



One Hundred Years of Clinical Toxicology in Florence: The Past and the Present

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Abstract

A survey of one hundred years of activity of the clinical toxicology of Florence is reported. The paper is focused on acute accidental and intentional poisonings, monitoring the changes taking place throughout the years from mercuric chloride to barbiturates and then benzodiazepines and opiates. Data on the improvement of the treatments are reported as well as results on validation of diagnostic and therapeutic protocols for opiate addicts and alcohol diseased patients, which were started in 1973. Acute and chronic intoxications are a mirror of the changes of our society.

Keywords: Mercuric acid; Barbiturates; Benzodiazepines; Opiates; Alcohol

Introduction

In the fall of 1917, about one hundred years ago, a toxicology unit was open within the emergency ward of the 600-hundred-year-old “Arcispedale di Santa Maria Nuova”, the main hospital of Florence, Italy, with the aim to treat, with specific competence, the accidental and intentional poisonings occurring in Florence and province. The unit was and is still manned by the staff of the Institute of Pharmacology with medical qualifications, supported by hospital’s personnel and is currently called Toxicological Clinic of Careggi, University Hospital of Florence. The establishment of a toxicology unit was a consequence of the long-lasting interest for toxicology existing in Florence. A chair of toxicology was established in Florence in 1859 and was held by professor Ranieri Bellini Pisano (1817–1878) who authored a book entitled “Lessons of Experimental Toxicology 1861-1862” (Lezioni di Tossicologia Sperimentale 1861-1862), that, according to Wallace-Hayes [1], is the first textbook of experimental toxicology ever published. After his death, the chair was discontinued but teaching and experimental and clinical research in toxicology continued in the Institute of Materia Medica and Experimental Pharmacology, then Institute of Pharmacology and Toxicology. A chair of toxicology was re-established in 1974.

The existence of accurate, although not homogeneous, records of 100 years of activity of the toxicological unit offers us the unique opportunity to overview the natural history of poisonings in the city of Florence and to draw a statistic on the number and causes of the recoveries. The purpose of this paper is to present them and to describe the changes over time in the agents used for intentional poisoning, from mercuric chloride to barbiturates and then benzodiazepines, the recurring of some accidental poisonings and the sudden, late, explosion of drug addiction. The treatment improvements will be discussed. The changes in the activity of the unit are a mirror of the development of the Italian society and offer a picture of the evolution of medicine in the last century.

Materials and Methods

The information on the activity of the toxicological clinic presented in this paper originates from two types of source. The activity of the years from 1917 to 1964, almost 50 years, is covered by papers published in Italian or German journals, every 3 years, except during the years of Second World War that are included in a paper covering the years 1938 to 1949 [2-13]. The published data were obtained by examining the individual clinical records and document the activity of the clinic and list the toxic agents causing the admissions. The years from 1964 to 1979 are covered by published papers too, while for the following years internal reports only are available [14,15]. Adults of Caucasian race of both sexes from the city and province of Florence represented the totality of the referrals to the clinic until the last decade. Presently, many subjects of different ethnicity are admitted as a consequence of the changes in the Italian population due to immigration. The catchment area of the clinic was

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Table 1: Statistics of admissions in the Toxicological Unit from 1917 to 1964. In parenthesis the number of food-borne infections.

Years	N° totaladmissions	Deaths	N° attempted suicides			Ref
			Tot	♀	♂	
1917 – 19	282	10.9	-	-	-	[2]
1920 – 22	303	-	-	-	-	[3]
1923 – 25	342	9.64	251	179	122	[4]
1926 – 28	441	7.48	302	-	-	[5]
1929 – 31	323	11.18	230	153	77	[6]
1932 – 34	270	10.37	142	97	44	[7]
1935 – 37	272	11.02	133	75	58	[8]
1938 – 40	262	9.16	126	94	32	[9]
1941 – 43	343	7.87	104	84	20	[9]
1944 – 46	338	5.91	72	55	17	[9]
1947 – 49	602 (364)	4.48	174	119	55	[9]
1950 – 52	1396 (640)	0.96	228	-	-	[10]
1953 – 55	1126 (628)	0.79	265	180	85	[11]
1956 – 58	1201 (787)	1.08	291	222	69	[12]
1959 – 64	3483 (688)	0.71	961	711	250	[13]

about 700.000 inhabitants in 1921, it increased to 866.000 in 1961 and to 1.015.000 in 2015 [16]. All subjects referred with symptoms of poisoning or suspected of being poisoned are formally admitted even if the recovery lasts a few hours and a clinical record is drafted. With few exceptions, poisoned children were recovered in the pediatric hospital and are not reported here. In the first decades, very few cases of acute ethanol intoxication were referred to the toxicological clinic and no case of chronic ethanol abuse.

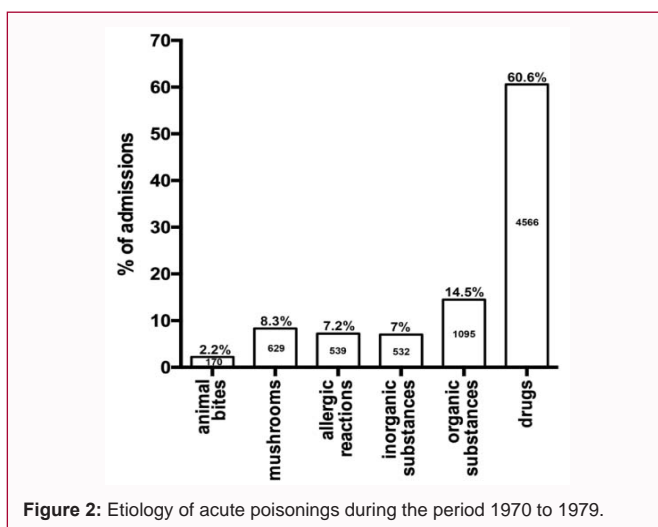
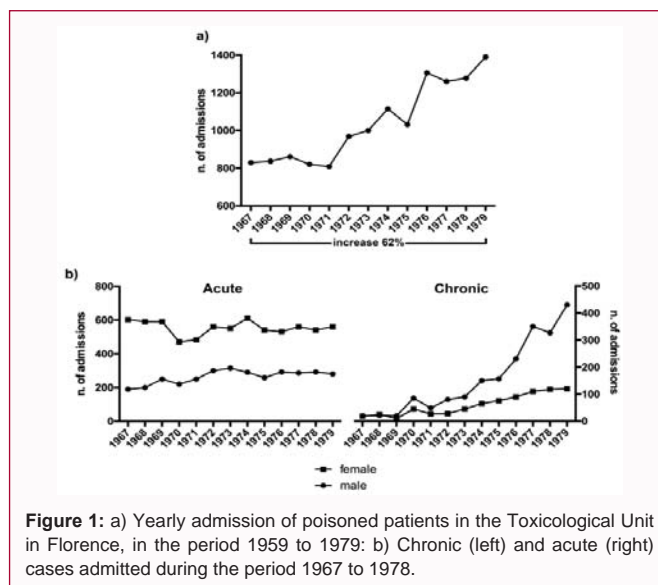
Results

The first 50 years: 1917 to 1967

Number of admissions and poisoning agents: Table 1 shows the total number of cases admitted between 1917 and 1964, the death rate and the number of attempted suicides. The mean number of admissions was about 300 per year from the triennium 1917-1919 to 1944-1946. The sharp increase in the following trienniums was due to the administrative decision to consider “poisoning” the food-borne infections and admit this type of patients to the toxicological clinic. The infections, sometimes collective episodes, were caused mostly by different strains of *Staphylococci* and in a minority of cases by *non-typhoidal salmonellae* [10]. Since 1968, these patients are more properly referred to the Infectious Disease Unit.

Table 2 lists the agents causing frequent admissions such as mercuric acid, barbiturates and mushrooms and a variety of toxic agents and drugs responsible of single or few cases of accidental or voluntary poisonings. In some cases, two or more substances were assumed simultaneously. The mortality was about 10% or more in the first two decades of activity and then gradually decreased to less than 1% in the year's 1959 to 1964 as a result of a shift toward less toxic agents and treatment improvements.

Attempted suicides: In the twenties, the number of attempted suicides was around 70% of total admissions. In 1928, the Fascist government censorship discouraged the press to publicize suicide stories in order to avoid a suggestion/contagion effect. This resulted in a reduction in the number of admissions due to suicide attempts. A



further decrease to 21% of total admissions occurred during Second World War, in the years 1941 to 1946, confirming the well-known observation that suicide rate is lower during wars [17]. The number of attempted suicides began to increase after the end of the war reaching 199 cases in 1964. As previously reported, the number of females attempting suicide was always larger than that of males [17,18].

In the first years of activity of the clinic, suicide was attempted and accidental poisoning occurred mostly with household products available at that time, primarily mercuric chloride that was largely used as a disinfectant. Its ingestion leads to death by renal failure in about 70% of cases. Some intentional, rarely accidental, poisonings with inorganic acids, namely hydrochloric acid and sulfuric acid were admitted every year with unexplained peak in some triennia [2-10]. This poisoning caused 40% mortality [9]. Strict limitations of mercuric chloride sales and the diffusion of low toxicity disinfectants, such as iodine, brought a gradual decrease in the number of cases of mercuric chloride poisoning and in the following decade, they became sporadic. Iodine substituted mercuric chloride as the drug of choice for attempting suicide for a decade during which only one death after iodine ingestion was reported [5]. Iodine was, in turn, gradually substituted by the more appealing but more dangerous

Table 2: The agents most frequently responsible for admission to the Toxicological Clinic. In parenthesis the number of cases.

Years	Agents	Ref
1917 – 19	Mercuric chloride (85), Iodine (65), Inorganic acids (15), Phosphorus (15)	[2]
1920 – 22	Iodine (75), Mercuric chloride (59), Sodium hypochlorite (9), Phosphorus (6)	[3]
1923 – 25	Iodine (85), Mercuric chloride (39), Hypnotics (31), Sodium hypochlorite (18)	[4]
1926 – 28	Iodine (86), Hypnotics (37), Mercuricchloride (30), Sodiumhypochlorite (25), Mushrooms (55), Potassiumpermanganate (20)	[5]
1929 – 31	Hypnotics (49), Iodine (43), Inorganic acids (34), Mercuric chloride (8),	[6]
1932 – 34	Hypnotics (51), Iodine (27), Carbon monoxide (18), Mercuric chloride (11)	[7]
1935 – 37	Hypnotics (37), Mushrooms (27), Sodium hypochlorite (26), Iodine (26), Carbon monoxide (17)	[8]
1938 – 49	Hypnotics (204), Carbon monoxide (147), Sodiumhypochlorite (101), Inorganicacids (56), Iodine (44)	[9]
1950 – 52	Hypnotics (125), Carbon monoxide (65), Sodium hypochlorite (61), Inorganic acids (21)	[10]
1953 – 55	Hypnotics (125), Analgesics (61), Carbon monoxide (61), Sodium hypochlorite (53), Various drugs (53), Mushrooms (30)	[11]
1956 – 58	Analgesics (100), Various drug (100), Carbon monoxide (89), Hypnotics (76), Mushrooms (61), Sodium hypochlorite (57), Tranquillizers (35)	[12]
1959 – 64	Hypnotics (318), Sodium hypochlorite (307), Carbon monoxide (255), Tranquillizers (243), Drug allergy (223), Analgesics (199)	[13]

barbiturates, the “sleeping pills”. Diethyl barbituric acid (Veronal) was the barbiturate most frequently used, followed by phenylethylbarbituric acid (Luminal).

As shown in Table 3, overall barbiturate mortality decreased from a peak of 32% in the triennium 1935 to 1937 to about 1% to 2%, due to an effective therapy with the analeptics metrazol, picrotoxin and antibiotics to prevent the onset of pneumonia. The analeptic therapy versus a purely supportive therapy was matter of an extensive debate and was eventually abandoned [19,20]. In the second part of the fifties the less toxic “tranquillizers”, including chlorpromazine, reserpine, meprobamate, benactyzine and the antidepressants replaced barbiturates [13]. The first antidepressant, the monoamine oxidase inhibitor, iproniazid, was introduced in USA in 1955 followed by imipramine and amitriptyline, the first monoamine reuptake inhibitors, in the early sixties. The problem of self-poisoning with antidepressants in depressed patients with suicidal ideation has accompanied the therapeutic success of these drugs in the treatment of the depressive disease [21,22]. Table 3 lists the CNS drugs used for suicide or involved in accidental overdoses and the number of cases.

Addicting drugs: As shown in Table 3, every year a small number of opiate intoxications was admitted. The opiates included mostly laudanum, followed by morphine and “Pantopon”, a mixture of opium alkaloids. The cause of admission was overdose for attempted suicide or therapeutic errors. No cases of addiction overdoses were recovered in the first 50 years of activity of the clinic. The cases of opiates addiction began in the early seventies [23]. The fashionable

abuse of cocaine, described in several novels at the end of the 19th and in the first part of the 20th centuries, resulted in a small number of overdose admissions in the early twenties [24,25]. Then for a long period until the end of the last century rare cases of cocaine overdose, mostly assumed together with heroin (speedball) were admitted but every year single cases of amphetamine poisoning were seen).

Accidental poisonings: The most common causes of accidental poisoning were carbon monoxide and mushrooms. A small number of admissions for carbon monoxide poisoning, usually accidental, occurred every year but occasionally there was a sharp increase in the number of cases, in concomitance with cold spells, for the improper use of braziers or malfunctioning stoves. Not always, the prognosis was favorable for the delayed neuropsychological sequelae [26]. Mushroom poisonings were admitted every year, sometimes with epidemic episodes. The epidemic episodes and in general most cases of poisoning resulted from the ingestion of mushrooms, belonging to various genera, containing gastrointestinal toxins [27].

A possible explanation for the epidemics is that also some edible mushrooms contain small amounts of poisonous compounds and in some years, mushrooms growth in larger number and their content in gastrointestinal toxins is higher [28]. A small number of cases of *Amanita Phalloides* (death cap) or *Amanita Verna* poisonings was also seen with a high rate of death [29].

In the period 1959 to 1964 [13], a new cause of accidental admission turned up: drug allergies. For many years, drug allergies have been rare events and were defined as drug intolerance. The sudden increase of drug allergies, particularly penicillin allergy, is presumably a consequence of a larger drug consumption associated with the improvement of the economic situation of the country and a better access to the health service.

The last fifty years: 1967 to 2017

Unit admissions and poisoning agents in the period 1967 to 1979: The temporal trend of the acute intoxication in the period 1967-1979 is reported in Figure 1a. The annual admissions for acute and chronic intoxications increased by 62% in the years 1967 to 1979. Interestingly, the number of admissions for acute intoxications did not significantly change in the years 1967 to 1979, while patients affected with chronic poisonings have increased greatly since 1974, mainly due to alcohol and opiate addiction (Figure 1b). The overall

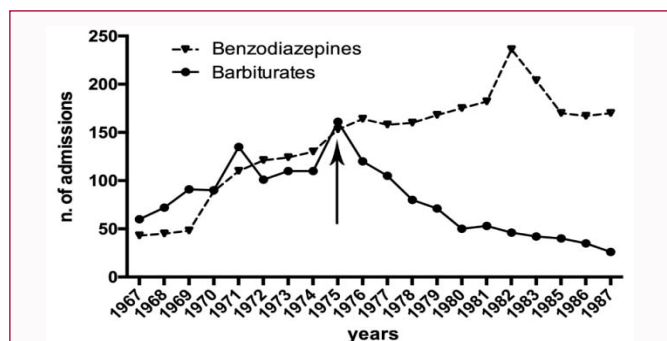


Figure 3: Yearly admissions for benzodiazepine and barbiturate acute intoxications. The arrow indicates that in 1975, barbiturate prescription modalities changed.

Table 3: Central Nervous System drugs: number of cases admitted in toxicology unit between 1917 and 1964. In parenthesis the number of deaths.

Years	Barbiturates	Opiates	Cocaine	Others	Ref
1917-19	1	6	1		[2]
1920-22	3	6	11	Strychnine 1	[3]
1923-25	21 (4)	4	5	Strychnine 4	[4]
1926-28	37 (4)	6	2		[5]
1929-31	45 (12)	5		Strychnine 2	[6]
1932-34	28 (7)	5		Hashish 1	[7]
1935-37	40 (13)	3			[8]
1938-40	36 (7)	8		Amphetamine 1	[9]
1941-43	47 (8)	5		Amphetamine 1	[9]
1944-46	33 (5)	5		Amphetamine 1	[9]
1947-49	88 (12)	15(2)		Amphetamine 2	[9]
1950-52	125 (5)	9		Amphetamine 1, Strychnine 1	[10]
1953-55	105 (1)	4		Analgesics 33	[11]
1956-58	79 (2)			Tranquillizers 35, Analgesics 91	[12]
1959-64	240 (3)	29(1)		Tranquillizers 243, Analgesics 199, Antidepressants 45	[13]

Table 4: The trend over time of acute intoxication admissions in the years 1980-2014.

Years	N° cases/year	Deaths %	Main poisonings
1980 - 83	976	0.3	Benzodiazepines, alcohol, pesticides, analgesics
1984 - 88	1156	0.4	Benzodiazepines, opiates, mushrooms
1989 - 93	1040	0.4	Benzodiazepines, opiates, alcohol
1994 - 98	1125	0.4	Alcohol, opiates, benzodiazepines, neuro-depressants
1999 - 2006	1346	0.3	Benzodiazepines, drug in association, neuroleptic
2007 - 2014	1084	0.4	Alcohol, benzodiazepines, neuro-depressants in association, carbon monoxide

sex ratio of acute poisonings was constant over the period, with a male:female ratio being 1:2.5; female outnumbering male in all age groups except in the 30 to 49 age group (data not shown). Children were not admitted to our clinic up to 1973 when a consultation service with the Department of Pediatrics was started. Interestingly, in chronic intoxications the male/female ratio is 3:1, 55% of patients being under 30 years [14].

The frequency distribution according to the type of toxic agent shows that the most frequent cause of intoxications is due to drug overdose, 4566 cases, about 60% of total, followed by organic substances like trichloroethylene and oil derivatives, 1095 cases, the 14.5% of total, whereas the total number of poisonings due to inorganic substances, 532 cases, the 7% of total, dropped significantly in the years 1970 to 1979, mainly because of a decreased number of carbon monoxide intoxications. The number of patients admitted for poisonous mushrooms was 628, the 8.3% of total. The harmful drugs of choice have changed over the years.

Barbiturate and benzodiazepine intoxications: The rise in benzodiazepines poisonings due to the increase in their prescription is coupled with a significant decrease in barbiturate poisonings, whose prescription became less popular; particularly after 1975, when barbiturate prescription modality changed (Figure 2). In the sixties and seventies of the last century barbiturates were responsible for the 85% of all comas, with 8% mortality, of the comatose patients. For this group of severely poisoned patients we validated charcoal hemoperfusion as the most effective measure for drug removal from the blood in association with intensive supportive therapy [30]. The

plasma barbiturates' concentration profile clearly demonstrated that hemoperfusion with charcoal columns and hemodialysis by polyacrylonitrile membranes were the preferential ways for an active removal of drugs [30].

In the early seventies, a significant percentage of poisonings was represented by analgesic-antipyretic drugs; the frequency of these intoxications notably decreased in the period 1976 to 1979, since the sale of these drugs over the counter was controlled.

In the years 1970 to 1979, 63 patients died, with a mortality rate of 0.67. The overall percent of mortality did not significantly change since 1959; but variations in the specific causes of death were observed. Strong acids were the main cause of death (21 patients, 15 females and 6 males); followed by poisoning with drug combination (12 patients, 7 males and 5 females), a figure higher than barbiturates alone (8 patients); while 3 patients died for narcotic overdose [15]. Of note, mortality due to caustic agents significantly decreased since the adoption of explorative laparotomy, early gastrectomy and the use of Sorensen buffer [31]; also the mortality due to barbiturate overdoses significantly decreases after the validation of charcoal hemoperfusion [30].

Accidental poisonings in the years 1980 to 2014

The number of intoxications in the period 1980 to 2014 is reported in Table 4: The temporal trend of the acute intoxication in the period from 1980 to 1988 shows a significant increase of benzodiazepine poisonings (Figure 3); the administration of flumazenil (2-10 mg e.v.) for a quick reversal of neuronal depression,

Table 5: The out-patient activity in three different periods.

	Mean number of consultations/year		
	2003-2007	2008-2012	2013-2016
Perinataltoxicology	184	135	102
Toxicologicalproblems	235	249	223
Drug and alcoholaddiction	2772	3156	3125

mainly in old patients and in mixed drug overdoses, was successfully validated in that period [32].

Beside benzodiazepines overdoses, opiates, alcohol, neuro-depressants in association and poisonous mushrooms were the main causes of acute poisonings. Since the early observations that Penicillin G decreases the toxicity of *Amanita Phalloides* toxins, a successful protocol for the treatment of these severe intoxications with benzylpenicillin, thioctic acid and corticosteroids was started. Several hypotheses have been proposed to explain the mechanisms of the antidotal action of benzylpenicillin in amatoxin poisoning. It was initially thought that penicillin G could displace α -amanitin from albumin, allowing better renal elimination [14]. Such hypothesis was not completely satisfactory and studies with amatoxins in human hepatocytes have been performed, demonstrating that benzylpenicillin blocks α -amanitin-amanitin hepatic uptake, being a potent inhibitor of OATP1B3 transporter [33].

However, this protocol, although used with success in our Unit and by American clinical toxicologists, is not widely accepted [34].

Chronic intoxications: Starting from the middle seventies, alcohol-related problems and heroin addiction became a growing concern in our country and we started treatment modalities both for chronic alcohol intoxication and opiate addiction. Protocols for early diagnosis and evaluation of the biological consequences of alcohol abuse were validated together with a detoxification program using a combination of two drugs: chlordiazepoxide, for avoiding alcohol withdrawal reaction, and tiopronin or reduced glutathione for their protective role in alcohol liver injury [35]. Protocols for the treatment of opioid overdose and chronic addiction were also introduced [23].

Methadone for the outpatient treatment of opioid use disorders is now recognized as a widely diffused and validated therapy. However, the beginning of methadone use in Italy was controversial causing hard discussions among physicians, law enforcement officials, and legislators. The controversy involved not only the technicality of low-dosage vs. high-dosage programs and their respective therapeutic outcomes but also their ethics, which are often denied on anti-pharmacological grounds [36-38]. On June 6, 1978 an Italian law [39], forbidding the sale of methadone in pharmacies and limiting the dispensing of methadone to "official" clinics, was approved. Therefore, methadone doses had to be taken on a daily basis in the approved clinics, in the presence of medical doctors and/or nursing personnel. On August 7, 1980 a new law reintroduced the sale of methadone in the pharmacies and restored the take-home medication treatment [40]. Since then, alternative programs were developed, such as the experimental legalization of morphine, up to 1985, the naltrexone protocol to minimize relapses in detoxified patients, as well as outpatient's short-time and residential long-term therapeutic communities. The out-patient activity in three different periods is reported in Table 5.

In October 2014, the clinical activities of the Florentine

Toxicological Unit underwent to a complex reorganization and acute intoxicated patients were admitted in the Emergency Department and an intense consultation activity, with a perpetual revision of our protocols for acute and chronic intoxicated patient, has been developed. Moreover, since the early seventies, of the last century, the medical personnel of the Florentine Toxicological unit operate as a Poison Control Center (PCC), providing immediate, free and expert treatment advice and assistance over the telephone in case of exposure to poisonous substances. This activity was formalized in 1990, together with the activity of the Center for Perinatal Toxicology, and both Centers were registered as Regional Reference Centers in 1992. The PCC of Florence is also responsible for keeping a stock of some rare and expensive antidotes for the Emergency Departments of Tuscany Region. In 2016, the number of consultations for Perinatal Toxicology and PCC were 6,765 and 4,699 respectively. It is noteworthy that these activities increase every year.

Conclusion

In conclusion, the natural history of intoxications analyzed throughout 100 years of activity of the Toxicological Clinic reveals two common patterns, increase in the number and a changing profile. The activity of the Clinic is the mirror of the changes of the society and of the evolution of medicine in the last century. Of note, in the last fifty years, alcohol, benzodiazepines and neuro-depressants continue to be the most commons substances involved in poisonings.

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