TREATMENT OF HÆMOPTYSIS BY NITRITE OF AMYL.

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IN a recent article Dr. W. E. Dixon reviews the drugs most commonly used in this country for internal hæmorrhage, and shows that most of them—namely, “the tannins, adrenalin, digitalis and its allies, ergot, veratrine, barium, and lead—are all worse than useless for hæmoptysis.”¹ He concludes that morphia “will probably do more good than any other drug,” but speaks favourably of calcium chloride. He omits, however, any mention of the drug which, in the opinion of those who have used it, is by far the most powerful pulmonary hæmostatic of all—namely, nitrite of amyl.

The considerations which led to the employment of nitrite of amyl in hæmoptysis were almost solely physiological, and therefore *a priori*, or deductive. It was recognised—(1) that one essential factor in the pulmonary hæmorrhage was the existence at the bleeding-point of a certain intravascular pressure; (2) that this intravascular pressure might be reduced passively “by a fall of pressure in the left auricle, due to diminished resistance in the aortic outflow” (Shäfer²); and (3) that the resistance in the aortic outflow might be precipitately diminished through the promotion of widespread vaso dilation of the systemic periphery by means of inhalation of nitrite of amyl. Before the clinical test, then, it was anticipated that this therapeutic procedure would be followed by an immediate retardation, if not a cessation, of the bleeding. But, in accordance with the notoriously fleeting action of the drug, it was not anticipated that this result would prove of great practical utility.

In 1903 I published two cases of hæmoptysis (one mitral, one phthysical) treated by inhalation of this drug.³ These, so far as I can discover, were the first published cases so treated. Subsequently seven more cases (all phthysical) were published by me.⁴ In April, 1905, Professor Rouget published ten cases.⁵ In May, 1905, Dr. Horace C. Colman published one case.⁶ Early in the same year Professor

¹ Dixon, W. E., *Lancet*, March 24, 1906, p. 826 *et seq.*

² Schäfer, “Text-book of Physiology,” vol. ii., p. 150, Edinburgh and London, 1900.

³ Hare, F., *Australasian Medical Gazette*, October, 1903.

⁴ Hare, F., *Australasian Medical Gazette*, February, 1904. *Lancet*, August 20, October 1, and November 19, 1904; January 21, 1905. *Clinical Journal*, March 22, 1905.

⁵ Rouget, *Société Médicale des Hôpitaux de Paris*, April 20, 1905.

⁶ Colman, H. C., *Scottish Medical and Surgical Journal*.

Pic began to use the drug, and his cases, together with others by Leclerc, Lemoine, Mouisset, and Bourland, were published by the last-named in a graduation thesis, dated the following November.¹

Taken together, these various articles include about sixty attacks of hæmoptysis occurring in thirty-three patients. All the attacks were treated by inhalation of nitrite of amyl, and in every instance except one the bleeding ceased, or became reduced to a mere staining of the sputa, immediately—that is, within a minute or so. In the single exception published by myself the bleeding was greatly reduced, but continued for ten minutes, ceasing spontaneously. I have now no doubt that a larger dose—the dose given did not exceed 5 minims—or a second inhalation would have been completely successful. I cannot find recorded nor have I heard of any instance of complete failure, or a second instance of partial failure. In some of the published cases the hæmoptysis is referred to as profuse or even violent; in some it had continued for days, in spite of complete rest, morphia hypodermically, ergotin, chloride of calcium in large doses, ipecacuanha pushed *ad nauseam*, dry cupping, and the use of ice internally and externally.

Besides the above published cases, many others have been reported privately to me. Dr. C. Reissmann, physician in charge of the Kalyra Sanatorium, and of the department for advanced cases in the Adelaide Hospital, South Australia, fully confirms the action of the drug. He directs that all patients in both the institutions in his charge who have had, or may be expected to have, hæmoptysis should carry the drug about with them for instant use. This plan has now been in use for the last three years at the Jubilee Sanatorium and the Diamantina Hospital for Chronic Diseases in Queensland.

It has been stated that “the cessation of hæmorrhage after the exhibition of a drug is in itself no proof that the effect was produced by the drug.”² This is doubtless true of the majority of drugs, more especially, of course, of those which act tardily. But it is obviously untrue of nitrite of amyl. The cessation of hæmoptysis after the exhibition of nitrite of amyl is definite proof that the effect was produced by the drug, for, as just stated, the effect is practically immediate and practically constant.

In a moderately severe case of hæmoptysis there is a definite periodicity in the expectoration of blood. The blood accumulates in the damaged lung tissue and bronchial passages up to a certain point, then cough is induced, and the accumulation expectorated. This recurs at short intervals. The time of election for the administration of the inhalation is immediately after the expectoration of a mouthful of blood. When so administered, the mouthful preceding the inhalation

¹ Bourland, “Traitement des Hémoptysies par le Nitrite d’Amyl,” Lyon, 1905.

² Dixon, W. E., *Lancet*, March 24, 1906, p. 828.

is the last of the series; it is then seen that the bleeding has ceased synchronously with the flushing of the face. The succeeding cough brings up merely blood-stained mucus or muco-pus, and in the majority of cases even this staining rapidly ceases.

The duration of the subsequent freedom from bleeding came as a distinct surprise. Taking the nine cases published by myself, in five there was no recurrence; but in one of these—a very advanced case, in which there had been free hæmorrhage for some days—the patient died from exhaustion a few hours later. In four there was recurrence. In one of these the recurrence took place in half an hour; this marked the shortest period of freedom recorded. In the three remaining cases the recurrence was delayed for several or many hours, and, as already pointed out, was promptly stopped by a fresh inhalation. Whatever the duration of the reduction of blood-pressure induced by nitrite of amyl, it must, I think, be conceded that—in many cases, at least—it is sufficiently prolonged to permit of adequate coagulation at the site of the lesion.

There is obviously room for considerable variation in dosage. In my own published cases the treatment was, of course, tentative. For the most part 3-minim capsules were given; no single inhalation contained more than 5 minims. Such dosage probably errs on the side of caution. Professors Rouget, Pic, and others have frequently given 9 or 10 minims without disquieting result. It would seem that the dose should vary within the limits specified directly with the severity of the bleeding.

Most of the advantages of nitrite of amyl inhalations are obvious, and have been dwelt upon by the writers quoted in this article. They comprise—accessibility; safety and facility of application and reapplication even in the absence of skilled assistance; rapidity, constancy, and duration of action; and general applicability from the absence of all known contra-indications. But there is a further advantage, less obvious perhaps, but none the less important. Before using the nitrite I had in most cases of severe hæmoptysis used morphia hypodermically. Morphia acts as a respiratory sedative, markedly diminishing cough; and this action undoubtedly tends to the cessation of pulmonary hæmorrhage. But the blood already effused is more or less retained in consequence. Under the thermal and microbic conditions obtaining in the ulcerated lung tissue the retained blood tends to decompose, and thus not rarely is set up septic pneumonia, high temperature, and prolonged exhausting illness. The result may be fatal; but in any case the patient is put far back on the road to convalescence, along which under modern treatment he may have made great advance. In my experience the incident of hæmoptysis, not dangerous in amount, has thus proved a grave misfortune for many phthisical patients; but with nitrite of amyl

the septic danger is avoided. It is the influx of blood to the ulcerated lung tissue which is checked, not the efflux from the air-passages; nor does the drug interfere in any way with coughing. Hence the blood already effused is rapidly got rid of. Conformably, in none of my own cases was there the least subsequent additional rise of temperature; the interruption in the usual hygienic routine did not exceed a few days.

Until quite recently the mechanism of the action of nitrite of amyl already suggested has remained unquestioned; the drug has been supposed to act solely through a passive reduction of the pulmonary blood-pressure. But from a series of laboratory experiments, Soulier, Pic, and Petitjean have been led to claim that this undoubted indirect action is not the only, nor even the chief, hæmostatic action exerted.¹ The experiments were made on curarized dogs of from 15 to 20 kilograms in weight. The anterior portion of the chest wall is removed, and life maintained by artificial respiration. The lung thus exposed exhibits the normal rose colour. One cubic centimetre of nitrite of amyl is then injected into the isolated femoral vein. Quickly white patches commence to form on the lung. These increase in size, coalesce, and soon cover the whole surface: the lung has become exsanguine. The process commences ten seconds after the femoral injection. The exsanguine condition endures, with an intensity which is often extreme, for several minutes before it begins to lessen; nor does the lung resume its normal rose colour for from seven to ten minutes after the injection. No reactionary hyperæmia ensues.

The intensity of the pulmonary anæmia is gauged by the following experiment: Some seconds after the injection the lung tissue is snipped with scissors. Usually profuse hæmorrhage follows such an injury, but in the case of the dog under the influence of nitrite of amyl no single drop of blood issues from the wound. The action of the drug is so energetic that the observers compare it to that of an Esmarch's bandage applied to the lung. Further, they point out that it is obviously indicated in all wounds of the lung parenchyma, whether occurring in war, in the duel, or accidentally.

The above laboratory observations undoubtedly explain the duration of the hæmostatic action in cases of hæmoptysis. But Soulier, Pic, and Petitjean claim that they demonstrate also that nitrite of amyl causes, not only vaso-dilation of the systemic periphery with secondary anæmia of lung tissue from fall of blood-pressure, but also a direct concurrent vaso-constriction of the pulmonary periphery. And in further confirmation they assert that the passing anæmia of the lungs

¹ *Comptes rendus hebdomadaires des Séances de la Société de Biologie*, January 20, 1906, p. 131; also *Lyon Médical*, February 18, 1906, p. 309 *et seq.*; and thesis by Georges Bourland, entitled, "Traitement des Hémoptysies par le Nitrite d'Amyl," Lyon, 1905.

coincides with an actual rise of blood-pressure in the pulmonary trunk artery, as shown by careful manometric observation.

Whether or no the experiments quoted necessarily bear the above interpretation, I am myself incompetent to judge; but if they do—if it be accepted that nitrite of amyl checks hæmoptysis by inducing, *inter alia*, an active, energetic pulmonary vaso-constriction—it must not be forgotten that the vaso-dilation of the systemic periphery, and the consequent fall of blood-pressure, remain important factors in the hæmostasis; otherwise it would be impossible to explain the fact now amply demonstrated that nitrite of amyl operates quite as rapidly, though perhaps not quite so powerfully, to check hæmorrhage from many parts of the systemic circulation. Inhalation of the drug may completely stop the normal menstrual flow;¹ it is capable of checking menorrhagia for many hours together;² and it has proved successful in the reactionary hæmorrhage following removal of parovarian cysts, and in the hæmorrhage from ruptured extra-uterine gestation.³

¹ Hare, Francis, M.D., "Medical Treatment of Deep-seated Hæmorrhage," *Lancet*, August 20, 1904, p. 524.

² Colman, Horace C., M.D., "Treatment of Menorrhagia, etc.," *Scottish Medical and Surgical Journal*, May, 1905, p. 390.

³ Moss, C. A. F., M.D., "Nitrite of Amyl in Gynæcology," *Lancet*, October 14, 1905, p. 1107.