent pains of the ordinary description in the lower extremities, with girdle sensations there and in the trunk, and she also often suffers from headache. One evening, while these conditions were present, she received 1 grain of exalgine. In twelve minutes the pain in the legs was greatly lessened, and in twenty-five minutes pain had entirely disappeared, the girdle sensations were less marked, and she was free from headache. This relief was maintained for three hours, when the symptoms gradually returned. One hour afterwards, when the symptoms were apparently present in their former severity, another grain of exalgine was administered; in twenty minutes the patient was asleep. She remained asleep for three hours and a half, and, on awaking, she stated that pain was completely absent, although an uneasy heavy sensation, which she nearly constantly experiences, was felt in the back. A third 1-grain dose was given to this patient when she was suffering only from girdle sensations in the back, but only a slight diminution in the sensation appeared to be produced.

The second case of ataxy in which exalgine was given was that of a man, W. L., aged 48, who had suffered from this disease for four years. On the occasion of administration, "gnawing" and "aching" pain was stated to be present in the lumbar region, causing much distress. In fifteen minutes after 2 grains of exalgine had been administered, pain had almost completely disappeared, and soon after the patient was asleep. He slept all night, and had no pain when he awoke next morning.

I have been able to make observations on four patients suffering from toothache. In one patient, half a grain gave complete relief on two occasions; in the second patient the same result was obtained, also on two occasions, by 1-grain doses, but the relief lasted for only one and two hours; in the third patient, 1 grain completely removed severe pain for twenty minutes, and, on its return, 1 grain followed in twenty-five minutes by 2 grains eased the pain in seven minutes after the second dose, and nearly completely removed it in about eighteen minutes, soon after which time the patient fell asleep, and pain was absent on the following morning; and in the fourth patient, with a number of decayed

teeth, only slight relief was produced by a half-grain dose on two occasions.

I have had only one opportunity of testing exalgine in cardiac angina. The patient, J. F., aged 45, suffers from aortic disease. On each of the seven days during which he had been under my care before exalgine was given, severe, sharp, and burning pain had occurred in the pericardium, and pain frequently shoots down the left arm, and is accompanied with a choking sensation in the throat, and with palpitation and much sweating. The attacks usually occur between 6.30 and 7 A.M., but they last only for from a quarter of an hour to half an hour, and during them the patient is obliged to sit up in bed. The first dose of half a grain was given at 6 A.M., in order to anticipate an attack, and on that day, for the first time since he had been under observation, he remained entirely free from an attack. The second dose, also of half a grain, was given a few minutes after an attack had commenced; in three minutes he said he was much better, and in five minutes that the pain and every symptom had disappeared, and he was now able to lie down.

I have given exalgine in two cases of pleuritic pain. In one, only an imperfect observation was made with a single 1-grain dose; but, on the whole, the evidence led to the conclusion that no relief was obtained. In the second case, in an adult patient, the pleurisy was recent, acute, limited to the right base behind, and accompanied with friction and considerable pyrexia. The pain was so acute that movement was nearly impossible, the chest expansion was almost limited to the left side, and the cough, excited mainly by bronchitis of the left side, was accompanied with a distressing pain in the region of the pleurisy. While these conditions were present, half a grain of exalgine was given in the evening. The pain was much relieved in twenty minutes, it had almost disappeared in thirty minutes, and it did not again become severe until two hours and a half. Forty-five minutes thereafter a second dose of half a grain was given; in nine minutes pain had nearly gone; a deep inspiration could easily be taken, and the right arm could be moved without inconvenience. One hour and fifteen minutes afterwards, pain again appeared, and it had become severe in one hour and twenty-five minutes, when it was not relieved by a dose of anodyne cough mixture containing a little opium. A third half-grain dose of exalgine was given three hours and fifteen minutes after the second dose; in ten minutes there was scarcely any pain, and the patient slept for five hours, when he awoke with pain of nearly original severity. A fourth half-grain dose was therefore administered; in four minutes there was almost no pain, in five minutes the right arm could be freely moved about, a deep inspiration could be taken without pain, and the cough was less frequent than it had been. This absence of every painful symptom continued for at least an hour and a half, when other treatment was commenced for the pleuritic inflammation.

I have also administered exalgine in several cases where the pain was not so distinctly of a neuralgic character as in the preceding cases.

Thus, in a case of rheumatic synovitis of one wrist, with intermittent attacks of severe pain occurring each evening, and lasting for from an hour and a half to two hours, on one occasion, half a grain of exalgine relieved the pain in forty minutes and for half an hour; on a second occasion, in half an hour, and for a whole night; on a third occasion, the same dose produced no marked effect until fifty minutes, when the pain suddenly disappeared, and remained absent during a whole night, a sudden cessation having never previously occurred; and on a fourth occasion, half a grain caused complete removal of pain in twenty minutes, which was maintained all night; and, indeed, after this dose no further pain has occurred of sufficient severity to require special treatment.

In a case of blennorrhagic arthritis with severe continuous pain in both knee-joints, and much swelling there, the pain was much relieved in ten minutes by 1 grain, and for two hours; but on a second occasion, 2 grains produced only slight relief, which, although apparently sufficient to allow the patient to fall asleep in twenty minutes, did not last long, as the sleep was soon interrupted by a return of the pain.

In each of these two cases, even when marked relief from pain was obtained, no effect seemed to be produced on the tender condition of the joints.

In two cases of gastric pain, due to organic disease of the stomach, exalgine was found to give a certain amount of relief.

In the first, that of a woman, J. H., aged 49, the pain was caused by malignant disease. It was most severe during the

evening and night, and was of a "burning" character, with "tearing" and "dragging" sensations during movement, and it usually prevented sleep. One evening she received 1 grain of exalgine while suffering greatly from pain; in ten minutes the pain was lessened, and she soon fell asleep, and slept well for the greater part of the night. On another occasion when the pain, however, was less severe, 1 grain again produced marked relief. In the second case, much pain and tenderness were present in a young patient, I. J., aged 19, suffering from a cicatrised ulcer and catarrh of the stomach. While the pain and tenderness were present, half a grain of exalgine on two occasions gave slight but only brief relief; and on other two occasions, the same dose appeared to give marked relief for several hours.

To conclude this detailed statement of the observations that have been made, in a case of cancer of the mesentery, ten administrations of from 1 to 4 grains each were successful in giving partial relief from severe pain on six occasions, but entirely failed on four occasions; in a case of extensive carcinoma of the liver, 2 grains did not have any effect on the pain on two occasions; in a case of large aneurysm of the descending portion of the thoracic aorta with erosion of several vertebrae, half a grain and 1 grain several times failed to give distinct relief; and in a case of lumbar abscess of long standing, and discharging through a drainage tube, where morphine had for several weeks been subcutaneously injected, three separate administrations of half a grain of exalgine did not affect the pain.

The observations I have briefly described were made on twenty-one patients, and in sixteen forms of disease. The majority of the patients were inmates of the hospital, and I have to thank my resident physician, Dr. Gibson, for the large amount of careful work he has done in connection with the observations. In order to place the results clearly before you, I have summarised them in the following table:—

Disease.	Number of Observations.	Number Successful.	Number Unsuccessful or Doubtful.
Facial neuralgia	8	8	—
Sciatica	10	9	1
Herpetic neuralgia	10	9	1
Neuralgia of arm, in hemiplegia	11	11	—
Locomotor ataxy, 1st case	2	2	—
2nd case	1	1	—
Toothache, 1st case	2	2	—
" 2nd case	2	2	—
" 3rd case	2	2	—
" 4th case	2	—	2
Cardiac angina	2	2	—
Pleuritic pain, 1st case	1	—	1
" 2nd case	4	4	—
Rheumatic synovitis	4	4	—
Blennorrhagic rheumatism	2	1	1
Gastric pain, cancer	2	2	—
" catarrh and cicatrised ulcer	4	2	2
Cancer in abdomen	10	6	4
Carcinoma of liver	2	—	2
Aneurysm of aorta	4	—	4
Lumbar abscess... ..	3	—	3
	88	67	21

The table shows that 88 separate administrations of exalgine were made, that in 67 of them pain was relieved, and that in 21 no distinct benefit was gained. The condition of some of the patients, however, was not one in which the pain that existed was likely to be removed by any substance that did not produce general narcotism; as, for example, that of the patients represented in the three last diseases in the table. The best results, undoubtedly, were obtained in neuralgia; and if we consider separately the observations in that disease, included in the table between "Facial neuralgia" and "Cardiac angina," we shall find that in 52 administrations, 48 were successful, and only 4 unsuccessful. Allowing for fallacies in estimating therapeutic effects where reliance has almost solely to be placed on the statements of patients, these results are satisfactory, and justify the hope that exalgine may take a useful and important place among the remedies by which pain is relieved. Its analgesic power is not a very powerful one, but it has the enormous advantages of being free from the disturbances and inconveniences that are associated with the action of nearly all other pain-subduing agents and from the dangers inseparable from the use of the more powerful of these agents.