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A Study of the Myocardial Depressant Factor and Its Relative Influence in Drug/Alcohol Mortality

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ABSTRACT: A shock factor, a low molecular weight peptide, has been isolated from postmortem blood. High levels of this peptide, which depresses the myocardium, were seen in cases where drug overdose or alcoholism, or both, were the cause of death. An elevated myocardial depressant factor (MDF) level was also demonstrated in a fire victim and a patient in cardiogenic shock. The peptide analysis was accomplished by using an isolated cat papillary muscle followed by paper chromatographic confirmation. Postmortem electrolytes, alcohol, and various toxic agents were eliminated as causes of myocardial depression in the isolated cat papillary muscle assay. The presence of elevated MDF levels may be significant in the overall death process.

KEY WORDS: pathology and biology, cardiovascular system, death

Death is generally not the sudden event we often assume it to be. There are progressive biochemical determinants involved in the deteriorative process that ultimately terminates life. For quite some time researchers have entertained the possibility that a toxic factor, a myocardial depressant factor (MDF), exists in the blood [*1*]. In cases of irreversible shock, this low molecular weight peptide acts as a depressant to the heart [*2*]. This study deals with the implication that elevated MDF may be significant in the overall death process.

The level of MDF was measured in a variety of postmortem blood samples from medical examiner's cases in which death was attributed to sudden infant death syndrome, acute congestive heart failure, myocardial infarction, acute and chronic alcoholism, accidental fatal injury, or toxic substance ingestion.

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Experimental Procedure

Sample Preparation

Blood samples (100 mL) were collected from 250 victims at autopsy (by aortic transection and cardiac puncture). These samples were immediately centrifuged at 10 000 rpm for 20 min. In cases that showed hemolysis, or when death had occurred more than 4 or 5 h before the autopsy, specimens were discarded. Of the 250 samples drawn, only 65 were suitable for this study.

The suitable serum samples were frozen at −10°C and stored until the MDF could be isolated, which was done within two weeks of the time the samples had been drawn.

The literature suggests two methods of sample preparation; one involves precipitation of large proteins with trichloroacetic acid [3]; the other uses selective membrane filtration [4]. Most samples in this study were processed by the latter method, which took approximately 5 h and was performed in a room maintained at 4°C. All samples were then frozen or assayed immediately following dialysis.

Assay with Cat Muscle

Before each run the "Physiograph"[4] and the force displacement transducer[5] were calibrated so that a 1-g weight produced a 5-cm pen displacement.

Cats of either sex, weighing 2 or 3 kg, were intravenously anesthetized with sodium pentobarbital. The heart was removed and placed in a porcelain dish containing freshly prepared Kreb Henseleit (KH) buffer [5], which was continuously oxygenated with tank-supplied 95% oxygen/5% carbon dioxide at 37°C. Cardiectomy performed in this manner took less than 1 min.

The papillary muscle was removed and mounted in a 10-mL glass-jacketed muscle chamber,[6] containing 10 mL of KH buffer, continuously oxygenated with 95% oxygen/5% carbon dioxide while being maintained at 37°C with a circulating water bath. After the muscle was allowed to equilibrate for a minute or two, the chamber was lowered and two stainless steel pin-type electrodes were implanted in the tissue approximately 1 cm apart. The muscle was then immediately resubmerged in the chamber.

Muscle stimulation was accomplished with an impulse from a stimulator,[7] operating continuously at a rate of 1 pulse/s. In most cases the voltage was 7 V (5 V above threshold). The muscle was then allowed to equilibrate for about 30 min, during which time the KH buffer was replaced with fresh KH buffer at approximately 5-min intervals.

The equilibration period having been completed, the test samples were used to replace the buffer in the chamber. Between each test sample, the muscle was washed and allowed to re-equilibrate with fresh KH buffer. To avoid having all positive samples run on the same muscle, samples were chosen at random from each group. All results were reported in units as described by Lefer et al [2]: 1 U = 1% depression of contractile force when compared to KH buffer.

Paper Chromatographic Assay

Confirmation of the presence of MDF in the test samples was done by paper chromatography according to the method of Leffler et al [6]. The chromatograms were immediately

[4] Grass Medical Instrument Corp., Quincy, Mass., Model P-1A.
[5] Grass Medical Instrument Corp., Quincy, Mass., Model FT-03.
[6] Metro Scientific Inc., Plainview, N.Y.
[7] Harvard Apparatus Co., Dover, Mass., Model 340.

placed between two clean thin-layer chromatography (TCL) glass plates and subjected to densitometry by employing a spectrofluorometer[8] equipped with a TLC scanner.

When the chromatographic scan was completed, the area produced by the density of Spot G was measured by using the standard triangulation method [7].

Statistical Analysis

In a study of this nature, it would be statistically invalid to compare groups where each member of the group died in a different situation. Therefore, each case had to be considered separately for MDF values.

For the collected data to have proper significance, the following protocol was observed: the acute accident death group, where death was instantaneous, was used as a control. The mean and standard deviations of the MDF values were first ascertained in this group. All other samples showing MDF values higher than two standard deviations above the mean of the control group were considered significant.

All graphic representations were subjected to computer analysis to assure the best line fit. Tables 1 through 7 indicate "neg" when the sample was analyzed but found to be negative and "—" when a sample was not analyzed.

Results

Within 4 to 5 min after a sample (containing MDF) was added to the isolated tissue chamber, there was a decrease in papillary muscle contractile force (Fig. 1). In some cases, however, depression did not occur as rapidly, but took as long as 10 min to occur. This depression was completely reversed by replacing the test sample with fresh KH buffer.

TABLE 1—*Postmortem MDF levels in instantaneous deaths caused by acute cardiac failure.*

Case	Age	Sex	MDF, units[a]	Area,[b] cm^2	Toxicology
1[c]	49	m	21	4.4	neg
2[c]	57	m	2	neg	neg
3[c]	53	m	4	neg	neg
4[c]	32	m	8	3.0	neg
5[c]	62	m	12	neg	neg
6	65	m	17	neg	neg
7	54	f	19	2.4	neg
8	46	m	6	2.0	neg
9	46	m	8	neg	neg
10	72	m	14	—	neg
11	60	m	14	neg	neg
12	83	m	17	4.2	neg
13	67	f	7	neg	neg
14	65	m	18	neg	salicylates, 2.5 mg/100 mL in blood
15[d]	45	f	8	—	—

[a] Where 1 unit = 1% depression of contractile force of the isolated cat papillary muscle.
[b] Densitometric area of Spot G from paper chromatogram.
[c] Trichloroacetate filtration.
[d] No autopsy was done.

[8] Farrand Optical Corp., New York, N.Y., Model Mark I.

TABLE 2—*Postmortem MDF levels in victims of acute accidental death (dead on arrival at hospital).*

Case	Age	Sex	MDF, units[a]	Area,[b] cm^2	Cause of Death	Toxicology
16	24	m	0	neg	fractured skull	lidocaine
17	54	f	9	neg	hemothorax	neg
18	13	m	2	neg	massive injuries	neg
19[c]	29	m	10	neg	fractured cervical vertebra	neg
20	19	f	9	—	lacerated aorta	neg
21	28	m	14	10	lacerated aorta	0.17% alcohol
23	23	m	7	neg	fractured skull	neg
24[c]	24	m	4	—	fractured skull	0.24% alcohol
25	25	m	26	14	lacerated aorta	salicylates
27[c]	42	m	7	neg	fractured skull	0.22% alcohol
28	34	m	14	6	fractured skull	neg
Mean	...	...	9.3	3.3	...	...
Standard deviation	...	...	±6.7	±5.1	...	...

[a] Where 1 unit = 1% depression of contractile force of the isolated cat papillary muscle.
[b] Densitometric area of Spot G from paper chromatogram.
[c] Trichloroacetate filtration.

TABLE 3—*Postmortem MDF levels from victims of sudden infant death syndrome.*

Case	Age	Sex	MDF, units[a]	Area,[b] cm^2	Toxicology
39[c]	3 months	m	7	neg	—
40[c]	1 month	m	16	3.0	—
41[c]	6 weeks	m	9	—	—
42	3 months	m	—	neg	—
43[c]	2 months	f	—	neg	—

[a] Where 1 unit = 1% depression of contractile force of the isolated cat papillary muscle.

[b] Densitometric area of Spot G from paper chromatogram.

[c] Trichloroacetate filtration.

Since most of the samples were postmortem specimens, a confirmatory method had to be applied. The large number of samples dictated that the method be relatively inexpensive and minimally time-consuming. The paper chromatographic technique met these requirements and was therefore used.

Multiple spots were eluted from paper chromatograms by the method of Leffler et al [6]. As noted in Fig. 2, most of the MDF activity was seen in Area G. This area, which was ninhydrin-positive, had an R_f value of approximately 0.7 and compared well with the data obtained by Leffler et al.

Densitometric analysis was then applied to the MDF-active area. As noted in Fig. 3, a linear relationship existed between the MDF assayed by the isolated cat papillary muscle technique and the densitometric area produced by Spot G from the paper chromatographic method. The MDF level is plotted versus its corresponding densitometric area of Spot G.

Acute Cardiac Failure

To categorize each case properly, the medical examiner's reports were reviewed with extreme care. The criterion for selecting cases in the acute cardiac failure group was that death had been instantaneous, that is, that there was no indication of a prolonged period between the fatal attack and death.

As seen in Table 1, a majority of these victims were males between the ages of 32 and 83. The MDF activity in these cases ranged from 2 to 21 U, and only 5 of the 15 samples showed ninhydrin-positive areas in the G region of the paper chromatogram. The slight depression seen in the papillary muscle assay was probably due to the differences between the samples' sodium, potassium, and calcium levels and the KH buffer to which they were compared.

Accidental Death

The accidental fatal injury group originally consisted of twelve vehicular-involved deaths and one fall from a roof in which all victims were dead on arrival. Again the criterion for selection was instantaneous or near-instantaneous death as evidenced by a determination of dead on arrival at the hospital or pronounced dead at the scene of occurrence. Two cases were subsequently placed in the miscellaneous group when it was found they had survived for short periods in the hospital (Cases 22 and 26 in Table 6).

As seen in Table 2, a majority of these victims were males between the ages of 13 and 34. The MDF activity in these cases ranged from 0 to 26 U, and only three of the ten cases showed ninhydrin-positive areas in the G region of the paper chromatogram.

TABLE 4—*Postmortem MDF levels in cases of suspected alcoholism.*

Case	Age	Sex	MDF, units[a]	Area,[b] cm^2	Cause of Death	Liver Pathology	Known History
29	41	m	13	3.0	pneumonia	marked fatty	yes
30	38	f	41[c]	25.2[c]	chronic alcoholism	nutritional cirrhosis	yes
31[d]	62	m	0	neg	subdural hemorrhage	marked fatty	yes
32	53	m	51[c]	32[c]	aortic aneurysm	nutritional cirrhosis	yes
33	49	f	63[c]	44[c]	pulmonary embolism	cirrhosis	no
34[d]	62	f	54[c]	42.4[c]	cardiac failure	marked fatty	?
35	51	f	80[c]	54[c]	cardiac failure	marked fatty	no
36	56	f	18	—	pneumonia	nutritional cirrhosis	yes
37	78	m	36[c]	—	cardiac failure	nutritional cirrhosis	yes
38	44	m	7	neg	cardiac failure	marked fatty	yes

[a] Where 1 unit = 1% depression of contractile force of the isolated cat papillary muscle.
[b] Densitometric area of Spot G from paper chromatogram.
[c] Significant, as described in the text; more than two standard deviations above the mean of the control group (see Table 7).
[d] Trichloroacetate filtration.

TABLE 5—*Postmortem MDF levels in deaths by ingestion of a poison.*

Case	Age	Sex	MDF, units[a]	Area,[b] cm^2	Cause of Death
44	55	m	60[c]	42.4[c]	chronic arsenic poisoning
45[d]	27	m	47[c]	30[c]	multiple drug intoxication (benzodiazepine, methadone, secobarbital)
46[d]	39	f	59[c]	41.4[c]	barbiturate intoxication
47	27	m	39[c]	21.6[c]	multiple drug intoxication (methadone, Sinequan®, hydroxyzine)
48	62	f	59[c]	46.2[c]	pneumonia secondary to ingestion of Isotox
49	34	m	64[c]	56[c]	methadone intoxication
50	30	m	47[c]	31.2[c]	drug and alcohol intoxication (propoxyphene, salicylates)
51	35	m	38[c]	28.4[c]	acute arsenic intoxication
52	50	f	—	3.0	amitriptyline intoxication
53[d,e]	24	m	—	18.6[c]	barbiturate and opiate intoxication
54[d,f]	...	...	73[c]	52.8[c]	...
55	82	m	19	3.6	opiate intoxication

[a] Where 1 unit = 1% depression of contractile force of the isolated cat papillary muscle.
[b] Densitometric area of Spot G from paper chromatogram.
[c] Significant, as described in the text; more than two standard deviations above the mean of the control group (see Table 7).
[d] Trichloroacetate filtration.
[e] Antemortem specimen.
[f] Postmortem specimen.

Toxicological analysis revealed the presence of ethyl alcohol in three cases and lidocaine in one case (administered in the ambulance en route to the hospital, where the victim was pronounced dead on arrival). As with the cardiac failure cases, the slight depression seen in the papillary muscle assay was probably due to electrolyte imbalances. The suddenness of death in apparently healthy individuals made this group an optimal choice for use as a control for this study.

Suspected Alcoholism Cases

One of the more difficult categories to classify was that of alcoholism since, in most cases, this factor was not indicated on the death certificate and embarrassed families were reluctant to volunteer this information when giving a history of the decedents' habits and medical past.

To ensure the veracity of this research, the only cases selected for this category were those in which "fatty metamorphosis" or "cirrhosis of the liver" was certified as either a primary or secondary cause of death.

As seen in Table 3, an elevated MDF level was noted in six of the ten cases, and five of these six samples showed strong ninhydrin-positive spots in the G region of the paper chromatogram. The sixth sample was not analyzed chromatographically. Although the electrolytes differed from the KH buffer, they were not significantly altered from those of the control group.

Sudden Infant Death Syndrome

In this still-puzzling type of death, five cases were studied (see Table 4). Autopsy disclosed no pathological findings; toxicological analyses were also negative. Since it was

TABLE 6—*Postmortem MDF level in deaths from miscellaneous causes.*

Case	Age	Sex	MDF, units[a]	Area,[b] cm^2	Cause of Death	Other Findings
22	37	m	14	8	fractured skull	1 h in hospital
26	34	m	44[c]	14[c]	fractured skull	2 h in hospital; lidocaine
56	67	m	4	neg	asphyxia, hanging	—
57	58	f	6	neg	asphyxia, hanging	alcohol, diazepam, salicylates
58[d]	45	m	48[c]	30[c]	acute cardiac failure	3 h in hospital
59[e]	...	...	54[c]	36[c]	...	...
60	55	m	48[c]	—	third-degree burns	24 h in hospital
61	26	m	26	6.4	rheumatic heart disease	—
62	47	f	0	neg	cerebral infarction	—
63	72	m	13	neg	aortic aneurysm	—
64	53	m	0	neg	aortic aneurysm	—
65	68	m	18	—	necrotizing arthritis	—

[a] Where 1 unit = 1% depression of contractile force of the isolated cat papillary muscle.
[b] Densitometric area of Spot G from paper chromatogram.
[c] Significant, as described in the text; more than two standard deviations above the mean of the control group (see Table 7).
[d] Antemortem specimen.
[e] Postmortem specimen.

TABLE 7—*Summary of results.*

Cause of Death	Ratio[a]		Sodium,[b] Mean ± SD	Potassium,[b] Mean ± SD	Calcium,[b] Mean ± SD
	Papillary Muscle	Paper Chromatography			
Acute cardiac failure	0/15	0/15	128 ± 23.6	7.3 ± 3.0	4.3 ± .9
Acute accidental death	control group		110 ± 19.7	6.6 ± 2.4	4.0 ± 1.7
Suspected alcoholism	6/10	5/8	115 ± 18.5	5.6 ± 2.1	4.5 ± 1.2
Sudden infant death	0/5	0/3	—	—	—
Poison ingestion	9/10	10/12	132 ± 16.5[c]	7.1 ± 1.9	4.8 ± 2.1
Burn shock	1/1	1/1	—	—	—
Cardiogenic shock	1/1	1/1	—	—	—
Acute arthritis	0/1	0/1	121 ± 15.8	5.6 ± 1.7	4.3 ± 1.4
Rheumatic heart disease	0/1	0/1	—	—	—
Acute accidental death (in hospital)	1/2	1/2	—	—	—

[a] Ratio of samples showing significant elevation in postmortem MDF to the number of samples tested.
[b] All values are in meq/L.
[c] Significantly different from control group by student's t test ($P = 0.012$).

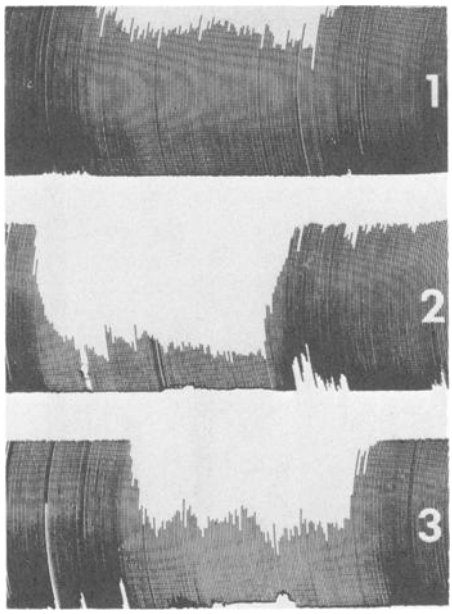

FIG. 1—*Typical physiological tracings of isolated cat papillary muscle response to a sample containing MDF;* (1) *auto accident victim,* (2) *drug overdose case, and* (3) *alcoholic.*

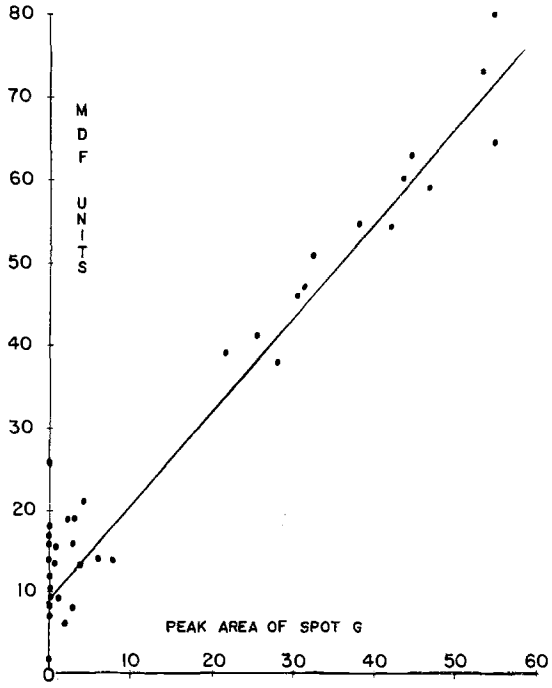

FIG. 2—*Eluates of MDF activity from paper chromatography.*

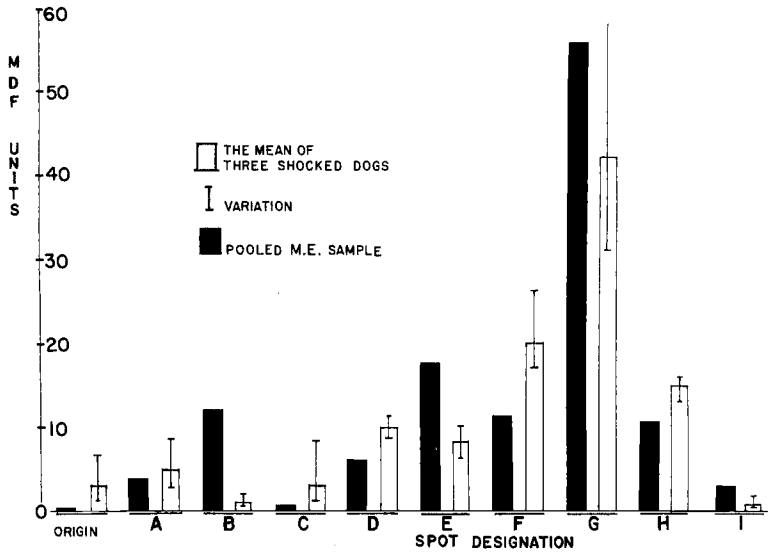

FIG. 3—*Correlation of MDF units obtained by the isolated cat papillary muscle technique with the densitometric area produced by ninhydrin-sprayed Spot G on the paper chromatograms.*

difficult to obtain sufficient quantities of blood from these infants, the isolated papillary muscle technique could be used on only three samples. None of these samples, assayed by either isolated cat papillary muscle or paper chromatographic techniques, showed elevated levels of MDF.

Poisonous Substance Ingestion

Twelve deaths certified as "accidental/suicidal ingestion of toxic substances" were studied (see Table 5). In all but two cases, an elevated MDF level and corresponding paper chromatographic confirmation were seen.

Cases 53 and 54 were of particular interest because they were antemortem (Case 53) and postmortem (Case 54) samples from the same individual. The deceased had been in a coma for ten days prior to death, enabling us to obtain blood specimens drawn upon his admission to the hospital and at autopsy.

Both specimens were assayed. Antemortem blood showed opiates and barbiturates present in toxic concentrations. The MDF was also present, as shown by a ninhydrin-positive spot in the G region of the paper chromatogram. Because there was insufficient serum, MDF activity could not be shown by isolated papillary muscle technique. Postmortem blood showed no evidence of toxic substances. However, the MDF level (ascertained by paper chromatographic technique) was approximately three times higher than it had been in the antemortem specimen. This was confirmed when the isolated papillary muscle assay showed 73 U in the postmortem sample.

To prove that the effect on the papillary muscle assay was not drug- or alcohol-induced, KH buffer containing the toxic compound found in each case was also assayed. The concentration of these compounds was based on previously determined postmortem blood levels. Only butalbital, at 2.3 mg/100 mL of buffer, showed significant depression (16%). Ethyl alcohol depressed the muscle only when its concentration was above 0.30% (v/v), and that depression was only in the range of 10 to 15%.

Miscellaneous Causes

As in all research of this scope, there were certain cases that did not specifically fit into any of the aforementioned categories. The results of these cases are listed in Table 6.

Cases 22 and 26, originally grouped with accidental deaths, were transferred to the miscellaneous causes category when it was ascertained the victims had survived for some time in the hospital after the accidents.

Cases 58 and 59 were drawn from the same person. A 50-mL blood specimen was drawn just prior to the victim's death, which occurred approximately 3 h after admission to the hospital in "cardiogenic shock and coma." The postmortem specimen was drawn 3 h after death occurred.

Assay for MDF by isolated papillary technique, followed by paper chromatographic confirmation, revealed elevated MDF levels in both antemortem and postmortem samples.

Case 60 was a fire victim who survived for 24 h in a hospital burn unit. Postmortem serum showed an elevated MDF level. However, the sample finding was not confirmed by paper chromatography. A summary of all data collected is presented in Table 7.

Discussion

In our study we have isolated a substance with myocardial depressant activity. This substance demonstrates all of the characteristics reported for MDF in the literature [*8*]. The substance we have isolated has a molecular weight of less than 1000, is dialyzable, has the ability to depress the contractile force of the isolated cat papillary heart muscle, chromatographs to an R_f of 0.7 on paper in an acid solvent system, and is ninhydrin-positive. The depression of isolated cat papillary muscle is probably not a result of electrolyte imbalances because the major salt components were not significantly different from group to group even though they differed slightly from physiologic KH buffer (see Table 7).

Our studies also indicated elevated MDF levels in postmortem blood of victims of alcoholism, fire, cardiogenic shock, and poison ingestion. In the cases of alcoholism, elevated MDF values could be a manifestation of pancreatitis since it has been hypothesized that the pancreas is responsible for MDF production [*4*]. Although postmortem examination showed no indication of pancreatic involvement, a definitive diagnostic opinion could be made only if amylase or lipase activity had been determined in the victim's antemortem blood.

The most striking results were obtained from the group of twelve individuals whose deaths were the result of poison ingestion; ten cases showed a marked elevation of MDF levels in postmortem blood samples. This suggests the possibility that chemically induced deaths are not only the result of the ingested substance's toxic effect but also the result of the release of a toxin (MDF) indigenous to the body itself.

Assuming these results will be confirmed by others doing similar research studies (but with a larger sample group), two major toxicological questions may have been answered. The first is, "Why, after all toxic substances have effectively been removed from the victim's circulation, does the victim still die?" and the second is, "What is synergism?"

The answer to the first question: In drug overdose or poison ingestion, the victim's death is the result not solely of drug-induced depression, but rather the progression of ingestion leading to shock, shock leading to pancreatic hypoxia, and pancreatic hypoxia leading to the release of high MDF levels, which, in turn, precludes recovery.

It is possible that, in at least two cases, the initial poison ingestion caused the victim to go into shock resembling (with respect to MDF production) hemorrhagic shock. The depressant effect of the toxic substance could have caused hypoxia to the pancreas, resulting in the release of MDF.

The two illustrative cases are Cases 53 and 54 wherein a patient, comatose with a toxic barbiturate and opiate blood level and presenting a slightly elevated level of MDF in his blood, was admitted to the hospital. After ten days in coma, he died. Postmortem toxicological analysis showed the tissues to be drug-negative, but postmortem MDF levels were almost triple those found in this person's antemortem blood. A similar instance is Case 48, wherein investigation confirmed the patient's intentional ingestion of 112 g (4 oz) of insecticide (Isotox®). Admitted to the hospital in coma, the patient died four days later without regaining consciousness. Postmortem toxicological analysis showed the tissues to be insecticide-negative, but once again MDF levels were significantly elevated. The authors do not mean to imply that MDF actually caused death, but MDF may be of some significance in cases where death is attributed to "brain death."

The answer to the second toxicological question may be that synergism is defined as "the joint action of agents so that their combined effect is greater than the algebraic sum of the effect" [*9*]. In essence, for the toxicologist, the combined effect of *two* depressant agents, each far below lethal concentrations in the tissue, produces death. No one has thus far suggested that three agents might be involved in synergism. This study suggests just that.

One could postulate, at least in the case of depressant drugs, that death is caused not only by the ingested drug's depressing effects but rather by the combined effect of drug depression and decreased cardiac output, which is caused by elevated circulating MDF levels. Though there may be exceptions to this study's conclusions (as in cases of brain anoxia), the MDF demonstrated by this study would appear to have significantly contributed to causing death.

As a result of our findings, it would seem of optimal importance that a faster method be found for determining MDF in both clinical and forensic science situations. It would also appear that the need for further studies (of this peptide) are indicated.

Only studies that include its chemical structure, its pharmacology, and its mode of action will tell us exactly what role MDF plays in our body's life-and-death struggle and further prove that death is generally not the sudden event we often assume it to be.

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