HANDBOOK OF CLINICAL NEUROLOGY

VOLUME 37

Edited by

P. J. VINKEN and G. W. BRUYN

INTOXICATIONS OF THE NERVOUS SYSTEM

PART II

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P. J. VINKEN and G. W. BRUYN

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PART II

Edited by

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Foreword to volumes 36 and 37

It would appear at first glance that the volumes on toxic disorders of the nervous systems would be among the easiest to organize; after all it is fairly clear which neurologic disorders are due to exogenous toxins and which are not. This superficial view however ignores three significant problems. The first is individual sensitivity to a specific exogenous toxin. This variability, the basis of which remains unclear, must play a role in determining why some manganese miners develop toxic symptoms while others with similar or even greater exposure do not. Although we are unaware of the biochemical basis of this phenomenon it is clear that manganese poisoning is a toxic disease. We do understand the biochemical basis of Refsum's disease, however, and therefore recognize why exogenous phytanic acid is toxic only to those individuals with a specific gene-related enzymatic deficit. Nonetheless, in susceptible individuals, phytanic acid is an exogenous toxin which causes neurologic disease that can be prevented and reversed by decreasing exposure to the toxin. In much the same way, many other neural metabolic disorders are really intoxications. The neuropathology of Wilson's disease may reflect nothing more than chronic copper toxicity. Neurologic symptoms in acute intermittent porphyria are often precipitated by exposure to an exogenous toxin. These are, of course, only two of an entire host of metabolic disorders in which exogenous toxins or metabolites play a significant role.

As a result, the editors are faced with the ever recurring problem of trying to put together a single topic outline which is comprehensive but does not overlap too much with other volumes and therefore result in costly repetition. The contents of these two volumes must be viewed as complementing the three volumes, 'Metabolic and Deficiency Diseases of the Nervous System' (Volumes 27, 28 and 29). The reader is specifically referred to these volumes for such toxic related subjects as: Wilson's disease (Volume 27); Bilirubin encephalopathy (Volume 27); Porphyria (Volume 27) and Oxygen toxicity (Volume 29).

All of the disorders of amino acid metabolism, many of which can be controlled by dietary management, have been presented in detail in Volume 29. The problems due to vitamin toxicity have been presented in Volume 28 in conjunction with discussions of vitamin deficiency syndromes. The role of alcoholism in the pathogenesis of numerous neurologic disorders has also been presented in Volume 28 and has therefore not been included here. The brief chapter on Refsum's disease (Chapter 13) must be read in conjunction with other chapters already published: Heredopathia atactica polyneuritiformis. Phytanic acid storage disease (Volume 21) and Biochemical aspects of Refsum's disease and principles for dietary treatment (Volume 27).

Another problem is related, again, to the internal organization of the Handbook

itself. Several chapters on toxic neuropathy were already published in Volume 7, including contributions on: Toxic neuropathy, Iatrogenic neuropathy, and Differential diagnosis of toxic neuropathy. Despite the desire to make the present two volumes as complete and independent as possible in relation to such toxic states, topics which would only repeat subjects covered in these chapters have not generally been included in detail here.

The second major problem concerns the ever expanding field of iatrogenic neurologic disorders. The neurologic side-effects of neuroleptics have become an increasingly important medical and medicolegal problem. These were presented in detail in Volume 6 (Drug induced extrapyramidal syndromes) but, because of their importance, have also been included here. The neurotoxicity of anticonvulsants has not been previously included in a complete fashion and therefore was included. In the same way ergotism, amphetamines and other central nervous system stimulants are given separate chapters but levodopa toxicity is not. In general, any drug which causes specific neurologic toxicity, not just overdose related toxic encephalopathy, has been included unless previous chapters in the Handbook have discussed the drug thoroughly.

There seems to be no limit to the number of therapeutic agents which can be devised and result in neurotoxicity. Similarly there is an increasing number of industrial organic agents which under appropriate circumstances can produce neurologic disease. We have attempted to include those of significant clinical relevance at this time but fully acknowledge that it is impossible to catalogue and discuss all such agents and equally impossible to predict which will be widely disseminated in the next decade.

The third problem is closely related to many toxins, widely used for their clinical relevance that are now mostly of historic interest. Bromide toxicity and thallium poisoning are two subjects that were more important in the past than they are today. It is of course impossible to predict if any such poison will again become important. Although our judgment as to which of these agents deserve special attention may not agree with that of others we have attempted to include all agents of continuing clinical relevance.

P.J.V.
G.W.B.
H.L.K.
M.M.C.

Acknowledgement

Several illustrations and diagrams in this volume have been obtained from other publications. Some of the original figures have been slightly modified. In all cases reference is made to the original publications in the figure caption. The full sources can be found in the reference lists at the end of each chapter. The permission for the reproduction of this material is gratefully acknowledged.

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Contents

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CHAPTER 1

Snake bite and snake venoms: their effects on the nervous system

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The snake is the emblem of the healer and has long been associated with healing and with therapeutics in Western medicine, but the use of snake venoms or snake flesh in therapeutics is not confined to past centuries.

In the present century snake venoms have been used in the treatment of chronic pain, neuralgias, epilepsy and terminal cancer (see Russell and Scharffenberg 1964 for references). More recently ancrod (Arvin), the purified coagulant factor of the venom of the Malayan pit-viper Agkistrodon rhodostoma, has been used to anticoagulate patients (Pitney 1972). The purified neurotoxins of snake venoms may possibly in the future have a role in therapeutics but there is no doubt that they will continue to be used as neuropharmacological experimental tools of great value for some years to come.

The clinical manifestations of snake bite provide a field of great interest to the clinician. Its diverse neurological manifestations mean that snake bite must be considered in the differential diagnosis of cranial nerve palsies, myasthenic syndromes, symmetrical limb weakness, acute myopathies and even of coma.

There are recent important books on the subject of snake venoms and snake bite (Bücherl et al. 1968; Bücherl and Buckley 1971; Lee 1977), and there are reviews on: the action of cobra venom and its toxins (Lee 1971), snake venoms (Boquet 1948, 1964, 1966; Russell 1967; Simpson 1971) and their effects on the nervous system (Meldrum 1965b; Lee 1970; Campbell 1975); the biochemistry of snake venoms (Slotta 1955; Kaiser and Michl 1958; Jiménez-Porras 1970); and on the toxins of the venoms (Jiménez-Porras 1968; Lee 1972; Yang 1974). Lee et al. (1974) highlight the most recent developments.

History

In the history of Western medicine, snake bite was synonymous with viper bite up until the late eighteenth century when information from India about elapid bites began to be published (Russell 1796).

While the clinical picture of viper bite was well known by the sixteenth century (Johnson 1678), as late as 1673, the ill effects of the bite could be attributed by some to the 'enraged spirits of the viper' (Charas 1673). But the experiments of Redi (1673) and Mead (1702) correctly attributed the effects of the bite to the venom voided out of the larger teeth of the snake. The Abbate Felice Fontana (1795) turned venom studies into an exact science performing 6,000 experiments involving the use of 3,000 vipers and 4,000 animals (Earles 1960), while the study of rattlesnake bite and venom was established on a firm scientific foundation by Mitchell (1860) and Mitchell and Reichert (1886).

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The study of elapid venoms was initiated by Fayrer (1872a, b; 1873) and Ewart and Richards (1872, 1885) in India (see also Indian Snake Bite Commission 1874), by Brunton and Fayrer (1873, 1874) in England and by the Snake Bite Committee of the Medical Society of Victoria in Australia (Australian Medical Journal 1876).

Fayrer (1872a), observing that artificial respiration abolished the cyanosis and convulsions produced by cobra venom in fowls, thought that there might be a resemblance between the action of cobra venom and curare. Despite over 100 experiments in tracheotomised, envenomated dogs, life was prolonged by artificial respiration but not saved (Indian Snake Bite Commission 1874). Mainly because of the results of these experiments and because of the prominence of bulbar muscle palsies in the clinical picture (Wall 1883), it was postulated that cobra venom must act on the spinal cord, brain stem nuclei and on the respiratory centre. This hypothesis was to persist right up to the present day even though there was soon experimental evidence that cobra venom acted at the neuromuscular junction (Brunton and Fayrer 1874; Wall 1883).

Ragotzi (1890), appreciating that if the neuromuscular blocking action of cobra venom was to be demonstrated in the intact animal a small lethal dose of venom must be used, proved that cobra venom was a curarising poison and that the respiratory failure was peripheral in origin. Despite Ragotzi's convincing proofs, dispute was to continue over the next 70 years between those who believed that the respiratory failure induced by elapid venoms was peripheral in nature and those who claimed that it was due to respiratory centre involvement.

Arthus (1910, 1911), Cushny (Cushny and Yagi 1918), Houssay (Houssay and Pavé 1922; Houssay et al. 1922) and Kellaway (Kellaway and Holden 1932; Kellaway et al. 1932) led the vanguard of those who repeatedly proved the peripheral nature of the muscle paralysis caused by elapid or sea snake venoms. The failure to realize that different species of animal vary considerably in their susceptibility to snake venom (Tseng and Lee 1962) was the cause of wrong conclusions in this debate (Epstein 1930). The cat in particular is very resistant to the curare-like action of cobra venom as it is to the action of curare itself (Lee and Tseng 1969) and to viper venom (Fontana 1795). More recent work with cobra and krait venoms in dogs and cats has confirmed that the respiratory centre is still active when respiration ceases and that 'curarisation' of the diaphragm is present (Lee and Peng 1961; Ciuchta and Polley 1964; Vick et al. 1965).

Over the last 25 years, research work has been concerned with defining the nature of the peripheral neuromuscular block induced by snake venoms; with a study of the venoms of the less common elapids; with the fractionation of the venoms and isolation of the neurotoxins and their characterization; with the use of tagged neurotoxins to isolate the cholinergic receptor protein; and with a clarification of the clinical picture of several types of snake envenomation. These developments will be considered in more detail below.

The venomous snakes

The important venomous snakes of the world belong to three families of snakes – the Viperidae, the Elapidae and the Hydrophiidae. The Viperidae or family of vipers is made up of two sub-families, the Viperinae or true vipers and the Crotalinae or pit-vipers. Members of the Viperidae are found on every continent except Australia. Pit-vipers are found in Asia and the Americas. They are most numerous in the New World where they dominate the population of venomous snakes. The rattlesnakes (Crotalus, Sistrurus spp.) are included in this sub-family.

The Elapidae are found in every continent except Europe. This family includes the cobras (Naja spp. and other genera), the kraits (Bungarus spp.), the mambas (Dendroaspis spp.), the American coral snakes and all the venomous snakes of Australia and New Guinea. The Hydrophiidae or sea snakes are closely related to the Elapidae and are principally found in Asian and Australasian waters.

It should be remembered that, in every continent except Australia, the bulk of the snake population is composed of members of the Colubridae family. With the exception of one or two rear-fanged species, e.g. African boomslang Dis-

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pholidus typus and the bird snake Thelotornis kirtlandii, these snakes are harmless.

Venom yield and toxicity

Measurements of the venom yield of snakes expressed as the dry weight in milligrammes (Table 1) have been obtained in the laboratory by having the snake bite through a thin rubber diaphragm into a container. Then the venom glands are compressed or 'milked' to try and empty them completely. It is difficult to establish what relationship such artificially derived venom yields have to the amount of venom which is delivered in a natural bite. Careful early workers estimated, on the basis of their experiments, that the greater part of this venom yield – ten-sixteenths (Acton and Knowles 1914) or three-quarters (Fairley and Splatt 1929) – would be discharged at a bite. Acton and Knowles (1914) estimated that a cobra would inject 172 mg of venom, ten times the human lethal dose. Consequently they believed that the probability of recovery from a cobra bite would be only 3–4%. Yet the case fatality rate (CFR) of cobra bite is less than 10% (Reid 1964). So it must be exceedingly uncommon for this snake to discharge anything approaching ten-sixteenths of its venom yield.

The toxicity of the venom expressed as the LD_{50} for a given animal is the best guide to the potential lethal power of the snake but it is also generally accepted that snakes with large venom yields are dangerous.

Venom

Snake venom is an extremely rich source of enzymes; one of the richest biological sources of enzymes. Enzymes which have been identified in different snake venoms are: pseudocholinesterases, phospholipase A, B, C, proteases, esterases, dipeptidedases, L-amino acid oxidase, deoxyribonuclease, ribonuclease, phosphodiesterases, phosphomonoesterase, 5′-nucleotidase, bradykinin-releasing enzyme and hyaluronidase (Sarkar and Devi 1968).

Although acetylcholine (ACh) (Welsh 1967) and acetylcholinesterase (Chang and Lee 1955; Kumar et al. 1973) are present in many elapid venoms they do not appear to be responsible for the neurotoxic effects of snake venoms. Most venoms contain high concentrations of phospholipase A and its izoenzymes. Purified phospholipase A from elapid venoms is without neurotoxicity (Yang et al. 1959) and the postsynaptic neurotoxins are devoid of phospholipase A activity (Yang et al.

TABLE 1

Venom yield and toxicity of some snake venoms.

	Venom yield (mg)[a]	I.V. LD 50 mice (mg/kg)[a]	Estimated LD man (mg)
European viper *(V. berus)*	6–18	0.55	
Russell's viper *(V. russelli)*	130–250	0.08	15[f]
Saw-scaled viper *(E. carinatus)*	20–35	2.30	8[f]
Eastern diamondback rattlesnake *(C. adamanteus)*	370–700	1.68	
South American rattlesnake *(C. durissus terrificus)*	50[b]	–	18[b]
Cottonmouth *(A. piscivorus)*	90–145	4.00	
Indian cobra *(N. naja)*	170–325	0.40	12
Common krait *(B. caeruleus)*	8–20	0.09	6[f]
Green mamba *(D. augusticeps)*	60–95	0.45	
Tiger snake *(N. scutatus)*	47.2[c]	0.04[d]	7[g]
Death adder *(A. antarcticus)*	84.7[c]	0.40[e]	11[g]
Sea snake *(E. schistosa)*	7–20[a]	0.01[a]	3[h]

a) Russell (1967a) unless otherwise indicated; b) average maximum yield, Belluomini (1968); c) average maximum yield, Fairley and Splatt (1929); d) and e) CLD ≏ LD 100; d) Kellaway (1929a); e) Kellaway (1929b); f) Deoras (1965); g) Campbell (1964b); h) Reid (1956a).

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1959; Lee and Chang 1966). The phospholipase A in crotoxin from the South American rattlesnake venom (C. durissus terrificus) is however responsible for its neurotoxicity (Habermann et al. 1972). More recently Eaker (1975) has shown that the principal presynaptic neurotoxins from tiger snake and taipan venoms have weak phospholipase A activity. He is of the opinion that these toxins, β-bungarotoxin and crotoxin have all evolved from a phospholipase A.

The proteolytic enzymes and bradykinin-releasing enzymes play an important role in the toxicity of pit-viper and viper venoms. Indeed the local necrotic action of Viperidae venoms and their haemorrhagin activity are related to their proteolytic enzyme content. The principal toxic components of elapid and sea snake venoms are proteins which have no enzymatic activity at all. These toxic components are called neurotoxins, cardiotoxins, coagulant and anticoagulant factors.

Haemorrhagins, one of the major toxic factors in viper venoms, damage the walls of small blood vessels causing haemorrhages and exudations of fluid. Neurotoxins cause a peripheral muscle paralysis but the term neurotoxin is often used loosely in the literature for any toxic fraction which has an action on the nervous system. Cardiotoxins impair the action of the heart and have a direct action on voluntary muscle. Coagulant and anticoagulant factors impair blood coagulability. There may be several distinct neurotoxic and/or haemorrhagic, cardiotoxic or coagulant proteins in the one venom.

Absorption of venom

Snake venom is almost always deposited in the subcutaneous tissues. In mice, 60% of a subcutaneously injected dose of I^{131}-labelled Formosan cobra Naja naja atra neurotoxin was absorbed within 2 hours but after 4 hours only one-third of the dose of the labelled crude venom or its cardiotoxin was absorbed (Tseng et al. 1968).

The latent period between the bite and the development of paralysis is shorter after cobra and mamba bites than after krait and Australian elapid bites. The slow absorption of the crude venom might be held to be the explanation for this latent period and this is partly true. When, however, cobra venom is injected intravenously in experimental animals there is still a latent period before paralysis develops in the in situ nerve–muscle preparation and even the intra-arterial injection of the venom doesn't shorten this latent period (Cheymol et al. 1967b).

Slow absorption cannot wholly explain the longer latent period of krait and Australian elapid envenomation. When in two sheep the area bitten by tiger snakes was completely excised within 5 minutes of the bites, and presumably absorption of the venom ceased, paralysis still took 36 hours 56 minutes to develop in one sheep and 3 hours 39 minutes in the other (Fairley 1929c). In vitro experiments with Formosan krait Bungarus multicinctus venom (Chang 1960a, b) and one of its neurotoxins β-bungarotoxin (Chang and Lee 1963) would indicate that after absorption the presynaptic neurotoxins have a long latent period which cannot be shortened. During this latent period irreversible fixation of the neurotoxin in the nerve terminals occurs.

Incidence of envenomation and case fatality rate (CFR)

In Papua the incidence of envenomation in 260 definite or probable elapid snake bite cases was 23% (Campbell 1969a). Chapman (1968) found that only 11% of 897 cases of viper and elapid bite in Natal were serious. Of 47 identified cobra bites in Malaya, 21 (45%) had no evidence of envenomation and another 4 (9%) had negligible signs of local envenomation (Reid 1964). Sixty-eight per cent of 101 cases of sea snake bite were not envenomated (Reid 1975b).

The true incidence of envenomation if all bites were reported would be lower than the above hospital figures indicate. Reid (1968) from his extensive practical knowledge of the subject has suggested that over 50% of those bitten by venomous snakes develop no evidence of envenomation. Most snake bites are not 'business' bites. They are 'startled' or 'defensive' bites. Venom is not injected even though, if the snake (elapid, sea snake or viper) can be captured and the venom glands are milked, several human lethal doses of venom may be found in the glands (Reid 1957; Reid et al. 1963b; Reid 1964).

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The treated CFR of snake is low, less than 6% as a rule (Reid et al. 1963a; Reid 1964; Chapman 1968; Rosenfeld 1971; Bhat 1974).

The clinical picture of snake bite

The present discussion will primarily concern itself with the neurological manifestations of snake bite. The literature contains many case reports of snake bite but not so many in which the snake is identified with certainty. We are still ignorant of the clinical effects of the bites of some species of snake and the clinical picture of bites from other species may be based on only one or two case reports.

ELAPID ENVENOMATION

For purposes of discussion the course of elapid envenomation can be considered under the following headings: a) local evidence of envenomation; b) preparalytic symptoms and signs of envenomation, c) paralytic symptoms and signs and d) other systemic effects of envenomation.

Local signs

The cobra is the only elapid snake whose bite is constantly associated with local signs of envenomation. Pain, which is frequently severe, is a constant feature of a cobra bite which produces envenomation. It is followed within a few hours by, or is accompanied by, swelling which may eventually involve the whole limb. Local necrosis of the skin and subcutaneous tissue frequently follow and is the commonest manifestation of a serious cobra bite (Reid 1964; Warrell et al. 1976a). If pain is not present, and if swelling is absent 3–4 hours after the bite of a cobra, envenomation will not have occurred.

In bites from almost all the other elapid snakes local pain and swelling are inconstant features of envenomation being more often absent than present. The local effects, however, of the bites of many species of elapid snakes are not well documented.

After inspection of the local wound following an elapid bite, one is therefore often still in doubt as to whether venom has been injected or indeed, at times, as to whether an actual bite has occurred. The fangs of the elapid snakes are small (Fairley 1929b) and their tiny puncture wounds may not be visible among the many marks on the skin of the feet of people who are habitually bare-footed. The preparalytic symptoms and signs therefore assume great importance. Their recognition as evidence of envenomation may allow the prompt administration of antivenene and thus may prevent paralysis developing.

Preparalytic symptoms and signs

It must be stressed that these symptoms and signs are a more characteristic feature of viper envenomation and in this section some reference will be made to their occurrence after viper bites. They are an inconstant feature of elapid envenomation. None of these symptoms and signs may develop; particularly is this so in mamba and cobra envenomation. Even after Papuan elapid bite, 10% of envenomated patients did not develop such symptoms. The preparalytic symptoms and signs which involve evidence of bleeding are peculiar to some Australian elapid bites and to viper bites.

Among these symptoms and signs – headache, vomiting, loss of consciousness, abdominal pain, pain in the regional lymph nodes or tenderness of the regional lymph nodes, faintness, sweating, pallor, the passing of blood-stained urine, proteinuria, diarrhoea, the spitting of blood, the coughing of blood, the vomiting of blood and, less commonly, loss of vision and convulsions – there are some which are obviously of interest to the neurologist, namely, headache, vomiting, loss of consciousness, loss of vision and convulsions. These latter symptoms may arise within minutes of the bite (Flecker 1940, 1944; Le Gac and Lepesme 1940; Fitzsimons 1962; Reid 1976) and symptoms arising within half an hour of snake bite are not necessarily due to fear as is suggested by some (Wall 1913; Reid 1968; Seth 1974).

Headache and vomiting are the commonest preparalytic symptoms. One or both of these symptoms may develop within a few minutes of the bite (Knyvett and Molphy 1959; Trinca et al. 1971) or they may be delayed for some hours. The headache may commence gradually or suddenly;

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