Diffusion Anoxia:

A Critical Reappraisal

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Arterial blood gas changes were studied in 18 healthy spontaneously-breathing patients during the change from breathing approximately 79 per cent N_2O–21 per cent O_2 to breathing air. Normal patients who awoke without respiratory irregularity or depression maintained Sa_{O_2} values above 90 per cent, and usually above 93 per cent. If respiratory irregularity or obstruction occurred during breathing of air then significant desaturation values, *i.e.*, below 90 per cent, were found, which lasted only as long as the period of obstruction. Likewise, such desaturation can occur readily in patients whose Pa_{O_2} values are low (approximately 70 torr) while breathing room air. The authors conclude that the entity of "diffusion anoxia" does not exist as a clinically significant phenomenon in healthy patients who maintain normal ventilation. The clinical usefulness of administering 100 per cent O_2 during the first few minutes of awakening from N_2O is discussed.

FINK[1] directed attention to the phenomenon of "diffusion anoxia" which occurs at the termination of N_2O–O_2 anesthesia when the patient begins to breathe room air. Because N_2O is more soluble than N_2 in the blood, the excretion of N_2O into the alveoli is greater than the uptake of N_2 from the alveoli into the blood; the resultant dilution of alveolar O_2 by N_2O causes arterial O_2 desaturation, with an average maximum decline of 8 per cent. However, it was pointed out by Rackow, Salanitre and Frumin,[2] in a carefully controlled study of N_2O excretion in artificially ventilated patients, that this fall could not be attributed to alveolar O_2 dilution alone, since such a decrease in Sa_{O_2} would require a far greater N_2O dilution of alveolar O_2 than could be accounted for by the measured alveolar N_2O concentrations. Their study also showed that in healthy patients the average decline in Sa_{O_2} due to N_2O excretion alone was 2–3 per cent during the first 15 minutes of excretion. They also postulated and demonstrated experimentally a dilution of alveolar CO_2 as well as O_2, and suggested that the diminution in the volume of ventilation inspired—as the expired volume remained constant—also contributed to the observed drop in Pa_{O_2}. However, Fink's study, conducted under conventional clinical conditions but with less precise techniques than are now available, has received far more attention than the study by Rackow *et al.* Techniques for blood gas analysis now available permit more accurate appraisals of Pa_{O_2} and Sa_{O_2} than were possible in either of the above-mentioned studies. It appeared useful, therefore, to reappraise the role of N_2O excretion, as well as other factors in the production of postanesthetic hypoxia in spontaneously-breathing patients.

Methods

Eighteen patients without histories or clinical evidence of cardiopulmonary disease, who underwent a variety of surgical operations, were anesthetized with an N_2O–O_2 mixture for at least 90 minutes. Twelve were intubated with the aid of succinylcholine, and N_2O–O_2 anesthesia was supplemented with halothane; three patients also received *d*-tubocurarine or succinylcholine subsequent to intubation. Flow rates of N_2O and O_2 into the semiclosed system were adjusted so that during the last 30 minutes of anesthesia the inspired O_2 concentration was approximately that of room air and the total flow of the mixture was at least 8 l/min. Precautions were taken to insure a smooth transition from N_2O–O_2 to air breathing. In all instances but one, the patients were

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TABLE 1. Arterial O_2 Saturation (Per Cent) in Patients Changing from Breathing N_2O–O_2 to Breathing Air*

Patient	Minutes											
	−3	−1	1	2	3	4	5	7	10	15	20	60
1	94	94	92	92	93	92	93	92	91	93	93	—
2	95	95	94	92	92	93	91	92	93	94	93	—
3	95	96	93	93	94	95	95	95	96	95	95	—
4	96	97	96	96	94	97	93	93	96	97	96	—
5	96	96	95	95	94	95	95	93	95	95	94	94
6	97	97	96	94	96	96	96	96	96			98
7	98	98	97	97	97	97	97	97	98			98
8	95	94	91	89	89	90	89	88	90			96
9	95	95	95	91	91	92	92	92	92			93
10	97	97	95	94	*94*	96	*96*	*96*	*96*	97	97	97
11	98	97	—	95	97	96	*89*	*86*	*88*	93	92	96
15	96	96	96	*87*	*91*	—	*87*	97	95	95	95	—
16	96	96	96	90	91	*92*	*85*	92	97	95	96	96
17	98	94	90	*85*	94	92	93	90	93	92	95	96
18	98	97	*92*	95	*95*	*96*	97	96	96	97	97	—

* − 3 and − 1 = minutes before change; all other values refer to minutes after change. Patients 1–9 = no respiratory obstruction. Patients 10, 11, 15–18 = respiratory obstruction at some time. Values given in italics were obtained during respiratory irregularity or obstruction. Patients 12–14, see figure 2.

extubated while breathing N_2O–O_2, the mask reapplied, and the anesthesia maintained by mask for not less than ten minutes. This was done to minimize or eliminate irregularities of respiration during the recovery due to the presence of the endotracheal tube. The mask was removed only after respiration had returned to a regular rhythm and pattern, the volume of spontaneous respiration appeared clinically adequate, supplemental agents such as halothane had been discontinued and, in two instances where *d*-tubocurarine had been used, atropine and prostigmine had been given i.v. to reverse the neuromuscular block. Nevertheless, in some instances respiratory irregularities from various causes did occur during the transition to air breathing; the data for these eight patients were treated separately.

Arterial blood samples were drawn anaerobically from indwelling needles into heparinized syringes and analyzed for P_{O_2}, *p*H and P_{CO_2} using the Radiometer electrode system incorporating a Radiometer Clark P_{O_2} electrode, E5046; a Radiometer Severinghaus P_{CO_2} electrode, 5036; and a Radiometer *p*H electrode. When blood samples were being analyzed, the P_{O_2} and P_{CO_2} electrodes were calibrated using a 20 per cent glycerin solution through which was bubbled an O_2–CO_2 mixture from a gas mixing pump whose output had been calibrated by the Scholander technique. When gas was being analyzed, the electrode was exposed directly to the output of the mixing pump. All samples were analyzed at 37 C and it was assumed that the patient temperature was also 37 C except in four patients (6–9) in whom rectal temperatures were measured and the appropriate corrections carried out. The majority of the samples were analyzed within five minutes after withdrawal. Duplicate P_{CO_2} measurements agreed within 1 torr, and P_{O_2} measurements (below 150 torr) also varied less than 2 torr. In the few instances when analysis was delayed, the samples were stored under ice for as long as two hours until the analysis could be carried out. In this laboratory, samples with Pa_{O_2} values between 30 and 90 torr treated in this manner showed decreases of not more than 2 torr during four hours of such storage. Samples were drawn three minutes and one minute before the resumption of air breathing and then 1, 2, 3, 4, 5, 7, 10, 15, 20, and occasionally 60, minutes after the resumption of air breathing.

A gas sample was drawn from the inspiratory limb of the circle system shortly before the mask was removed and was analyzed with the electrode system for P_{O_2}. Sa_{O_2} was calculated from Pa_{O_2} and *p*H values, using the blood gas calculator of Severinghaus [3] and assuming a blood temperature in the body of 37 C. In the periods just before and after resumption of breathing air, the occurrence of coughing, vomiting, retching, breath-holding or any irregularity in respiration was noted and was then correlated with the blood gas findings. Depression of ventilation was assessed using the Pa_{CO_2} values.

Results

The patients were divided into three groups. The first group, patients 1 to 9, (a) had no respiratory irregularities at any time; (b) while breathing N_2O–O_2 had Sa_{O_2} values of 94 per cent or more (table 1); and (c) had Pa_{CO_2} values which rarely exceeded 45 torr (table 2). Pa_{O_2} values during the first five minutes and after 20 or 60 minutes of air breathing are shown in table 3. Sa_{O_2} values of all patients in this group except patient 8 were 90 per cent or greater while they were breathing room air. Patient 8, while breathing N_2O–O_2 with a PI_{O_2} of 160 torr, had a Pa_{O_2} of 74 torr and, after breathing room air for one hour, had a Pa_{O_2} of only 71 torr. The results in patient 7, who showed the maximum fall in Pa_{O_2}, are shown in figure 1.

TABLE 2. Ages, PI_{O_2} and Pa_{CO_2} Values of Patients Changing from Breathing N_2O–O_2 to Breathing Air

Patient	Age (years)	PI_{O_2} N_2O–O_2 (mm Hg)	$Paco_2$ N_2O–O_2 (mm Hg)	$Paco_2$ Air Range (mm Hg)
1	11	142	40	41–43
2	29	149	42	37–40
3	23	—	43	40–47
4	26	160	45	42–48
5	78	158	36	29–34
6	18	131	32	28–36
7	32	156	36	25–33
8	49	160	42	28–39
9	46	—	45	39–44
10	30	133	42	39–43
11	40	—	38	28–40
15	39	160	49	45–47
16	61	147	35	33–38
17	26	153	43	36–45
18	32	178	23	26–31
12	28	151	54	47–55
13	60	210	38	40–60
14	75	160	42	43–42

TABLE 3. Arterial O_2 Tensions (mm Hg) during Change from Breathing N_2O–O_2 to Breathing Air in Patients Who Showed No Respiratory Obstruction

Patient	Minutes of Breathing Air						
	1	2	3	4	5	20	60
1	61	64	66	64	65	65	
2	68	64	64	67	64	68	
3	64	63	70	77	76	78	
4	88	88	74	84	70	88	
5	81	78	71	78	78	76	
6	81	68	79	75	78		88
7	91	84	84	86	89		104
8	60	55	55	56	55		71
9	69	58	58	60	60		62

The second group consisted of six patients (10, 11, 15, 16, 17 and 18) who had occasional bouts of respiratory irregularity during excretion of N_2O. All Sa_{O_2} values during breathing of N_2O–O_2 were 94 per cent or more. Sa_{O_2} values below 90 per cent always were accompanied by obstruction. However, in two patients (10 and 18), even though respiratory irregularities did occur, Sa_{O_2} values were maintained above 92 per cent. When no respiratory irregularities were present, all Sa_{O_2} values were 90 per cent or more as in the group 1 patients.

The third group consisted of three patients, 12, 13, and 14 who had Sa_{O_2} values below 94 per cent while breathing N_2O–O_2 or after 20 minutes of breathing air (fig. 2). In two of these cases (12 and 13), persistent respiratory depression was present, and Pa_{CO_2} values were above 50 torr during most of the excretion period. Although respiratory obstruction was not present in patient 14, she was 75 years old, and her Sa_{O_2} did not exceed 90 per cent during breathing of room air. Ages, inspired P_{O_2} values during breathing of N_2O, and ranges of Pa_{CO_2} values of all patients are given in table 2.

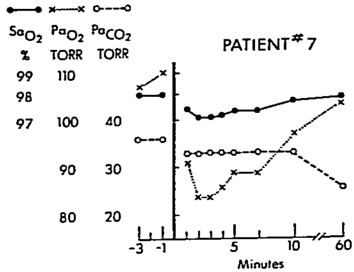

FIG. 1. Pa_{O_2}, Pa_{CO_2} and derived Sa_{O_2} values in patient 7, who showed the largest Pa_{O_2} decrease without respiratory obstruction during the change from breathing N_2–O_2 to breathing air.

Discussion

Three points are suggested by these findings: (1) the entity of "diffusion anoxia" does not exist as a clinically significant phenomenon; (2) normal patients who awaken from N_2O anesthesia without respiratory irregularity or depression do not have any clinically significant degree of arterial O_2 desaturation; (3) respiratory irregularities commonly met during awakening from general anesthesia, such as coughing, straining or soft-tissue obstruction, can cause significant arterial desaturation, but this desaturation is transient and lasts only as long as the respiratory irregularity exists.

If diffusion anoxia were, by itself, a clinically significant entity, then the expected changes should have been clearly evident in the subjects in group 1 who had relatively normal control O_2 and CO_2 values and never showed obstruction. The evaluation of these subjects would not have been complicated by the simultaneous occurrence of other causes for hypoxia, chiefly clinical repiratory obstruction or the presence of pre-existing low Pa_{O_2} values which would produce desaturation with small decreases in Pa_{O_2}. If we use as a criterion for significant hypoxia an Sa_{O_2} below 90 per cent, no patient in this group except patient 8 became hypoxic. Patient 8's control Pa_{O_2} of 71 torr placed her values near the sharply-falling segment of the dissociation curve where small P_{O_2} changes produce large saturation changes.

The selection of Sa_{O_2} values of 90 per cent or less as the criterion of clinically significant hypoxia was made arbitrarily. The earliest objective signs of hypoxia appear at a Pa_{O_2} of 60 torr, which under normal conditions will result in an Sa_{O_2} of about 90 per cent. It is also very difficult, if not impossible, to appreciate clinical cyanosis with any confidence above 90 per cent Sa_{O_2}. In any case, it is a reasonable value, and one which was selected before the results of the study were obtained.

Since body temperature corrections for Pa_{O_2} were applied to determinations in only some of the subjects, it is possible that some of the absolute P_{O_2} values given in the remaining samples may be incorrect. However, since body temperature would change only very little during the crucial ten minutes of the study, the error introduced in the Pa_{O_2} values would be systematic and would not affect interpretations based on relative changes. More importantly, there appears to be no significant error introduced in the Sa_{O_2} determinations even if no temperature corrections are made in the Pa_{O_2} measurement. For example, if the blood is drawn while the patient's temperature is 35 C, but the measurements of P_{O_2}, *p*H, and P_{CO_2} are made at 37 C without correcting for this temperature discrepancy, then with an observed *p*H of 7.40, a P_{O_2} of 80 torr and a P_{CO_2} of 40 torr, one would arrive at an Sa_{O_2} of 95.8 per cent. If the temperature corrections are made, the true P_{O_2} would be 69 torr and the corrected *p*H 7.43. The Sa_{O_2} calculated from these values would again be 95.8 per cent. Hence, there is no error in the Sa_{O_2} measurement due to failure to correct for temperature deviations. For this reason, as well as others, we tended to rely more upon Sa_{O_2} values in the interpretation of this study.

When the hypoxia is viewed from the standpoint of Pa_{O_2} changes, only patients 8 and 9 in group 1 had values below 60 torr during the N_2O excretion period. In both cases, the control Pa_{O_2} values—one hour after termination of the anesthesia—were only 71 and 63 torr, respectively, indicating probably persistent significant shunting which might also have occurred early during excretion. This factor appears to have been far more impor-

tant in these two patients than the effects of O_2 dilution. The maximum decrease in Pa_{O_2} usually was observed in the second or third minute of the excretion period (table 3). This time agrees well with the theoretical value of two minutes predicted by Rackow *et al.* They arrived at this figure on the basis of subtraction of an N_2 lung washout curve from the average curve of N_2O excretion during circumstances similar to the present study to arrive at the extent of dilutional N_2O in the alveoli as differentiated from N_2O originally present there at the beginning of the washout period, which does not contribute to dilutional hypoxia. They predicted that the maximum decrease in $P_{A_{O_2}}$—and hence, Pa_{O_2}—should be about 20 per cent of the initial value, and thus the maximum expected decrease in $P_{A_{O_2}}$ and Pa_{O_2} would be 20 torr from a conventional normal control value of about 100 torr. Table 3 shows that, using as control the 20- or 60-minute Pa_{O_2} values, changes as great as 20 torr were seen in patients 6 and 7, but the changes were usually smaller, with a range of 4 to 16 torr, in the balance of the subjects. The results in patient 7, who had the largest decrease in Pa_{O_2} are shown in figure 1. It is interesting to note, again in confirmation of the prediction by Rackow *et al.* from considerations of the dissociation curve, that since patients 6 and 7 had control Sa_{O_2} values of 97 and 98 per cent, then at the time of the maximum Pa_{O_2} drop of 20 torr, their lowest Sa_{O_2} values were 94 and 97 per cent, respectively.

In summary, 103 samples were drawn from these 15 subjects during the first ten minutes of N_2O excretion. Sixteen were taken during some degree of respiratory irregularity, leaving 87 samples for consideration of dilutional hypoxia uncomplicated by respiratory irregularity. Of these, only four showed Sa_{O_2} values below 90 per cent; these four all occurred in patient 8, who had a control Pa_{O_2} of only 71 torr and whose Sa_{O_2} values were only 88 and 89 per cent during the excretion period. Hence, we conclude that the entity of "diffusion anoxia" does not exist as a clinically significant phenomenon in normal healthy patients without respiratory obstruction.

The transient hypoxia (Sa_{O_2} below 90 per cent) noted in the patients in group 2 was in each instance associated with some respiratory irregularity, and the persistent hypoxia in two of the group 3 subjects also was associated with persistent ventilatory depression. This relationship of lowered Sa_{O_2} to hypoventilation rather than to N_2O diffusion into the alveoli also is supported by the trend toward increased Pa_{CO_2} which accompanied the lowered Sa_{O_2}. As Rackow *et al.* pointed out, when N_2O diffuses into the alveoli both the alveolar O_2 and CO_2 should be diluted, and one should observe a trend toward decreased Pa_{CO_2} along with the decreased Pa_{O_2}. However, if respiratory obstruction caused the hypoxia, Pa_{CO_2} should rise as Pa_{O_2} falls: this was indeed observed in all such instances in the patients in group 2. Whenever Pa_{O_2} or Sa_{O_2} decreased, Pa_{CO_2} rose between 2 and 8 mm Hg when compared with the Pa_{CO_2} value just before

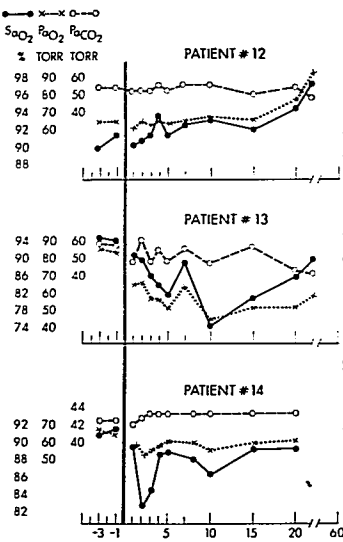

FIG. 2. Pa_{O_2}, Pa_{CO_2} and derived Sa_{O_2} values in patients who had either ventilatory depression (elevated Pa_{CO_2}) or low control Sa_{O_2} values before changing from breathing N_2O–O_2 to breathing air.

the obstruction. In no instances did Pa_{CO_2} decrease as Sa_{O_2} decreased.

The ventilatory factor in producing hypoxia was particularly evident in patient 12, who had extensive plastic surgery on the neck and was still depressed from halothane, and in whom a clear airway could not be maintained after extubation even with manual assistance. Her Pa_{CO_2} persisted at 54 mm Hg for almost 20 minutes, during which time Sa_{O_2} values were at their lowest level (90–93 per cent). At 60 minutes, when spontaneous ventilation was adequate and unobstructed, Sa_{O_2} reached 97 per cent and Pa_{CO_2} fell to its lowest value.

Patient 14 demonstrates a significant aspect of blood oxygenation which, if ignored, could result in an incorrect generalization about the role of N_2O diffusion in producing significant reductions in Sa_{O_2} values. This 75-year-old woman showed no gross respiratory irregularities and had normal Pa_{CO_2} values throughout her recovery. Yet, her Sa_{O_2} values were all below 90 per cent; 83–85 per cent after the first two minutes and 89 per cent after 20 minutes, when the effects of N_2O dilution upon alveolar O_2 must have been negligible. Pa_{CO_2} was at its lowest, 51 mm Hg, after two minutes, and was 59 mm Hg after 20 minutes. If we assume that the difference of 6 per cent in Sa_{O_2} or 8 mm Hg in Pa_{O_2} between the two- and 20-minute samples was due to O_2 dilution by N_2O, then this corresponds to a 12 per cent dilution of alveolar O_2 by N_2O at a time when one would see the maximum dilutional effect. However, a similar 12 per cent change in Pa_{O_2} would only cause a 1 per cent change in Sa_{O_2}, if the control value were in the region of 96 per cent Sa_{O_2}. Elderly patients commonly have low "normal" Sa_{O_2} values.[5] In such situations, small degrees of alveolar dilution would produce similar small changes in Pa_{O_2} but large changes in Sa_{O_2}. Although the ages of the patients are not listed in Fink's study, his illustrative protocol (patient MR) closely resembles the findings in patient 14 of the present series. At least three others of his eight patients also resemble our patients in that the highest Sa_{O_2} at any time during breathing of N_2O–O_2 or air was 91 per cent. It is reasonable to assume, therefore, that our patient and some of Fink's patients had "normal" Sa_{O_2} values of approximately 90 per cent while breathing room air, and that the sharp fall in O_2 saturation was due primarily to the positions of these samples on the O_2 dissociation curve, which tends to exaggerate Sa_{O_2} changes in relation to Pa_{O_2} changes. When control Sa_{O_2} values are approximately 95 per cent or higher and the observed decreases in O_2 saturation are large, the fall in Pa_{O_2} required to account for this desaturation on the basis of dilution alone is manifestly unreasonable. For example, a 5 per cent alveolar dilution and a corresponding 50 mm Hg fall in Pa_{O_2} would have been required to produce the Sa_{O_2} fall from 98 to 89 per cent which Fink reported in subject SA.

Without reviewing here the principles and supporting data presented by Rackow *et al.* their report demonstrated that when the average control Sa_{O_2} value was 97 per cent, the average decrease in Sa_{O_2} was 2 to 3 per cent, which corresponds to changes in Pa_{O_2} as high as 20 mm Hg. In the present study, when greater changes in O_2 saturation occurred they were clearly due to respiratory irregularity and, importantly, were transient and limited to the period of inadequate ventilation or had occurred in patients who had "normal" Sa_{O_2} values of about 90 per cent.

Even though we agree with the logical concept developed by Fink that N_2O diffusion at the termination of N_2O–O_2 anesthesia will dilute alveolar O_2, the degree of alveolar dilution caused by N_2O diffusion in healthy patients produces only inconsequential changes in Pa_{O_2} and Sa_{O_2}. The present study was not designed to test the various facets of N_2O excretion in the same manner that Rackow *et al.* did, but, more importantly, did evaluate the phenomenon in a common clinical setting of spontaneously-breathing patients awakening from N_2O anesthesia. The recent development of electrode techniques for accurate and reproducible P_{O_2} and P_{CO_2} determinations made it advantageous to repeat the previous studies, which were carried out before the techniques were generally available, and thereby to reassess quantitatively the effect of N_2O diffusion.

One result of Fink's work has been the widespread clinical practice of administering

100 per cent O_2 to patients for at least five minutes before discontinuing N_2O–O_2 anesthesia. The results of this study should not be interpreted as making this practice unnecessary or undesirable. Although "diffusion anoxia" does not exist as a clinical entity, hypoxia may occur in the immediate postanesthetic period, either because of respiratory irregularity or because of ventilation–perfusion changes which occur as part of the aging process or for other reasons and which result in low "control" Sa_{O_2} values. In either instance, the breathing of high concentrations of O_2 will eliminate or reduce considerably any hypoxemia which would result from such causes.

The authors thank Jordan D. Smith, B.S., for technical assistance.

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Drugs

ISOPROTERENOL The effects of isoproterenol infusion (.005 to .006 mg per minute) were studied in anesthetized dogs. Blood pressure decreased from 150 to 100 mm Hg. Vertebral artery flow increased from 50 to 150 ml per minute. Left circumflex coronary artery flow increased from 50 to 75 ml per minute. Aortic blood flow increased from 4.0 to 4.8 l/min. Vascular resistance decreased 58 per cent in the left coronary artery, 70 per cent in the vertebral artery, and total resistance decreased 45 per cent. Cardiac work increased 27 per cent; cardiac output increased 58 per cent; and coronary perfusion increased 94 per cent. The changes are considered to be due to beta-adrenergic receptor stimulation and vasodilatation. Similar results were obtained when animals were given norepinephrine and phenoxybenzamine simultaneously. (*Dedichen, H., and Schenk, W. G.: Hemodynamic Effects of Isoproterenol Infusion, Arch. Surg. 97: 934 (Dec.) 1968.*)

PHYSOSTIGMINE Physostigmine salicylate in doses of one to two mg administered parenterally was found to be an effective antidote to intoxication with centrally-active anticholinergic agents. Confusion, agitation, hallucinations, stupor, ataxia, dysarthria, and other symptoms were reversed promptly in 26 consecutive patients in whom toxic reactions developed after they received scopolamine, atropine or drugs for Parkinson's disease. Physostigmine deserves a place in therapeutics as an antidote to anticholinergic intoxication. (*Duvoisin, R. C., and Katz, R.: Reversal of Central Anticholinergic Syndrome in Man by Physostigmine, J.A.M.A. 206: 1963 (Nov.) 1968.*)

IMIPRAMINE INTOXICATION A 2½-year-old boy died as a result of cardiovascular complications of imipramine hydrochloride overdosage. Through a direct toxic effect on the myocardium, imipramine lowers myocardial contractility and cardiac output, with resultant hypotension. Cardiac arrhythmias are also a constant feature of imipramine toxicity. Since there is no specific antidote to imipramine, treatment of overdosage with this drug must be directed at its life-threatening circulatory and respiratory manifestations if the patient is to survive. (*Sacks, M. H., and others: Cardiovascular Complications of Imipramine Intoxication, J.A.M.A. 205: 588 (Aug.) 1968.*)