

THE INFLUENCE OF SCOPOLAMIN-MORPHIN NARCOSIS ON METABOLISM *

F. M. BARNES, JR., M.D.

BALTIMORE

During the course of some studies of metabolism it was desired to bring about a moderate grade of anesthesia in order that a diagnostic lumbar puncture might be made possible, and for this purpose a mixture of scopolamin (hyoscin), hydrobromate and morphin (sulphate) was given subcutaneously a short time before the operations were carried out.¹ It is stated² that morphin and several of its derivatives when given in therapeutic doses will cause no alteration in the respiratory metabolism, while conclusions concerning the protein metabolism are at variance, some observers having found an increase and others a decrease in the intensity. In either case the variation seems to have been quite slight. With atropin and several of its congeners, however, a somewhat more definite result seems to have been obtained. De Stella,³ after long-continued small doses of scopolamin, noted in four experiments on rabbits and dogs that there occurred a decrease in not only the volume of the urine, but also in the content of nitrogen, phosphorus and chlorin. These experiments do not seem to be entirely conclusive, and it was determined to employ the drugs as usual and to keep watch for any effect on the metabolic functions.

The accompanying table picturing that portion of the investigation particularly related to the administration of the drugs is composed of the results obtained from the observation of five individuals, the first four of whom were subjects of undoubted paresis. The fifth was a healthy man, 23 years of age, employed as a nurse, who willingly offered his services for experimentation. The histories of the patients are not of importance in this consideration, with the exception that in the two cases (those of P. L. F. and R. B. S.) scopolamin-morphin had been given almost daily

* From the Clinical Laboratory of the Sheppard and Enoch Pratt Hospital.

1. In order to perform a lumbar puncture for the purpose of diagnosis in these patients it is desirable and generally necessary to administer some sedative medicine to allay the attacks of motor restlessness and irritability to which persons with general paresis are so frequently subject. The effects of the drugs thus administered for diagnostic and therapeutics measures are recorded here in so far as the metabolic functions are concerned.

2. Von Noorden: *Pathologie des Stoffwechsels*, ed. 2, 1907, ii, 775.

3. De Stella: *Ibid.*, 1907, ii, 807.

TABLE SHOWING EFFECT OF SCOPOLAMIN AND MORPHIN ON METABOLISM

24 hours ending 7 a. m., Vol- 1909, uue. Date. In c.c.	Sp. Gr.	Total.	Urea.		Nitrogen		Creatinin.		Uric Gm. %	Acid. Gm. %	Rest. Gm. %	Total.	Sulphur		Ethereal.		Chlorine.		Phos- phorus. Gm. P ₂ O ₅ .	Remarks.	
			Gm.	%	Ammonia. Gm. %	Gm. %	Gm. %	Gm. %					Inorganic. Gm. %	%	Gm.	%	Gm.	%			NaCl.
4/19 2300	1015	12.10	0.87	7.13	0.40	3.27	0.07	0.57	2.07	0.25	10.58	2.46	R. N. H.—Paresis.	
4/20 1510	1019	10.49	0.61	5.73	0.45	4.23	0.10	0.90	2.25	0.20	8.88	1.85	82.14	0.20	8.88	2.48	Hyoscin, gr. 1/75; morphin, gr. 1/4 at 2:00 p. m.	
4/21 1090	1026	10.71	0.48	4.46	0.39	3.63	0.10	0.93	2.21	0.20	9.00	1.88	84.60	0.13	5.85	2.26	Hyoscin, gr. 1/75; morphin, gr. 1/4 at 2:00 p. m.	
4/22 3120	1024	12.84	10.43	80.31	1.49	11.47	0.38	2.93	0.06	0.42	0.48	3.70	0.32	11.55	2.45	88.45	0.00	0.00	15.16	2.93	
4/19 2050	1021	15.21	0.64	4.16	0.50	3.24	0.15	0.98	3.02	0.25	8.28	2.64	87.38	0.13	4.31	11.07	3.73	P. L. F.—Paresis. Hyoscin, gr. 1/100; morphin, gr. 1/4.
4/20 1260	1028	14.64	12.56	85.41	0.69	4.69	0.52	3.54	0.16	1.09	0.51	2.47	0.33	10.36	2.66	83.52	0.19	5.97	7.56	4.02	Hyoscin, gr. 1/75; morphin, gr. 1/4 at 4:30 p. m.
4/21 920	1031	12.84	0.51	3.93	0.43	3.31	0.13	1.00	2.99	0.28	9.35	2.57	85.84	0.14	4.68	7.18	3.38	Hyoscin, gr. 1/100; morphin, gr. 1/4 at 1:45 a. m., 1:00 p. m. and 10:00 p. m.
4/22 965	1029	13.14	11.13	84.59	0.53	4.03	0.38	2.89	0.14	1.06	0.96	7.30	0.24	8.88	2.34	86.58	0.12	4.44	7.53	2.80	Hyoscin, gr. 1/100; morphin, gr. 1/4.
5/ 3 1990	1021	17.75	15.21	85.18	0.56	3.14	0.63	3.53	0.14	0.78	1.41	7.90	0.37	7.56	3.06	85.71	0.24	6.72	12.74	4.40	E. J. D.—Paresis.
5/ 4 1500	1022	14.49	12.68	87.50	0.48	3.32	0.54	3.73	0.13	0.90	0.66	4.55	0.27	9.13	2.52	85.18	0.16	5.44	10.50	3.53	Hyoscin, gr. 1/75; morphin, gr. 1/4 at 3:30 p. m.
5/ 5 1675	1022	18.85	16.07	86.17	0.64	3.39	0.59	3.13	0.16	0.85	1.39	7.37	0.39	9.04	3.34	83.83	0.28	7.03	9.71	3.87	
5/17 1670	1019	12.90	0.58	4.50	0.40	3.10	0.10	0.77	2.83	0.24	8.47	2.37	83.66	0.22	7.77	11.02	2.77	R. R. S.—Paresis.
5/18 1890	1018	13.47	12.01	89.11	0.59	4.38	0.43	3.19	0.07	0.52	0.37	2.75	0.29	10.85	2.25	83.15	0.13	4.86	11.34	2.67	Hyoscin, gr. 1/75; morphin, gr. 1/4 at 3:00 p. m.
5/19 1440	1017	10.92	9.42	86.19	0.47	4.30	0.34	3.11	0.04	0.37	0.65	5.95	0.24	7.92	2.08	86.65	0.13	5.41	7.20	2.46	Hyoscin, gr. 1/75; morphin, gr. 1/4 at 12:30 a. m., and 1:30 p. m. Cheyne-Stokes respiration during p. m.
5/20 1400	1021	13.99	0.53	3.78	0.44	3.14	0.11	0.79	2.56	0.28	10.94	2.12	82.81	0.16	6.25	9.52	2.80	
7/12 880	1040	17.49	13.74	78.47	0.53	3.03	0.78	4.43	0.14	0.80	2.29	13.08	0.42	12.04	2.86	82.24	0.20	5.69	8.80	4.73	R. W.—Normal—Nurse.
7/13 890	1039	16.98	0.52	3.06	0.78	4.57	0.13	0.76	3.50	0.39	11.07	2.88	82.29	0.23	6.63	9.08	4.61	
7/14 940	1041	19.78	0.67	3.37	0.93	4.72	0.16	0.73	4.14	0.46	11.06	3.45	83.23	0.23	5.57	9.21	5.24	Hyoscin, gr. 1/100 at 4:45 p. m.
7/15 475	1043	10.68	0.28	2.66	0.51	4.73	0.08	0.78	2.17	0.22	9.96	1.79	82.67	0.16	7.21	4.47	2.29	

* Three duplicate determinations.

for months preceding these observations. The other two patients (R. N. H. and E. J. D.) had had only very occasional doses of these drugs, and none at all for several months past. During these observations it so happened that the scopolamin-morphin was given during two successive twenty-four hours, with the exception of the one patient (P. L. F.) to whom it was given daily to allay excitement and motor restlessness. The hour of giving the drugs, together with the amount, is indicated in the table.

The plan of the work and the analytical procedures employed have not differed essentially from those previously described as used in this laboratory.⁴ A liquid diet (the Folin milk and egg diet) prepared in the laboratory was taken throughout each of these separate periods. The collection of the urine began on the fourth morning after beginning the diet. Patients were kept in bed during the period of observation and were constantly under the watch of special nurses. The nurse experimented on engaged in the usual routine duties of the ward, with the exception of the evening when he was given the scopolamin.

The tabulation of the results makes patent the influence of the narcotic mixture, and only a few general points call for further textual notice. The narcotic effect of the drugs was evidenced in a fairly uniform manner so that, with the exception of one patient (E. J. D.), in whom only a decided drowsiness ensued, a profound sleep of from four to five hours was produced. The nurse who received the scopolamin alone showed an entirely different train of symptoms, which will be more fully mentioned later. It may be seen at a glance that the two patients (R. N. H. and E. J. D.), who had not been more or less accustomed to the drugs by frequently repeated doses, show very sharply the action of a single dose in so far as the urine and its several constituents are concerned. In the first instance (R. N. H.) a definite drop in almost every urinary constituent is evident, and this is perhaps even better shown in the other patient (E. J. D.). Such daily variations of so extensive degree have not been noted in the cases of paresis similarly studied, in which the drugs have not been administered. In these two patients on the day following the scopolamin-morphin there is to be noted an increase in the various urinary bodies, which in general gives amounts that are slightly higher than those of similar bodies on the days before the drugs were given. This increase, however, is not enough to compensate fully for the reduction following the giving of the drugs.

4. Barnes: A Study of the Metabolism of Two Atypical Cases Related to the Dementia Præcox Group, *Am. Jour. of Insanity*, 1909, lxxv, 593. ,

When one examines the figures obtained from the other two observations on the patients (P. L. F. and R. B. S.) it is found that the same regularity of variation in the amounts of the different urinary constituents is not present in relation to the time of the administration of the drugs. The first patient (P. L. F.), during the four days of the observation, received in all six doses of the drug mixture; and, of these, three were given on the third day of the period (April 21). The second patient (R. B. S.) was given three doses in all during the entire period, and all of these during the twenty-four hours ending May 19. Although there is, in general, more irregularity shown in the influence of the drugs on the urinary secretions, there is one point which seems quite clearly shown in the table; that is, on those days during which three doses of the drugs were given there occurred a decrease in the excretion directly analogous to that which has been observed in the other two patients when only one dose was given, and, further, it is seen that this reduction is not so quickly recovered from, and that on the next day the amounts are still lower than might be expected. This is particularly true with the first patient (P. L. F.) and is not so entirely unexpected in accordance with the other results here obtained, as he received more of the drugs. In the other case it is to be noted that the volume of the urine particularly remains low, whereas the other constituents show a definite tendency to resume former levels. The points above indicated in these two cases would seem to show that in individuals who have become accustomed to these drugs by frequently repeated doses given over a long period of time some form of tolerance is produced which makes necessary the use of larger quantities of the drugs in order to bring about conditions of metabolism which occur with smaller doses when given to individuals not possessing such resistance from custom.

In none of these four cases was there noticed any especially constant disturbance of the relative amounts of the various urinary constituents, although there is shown a slight tendency toward an unequal variation. This is seen in the slight elevation of the nitrogen, phosphorus and sulphur ratios.

The outward action of the scopolamin alone on the nurse was opposite to that of the scopolamin-morphin on the patients; instead of drowsiness or sopor, a distinct elevation of function was occasioned. This was evidenced by motor restlessness and activity within a few minutes; soon unsteadiness in walking and general confusion of psychic processes were easily determinable. Within half an hour after the injection was made the nurse was put to bed and there remained until the following morning. For the succeeding hour and a half after going to bed there was present a

condition not entirely dissimilar to a mild delirium, during which a conglomeration of pseudohallucinatory experiences and incomplete delusions, largely resultant from disturbances within the scope of the visual apparatus, together with an uncertain ability in personal identification, occurred. By 9 o'clock nearly all of these symptoms had vanished, although sleep did not occur until 1 o'clock the next morning. The sole unpleasant result of the experiment was the thirst following the wearing away of the effect of the drug. The results of the urinary analysis for these twenty-four hours show an increase in output which is not less interesting than the extraordinary decrease of the following day.⁵ These daily variations are far too extensive to be entirely accidental. With several other "normal" persons on whom similar studies of metabolism have been made in this laboratory no such results have been obtained. The ratios, which in the four patients showed some tendency to variability, were not affected in this experiment, except that on the last day they were somewhat lower than previously. In general, there was in this individual an effect almost the exact opposite of that produced by the drugs given the four patients. Instead of the initial drop there occurred an increase followed by a fall.

Can these apparently divergent results be brought into accord? In this connection it is necessary to bear in mind that all four of the patients received sufficient of the two drugs to bring about a depression of activities, whereas the nurse was given the scopolamin alone, and this resulted in a state of mild excitement. Individual idiosyncrasy must be given due consideration, and especially in this instance, as the nurse reports that, although he has had no experience with drugs, he is particularly susceptible to alcohol, and small quantities will produce effects quite similar to those here noted to have followed the administration of the scopolamin.

The most striking point thus far met is that with the patients there is a decreased output through the kidneys coincident with a varying grade of outwardly apparent depression of general activities, while with the nurse the opposite state obtains. Certainly it is suggestive that these results may be due in part to secondary factors, whether the given individual is in a state of activity or rest. At least, in these experiments the parallelism between the degree of activity and the variation in the urinary findings seems most direct. The four patients were in bed throughout the entire period of observation, but were frequently restless and

5. Although this last day at first suggests some loss of material, I feel quite certain that all urine voided during the twenty-four hours is here represented. This experiment would no doubt have been of more complete value if continued for at least another day, but this could not be done.

uneasy, perhaps because previously they had been allowed to be up and about and could not accommodate themselves sufficiently well to the enforced rest necessitated by these studies. When the drug was in effect, even this restlessness was annihilated. On the other hand, the nurse was engaged with his routine duties up to the moment the hyoscin was given, and the added abnormal activity which this occasioned persisted for several hours. It has been shown,⁶ however, that when the diet contains a sufficient amount of carbohydrates and fat the protein metabolism is not appreciably altered by muscular activities. The diet used here conforms to these requirements and, therefore, it is necessary to throw aside this factor as a possible explanation of the variations in the protein metabolism as found in these observations.

Whatever may be the cause or the specific manner in which the variations in the urinary constituents were produced, there has been apparently some interference through the action of these drugs with one or more steps at some point in the process of metabolism which has led to a general deviation from the normal in the amounts of the various urinary bodies as determined in these analyses. And the very fact that this deviation, whether an increase or the reverse, has been such that the usual ratios have not been changed, would seem to indicate that the force in effect has been of such a nature and has been applied at such a point as to occasion a retardation (or acceleration) of the metabolic processes at a stage at which all elements would be influenced equally. Looking at the question from this point of view, the following possibilities need to be considered:

1. There may have been some delay in the processes of absorption from the alimentary tract.
2. There may have been a variation in the intensity of tissue metabolism.
3. An interference with the elimination of normally formed products may have occurred.

That there may have occurred some delay in the absorption seems possible. The effect of morphin alone on the intestinal movements has been known for some time, but the work of Magnus has added much to this knowledge. Magnus⁷ has shown that morphin causes a very high grade of retardation in the passage of food along the alimentary canal and that after the administration of morphin food remains in the stomach

6. Wait: Experiments on the Effect of Muscular Work on the Digestibility of Food and the Metabolism of Nitrogen, U. S. Dept. of Agric., O. E. S. Bull. 117, 1902, p. 40.

7. Magnus, R.: Die stopfende Wirkung des Morphins, Arch. f. d. ges. Physiol., 1908, cxxii, 210.

many hours longer than is normal. Such a stasis of the food would lead to a delay in absorption which would very probably cause a decrease in the amount of food metabolized, and this in turn would show itself in a decrease in the output of metabolic products during the period over which the drug was in action. And yet the reduction on the days when the drugs were given is not so very extensive—not so much as one might expect from the enormous delay that Magnus has shown to occur as the result of morphin alone. This suggests that the scopolamin may exert some antagonistic action, so that the full effect of the morphin is not brought into action. The effect of the scopolamin alone on the nurse might offer additional weight tending to corroborate this suggestion. Whether or not it would be justifiable to accept this, it seems that without doubt the effect of morphin in producing delayed absorption from the alimentary tract is one of the most important and prominent factors in explaining the deviation of metabolism as found in this study.

A decrease in the tissue metabolism is the second stage at which a general action of the drugs might be looked for. It would not be expected that a variation that would affect the metabolism of nitrogen would occur at this point; and, although such may be the case, there is no tangible evidence to support the conclusion that any of the metabolic processes were here interfered with so as to cause such variations in the urinary output as have been found.

The action of morphin on the intestinal movements would perhaps be of considerably more importance in considering the elimination of normally formed metabolic products through the feces. The slowing of bowel evacuations due to morphin was not particularly well marked in these cases. Unfortunately, as the feces were not divided into twenty-four-hour periods corresponding to the times when the urine was collected, the determination of the average daily output of the fecal constituents for the whole period of the experiment would offer no data of value in this connection. On this account these figures are not given here. The action of the members of the atropin group on the secretions in general might lead to the idea that it had exerted some effect on the renal secretion in the case of the patients. Besides the fact that the atropin is not supposed to exert directly much effect on the kidneys, however, we have the diametrically opposite effect produced in the nurse to whom the scopolamin was given alone. It is notable, too, that with the nurse the water content of the urine was but very slightly increased, so that the enormous relative increase in the amounts of the other constituents cannot be due to a flushing-out action of a sudden, large increase in the amount of the urine voided. That the entire variation may not be

imputed to an incompletely emptied bladder, it might be stated here that with all of the patients it was deemed advisable to use the catheter frequently in order to avoid, as far as possible, errors from this source. The third patient (E. J. D.), for instance, in whom the decrease is exceedingly clearly shown on the second day, was catheterized both during the twenty-four hours and each day exactly at the time of ending of the period.

In the patients the decrease noticed was not merely a return to normal from a level already heightened by some unknown process incident to the diseased state. That this is true is seen in the fact that the amounts of the various urinary constituents excreted before the drugs were given is in most instances already decidedly lower than that which is considered the "normal" for this particular diet. With the nurse the amounts were definitely higher than this normal for the twenty-four hours during which the drug was administered.

CONCLUSIONS

Although generalizations cannot be drawn with final security from so limited a series of observations, it seems that the points brought out by these observations justify the following conclusions:

1. Scopolamin-morphin when given together in sufficient quantity and when leading to a depression of activities cause a decrease in the absolute amounts of nearly all of the normal constituents of the urine.
2. Scopolamin alone, when it leads to an elevation of activities, causes an increase of such constituents.
3. The increase or decrease affects all constituents about equally.
4. The effect of both drugs together or of the scopolamin alone is shown transiently not more than twelve hours and perhaps less, and on the day following the administration of the drugs the variation is partly counterbalanced by an increase or decrease, as the case may be.
5. Repeated doses of both drugs together over a long period of time will lead to a form of tolerance.
6. The influence on metabolism, as indicated by the variations in the urinary secretion, seems due to an indirect and secondary action of the drugs. The retardation of absorption from the alimentary tract is considered the prime cause for the variations found in the urine during these studies.