Update Article

Clinical Aspects of Chronic Arsenic Toxicity

DNG Mazumder

Humans are exposed to arsenic (As) primarily from air, food and water. Drinking water may be contaminated with As from arsenical pesticides, natural mineral deposits or improperly disposed arsenical chemicals. Elevated As levels in drinking water is the major cause of As toxicity in the world. Reports of such contamination are available from Taiwan, Chile, China, Argentina, Mexico, India, Hungary, Bangladesh, USA and Thailand. However, largest number of people in the world affected from chronic As toxicity due to drinking of As contaminated ground water belongs to Bangladesh, India and China. Data derived from various studies show that inorganic As adversely affect multiple organ systems of human body.[1]

Biochemical effect and cellular mechanism of As toxicity have been frequently reviewed. In 1925, Voegtlin demonstrated that the sulfhydryl (SH) groups within cells were receptors for trivalent As. He also showed that glutathione and other sulfhydryl containing chemicals prevented the toxic effects of As. Voegtlin postulated toxic reversible interaction of arsenite (As III) with the SH groups of glutathione in cells or with other SH groups occurring in cell protoplasm.[2] This conclusion has been supporting the concept that the major toxic action of trivalent arsenicals is their interaction with thiol groups.[3] The biologic toxic action of As is due to more functional activity than to any damage to the structural integrity of the tissues. Arsenite inhibits number of thiol dependent enzymes in exerting its toxic effects, arsenite is thought to combine with SH groups and inhibit about 100 different enzymes. It has been shown that the SH groups decrease in whole blood after exposure to arsenite. Arsenic binds to two thiol groups per molecule to form stable ring compounds, in preference to reacting with two thiol groups of two separate molecules.[4] After prolonged feeding of As contaminated water (3.2 mg/l) in mice, increased lipid peroxidation and plasma membrane damage in association with reduction of hepatic glutathion and enzymes of anti oxidant defense system (G6PDH, GPx, GST and GR) were observed by Santra *et al*.[5] According to Casarett and Doul (1986),[6] mitochondria accumulate As. Respiration mediated by NAD linked substrates is particularly sensitive to As. The most As sensitive enzymes are those which are not reactivated by simple monothiol compounds. These sensitive enzymes includes lipoic acid dehydrogenase and the oxidases which use lipoic acid as coenzymes. For these enzyme systems, 2, 3-dimercapto propanol and dithiol compunds are far more effective in reversing the action of As. The As sensitive enzymes have been found to contain vicinal SH groups which can form stable five or six membered rings when bound to monosubstituted As. Disruption of oxidative phosphorylation and concomitant decreases in cellular levels of ATP[7] are thought to be important central events in the onset of cellular injury and death, in arsenic intoxication because ultrastructural morphometric alterations in mitochondrial structure, and disruption of mitochondrial respiratory function, are closely correlated.

Most of the reports of chronic As exposure in man focus attention on skin manifestations because of their diagnostic specificity. Data derived from population based studies, clinical case series and reports relating to intake of inorganic As in drinking water, medications or occupational and environmental exposure show its capacity to adversely affect multiorgan system. The clinical appearance of the non carcinomatous manifestations of As intoxication in humans is dependent on the magnitude of the dose and the time course of its exposure.

Protean clinical manifestations have been described by Guha Mazumder *et al*[8-11] on the basis of detail clinical and relevant investigations (with individual As exposure data) on people drinking As contaminated water in seven affected districts of West Bengal, India.

Member, Task Force on Arsenic Pollution in Ground Water in West Bengal, Government of West Bengal, Formerly, Head of the Department of Medicine and Gastroenterology, Institute of Post Graduate Medical Education and Research, Calcutta - 700 020. **Received : 12.10.1999; Revised : 24.4.2000; Re-revised : 28.9.2000; Accepted : 25.2.2000**

Clinical features of 248 patients investigated are given in Table 1. Though pigmentation was seen in most cases (94.35%), keratosis was found in 162 patients (65.32%), and skin cancer was detected in five (2.02%) cases. Association of As with several internal cancers have also been established by epidemiological studies at exposure concentrations of several hundred microgram per liter of drinking water.[1]

Table 1 : Clinical features of 248 cases studied

Presenting features	No of patients	Percentage
1. Rain-drop pigmentation	234	94.35
2. Weakness	163	65.73
3. Keratosis (sole and palm)	162	65.32
4. Dyspepsia	165	66.53
5. Cough (± expectoration)	154	62.10
6. Burning sensation of eyes	74	29.84
7. Anaemia	109	43.95
8. Hepatomegaly (firm, non-tender 2-6 cm below costal margin)	190	76.61
9. Splenomegaly (1.5-8 cm below costal margin)	73	29.43
10. Crepitation ± rhonchi	75	30.24
11. Polyneuropathy	74	28.83
12. Pedal oedema (non-pitting)	23	9.27
13. Blackfoot disease (Gangrene)	3	1.20
14. Skin cancer	5	2.02
15. Kideny cancer	1	0.4

Though chronic As toxicity produces varied non carcinomatous manifestations and cancer of skin and different internal organs, cutaneous manifestations are more specific features of chronic arsenicosis. The hyperpigmentation of chronic As poisoning commonly appears in a finely freckled, "raindrop" pattern that is particularly pronounced on the trunk and extremities distributed bilaterally symmetrically. But that might also involve mucous membranes such as undersurface of tongue or buccal mucosa. The raindrop appearance results from the presence of numerous rounded hyperpigmented macules (typically 2-4 mm in diameter) widely dispersed against a tan-to-brown hyperpigmented background. Although less common, other patterns include diffuse hyperpigmentation (melanosis); localized or patchy pigmentation, particularly affecting skinfolds; and so-called leukodermia or leukomelanosis, in which the hypopigmented macules take spotty, white appearance. Pigmentation is not histopathologically related to arsenical hyperkeratosis, nor is it a direct precursor to cancer[1] (Fig. 1).

Arsenical hyperkeratosis appear predominantly on the palms and the plantar aspect of the feet, although involvement of the dorsum of the extremities and the trunk have also been described. In early stages, the involved skin might have an indurated, gritlike character that can be best appreciated by palpation; however, the lesions usually advance to form raised, punctuate, 2-4 mm wartlike keratosis that are readily visible. Occasional lesions might be larger (approximately 1 cm) and have a nodular or horny appearance. In severe, cases, the hands and soles present with diffuse verrucous lesions. Cracks and fissures may be severe in the soles[12,10] (Figs. 3 and 4).

History of As exposure through inhalation or ingestion is helpful for corroborative evidence for diagnosis of chronic arsenic toxicity as skin manifestation like diffuse melanosis could not be differentiated from normal dark complexioned farmers in the tropics who work in the field bare bodied under direct sun exposure. However, spotty rain drop pigmentation of the skin distributed bilaterally symmetrically over trunks and limbs are most diagnostic feature of arsenical hyperpigmentation. Though spotty depigmented spots, similarly distributed are also diagnostic for this condition, sometimes blotchy depigmented spots are seen and these need to be differentiated from other depigmented skin lesions like Tinea versicolor, seborrheic dermatitis. Diffuse hyperkeratitic lesions of the palms and soles are distinctive lesions of chronic arsenicosis. However, manual labourors, who used hands might have thickening of the palms. Similarly bare footed farmers who work in the fields might have diffuse thickening of the soles. However, when the lesions become nodular the diagnosis

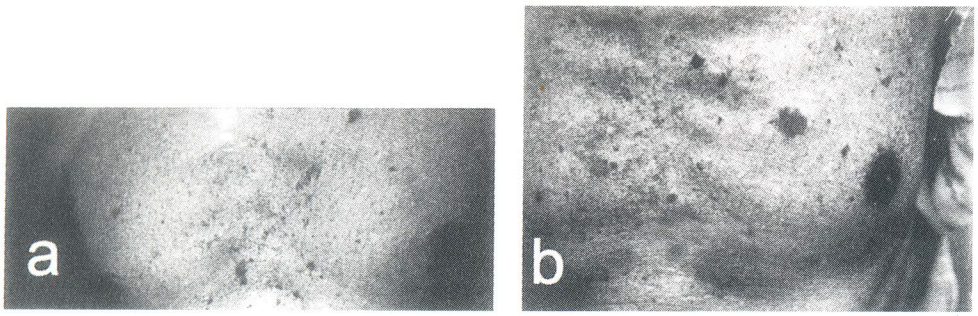

Fig. 1 : (a) Moderate pigmentation, (b) Severe pigmentation

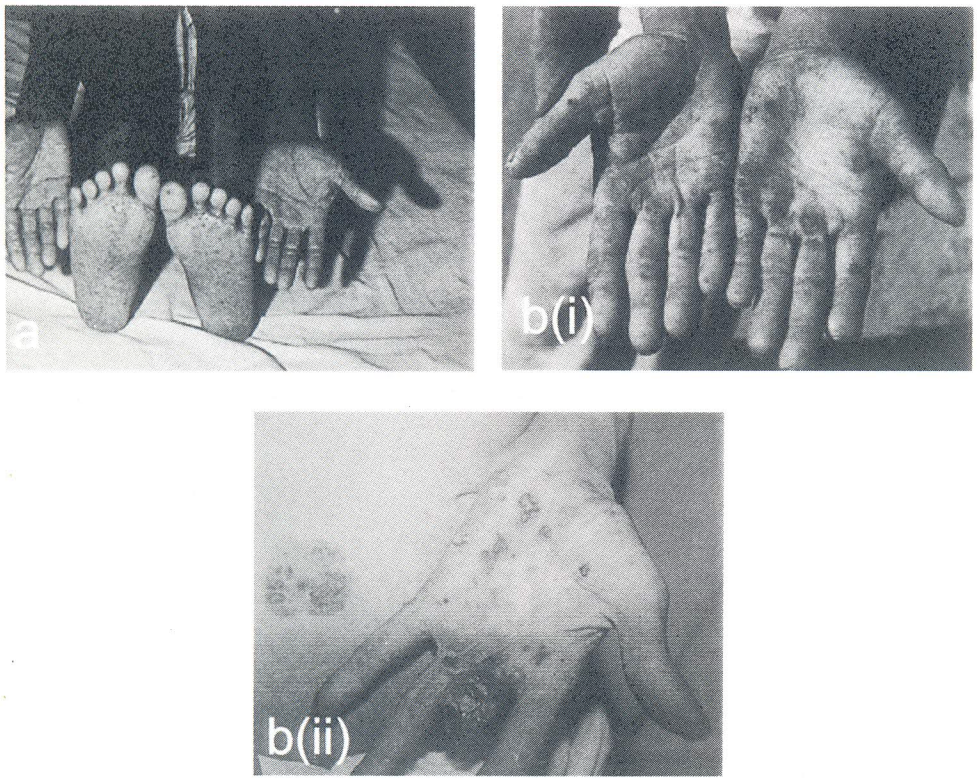

Fig. 2 : a) Mild keratosis, b) moderate keratosis (i) moderate diffuse thickening of the palm, (ii) A few nodules over thickened palm (associated lesions : Bowen's disease of the abdomen and squamous cell carcinoma on the finger)

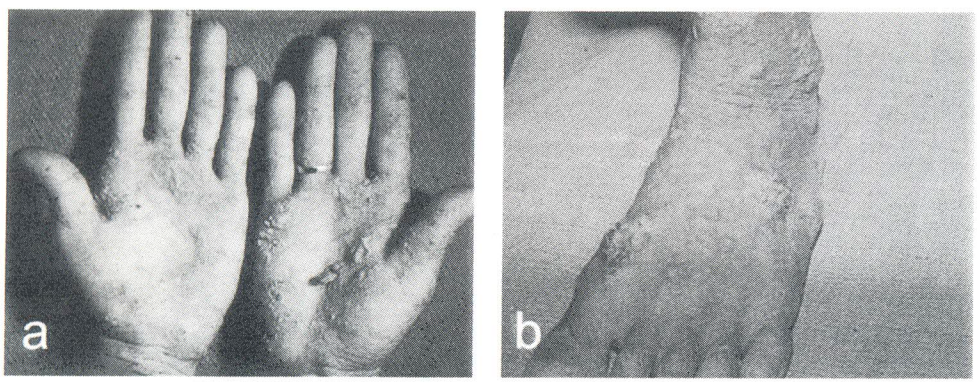

Fig. 3 : Severe keratosis a) verrucous lesion of the palm with keratotic horn, b) big nodules over the dorsum of feet (associated lesion : squamous cell carcinoma)

becomes obvious.

In the presence of history of chronic exposure of As other important predictors of chronic arsenicosis are weakness, anaemia, peripheral neuropathy, hepatomegaly with portal zone fibrosis with/without portal hypertension, chronic lung disease and peripheral vascular disease. However, these features are manifested variably in different exposed population and may be caused by As unrelated conditions. Infrequent manifestations, which have been reported to occur by some investigators in people giving history of chronic As exposure and which may also be As unrelated are : conjunctivitis, keratitis, hypertension, cardiovascular disease, cerebrovascular disease, perceptive hearing loss, cataract, nephropathy, solid edema of the limbs, diabetes mellitus etc. These have least diagnostic value of chronic As toxicity inspite of their reported occurrence among people giving history of chronic As exposure.

Skin cancer of chronic arsenicosis is quite distinctive. The lesions are frequently multiple and involve covered areas of the body, contrary to non arsenical skin cancer which is usually single and occur in exposed parts of the body.[13,14]

As with the exception of cutaneous manifestations, other symptoms and signs of chronic arsenicosis are non specific, evidence of As exposure from the environment and detection of high level of As in urine and/or in hair and nails in association with those

symptoms would be suggestive of chronic arsenicosis. But its normal value in those materials do not exclude the diagnosis of such toxicity. Diagnostic criteria, grading of severity of dermatological manifestations and case definition of chronic As toxicity are given in the Tables 2, 3 and 4.

Table 2 : Diagnostic criteria of chronic arsenicosis

1. At least six months exposure to arsenic levels of greater than 50 µg/L or exposure of high arsenic level from food and air.
2. Dermatological features characteristic of chronic arsenicosis.
3. Non carcinomatous manifestations : Weakness, chronic lung disease, non cirrhotic portal fibrosis of liver with/without portal hypertension, peripheral neuropathy, peripheral vascular disease, non pitting edema of feet/hand.
4. Cancers : Bowens disease, squamous cell carcinoma, basal cell carcinoma at multiple sites, occurring in exposed and unexposed parts of the body, cancer of urinary bladder, lungs.
5. Arsenic level in hair and nail above 1 mg/kg and 1.08 mg/kg respectively and/or arsenic level in urine, above 50 µg/L (without any history of taking seafood).

Table 3 : Dermatological criteria and grading of severity of chronic arsenic toxicity

Grade I	Mild	a) Diffuse melanosis. b) Suspicious spotty depigmentation / pigmentation over trunk/limbs. c) Mild diffuse thickening of soles and palms.
Grade II	Moderate	a) Definite spotty pigmentation / depigmentation on the trunk and limbs, bilaterally distributed. b) Severe diffuse thickening (with/without wart like nodules of the palms and soles).
Grade III	Severe	a) Definite spotty pigmentation/ depigmentation as above with few blotchy pigmented/depigmented macular patches over trunks or limbs. b) Pigmentation involving the undersurface of tongue and/or buccal mucosa. c) Larger nodules over thickened palms and soles occasionally over dorsal aspect of hands and feet. Diffuse verrucous lesions of the soles with cracks and fissures and keratotic horns over palms.

The concentration of total As in urine has often been used as an indicator of recent exposure because urine is the main route of excretion of most As species.[15,16] The half-time of inorganic As in human subject is about four days. Reported data on average

Table 4 : Case definition of chronic arsenic toxicity

Definite

1. Criteria 1 + Criteria 2 ± Criteria 3 ± Criteria 4 + Criteria 5
2. Criteria 1 + Criteria 2 (Grade II/III) ± Criteria 3 ± Criteria 4
3. Criteria 2 (Grade II/III) ± Criteria 3 ± Criteria 4 + Criteria 5

Probable

1. Criteria 1 + Criteria 2 (Grade I) ± Criteria 3 ± Criteria 4
2. Criteria 2 (Grade I) ± Criteria 3 ± Criteria 4 + Criteria 5
3. Criteria 2 (Grade II/III) ± Criteria 3 ± Criteria 4
4. Criteria 3 + Criteria 5
5. Criteria 4 + Criteria 5

background concentrations of As in the urine are generally below 10 µg/L in European countries, somewhat higher in some parts of the United States and around 50 µg/L in Japan.[17] Total As in urine has been used traditionally to assess occupational exposure to inorganic As. An average urinary concentration of 820 µg/L (median 580 µg/L) was reported by Pinto and McGill[18] in men exposed to As. Arsenic is normally found in higher concentrations in human hair and nails than in other parts of the body. This has been explained by the high content of kertin in these tissues.[19] Hair As levels can provide useful information in chronic As poisoning but the results should not be overinterpreted. In people with no known exposure to As, the concentration of As in hair is generally 0.02-0.2 mg/kg. Concentrations ranging from three to 10 mg/kg are reportedly common in people in areas in West Bengal that have high As concentrations in drinking water.[20] Normal As values in nails appear to range from 0.02 to 0.5 mg/kg[21,22] while four to 10 mg per kg have been reported in cases of chronic As poisoning.[23]

Though As level of hair and nails have been found to be elevated in people drinking As contaminated water there is no correlation regarding its level in hair and nail the degree of As exposure caused by drinking As contaminated water by the people.[10] Similarly there is no correlation regarding As level in hair and nails and clinical manifestation of chronic As toxicity among people drinking As contaminated water. In a village of West Bengal all the 17 people drinking As contaminated water had evidence of elevation of As level in hair and nail but only eight of them showed cutaneous lesion of As toxicity. Further out of 40 people with arsenical skin lesions in another village of West Bengal having history of drinking As contaminated water, normal As levels in their hair and nail samples were found in 31 and 26 cases respectively.[23]

Treatment

Chronic arsenicosis leads to irreversible damage in several vital organs and is a established carcinogen. Despite the magnitude of this potentially fatal toxicity, there is no effective therapy for this disease; patients once affected may not recover even after remediation of the As contaminated water. The need for an effective therapy for chronic arsenicosis is obvious.

Chelation therapy for chronic As toxicity is thought to be the specific therapy for relief of systemic clinical manifestations and reduction of As stores in the body, reducing subsequent cancer risk. Chelation therapy is presumed to be more effective with early features of the toxicity, as severe manifestation of polyneuropathy, chronic lung and liver disease, swelling of hand and legs, defect of hearing and vision are less likely to respond to this therapy. Chelating agents like, DMSA (Dimercaptosuccinic acid), DMPS (Dimercaptopropane succinate) and d-penicillamine have frequently been considered for treatment of chronic As toxicity. However, their usefulness are yet to be established.

Treatment for chronic As intoxication need to be directed towards a) stoppage of As exposure by providing As free safe water to the exposed population, b) providing specific drug for helping recovery and/or averting disease progression and c) general measures and symptomatic treatment. Stoppage of intake of As contaminated water and intake of nutritious diets can reduce some of the symptoms of chronic arsenicosis. Whether this could prevent the development of cancer is not known. No specific drug for altering the natural history of the disease has yet been available. However, supportive and symptomatic treatment could help a lot to reduce the suffering of patients. Early diagnosis of skin and bladder cancer caused by chronic arsenicosis could be managed successfully by surgery. But the prognosis of other cancers, e.g. lung cancer, liver cancer are bleak.

Conclusion

The diagnosis of chronic arsenic toxicity is based on history of exposure of As for porlonged period associated with demonstration of various non carcinogenic (specifically cutaneous) and/or carcinogenic manifestation of chronic arsenic toxicity. Though confirmation of the diagnosis is based on detection of high levels of As in urine, hair/nails, their normal value does not preclude such diagnosis. The treatment is mostly symptomatic as the efficacy of chealating agents are yet to be established. Arrangement of arsenic free water and surveillance programme for early detection of skin and bladder cancer could save many lives from the effect of chronic arsenic toxicity.

References

1. **National Research Council.** *Arsenic in drinking water.* National Academy press. Washington DC 1999; 84 : 131.
2. **Voegtlin C, Rosenthal SM, Johson JM.** *Pub Health Rep* 1931; 46 : 339-354. Quoted by Williams ML, Quantitative toxicological evaluation of inorganic arsenic, USEPA, Washington DC. 1988; VIII-24.
3. **Squibb KS, Fowler BA.** In : Biological and environmental effects of arsenic. *Elsevier and Fowler* (eds). 1983; 233-67.
4. **Goodman Gillman's.** The pharmacological basis of therapeutics. Ed.:Harman JG, Limberd LE, Molinoff PB, Ruddon RW and Gilman. MC Graw - Hill, New York 1996; 9 : 1661-2.
5. **Santra A, Maity A, Das S, Lahiri S, Chakraborty S, Guha Mazumder DN.** Hepatic damage caused by chronic arsenic (As) toxicity in experimental animal. *Clinical Toxicol* 1998; 36 : 683-90.
6. **Casarett LJ, Doul J.** Toxicology, Mc Millan Publishing Co., New York 1986. Quoted by Williams ML, Quantitative toxicological evaluation of inorganic arsenic, USEPA, Washington DC. 1988; VIII-24.
7. **Chen B, Burt CT, Goering PL, Fowler BA, London RE.** In vivo 31-P nuclear magnetic resonance studies of arsenite induced changes in hepatic phosphate levels. *Biochem Biophys Res Commun* 1986; 139 : 228-34.
8. **Guha Mazumder DN, Chakraborty AK, Ghosh A, *et al.*** Chronic arsenic toxicity from drinking tubewell water in rural West Bengal. *Bull Wld Health Org* 1988; 66 : 499-506.
9. **Guha Mazumder DN, Das Gupta J, Chakraborty AK, Chatterjee A, Das D, Chakraborty D.** Environmental pollution and chronic arsenicosis in South Cacutta. *Bulletin of the World Health Organization* 1992; 70 : 481-5.
10. **Guha Mazumder DN, De BK, Santra A, Das Gupta J, et al.** Chronic arsenic toxicity : Epidemiology natural history and treatment in arsenic : Exposure and health effects, WR Chappell, CO Abernathy, RL Calderon, and eds. London : Chapman and Hall. 1999; 335-347.
11. **Guha Mazumder DN, Das Gupta J, Santra A, Pal A, Ghosh A, Sarmar S.** Chronic arsenic toxicity in West Bengal - The Worst Calamity in the World. *JIMA* 1998; 96 : 4-7,18.
12. **Saha KC.** Melanokeratosis from arsenic contaminated tubewell water. *Ind J Dermat.* 1984; 29 : 37-46.
13. **Tseng WP.** Effects and dose-response relationships of skin cancer and blackfoot disease with arsenic. *Environ Health Perspect* 1977; 19 : 109-19.
14. **Zaldivar R, Prunes L, Ghai G.** Arsenic dose in patients with cutaneous carcinomata and hepatic hemangio-enothelioma after environmental and occupational exposure. *Arch Toxicol* 1981; 47 : 145-54.
15. **Buchet JP, Lauwerys R, Roels H.** Comparison of the urinary excretion of arsenic metabolites after a single oral dose of sodium arsenite, monomethylarsonate, or dimethylarsinate in man. *Int Arch Occup Environ Health*

1981; 48 : 71-9.

16. **Vahter M.** Species differences in the metabolism of arsenic compounds. *Appl Organomet Chem* 1994; 8 : 175-82.
17. **Yamauchi H, Takahashi K, Mashiko M, Saitoh J, Yamamura Y.** Intake of different chemical species of dietary arsenic by Japanese and their blood and urinary arsenic levels. *Appl Organomet Chem* 1992; 6 : 383-88.
18. **Pinto SS, McGill CM.** Arsenic trioxide exposure in industry. *Ind Med Surg* 1953; 22 : 281-7.
19. **Shapiro HA.** Arsenic content of human hair and nails. Its interpretation. *J Forensic Med* 1967; 14 : 65-71.
20. **Das D, Chatterjee A, Mandal BD, Samanta G, Chakraborti D, Chanda B.** Arsenic in ground water in six districts of West Bengal, India : The biggest arsenic calamity in the world. Part 2. Arsenic concentration in drinking water, hair, nail, urine, skin-scale and liver tissue (biopsy) of the affected people. *Analyst* 1995; 120 : 917-24.
21. **Narang APS, Chawls LS, Khurana SB.** Levels of arsenic in Indian opium eaters. *Drug Alcohol Depend* 1987; 20 : 149-53.
22. **Takagi Y, Matsuda S, Imai S, et al.** Survey of trace elements in human nails : An international comparison. *Bull Environ Contam Toxicol* 1988; 41 : 690-5.
23. **Chowdhury TR, Mandal BK, Samanta G, et al.** Arsenic in groundwater in six districts in West Bengal, India : the biggest arsenic calamity in the workd : the status report up to August, 1995. *Arsenic Exposure and health effects*, Eds. CO Abernathy, RL Calderon and WR Chappell, Chapman and Hall, London. 1997; 9 : 93-111.