SPONTANEOUS HYPOGLYCAEMIA, HEPATIC AND RENAL NECROSIS FOLLOWING THE INTAKE OF HERBAL MEDICINES

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During an investigation of hypoglycaemia in African patients, it was noticed that some did not respond to intravenous dextrose solution and death occurred soon after admission. At necropsy there was an acute diffuse centrilobular zonal necrosis of the liver and, in many cases, a bilateral acute tubular necrosis. For a number of years these lesions had been found at necropsy but their aetiology remained unknown. The investigation of hypoglycaemia was therefore extended to cases presenting with jaundice and anuria. Many of the patients who died of the disease came from the outlying districts or African reserves and most of them had taken African herbal medicines immediately before the onset of the symptoms. Herbal medicine was obtained from the relatives of 2 sisters who died following its consumption. When this was administered to rats via the intraperitoneal route, typical lesions were produced in the liver and kidney.[1] The toxic role of herbal medicine thus became apparent. In this paper illustrative cases of the disease following the intake of herbs either orally or rectally as enemas, are presented. This toxic hepatitis is then compared with infective hepatitis.

MATERIAL AND MTEHODS

The clinical material consists of 11 patients in whom disease was considered to be the result of herbal medicines and 12 patients with infective hepatitis. Biochemical and haematological investigations were done on all. Biochemical investigations, using methods previously listed,[2] included total serum bilirubin, alkaline phosphatase activity (KA units), serum glutamic oxalacetic acid transaminase (SGOT, Karmen units), prothrombin index, blood-sugar and blood-urea. Routine testing of urine was done on all the patients.

RESULTS

1. *Patients who used Herbal Medicines*

(a) *Illustrative cases. Cases 3 and 4.* Two sisters aged 7 and 14 years respectively, were admitted to King Edward VIII Hospital in a state of collapse on 23 April 1960. The 7-year-old child died soon after admission. A history taken from the relatives revealed that both had taken herbal medicine with their supper 2 nights before admission and on the following morning were vomiting and complaining of epigastric pain. The older child was semi-comatose, mildly dehydrated and cold. The pulse was 120 per minute and the blood pressure was not recordable. This child also died on the day of admission.

Special investigations. Electrolytes: Na 117 mEq./l., K 7·2 mEq./l., Cl 103 mEq./l., Hb 17·5 G/100 ml.; white cells 15,000/cu.mm. The blood sugar was not done. Necropsy showed diffuse centrilobular hepatic necrosis in both and acute tubular necrosis of the kidneys in case 4. The plant from which the herbal medicine was made, was identified as *Adenia gummifera* (*imfulwa*).

Case 8. A male African child aged 16 months was admitted to hospital on 14 September 1960, semi-comatose. The history obtained from the father was that the child had had diarrhoea for 4 days without anorexia, nausea or vomiting. On the morning before admission he was given herbal medicine by a witchdoctor. The same evening the child was weak and the following day he became unconscious and was brought to hospital. On examination the child was found to have oedema of the feet, a slow pulse, blood pressure 95/65 and an enlarged liver. Hypoglycaemia was suspected.

Special investigations. Blood sugar 30 mg./100 ml.; CSF sugar 15 mg./100 ml., serum bilirubin 3·1 mg./100 ml., white cells 23,000/cu.mm. and blood urea 54 mg./100 ml. The remaining results are given in Tables II and IV. There was thus evidence of liver and renal damage. The child was placed on a protein-free diet, restricted fluids and terramycin syrup. He recovered completely, after a severe illness for the first 72 hours, and was discharged on 27 September 1960. Liver biopsy performed during the acute phase showed centrilobular zonal necrosis.

Case 9. An African female aged 24 years was admitted to hospital on 15 October 1960, with a history of abdominal pain of 10 days' duration. Her appetite was poor and she had nausea and vomiting. At the beginning of her illness she had had an enema made from herbs and she also consumed herbal medicine twice a day until the day of admission. She had apparently passed no urine for 6 days prior to coming to hospital. On examination the patient looked ill and toxic. There was marked icterus and subconjunctival haemorrhage. The temperature was 102°F and the liver was enlarged and tender. The diagnosis appeared to be between infective hepatitis and toxic hepatitis from herbal medicine.

Special investigations. The urinary urobilin was increased ++ and bilirubin +, prothrombin index 73%, Hb. 11·4 G/100 ml., white cells 20,000/cu.mm. with toxic changes in the leukocytes; blood urea 300 mg./100 ml., serum bilirubin 8·3 mg./100 ml., thymol turbidity 2 units, serum Na 139 mEq./l., serum K 5·1 mEq./l., serum Cl. 99 mEq./l. and SGOT 128 KA units. These findings suggested toxic hepatitis with tubular necrosis rather than infective hepatitis. Unfortunately, there was no record of the urinary output on the first 2 days but on the third day the patient passed 240 ml. of urine of SG 10·10. Pericardial friction rub, suggesting uraemic pericarditis, was heard. The urinary output on the fourth day was 600 ml. and on the fifth day 1,200 ml., after which the output was over 1,500 ml. per day. The patient was treated as a case of tubular necrosis and made a good recovery. Liver biopsy done on the sixth day after admission showed normal architecture and absence of inflammatory cell infiltration in the parenchyma and portal tracts. Table I gives the daily biochemical and haematological findings. The clinical, biochemical and haematological findings of patients with signs of toxic hepatitis are shown in Table II, while in Table IV a case of toxic hepatitis and renal damage

TABLE I. CASE 9

Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
SGOT					128	320	68	62	44			42	38	50			20
PT				73	68	76	70	78		83	80	85	85	100			100
S. bilirubin			8·3		6·2	4·8	2·1			1·5	1·3	1·1	1·1	1·2			1·5
Alk. phos.					16	19	18			17	13		12	17			17
Blood urea			300	275	206	190	280	240	199	215	143	126	80	64	43		32
WBC × 1,000			20			17											
Electrolytes																	
Na				139	135	130	137	128	130	130	133	130	130	130	121		130
K				5·1	4·7	4·4	4·9	3·9	3·1	5·2	5·6	6·0	5·9	6·4	5·1		5·4
Cl.				99	106	104	106	101	102	107	121	117	106	106	104		107

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TABLE II. FINDINGS ON ADMISSION—HERBAL TOXIC HEPATITIS

Case no.	1*	2*	3†	4†	5	6	7	8	9‡	10	11
Age	13	6	7	14	21	65	34	16/12	25	5	2
Sex	F	M	F	F	F	M	F	M	F	F	F
Herbal medicine	?	?	Yes	Yes	?	Yes	?	Yes	Yes	Yes	Yes
History	Abd. pain	Epigastric pain, fits	Abd. pain	Abd. pain	Fits	Vomiting	Vomiting	Abd. pain	Abd. pain	Fits	Fits
Level of conciousness	Coma	Coma	Coma	Semi-coma	Stupor	Coma	Semi-coma	Semi-coma	Fully conscious	Coma	Coma
Jaundice	Nil	Nil	—	Nil	Nil	Nil	Nil	Nil	++	Nil	Nil
Foetor hepaticus	Nil	Nil	—	Nil	Nil	Nil	Nil	Nil	Nil	Nil	Nil
Liver	Tender	Nil	—	Nil	Nil	1 Fd. Tender	Tender RUQ	1 Fd.	1 Fd.	1 Fd.	Nil
Spleen	Nil	Nil	Nil	Nil	Nil	Nil	Nil	Nil	Nil	Nil	Nil
WBC × 1,000	33	36	—	15	21	20	20	23	20	32	35
Urea	123	35	—	—	28	26	220	54	300	41	—
Urine:											
Albumin	++	+						+	Nil	++	+
24 hr. output (ml.)								100	240	250	
SGOT	0	6	—	—	10	0	—	12	128§	36	0
PI	0	—	—	—	0	29	58	0	73	0	28
S. bilirubin	2·3	0·9	—	—	1·2	1·8	1·5	3·1	8·3	3·5	2·1
Alk. phos.	—	—	—	—	11	12	29	24	2	40	3
Blood sugar	13	9	—	—	15	27	160	30	—	23	20
Prognosis	D	D	D	D	D	D	D	A	A	A	D
Pathological findings	CZN ATN	CZN	CZN	CZN ATN	CZN ATN	CZN	CZN ATN	CZN	Liver NAD	—	CZN

*Sister and brother. †Sisters. ‡Biochemical tests 3rd day. §Test done on 5th day. D = Dead. A = Alive. CZN = Diffuse centrilobular zonal hepatic necrosis ATN = Acute tubular necrosis kidneys. NAD = Nil abnormal detected. (Cases 1—7, 11 Necropsy. Cases 8—9 Liver biopsy).

is compared with infective hepatitis.

(b) *Pathological findings.* Eight patients died. Necropsy revealed diffuse acute centrilobular necrosis while in 4 bilateral acute tubular necrosis was also observed. Macroscopically the liver resembled that found in acute passive congestion. Microscopically the liver showed centrilobular necrosis of variable degree ranging from mild to more extensive lesions. In the most severe cases only a rim of periportal parenchyma was present. The cytoplasm was often eosinophilic and pyknotic nuclei were present. In others lytic necrosis was noted.[3] Inflammatory cells were not seen in all sections but neutrophilic infiltration was present in most (Fig. 1). Liver biopsy

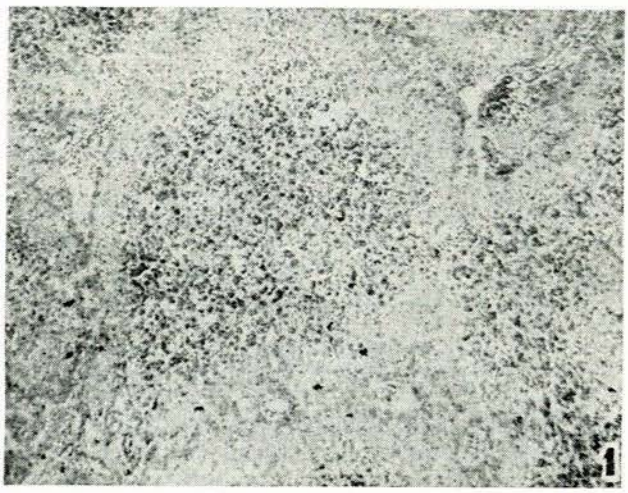

Fig. 1. Centrilobular zonal necrosis of the liver (H. & E. x 25).

was performed on 2 patients who survived. In 1 (case 8) centrilobular zonal necrosis was present, while in the other (case 9), no abnormality was noted, the biopsy being done on the sixth day after admission.

2. *Patients with Infective Hepatitis*

(*a*) *Table III* gives the relevant clinical, biochemical and haematological findings on admission.

(*b*) *Pathology*: One patient died. Necropsy showed acute massive necrosis of the liver. Histology showed extensive hepatic cell necrosis, destruction of liver-lobular structure and disruption of reticulum framework.

Liver biopsy was performed on 4 patients. In all the histology showed hepatic cell necrosis, round cell infiltration and hyperplasia of endothelial cells of sinusoids, the picture being compatible with infective hepatitis.

DISCUSSION

It soon became apparent from the study of patients that there were 3 main presentations of disease following the intake of toxic herbal medicines. Spontaneous hypoglycaemia was the commonest. Here the patient was admitted in coma and was found to have a low blood sugar. After administration of dextrose solution intravenously, recovery was rare though in some the level of consciousness improved. The majority died and necropsy revealed the typical hepatic and renal lesions. The second presentation was jaundice. In 1 case (case 9), in which jaundice was the presenting symptom, a history of imbibing herbal medicine, an accompanying acute renal failure and leukocytosis suggested the disease. The third presentation was acute renal failure. In 1 patient (case 7) who presented with anuria and a blood urea of 220 mg./100 ml., the finding of a mildly raised serum bilirubin suggested the diagnosis. At necropsy the typical lesions were observed. It should also be emphasized that herbs are often taken because of an associated illness, symptoms and signs of which may mask those produced by toxic hepatitis or *vice versa.*

The fact that most patients in hypoglycaemic coma failed to recover despite intravenous administration of dextrose suggested irreversible brain damage. Yet in these patients hypoglycaemia had not been prolonged as it usually is in the post-alcoholic group,[2] suggesting the possibility that there is, in addition, direct damage to the brain by the herbal medicine. It became apparent, therefore, that hepatic and renal failure were the dominant features with hypoglycaemia as a presenting symptom.

Although the evidence incriminating herbal medicine in the production of hepatic and renal lesions is substantial, it must be pointed out that herbs are commonly taken by Africans in Natal without any apparent ill-effect. Moreover, it has been noted that the same herbs may produce toxic effects in one individual and not in another. However, Bryant, as quoted by Watt and Breyer-Brandwijk[4] felt that *Adenia gummifera* (cases 3 and 4), frequently taken by Zulus, was poisonous. Possible toxic herbs are listed in Table V.

TABLE III. FINDINGS ON ADMISSION—INFECTIVE HEPATITIS

Case no.	1	2	3	4	5	6	7	8	9	10	11	12
Age	43	29	31	34	37	12	23	8	22	7	10	11
Sex	F	F	F	F	F	F	F	M	F	F	M	M
Herbal medicine	Nil	Nil	Nil	Nil	Nil	Nil	Nil	Nil	Nil	Nil	Nil	Nil
History	Pain RUQ.	General aches	Epigastric pain	Epigastric pain	Pain RUQ.	Jaundice	Anorexia pain RUQ.	Abd. pain	Anorexia	Abd. pain vomit	Anorexia	Anorexia
Level of conciousness	C	C	C	C	C	C	C	Stupor	C	C	C	C
Jaundice	++	++	++	++	++	++	++	+	+	+	++	++
Foetor hepaticus				+				++			+	++
Liver	2 Fd.	Nil	Tender RUQ.	2 Fd.	1 Fd.	1½ Fd.	Tender RUQ.	1½ Fd.	Nil	½ Fd.	3 Fd.	2 Fd
Spleen	Nil	Nil	Nil	Nil	Nil	Nil	Nil	+	+	Nil	Nil	Nil
WBC × 1,000	6	5	9	7	5	6	9	8	7	12	7	14
Urea	23	12	—	—	16	33	20	34	18	17	28	23
Urine:												
Albumin					Trace		Trace					
24 hr. output	N	N	N	N	N	N	N	N	N	N	N	N
SGOT	250	150	280	900	130	290	350	10	260	120	160	240*
PI	63	59	42	52	93	60	43	0	57	38	68	51
S. bilirubin	12·6	3·4	13	6·2	5·4	3·4	10·5	3·7	7·7	6·2	11·2	6·0
Alk. phos.	15	14	11	13	23	25	12	23	16	28	—	14
Blood sugar										48		
Prognosis	A	A	D	A	A	A	A	A	A	A	A	A
Pathological findings			Massive necrosis liver CIH					CIH		CIH	CIH	CIH

*Test on 5th day after admission. C = Conscious. CIH = Compatible with infective hepatitis. (Case 3 Necropsy; Cases 8, 10, 11, 12 Liver biopsy.

TABLE IV. COMPARISON OF CASE OF TOXIC HEPATITIS WITH INFECTIVE HEPATITIS

	*Herbal medicine—toxic hepatitis (case 8)**													
Days	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*	*14*
SGOT	12	4	90	200	112	100	88		50		54			60
PI	0		68	76	65	85	76		93		97			90
S. bilirubin	3·1	3·5	2·1	1·1	0·5	0·3			0·6					
Alk. phos.	24		17	16	15	14	11		11					
Urine:														
Urobilin		Trace	Trace	+	Nil	Nil	Nil							
Bilirubin		Nil	Nil	Nil	Nil	Nil	Nil							
Albumin		+	Nil	Trace	Trace	Trace								
Deposit		Rbc's	Rbc's											
Output	100		320	750	650	1520	1290							
Blood urea	54	73	82	46	31	25	20							
WBC × 1,000	23		8						10		9			

	Infective Hepatitis (case 11)											
Days	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*
SGOT	160				350					210	190	88
PI	68			71				89		83		86
S. bilirubin	11·2							4·5		3·8	3·1	3·1
Alk. phos.								17		17	14	15
Urine:												
Urobilin					+				+		Trace	Trace
Bilirubin					+				Nil		Nil	Nil
Albumin					Nil				Nil		Nil	Nil
Deposit	←							NAD				→
Output	←							NAD				→
Blood urea	28			23								
WBC × 1,000	7			5	5					9	7	9

*Blood sugar 30 mg. per 100 ml. on admission. NAD = Nil abnormal detected.

TABLE V. SOME PLANTS USED IN HERBAL MIXTURES

1. *Adenia gummifera Harms ('Imfulwa')*
2. *'Lwini—Livenkomo' ('cow's tongue')*
3. *Mixture spilanthus Mauritania + Iboza Riparia*
4. *Mixture spilanthus Mauritania*
   Iboza Riparia
   Syringa leaves
5. *Chenopodium Ambrosioides*

There appear to be certain clinical and biochemical differences between the patients with toxic hepatitis and infective hepatitis. These differences are shown in Tables IV and VI. It is of interest to note that patients with toxic hepatitis have unrecordable or low SGOT activity on admission. This is possibly due to an interfering substance or rapid diminution in the liver-transaminase level. Often the prothrombin index also shows a low value on admission. Other differences are the frequency of hypoglycaemia, renal damage and neutrophilic leukocytosis in the toxic hepatitis group. We have found the leukocyte count a valuable diagnostic aid in distinguishing toxic hepatitis from infective hepatitis, though we have on occasions seen cases of the latter, especially in association with massive necrosis of the liver, with leukocytosis. A further notable difference is seen when following the progress of the 2 diseases. In toxic hepatitis, daily biochemical tests suggest that there has been an initial, acute insult followed, if survived, by rapid recovery, while in infective hepatitis the findings have been more variable and have usually remained abnormal for a longer time (Table IV).

It is known that a toxic substance, such as carbon tetrachloride, when administered frequently in mildly toxic doses over a prolonged period may result in hepatic cirrhosis.[5] It would seem possible, therefore, that frequent

TABLE VI. COMPARISON OF HERBAL TOXIC HEPATITIS WITH INFECTIVE HEPATITIS

	Toxic hepatitis	*Infective hepatitis*
Environment	Often rural community	Urban community
History	Intake herbal medicine	Sometimes history of herbal medicine
Clinical findings	Sometimes non-specific illness before ingestion of herbs	Malaise, anorexia, nausea, vomiting, pain RUO, jaundice etc.
Level of consciousness	Often unconscious	Usually conscious
Jaundice	Absent or minimal jaundice—no foetor hepaticus	Jaundice—foetor hepaticus more common
Prothrombin index	Often very low on admission—soon returns to normal	Reduced or normal
Hypoglycaemia	Common	Uncommon—more common in children
SGOT	Often low on admission then raised	Raised
WBC	Leukocytosis	Leukopenia or normal, occasional leukocytosis
Kidneys	Often evidence of renal damage	Renal damage rare
Histology	Acute diffuse centrilobular hepatic necrosis, and often acute tubular necrosis	Liver comparable with infective hepatitis—kidneys usually no severe tubular damage
Prognosis	Death common	Death uncommon

use of mildly toxic herbs over a prolonged period might also lead to cirrhosis. Gillman and Gilbert[6] and Higginson *et al.*[7] have suggested this possibility. Much of the cirrhosis found in Natal and in Johannesburg[7] among Africans appears to be post-necrotic scarring and in some it is associated with primary carcinoma of the liver.[8] However, the aetiological role of toxic herbs in the production of cirrhosis of the liver is not yet proven.

SUMMARY

Eleven cases of toxic hepatitis and tubular necrosis owing to herbal medicine are presented. These are compared and contrasted with 12 cases of infective hepatitis. Hypoglycaemia was a common presenting feature in toxic hepatitis. The role of toxic herbs in the possible production of cirrhosis of the liver is discussed.

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