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Chronic arsenic toxicity from drinking tubewell water in rural West Bengal

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Hepatic damage caused by chronic exposure to arsenic has been frequently described. Here we report on 13 patients from West Bengal, India, who consumed large amounts of arsenic in drinking water. An epidemiological investigation of the study area showed evidence of chronic arsenical dermatosis and hepatomegaly in 62 (92.5%) of 67 members of families who drank contaminated water (arsenic level, 0.2–2 mg/l). In contrast, only six (6.25%) of 96 persons from the same area who drank safe water (arsenic level, < 0.05 mg/l) had non-specific hepatomegaly, while none had skin lesions. Hepatomegaly occurred in all the 13 patients who were studied in detail, although five had splenomegaly. Biopsy of samples of liver from these patients revealed various degrees of fibrosis and expansion of the portal zone that resembled non-cirrhotic portal fibrosis (NCPF).

In a few villages in West Bengal, India, arsenical dermatosis has been observed in individuals who drink subsoil water that contains a high level of arsenic (*1*). Among the noncarcinogenic effects of long-term exposure to arsenic are hyperkeratosis, hyperpigmentation, and peripheral vascular and neurological damage (*2*). Non-cirrhotic portal hypertension (NCPH) following chronic arsenic intake has also been reported (*3–5*), and cirrhosis due to the toxic effects of chronic arsenic exposure has been described (*2, 6–8*).

Non-cirrhotic portal fibrosis (NCPF) is frequently seen in West Bengal (*9, 10*) and chronic intake of arsenic may produce this condition. We therefore undertook a study to characterize the liver damage in a group of patients who, for prolonged periods, had been drinking water containing high levels of arsenic. An epidemiological study of the patients' area of residence was also carried out to determine whether there was an association betwen hepatic involvement and consumption of drinking water that contained arsenic levels greater than the tolerable limit recommended by WHO.

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MATERIALS AND METHODS

Thirteen patients (8 male, 5 female) from six families who lived in two hamlets in the village of Ramnagar, West Bengal, and who exhibited signs of chronic arsenical dermatosis, were admitted to the Institute of Post-Graduate Medical Education and Research, Calcutta, for investigation. Also, an epidemiological study of residents of the affected area was carried out by house-to-house visits. Ramnagar is situated 40 km south of Calcutta in the Ganges delta region, far away from industrial areas. The socioeconomic status of the people, their occupation, type of housing, dietetic habits, and source of drinking water were recorded. Those surveyed were examined clinically, paying particular attention to detection of skin manifestations and liver involvement. Also, water samples were collected from the tubewells used for drinking purposes. The level of arsenic in the water samples was determined spectrophotometrically in the Department of Sanitary Engineering, All India Institute of Hygiene and Public Health (*11*).

The 13 study patients admitted to hospital were thoroughly examined clinically and the following investigations were carried out: routine examination of blood, urine, stools, liver function tests (bilirubin, total protein and albumin, SGOT, SGPT, and alkaline phosphatase levels), determination of prothrombin time, 45 minutes' bromsulphthalein retention test, chest X-ray, and recording of electrocardiogram and electromyogram. All the patients studied were negative for hepatitis B surface antigen (HBsAg). Biopsies were carried out on two samples of liver tissue from

each patient. The first sample was stained with haematoxylin–eosin and reticulin, while the arsenic content of the second sample, together with that of samples of hair and nails, was estimated by neutron activation analysis (12). Upper gastrointestinal endoscopy and splenoportal venography were performed and the intrasplenic pressure was measured in order to detect any oesophageal varices or portal hypertension (*13*). Unfortunately, no haemodynamic studies could be performed since the patients refused permission.

RESULTS

The results of the epidemiological survey of the two affected hamlets of Ramnagar showed that most of the inhabitants were of a low socioeconomic class and lived in mud houses; only two of the families resided in brick houses. The source of drinking water for all the people in the village was a shallow tubewell (depth, 36.5–45.7 m). Most of the inhabitants worked the land or were day labourers, though a few belonged to middle-class families and were employed in offices. None of the people habitually ate seafood. A group of 48 persons from eight families who lived in one cluster drank water from a public tubewell (number 1) that contained a very high level of arsenic (2 mg/l) (see Table 1); in addition to mottled hyperpigmentation of the skin, 46 (95.8%) of these persons had hepatomegaly. The two members of the families who were not affected had lived elsewhere for some time. Also, of two unaffected members of the family that drank water from tubewell number 2, one was a baby aged 4 months and the other was a woman who had come to the village only a few months previously after her marriage. The one unaffected member of the family that drank water from tubewell number 3 was a baby aged 6 months. Although the overall prevalence of hepatomegaly was 92.6% (62 out of 67) among people drinking water that contained levels of arsenic considerably greater than the limit recommended by WHO (0.05 mg/l) (*14*), the prevalence was much lower (6 out of 96; 6.25%) among residents of the same area who drank water containing a level of arsenic below this limit.

The ages of the 13 patients investigated in detail ranged from 15 to 50 years (10 were aged 20–40

Table 1. Epidemiological data for Ramnagar village, West Bengal

Village hamlet and tubewell number		Arsenic concentration of tubewell water (mg/l)	No. of people drinking tubewell water	No. of people with skin pigmentation	No. of people with hepatomegaly	Attack rate of hepatomegaly (%)
Arsenic concentration > 0.05 mg/l						
Gharamipara	1	2.0	48	46	46	95.8
	2	0.2	8	6	6	75
	3	0.725	7	6	6	85
Bakerpara	4	0.2	4	4	4	100
Total			67	62	62	92.5
Arsenic concentration < 0.05 mg/l						
Gharamipara	5	ND[a]	11	0	0	
	6	0.035	8	0	0	
	7	ND	26	0	3	
	8	0.037	16	0	1	
Bakerpara	9	0.022	7	0	1	
	10	ND	12	0	0	
	11	0.031	16	0	1	
Total			96	0	6	6.25

[a] ND = not detectable.

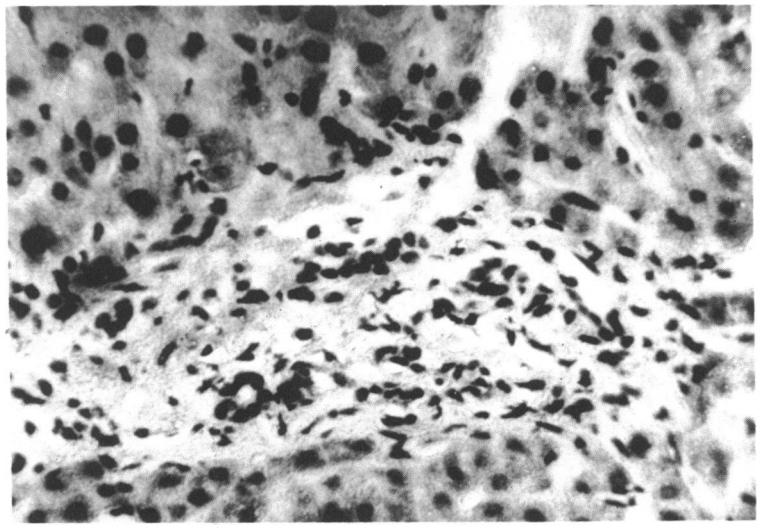

Fig 1. Photomicrograph of liver biopsy from a patient showing expansion of portal zone containing a few round cells (case 5) (haematoxylin–eosin stain, ×200).

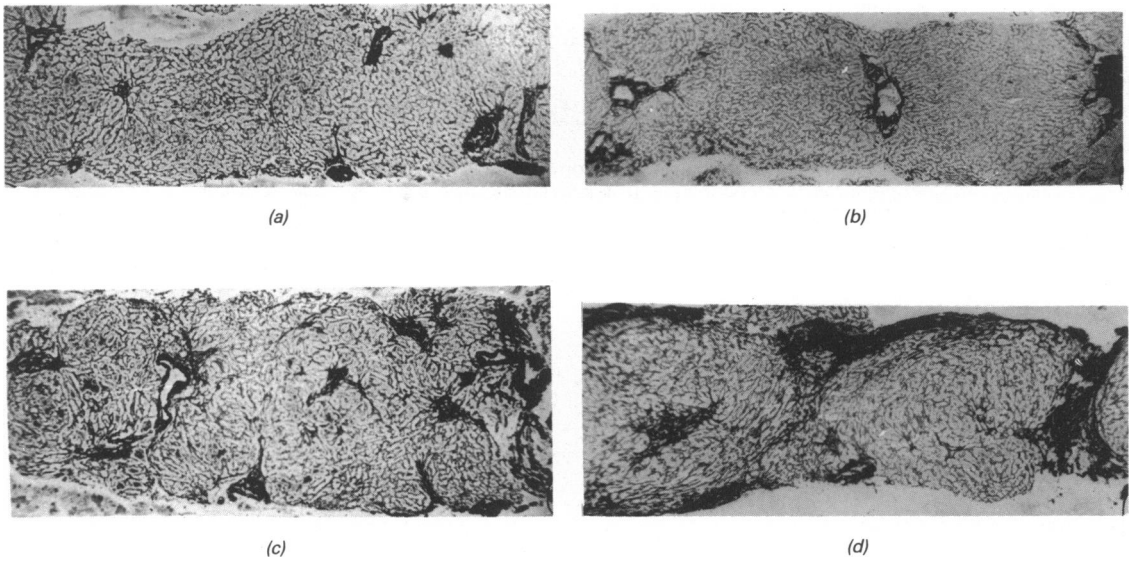

Fig 2. Photomicrographs of liver biopsy specimens from study patients. *(a)* Grade I fibrosis—mild fibrosis producing expansion of portal zone (case 8). *(b)* Grade II fibrosis—expansion of portal zone with thin fibrous extension producing septae (case 6). *(c)* Grade III fibrosis—moderate fibrosis in the portal zone with thick septae; tendency to mild pseudolobulation is seen with slender bands. *(d)* Grade IV fibrosis—dense fibrosis within the liver with a marked tendency to pseudolobule formation (case 4) (reticulin stain ×25).

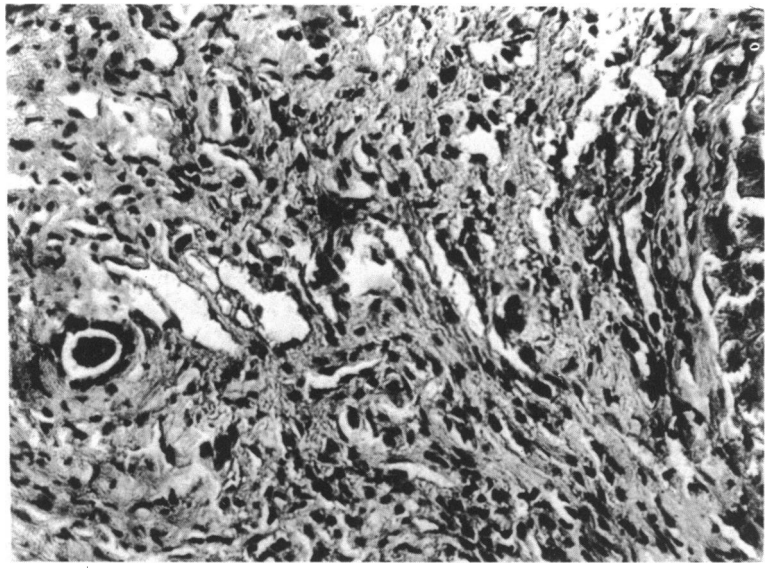

Fig 3. Photomicrograph of biopsy from a patient showing a portal zone with multiple vascular channels and significant fibrosis (case 10) (haematoxylin–eosin stain, ×200).

years). The clinical features presented by these patients are given in Table 2. All exhibited mottled dark-brown (rain drop) pigmentation distributed over the whole body and limbs, while 10 patients had hyperkeratosis of the palms and soles. Also, in six patients the pigmentation was present on the mucous membrane of the oral cavity, including the underside of the tongue. The liver was palpable and firm in all patients. Gross splenomegaly (7 cm) occurred in only one patient, who also had ascites and exhibited haematemesis and melena on two occasions during her stay in the hospital (1.5 months). The spleens of four other patients were also palpable ($\leqslant 3$ cm). The haemoglobin levels in the 13 patients varied from 10 g to 13 g per 100 ml blood. No abnormality was detected in the differential lymphocyte count or in the blood sugar, urea, and creatinine levels of any of the patients. Traces of albumin were found in the urine of two patients. Also, *Ascaris lumbricoides* was detected in the stools of six patients, *Entamoeba histolytica* in those of three patients, while *Ancylostoma duodenale* and *Trichuris trichiura* were found in the stools of one patient each.

Although the results of routine liver function tests were normal, the prothrombin time for one patient was elevated, while the bromsulphthalein retention tests of three patients were abnormal (13.8%, 13.1%, and 15.3%). The electrocardiograms of all patients were normal, but the electromyograms of the eight patients from whom these measurements were obtained showed mild to moderate neuropathic patterns. Histological studies of samples of liver showed enlargement and fibrosis of varying degrees in the portal regions (Fig. 1 and 2). Fibrous extensions from the portal tracts that produced septae were observed in 10 patients, six of whom showed a tendency to pseudolobule formation. The limiting plates of parenchyma were intact in most patients, but in some, advancing fibrous tissue (septae) divided the liver lobules into small segments. Slight-to-moderate accumulations of lymphoid cells were visible in the portal tracts and in the interlobular areas; however, frank cirrhosis was not observed in any case. In some patients, portal vein branches were replaced by multiple vascular channels (Fig. 3). Bile ductular proliferation occurred also in the dense fibrous portal tracts and septae. However, gross abnormalities were not observed in the liver parenchyma and there was no accumulation of cells in the sinusoids. A liver biopsy of the only patient who had ascites, haematemesis, melena, and gross splenomegaly (case 1) yielded only scar tissue and fragmented liver lobule. Unfortunately, this patient did not consent to a further biopsy or to other investigations except endoscopy. Oesophageal varices were observed in this patient and in two of the other four patients in whom splenomegaly was identified by upper gastrointestinal endoscopy. Splenoportal venography indicated that four of the five patients with splenomegaly had increased intrasplenic pressure (30–36 cm saline) and evidence of intrahepatic portal vein obstruction. The intrasplenic pressure in the other nine patients studied was normal (16–20 cm saline).

Table 2. Clinical features among the 13 patients investigated in the study

Clinical feature	No. of patients
Anorexia	4
Nausea	3
Vomiting	3
Diarrhoea	1
Abdominal pain	10
Heartburn	2
Tingling and numbness of hands and feet	10
Pigmentation	13
Thickening of palms and soles	10
Anaemia	13
Weakness of limbs	2
Hepatomegaly (2–4 cm)	13
Splenomegaly (3–7 cm)	5
Ascites	1

The level of arsenic in the tubewell water drunk by the patients, together with the duration of their intake and the level of arsenic in patients' hair, nails, and liver biopsy material are shown in Table 3. The level of arsenic in the water was much higher than the value of 0.05 mg/l recommended by WHO as the limiting concentration, while its level in hair, nails, and liver tissues was also greater than the levels in the controls.

DISCUSSION

The results of the study indicate chronic toxicity caused by drinking tubewell water that contained a high level of arsenic in a village in the Ganges delta region far away from sources of industrial pollution. Generally, the total arsenic level of ground and surface water in this area is less than 10 μg/l, although levels greater than 1 mg/l have been recorded for deep tubewell water or in areas where industrial effluent has led to severe contamination (2). It is therefore interesting that the village in our study used water

Table 3. Relationship between the amount of arsenic ingested by patients, its level in various body tissues, and the severity of hepatic lesions

Patient	Age (years)/ sex[a]	Arsenic concentration in tubewell water (mg/l)	Duration of water intake (years)	Arsenic level (mg/kg) in: Hair	Nails	Liver (dry weight)	Liver lesions[b]: Fibrosis in portal zone	Enlargement of portal zone	Tendency to pseudolobule formation	Multiple vascular channel in portal tract
1	43/F	0.75	10[c]	7.5	24	ND[d]	+ + + +[e]			
2	26/F	2	4	13.3	66	1.5	+	none	none	+
3	25/F	2	4	1.4	40	1	+ +	+	none	+
4	23/F	2	4	7.1	57	0.5	+ + + +	+	+	+
5	47/M	2	1[c]	7.7	27	3	+	+	none	+
6	22/M	2	1	3.8	16	1.5	+ +	+	+	+
7	36/M	2	4[c]	20	41	ND	+ +	+	none	+
8	31/M	2	4[c]	7.4	31	1.5	+	+	+	+
9	30/M	2	4	ND	24	1	+ + +	+	+ +	+
10	30/M	0.5	20[c]	4.7	26	ND	+ + + +	+	+	+
11	25/M	0.22	1	7.1	ND	2	+	none	none	none
12	40/F	2	1	6	29	6	+ + +	+	+	+
13	18/M	2	1	3.6	27	3	+ + +	+	none	+
Control values		<0.05 ($n = 96$)		0.15 ± 0.35 ($n = 5$); $P < 0.001$	0.34 ± 0.25 ($n = 5$); $P < 0.001$	0.16 ± 0.04 ($n = 5$); $P < 0.01$				

[a] M = male; F = female.

[b] Grading of fibrosis: + to + + + +.

[c] Presence of portal hypertension.

[d] ND = not detectable.

[e] Unsatisfactory liver biopsy showing scar tissue and fragmented liver lobule. The patient had ascites, gross splenomegaly, and a history of haematemesis.

from shallow tubewells located far away from industrial activity. Arsenic could not be detected in samples of water from deep tubewells in the area. None of the affected people was in the habit of eating seafood, which is known to contain a high level of arsenic (*2*). Similarly, samples of soil from the area did not contain any appreciable levels of arsenic (*15*). Thus, although the source of the arsenic was water from shallow tubewells, its origin was not determined. The results of the epidemiological study showed not only evidence of the typical mottled skin pigmentation caused by arsenic toxicity but also of hepatomegaly in most of those who drank water containing arsenic at levels greater than the 0.05 mg/l limiting concentration recommended by WHO (*14*). Hepatomegaly was observed in 92.5% of those (67) who drank the contaminated water (arsenic content 0.2–2 mg/l), while six of the 96 individuals (6.25%) who drank water containing less than 0.5 mg/l arsenic had mild non-specific hepatomegaly but no skin changes.

All of the 13 patients with arsenic toxicity who were investigated in the study had skin pigmentation and hepatomegaly. Evidence of neuropathy was found in the eight patients investigated by electromyography, although, in contrast to previous reports, none showed any ECG abnormality or sign of peripheral vascular disease (*2*).

Although liver damage caused by chronic arsenic toxicity has been reported frequently, its nature and effect on portal haemodynamics have been variously described (*2–8, 16–18*). We have presented here data on the largest reported series of patients who exhibited portal fibrosis following intake of drinking water contaminated with arsenic. However, definite evidence of portal hypertension was observed in only five cases. The almost normal liver function tests and absence of gross damage to hepatocytes in the study

cases are consistent with previous reports (*3, 5*). Also, the features of the periportal fibrosis and multiple vascular channels in expanded portal zones are in accord with the results of other studies of NCPF in India (*5, 9, 19–21*). The hepatic histology described by Morris et al. (*3*) in cases of NCPH caused by chronic arsenic toxicity did not include extension of fibrosis from the portal tract or any tendency to the pseudolobule formation that we saw in our cases. However, like us, they did observe an expansion of the portal zone. In contrast, Franklin et al. (*7*) reported periportal fibrosis that extended intralobularly in one of the three cases of arsenic toxicity they studied. Fibrosis of the portal tract with septae in two patients was also described by Rosenberg (*8*). Finally, Datta et al. (*5*) reported a higher level of arsenic in the livers of four out of nine patients who had NCPF with portal hypertension, although only two of them had drunk water containing a high concentration of arsenic. Also in the last-mentioned study, skin manifestations, such as typical pigmentation of the body or hyperkeratosis of the palms and soles, occurred in only one patient.

The arsenic level in the hair of five normal patients in our study was 0.15 ± 0.35 mg/kg, which is consistent with previously published values (*2*).

Although it has been established that chronic arsenic intake can produce NCPF, the results of the present study indicate that portal hypertension is not a necessary consequence. The absence of any precise correlation between the level of arsenic in liver tissue and portal venous pressure has been reported previously (*5*) as has the lack of clear correlation between the degree of portal fibrosis and the magnitude of portal pressure (*21*). The etiology of portal hypertension in patients with chronic arsenic toxicity has been ascribed to changes in the branches of veins in the portal tracts (*3, 5*), which is consistent with the vascular changes that we observed in patients with portal hypertension. However, we did not observe vascular lesions such as intimal thickening of arteries in the portal region or the cirrhotic changes described by Rosenberg (*8*) in children who drank arsenic-contaminated water. Although we examined only samples of liver obtained by needle biopsy, such changes have not been reported for wedge biopsy studies of liver on patients with chronic arsenic toxicity (*3, 5*).

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RÉSUMÉ

TOXICITÉ ARSENICALE CHRONIQUE DE L'EAU DE BOISSON PROVENANT DE PUITS INSTANTANÉS DANS LES RÉGIONS RURALES DU BENGALE-OCCIDENTAL

On observe dans quelques villages du Bengale-Occidental, en Inde, une dermatose arsenicale chez les sujets qui boivent de l'eau contenant de fortes concentrations d'arsenic. Par le passé, on a signalé diverses atteintes hépatiques chez des sujets souffrant d'une intoxication arsenicale chronique. Sont ici décrits les résultats d'une étude approfondie portant sur 13 malades atteints d'intoxication arsenicale chronique, étude au cours de laquelle on s'est particulièrement attaché à établir la nature des atteintes hépatiques.

Une étude épidémiologique de la région a indiqué que 62 personnes sur 67 (92,5%) buvaient de l'eau contaminée par de l'arsenic (concentration d'arsenic: 0,2–2 mg/l) et montraient tous les signes d'une dermatose arsenicale chronique et d'une hépatomégalie, tandis que 6 personnes sur les 96 étudiées qui ne buvaient pas d'eau contaminée (6,25%) (concentration d'arsenic inférieure à 0,05 mg/l) ne montraient qu'une hépatomégalie non spécifique et ne présentaient aucune manifestation cutanée.

Une hépatomégalie d'importance variable (2 à 4 cm) a été observée chez les 13 sujets de l'étude approfondie. On a également observé une splénomégalie (3 à 7 cm) chez 5 de ces malades. Les épreuves classiques de la fonction hépatique se sont révélées normales chez tous ces malades, mais le temps de Quick était anormal chez l'un d'eux, et 3 autres montraient des anomalies dans l'épreuve à la bromesulfonephtaléine. Tous les électrocardiogrammes étaient normaux, mais les électromyogrammes des 8 sujets chez qui on les a obtenus ont montré des lésions nerveuses bénignes à modérées. On a observé dans le foie de tous les sujets étudiés une hypertrophie des espaces portes avec divers degrés de fibrose. On a également observé des extensions fibreuses à partir des espaces portes, avec apparition de septums chez 10 malades, dont 6 montraient une tendance à

la pseudolobulation. Aucune cirrhose franche n'a été observée. Chez un des malades, les troncs veineux avaient été remplacés par des dérivations vasculaires multiples dans la zone porte. En outre, 5 malades ont montré une hypertension portale, mise en évidence par une pression intrasplénique élevée (30 à 36 cm de soluté physiologique). L'endoscopie a révélé des varices œsophagiennes chez 3 malades.

On a déterminé la concentration en arsenic de prélèvements de cheveux, d'ongles et de tissu hépatique chez tous les malades et elle s'est avérée plus élevée que chez les témoins. Cette étude a mis en lumière le fait que l'intoxication chronique par l'arsenic est relativement commune en Inde chez les personnes qui boivent de l'eau contaminée puisée dans le sous-sol. L'atteinte hépatique est un symptôme d'accompagnement important de cette intoxication et les lésions observées sont identiques à celles qui accompagnent une fibrose portale non cirrhotique.

REFERENCES

1. GORAI, R. ET AL. Chronic arsenic poisoning from tubewell water. *Journal of the Indian Medical Association*, **82**: 34–35 (1984).
2. *Arsenic*. Geneva, World Health Organization, 1981 (Environmental Health Criteria Series, No. 18).
3. MORRIS, J. S. ET AL. Arsenic and non-cirrhotic portal hypertension. *Gastroenterology*, **64**: 86–94 (1974).
4. DATTA, D. V. Arsenic and non-cirrhotic portal hypertension. *Lancet*, **1**: 433 (1976).
5. DATTA, D. V. ET AL. Chronic oral arsenic intoxication as a possible factor in idiopathic portal hypertension (non-cirrhotic portal fibrosis) in India. *Gut*, **20**: 378–384 (1979).
6. HUTCHINSON, J. Diet and therapeutics. *Archives of surgery*, **6**: 389–391 (1895).
7. FRANKLIN, M. ET AL. Fowler's solution as an etiologic agent in cirrhosis. *American journal of the medical sciences*, **219**: 589–596 (1950).
8. ROSENBERG, H. G. Systemic arterial disease and chronic arsenicism in infants. *Archives of pathology*, **96**: 360–365 (1974).
9. BASU, A. K. ET AL. Non-cirrhotic portal fibrosis with portal hypertension—a new syndrome. Parts I and II. *Indian journal of medical research*, **55**: 336–359 (1968).
10. GUHA MAZUMDER, D. N. ET AL. Search for aetiological factors of non-cirrhotic portal fibrosis. *Indian journal of gastroenterology*, **3**: 25–26 (1984).
11. *Standard methods for examination of water and waste water*, 14th edition. New York, American Public Health Association, 1967, p. 283.
12. OBRUSNIK, I. ET AL. Indication of environmental pollution by means of INNA of the hair of some free-living mammals. *Journal of radioanalytical and nuclear chemistry*, **83**: 397–406 (1984).
13. GUHA RAY, B. N. ET AL. Direct splenocaval shunt for selective decompression of portal hypertension in children. *Surgery*, **87**: 271–279 (1980).
14. *Guidelines for drinking water quality, Volume 1*. World Health Organization, Geneva, 1984.
15. CHAKRABORTY, A. K. ET AL. Arsenical dermatosis from tubewell water in West Bengal. *Indian journal of medical research*, **85**: 326–334 (1987).
16. CLINICOPATHOLOGICAL CONFERENCE. Chronic arsenical poisoning and non-cirrhotic portal hypertension—a case for diagnosis. *British medical journal*, **4**: 725 (1971).
17. HUET, P. M. ET AL. Non-cirrhotic presinusoidal portal hypertension associated with chronic arsenical intoxication. *Gastroenterology*, **68**: 1270–1277 (1975).
18. VIALLET, A. ET AL. Presinusoidal portal hypertension following chronic arsenic administration. *Gastroenterology*, **62**: 177 (1972).
19. *Workshop on Non-Cirrhotic Portal Fibrosis*. New Delhi, Indian Council of Medical Research, 1969, pp. 36–45.
20. SAMA, S. K. ET AL. Non-cirrhotic portal fibrosis. *American journal of medicine*, **51**: 160–169 (1971).
21. NAYAK, N. C. ET AL. Obliterative portal venopathy of the liver associated with so-called idiopathic portal hypertension or tropical splenomegaly. *Archives of pathology*, **87**: 359–369 (1969).