NITRO-GLYCERINE AS A REMEDY FOR ANGINA PECTORIS*

By William Murrell, M.R.C.P.

In 1879 Murrell reported that a 1 percent solution of nitroglycerin administered orally relieved angina and prevented subsequent attacks. His classic report is reproduced below. –Eds.

SOME TWENTY years ago a controversy took place in the pages of the *Medical Times and Gazette*, on the properties, physiological and therapeutical, of the substance known to chemists as nitro-glycerine. The discussion was opened by Mr. A.G. Field. then of Brighton, who described in detail the symptoms he had experienced from taking two drops of one per cent solution of nitro-glycerine in alcohol. About three minutes after the dose had been placed on his tongue, he noticed a sensation of fullness in both sides of the neck, succeeded by nausea. For a moment or two there was a little mental confusion, accompanied by a loud rushing noise in the ears, like steam passing out of a tea-kettle.

He experienced a feeling of constriction around the lower part of the neck, his forehead was wet with perspiration, and he yawned frequently. These sensations were succeeded by a slight headache and a dull heavy pain in the stomach, with a decided feeling of sickness, though without any apprehension that it would amount to vomiting. He felt languid and disinclined for exertion, either mental or physical. This condition lasted for half an hour, with the exception of the headache, which continued till the next morning. These symptoms Mr. Field described as resulting from a single dose of one-fiftieth of a grain. Thinking that possibly he might he unusually susceptible to the action of the drug, he induced a friend to take a dose. The gentleman experienced such decided effects from merely touching his tongue with the cork of the bottle containing the nitro-glycerine solution that he refused to have anything more to do with it.

A lady suffering from toothache, on whose tongue Mr. Field placed about half a drop of the same solution, experienced a pulsation in the neck, fullness in the head, throbbing in the temples, and slight nausea. The toothache subsided and she became partly insensible, disliking much to be aroused.

When fully sensible she had a headache, but the toothache was gone. Another of Mr. Field's patients, a stout, healthy young woman, accidentally swallowed a small piece of lint dipped in the nitroglycerine, whilst being applied to a decayed tooth. In about five minutes, after feeling giddy and sick, with headache, she became insensible. Her countenance, naturally florid, was unaltered, breathing tranquil, pulse full, and rather quickened. She recovered in about three minutes, after the administration of a stimulant. Some headache was complained of, but the toothache was gone. Mr. Field, in conclusion, offered some suggestions as to the therapeutical uses of the drug, and stated that he had not met with a single well-defined case of neuralgia or spasmodic disease in which it had failed to afford some relief.

This paper was followed by a letter from Dr. Thorowgood, in the main confirmatory of Mr. Field's observations. He, after taking a small dose, experienced "a tensive headache over the eyes and nose, extending also behind the ears, and soon followed by a tight, choking feeling about the throat, like strangulation. Neither loss of consciousness nor nausea was experienced, and a walk by the sea soon did away with the unpleasant feeling."

These statements did not long remain unchallenged, their accuracy being called in question by Dr. George Harley, of University College, and Dr. Fuller, of St. George's. Dr. Harley, having obtained some nitro-glycerine of the same strength as Mr. Field's, commenced his observations by touching his tongue with the cork of the bottle containing the solution. He experienced "a kind of sweet and burning sensation, and soon after a sense of fullness in the head, and slight tightness about the throat, without, however, any nausea or faintness." After waiting a minute or two these effects went off, and Dr. Harley was inclined to think "they were partially due to imagination." Determined, however, as he says, to give the drug a fair chance, he swallowed five drops more, and as this did not cause any increased uneasiness, he took, in the course of a few minutes, another ten drops of the solution.

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Being at the time alone he became alarmed lest he should have taken an overdose, and very soon his pulse rose to above 100 in a minute. The fullness in the head and constriction in the throat were, he thought, more marked than after the smaller dose. In a minute or two the pulse fell to 90, but the fullness in the head lasted some time, and was followed by a slight headache. To two medical friends Dr. Harley administered respectively twenty-eight and thirty-eight drops in divided doses without the production of any symptoms. Some pure nitro-glycerine was then obtained, and of this Dr. Harley took, in the course of a few minutes, a drop, equivalent to a hundred drops of the solution previously employed. The only symptoms produced were a quickened pulse, fullness in the head, and some tightness in the throat: but as these passed off in a few minutes, Dr. Harley considered that they were probably the effects of "fear and imagination."

On a subsequent occasion he took, in the course of three-quarters of an hour. a quantity of the nitro-glycerine solution equivalent to 1991/2 drops of the solution used by Mr. Field, with the production of no more disagreeable symptoms than those he had experienced in his former trials. The quickening of the heart's action he ascribed to fear, but the head and neck sensations were, he considered, "too constant to be attributed to the same cause," although he thought they were exaggerated by the imagination. Dr. Harley, in conclusion, states that he experimented on ten different gentlemen with nitro-glycerine solution, obtained from four different sources, without witnessing any dangerous effects when administered in the above doses: but he adds that, if taken pure, great caution should be used.

In a second communication to the same journal Mr. Field reasserted the correctness of his observations, and maintained that a reasonable explanation of the very different results obtained by different observers might be found in the great variation in strength to which the drug is liable. He considered, too, that the conditions under which the drug was taken had much to do with its action. When the system is worn out by fatigue, he says, it is more likely to act powerfully than when taken under less unfavourable conditions. On the occasion of taking the dose which produced in him such startling effects, his nervous energy had been impaired by an unusually hard day's work. He found that under more favourable conditions he could take the same dose with production of nothing worse than headache.

Having in his experiments on himself experienced the greatest variation in the strength of different specimens of nitro-glycerine, he was disposed to think, on reading the account given by Dr. Fuller and Dr. Harley, that they had used a less powerful agent. He accordingly called on Dr. Fuller, and induced him to take a dose of the solution he had used, hut, to his surprise, he experienced little beyond headache. On the same day Mr. Field administered to a hospital patient suffering from hemicrania two drops of the solution. In about a minute he became pallid, felt sick and giddy, his forehead was covered with perspiration, and he sank on the bed by which he was standing almost unconscious, his pulse failing so as scarcely to be felt. After the administration of a little ammonia the circulation became more vigorous, and in twenty minutes there was a marked diminution of the pain, and he experienced a great desire to sleep, a luxury of which his sufferings had almost deprived him on previous nights. Mr. Field administered small doses of the drug to several other people, all of whom were distinctly affected by it.

Being greatly interested in this curious controversy, and being quite at a loss to reconcile the conflicting' statements of the different observers, or arrive at any conclusion respecting the properties of the drug, I determined to try its action on myself. Accordingly I obtained some one percent solution. One afternoon, whilst seeing. out-patients, I remembered that I had the bottle in my pocket. Wishing to taste it, I applied the moistened cork to my tongue, and a moment after, a patient coming in, I had forgotten all about it. Not for long, however. for I had not asked my patient half a dozen questions before I experienced a violent pulsation in my head, and Mr. Field's observations rose considerably in my estimation. The pulsation rapidly increased, and soon became so severe that each beat of the heart seemed to shake my whole body.

I regretted that I had not taken a more opportune moment of trying my experiments, and was afraid the patient would notice my distress, and think that I was either ill or' intoxicated. I was quite unable to continue any questions, and it was as much as 1 could do to tell him to go behind the screen and undress so that his chest might be examined. Being temporarily free from observation, I took my pulse and found that it was much fuller than

natural and considerably over 100. The pulsation was tremendous and 1 could feel the beating to the very tips of my fingers. The pen I was holding was violently jerked with every beat of the heart. There was a most distressing sensation of fullness all over the body and I felt as if I had been running violently. I remained quite quiet for four or five minutes and the most distressing symptoms gradually subsided.

I then rose to examine the patient, but the exertion of walking across the room intensified the pulsation. I hardly felt. steady enough to perform percussion and determined to confine my attention to auscultation. The act of bending down to listen caused such an intense beating in my head that it was almost unbearable and each beat of the heart seemed to me to shake not only my head, but the patient's body too. On resuming my seat I felt better and was soon able to go on with my work, though a splitting headache remained for the whole afternoon. Were my symptoms due to nervousness or anxiety? Certainly not. I will not say that I discredited Mr. Field's observations, but after Dr. Harley's positive assertions I certainly did not expect to obtain any very definite results from so small a dose.

Moreover, at the moment of the onset of the symptoms I was engaged in the consideration of another subject and had forgotten all about the nitro-glycerine. I did nothing to intensify the symptoms, but, on the contrary, should have been only too glad to have got rid of them. The headache, I can most positively affirm, was anything but fancy. Since then I have taken the drug some thirty or forty times, but I never care to do so unless I am quite sure that I can sit down and remain quit for a time, if necessary. It uniformly produces in me the same symptoms, but they are comparatively slight if I refrain from moving about or exertion of any kind. The acceleration of the pulse is very constant, although sometimes it amounts to not more than ten beats in the minute. The temperature remains unaffected. The pulsation is often so severe as to be acutely painful. It jerks the whole body so that a book held in the hand is seen to move quite distinctly at each beat of the heart.

The amount of pulsation may be roughly measured by holding a looking glass in the hand and throwing the reflection into a dark corner of the room. Before taking the drug the bright spot may be kept steady, but as soon as the pulsation begins it is jerked violently from side to side. I have taken al doses from one minim to ten, sometimes simply dropped on the tongue, at others swallowed on sugar or in water. I have not ventured to take more than fifteen minims in a quarter of an hour. Once or twice a ten minim dose has produced less pulsation than I have experienced at other times in a single drop: but then with the larger quantity one is careful to avoid even the slightest movement. After a five minim dose I usually experience a certain amount of drowsiness – a lazy contented feeling, with a strong disinclination to do anything.

Thinking there might be individual differences of susceptibility to the action of nitro-glycerine, I have laid my friends and others under contribution and have induced as many as possible to give it a trial. I have notes of thirty-five people to whom I have administered it, twelve males and twenty-three females; their ages varying from twelve to fifty-eight. I find they suffered from much the same symptoms as I did, although it affects some people much more than others. Of the numbers above quoted, only nine took minim doses without experiencing decided symptoms. Women and those below par are much more susceptible to its action than are the strong and robust.

A delicate young lady, to whom, adopting Mr. Field's suggestion, I administered it in drop doses for the relief of neuralgia, experienced very decided effects from it, each dose producing a violent headache lasting from half an hour to three hours. A married woman, aged thirty-five, took one minim with very little inconvenience, but was powerfully affected by two. She was obliged to sit down after each dose and was positively afraid to move. It made her hot and caused such a beating in her head that she had to support it with her hands. She experienced a heavy weight on the top of the head and also a sharp darting pain across the forehead, which for a moment or two was very painful to bear. A friend, who, for some days took four drops every three or four hours, informs me that at times it affected his head "most strangely."

The pulsation was very distressing and often lasted an hour or more, being intensified by moving. It has relieved him of an old-standing facial neuralgia, and he is enthusiastic in its praise. A young woman, aged twenty-nine, complained that after every dose of the medicine – one minim – "it seemed as if the top of her head were being lifted off " and this continued sometimes for five minutes and sometimes longer. The medicine made her bewildered, and

she felt sick. A patient with a faint apex systolic murmur was ordered one minim in half an ounce of water four times a day. He took two doses, but it caused “such a beating, thumping, hot pain” in his head that he was unable to continue it.

A young man who was given nitro-glycerine in mistake for phosphorus said it made his temples throb, and he could see his pulse beat so distinctly that he was frightened. It caused a burning: and flushing in his face, and “took every bit of strength away.” This would last for twenty minutes or half an hour after each dose. There was no headache. That alarming symptoms may be produced by large doses, is shown by the following case. A woman, aged fifty-one, was ordered drop doses of the one per cent solution every four hours. This was taken well, and at the expiration of a week the dose was doubled. No complaint being made, it was then increased to four minims, and after a time to six. The patient said “the medicine agreed with her,” and even leading questions failed to elicit any complaint of headache or the like.

After the medicine had been taken continuously for five weeks the dose was increased to ten minims. The patient then stated that the medicine no longer agreed with her; it made her sick after every dose and took her appetite away. She always vomited about five minutes after taking the medicine, the vomiting being immediately followed by headache. The medicine made her “go off in a faint” after each dose. She had three “fainting fits” in one day and could not venture to take another dose. She became quite insensible and once remained so for ten minutes.

Each fainting fit was “followed by cold shivers,” which “shook her violently all over.” Her husband and friends were greatly alarmed, but she thought on the whole it had done her good. She had never noticed that the medicine produced drowsiness. In another case a three minim dose taken on an empty stomach caused a feeling of faintness; “everything goes dark,” the patient said, “just as if I were going to faint.” The patient could take the same dose after meals without the production of any unpleasant symptoms. Drowsiness is not an uncommon result of taking nitro-glycerine.

From a consideration of the physiological action of the drug and more especially from the similarity existing between its general action and that of nitrite of amyl, I concluded that it would probably prove of service in the treatment of angina pectoris, and I am happy to say that this anticipation has been realized.

As a preliminary step I was anxious to obtain a comparative series of sphygmographic tracings. . . . Judged by the sphygmographic tracings, the effects of nitrite of amyl and of nitro-glycerine on the pulse are similar. Both drugs produce a marked state of dicrotism and both accelerate the rapidity of the heart’s action. They differ, however, in the time they respectively take to produce these effects. The full action of the nitro-glycerine is not observed in the sphygmographic tracings until six or seven minutes after the dose has been taken. In the case of nitrite of amyl, the effect is obtained in from fifteen to twenty seconds after an inhalation or a dose has been taken on sugar. The influence of the nitrite of amyl is extremely transitory, a tracing taken a minute and a half after the exhibition of the drug being perfectly normal. In fact, the full effect of the nitrite of amyl on the pulse is not maintained for more than fifteen seconds. The nitro-glycerine produces its effects much more slowly; they last longer and disappear gradually, the tracing not resuming its normal condition for nearly half an hour. The effect may be maintained for a much longer time by repeating the dose.

Nitro-glycerine is more lasting in its power of producing a dicrotic form of pulse heat, and consequently in cases where the conditions of relaxation and dicrotism are desired to be maintained for a space of time, its exhibition is to he preferred to that of nitrite of amyl.

During the last nine months I have treated three cases of undoubted angina pectoris with nitro-glycerine with what success the cases themselves will show.

William A---. aged sixty-four, first came under observation in December, 1877, complaining of intense pain in the chest, excited by the slightest exertion. It was distinctly paroxysmal, the patient being perfectly well in the intervals. The first attack was experienced in September, 1876. Patient was at the time in his usual health and was, in fact, out for a day’s pleasure in the country. The pain seized him quite suddenly when walking. It was a most severe attack-as severe a one as ever he experienced in his life. It caused both him and his friends great alarm and they were most anxious that he should return home at once. He cannot tell at all what brought it on; he had been enjoying himself very quietly; it was not by any means a cold day, and he had not been running, or even walking faster than usual. He remained perfectly well until the

following April when he experienced another similar attack and since then he has been suffering from them with increasing frequency. From September, 1877, they have been a source of constant anxiety and it was only by a determined effort that he could continue to follow his occupation.

The attacks usually commence with a feeling of warmth, then, of heat, and then of burning heat in the chest immediately followed by a heavy pressure, from the midst of which proceeds an acute pain, so that in a moment the whole chest seems as if it were one mass of pain. It is almost impossible, he says, to describe it for he never felt anyting like it before. The pain is first experienced at a small spot on either side of the sternum, corresponding to its junction with fourth costal cartilages. From the chest the pain flies to the inner side of the arm at a point midway between the shoulder and the elbow. It runs down as far as the elbow, but never to the fingers. It is not more severe on one side than the other.

During the seizure the patient suffers most acutely and feels convinced that some day he will die in an attack. He usually experiences some shortness of breath at the time, but there is no feeling of constriction about the chest. He can speak during the seizure, though with some difficulty. The attacks are not accompanied by any sensation of warmth or chilliness, but patient is under the impression that he grows pale at the time. These attacks are induced only by exertion in some form or other, most commonly by walking, and especially by walking fast. Walking up hill is sure to bring: on a seizure. Stooping down has a similar effect and the act of pulling on the boots will excite a paroxysm almost to a certainty.

He is almost afraid to stoop down and when he wants to pick up anything from the floor he goes down on his hands and knees. He has a slight cough, but although it shakes him at times, it never brings on the pain. The attacks are not excited by food, but exercise taken after meals is more likely to induce them than when taken on an empty stomach. Patient has noticed that they are far more readily excited immediately after breakfast than at any other period of the day.

There could be no possibility of doubt respecting the diagnosis. It was a typical uncomplicated case of angina pectoris.

Patient was placed for a week on infusion of quassia in order that he might be observed and also to eliminate the effects of expectation. It need hardly be said that he derived no benefit from this treatment. He was then ordered drop doses of the one per cent nitro-glycerine solution in half an ounce of water three times a day. At the expiration of a week he reported that there had been a very great improvement.

The attacks had been considerably reduced in frequency and for two or three days he had had only one attack in the morning after breakfast. The attacks, when they did occur, were much less severe. He found, too, that a dose of medicine taken during an attack would cut it short. He had tried it several times, and it had always succeeded. It would not act instantly, but still very quickly so that the attacks were considerably shortened. He was thoroughly convinced that the medicine had done him good and said he was better than he had been since first he had the attacks.

Patient had adopted the plan of carrying his medicine with him in a phial and taking a dose if an attack seized him in the street. It never failed to afford relief.?

Medical Humor

Doctor: I have some bad news and some very bad news.

Patient: Well, might as well give me the bad news first.

Doctor: The lab called with your test results. They said you have 24 hours to live.

Patient: 24 hours! That's terrible! What could be worse? What's the very bad news?

Doctor: I've been trying to reach you since yesterday.