about 2·5%. These calculations suggest that the failure rate might be about 2% higher with dose 4 than with dose 1. The observed difference (about 1·5%) was in reasonable agreement.

There was evidence of an association between transplacental haemorrhages of 4 ml or more and failures with dose 4. Twelve women had an estimated transplacental haemorrhage of 4 ml or more after a first pregnancy, and there were three additional women with a transplacental haemorrhage of this extent who were excluded from the trial. If it is assumed that these three women would, if they had been included, have distributed themselves at random among the dose groups then there would have been only about one additional woman with a transplacental haemorrhage of 4 ml or more treated with dose 4. It seems evident that this could not have had any substantial effect upon the results.

The fact that the observed failure rate with a dose of 200-300 μg anti-D seemed to be about 1-2% by the end of a second D-positive pregnancy, as shown by the present trial and by several other series (for example, Eklund and Nevanlinna, 1973), suggests that many apparent failures of treatment when anti-D is given at the time of delivery are due to the occurrence of Rh sensitization before delivery.

Unless "failures" are carefully defined estimates of the failure rate are bound to vary from one series to another. For example, in the present series women whose serum contained anti-D at the end of their first pregnancy were excluded. No accurate estimate is available of the number of such women excluded but published data suggest that the figure would be about 0·5% (Woodrow, 1970; Eklund and Nevanlinna, 1973). On the same reasoning it may be assumed that about 0·5% of women develop anti-D at the end of the second pregnancy as a result of primary immunization in that pregnancy. Such women will falsely be included as failures of treatment.

The criterion of "serologically detectable anti-D" must also affect the reported failure rate. In the present series only women who developed a positive I.A.G.T. result were counted as failures. The five women with anti-D detectable only with enzyme-treated cells at the end of their second pregnancy were not counted as failures. Nevertheless, even if they had been included the overall failure rate would have risen by less than 1%.

In the United Kingdom and in a few other countries a dose of 100 μg anti-D has for some time been used for routine administration to unimmunized D-negative women recently delivered of a D-positive infant. Our results support the contention that this dose has a success rate which is not appreciably different from that observed with a dose of 200-300 μg. Whatever standard dose is adopted it is desirable to perform a screening test to detect large transplacental haemorrhages because it is likely that in such cases the risk of Rh immunization can be reduced by giving an appropriately increased dose of anti-D.

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Hepatic Disorders Associated with Liver/Kidney Microsomal Antibodies

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Summary

A study of the clinical associations of a recently defined tissue autoantibody, the liver/kidney microsomal (L.K.M.) antibody, showed that out of 33 patients 26 had clinical liver disease. Fifteen of the patients had active chronic hepatitis and there were seven cases of acute hepatitis, precipitated by presumed virus A infection in three instances and by drug hypersensitivity in the other four. The remaining cases with liver disease included two with subclinical hepatitis and two with hepatocellular carcinoma. Evidence is presented that the patients with active chronic hepatitis may represent a distinct subgroup of the disease with a young mean age, an even male to female ratio, and a striking lack of other non-organ-specific autoantibodies—that is, antinuclear and smooth muscle—which are usually present in the other autoimmune variant of the disease.

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Introduction

Immunofluorescent tests are helpful in the differential diagnosis of certain chronic liver diseases. The most useful markers have been the antinuclear (A.N.A.) and smooth muscle (S.M.A.) antibodies (Holborow, 1972), present in some cases of active chronic hepatitis, and the mitochondrial antibodies (A.M.A.), which are found in almost all patients with primary biliary cirrhosis (Walker *et al.*, 1965; Klatskin and Kantor, 1972; Sherlock and Scheuer, 1973). Mitochondrial antibodies react with all organs and all types of mitochondria and the immunofluorescent pattern is now well characterized (Doniach, 1972). The antigen has been localized to a lipoprotein in the inner mitochondrial membranes (Berg *et al.*, 1969; Ben-Yoseph *et al.*, 1974). Binding of immunoglobulins

from patients with primary biliary cirrhosis to these membranes has also been shown by immunoelectronmicroscopy with peroxidase conjugates (Bianchi *et al.*, 1973).

In the past four years other immunofluorescent patterns closely resembling A.M.A. have been recognized. Of particular interest for liver disorders is an antibody which has now been named the liver/kidney microsomal (L.K.M.) antibody as it reacts mainly with hepatocytes and proximal renal tubules. At first it was thought to represent a variant of A.M.A. since it occurred mostly in liver patients and certain sera fixed complement with mitchondrial preparations (Doniach and Walker, 1972). This antibody has now been further characterized, however, and the antigen localized to microsomal membranes (Rizzetto *et al.*, 1973). Separation of A.M.A. and L.K.M. antibodies was finally achieved by quantitative complement fixation studies and absorption of the immunofluorescence with purified subcellular fractions. Localization to rough endoplasmic reticulum was also confirmed by immunoelectronmicroscopy (Rizzetto *et al.*, 1974).

L.K.M. antibodies are uncommon and we describe here the clinical conditions in which they were found.

Patients and Methods

A total of 33 patients (16 male, 17 female) were found to have L.K.M. antibodies in the serum. This antibody was detected in 0·12% of the patients whose serum was sent to the laboratory for testing after December 1972. Most of the 33 were retested at intervals over periods up to four years. The results were persistently positive except in three patients in whom the antibody could no longer be detected after intervals of two months to one year. Sera could be kept at −20°C for several years without loss of antibody activity.

Sera were screened at 1/10 dilutions by indirect immunofluorescence with polyvalent anti-γ FITC conjugates. To distinguish L.K.M. from mitochondrial antibodies it was essential to include both renal cortex and medulla, which necessitated changing from human to rat kidney. A.M.A. stains all renal tubules with maximum fluorescence on distal tubule and ascending loop of Henle whereas L.K.M. antibody reacts mostly with the P_3 portion of proximal tubules and gives no staining of the renal medulla. On liver the staining patterns of these two antibodies are difficult to distinguish, while thyroid and stomach are awkward substrates owing to the organ-specific thyroid and gastric parietal cell antibodies which are sometimes present together with L.K.M. in liver patients. All other antibody tests were as described in the W.H.O. manual for autoimmune serology (Roitt and Doniach, 1969). Serum immunoglobulin (Ig) levels were measured by single radial immunodiffusion (Mancini *et al.*, 1965). Hepatitis B antigen (HBAg) and antibodies were detected by radioimmunoassay and by haemagglutination inhibition tests.

Clinical and Serological Data on 33 Patients with L.K.M. Antibodies

Case No.	Clinical Diagnosis	Age and Sex	Duration of Liver Disease	Cirrhosis	Associated Features	Autoantibody Titres							Immunoglobulins (mg/100 ml)		
						L.K.M.†		A.N.A.	S.M.A.	Thyroid		G.P.C.	IgG	IgA	IgM
						Fluorescence	C.F.T.			T.R.C.	Fluorescence				
					Cases with Liver Disease										
1	Active chronic hepatitis	11 M.	1 year		Diabetes	1,200	512						3,500	22	210
2	,,	31 M.	12 years	+	None	160	8						2,100	80	46
3	,,	64 M.	2 years		None	20							1,200	200	220
4	,,	38 M.	11 years	+	Urticaria	40	16					10	1,500	330	125
5	,,	44 M.	1 year		None	40			80				3,760	387	280
6	,,	29 M.	4 years	+	Ulcerative colitis	80		40	40	10	10	20	3,400	610	290
7	,,	18 F.	2 years	+	Urticaria, thyrotoxicosis	800	32					40			
8	,,	26 F.	1 year		Cutaneous vasculitis	1,200	256				10		1,600	150	200
9	,,	25 F.	1 year	+	None	640	64						2,000	205	180
10	,,	12 F.	2 years		None	640	32						3,600	360	55
11	,,	4 F.	2 years		None	320	256						1,260	22	41
12	,,	31 F.	6 years	+	Nephrotic syndrome	320			10				2,200	640	200
13	,,*	30 M.	12 years	+	None	Not titred			10				2,650	305	205
14	,,*	25 M.	3 years	+	Heroin addiction	160							2,350	300	74
15	Active chronic hepatitis,* hepatoma	67 M.	5 years	+	Neuropathy	200	64	10	10	10	10		2,010	320	440
16	Presumed viral hepatitis	33 F.	1 year		Thyrotoxicosis	80					10		1,150	99	120
17	,,	48 M.	1 year		None	40									
18	,,	31 F.	4 weeks		None	Not titred				320	Not titred		1,400	380	62
19	Drug-associated hepatitis	59 F.	4 weeks		None	40				320	40		960	180	54
20	,,	61 F.	4 weeks		None	80							1,180	380	
21	,,	21 F.	8 weeks		None	80			10	160	20		620	120	92
22	,,	51 M.	2 months		None	20							1,850	465	125
23	Subclinical hepatitis	64 F.	Not known		Rheumatic arthritis, goitre	640	256		20	20	10	40	1,600	390	380
24	,,	57 M.	1 year		Hydrocephalus, neuropathy	600‡							1,350	320	140
25	Hepatocellular carcinoma	75 M.	9 months	+	None	160							1,700	975	350
26	,,	42 M.	1 year		None	40					20		1,700	460	60
					Cases without Evidence of Liver Disease										
27	Non-toxic goitre	21 F.			Chronic B.F.P. reactor	320				10	10	10	1,700	150	145
28	Vitiligo	26 F.			Asthma, hay fever	80	16			320	20	10	1,170	130	225
29	Cancer of colon	50 M.			None	40		20	10	10	Not titred	10			
30	Polyarthritis	40 F.			Non-toxic goitre	40			20				3,300	310	200
31	Collagen disease	70 M.			None	20		10				10	960	500	110
32	Hashimoto's thyroiditis	54 F.			None	40			10	10					
33	Polyarthralgia	40 F.			Ulcerative colitis, Raynaud's phenomenon	20		40	10		10		1,220	115	330

B.F.P. = Biological false positive test for syphilis.
C.F.T. = Complement fixation test.
T.R.C. = Tanned Red Cell agglutination test for thyroglobulin antibodies.
G.P.C. = Gastric parietal cell.
* On repeated testing HBAg was positive in serum.
† Maximum L.K.M. fluoresence titre is given where repeated specimens were tested.
‡ Monoclonal IgG_3 Kappa.

Results

Clinical and serological data are shown in the table. Twenty-six patients had confirmed liver disease and L.K.M. antibodies were also found in seven patients who presented with non-hepatic conditions and whose liver function tests gave normal results.

LIVER DISORDERS

Active Chronic Hepatitis

The 15 patients with active hepatitis (9 male, 6 female) ranged in age from 4 to 67 years (mean 30 years). The known age of onset of the chronic liver condition ranged from 2 to 62 years (mean 26 years) and the duration of the illness ranged from one to 12 years (mean five years). Twelve cases presented with jaundice and two of the three remaining patients had had episodes of jaundice 10 and 20 years previously. Cirrhosis was present at the time of initial diagnosis in two patients and was seen to develop during follow-up in seven further cases while three others showed progressive liver damage and heavy fibrosis. All but two of the 15 patients had received corticosteroid therapy, alone or in combination with azathioprine. Two patients who developed cirrhosis died four and six years after the onset of symptoms, one with a hepatocellular carcinoma. The three patients with positive tests for HBAg in the serum —the only such cases in the complete series—were all men and two had special reasons for contracting the virus (one was a chronic heroin addict and the other had had homosexual contacts). Associated clinical disorders included diabetes mellitus in one patient, severe chronic urticaria in two, thyrotoxicosis in one, colitis in one, cutaneous vasculitis in one, and peripheral neuropathy in one.

Microsomal fluorescence titres varied between 20 and 1,200 and were 160 or higher in two-thirds of the active chronic hepatitis cases. Complement fixation with liver microsomes was positive in nine cases, with titres up to 512. In some patients tested repeatedly there were marked fluctuations. Rising titres were observed during active progression of the disease (cases 8 and 10) and a decrease occurred when the hepatitis became quiescent, as seen in case 1, or when an established cirrhosis became inactive, as in case 7. Other antibodies were found in trace amounts. Only one patient (case 6) had significant A.N.A.; L.E. cells were shown to be present at the onset of the disease, with A.N.A. of 40 on one occasion, but the A.N.A. was practically negative on subsequent occasions. Four patients had traces of S.M.A., one reaching a titre of 80, and five had low titres of organ-specific thyroid or gastric parietal cell antibodies. Serum IgG levels were above 3,000 mg/100 ml in four patients, three of whom had not developed cirrhosis. IgA showed no strikingly high values and was abnormally low (80, 22, 22 mg/100 ml) in three patients. IgM values were significantly raised in two patients, both with cirrhosis.

Comparison of Patients with L.K.M.-positive and L.K.M.-negative Active Chronic Hepatitis.—To determine whether patients with L.K.M.-positive active chronic hepatitis could be distinguished as a group from other patients with this disease statistical comparisons were made with a series of 89 patients with active chronic hepatitis seen at King's College Hospital in the last five years (Reed *et al.*, 1973). The latter included 13 patients with persistent hepatitis B antigenaemia. The mean age of 26 years at the onset of liver disease in the L.K.M.-positive group was lower than that of the L.K.M.-negative patients (mean 41 years; range 9 days — 77 years; $P < 0.005$). There was a slight male preponderance among the L.K.M.-positive patients—60% compared with 34% in the L.K.M. negative patients—but this was not statistically significant. The mean duration of liver disease was about five years in both groups and a similar percentage of each presented with an acute illness resembling viral hepatitis. Non-organ specific S.M.A. and A.N.A. were found much less often overall among the L.K.M.-positive patients; only five of the 15 showed any trace of these antibodies compared to 76 of the L.K.M.-negative subjects. When antibody titres of 80 or more only were considered and related to sex for the comparison, however, this clear-cut difference was restricted to the female patients. None of the six female patients in the L.K.M.-positive group had more than trace amounts of A.N.A. or S.M.A. compared to 31 out of 58 L.K.M.-negative female patients ($P = 0.014$). In contrast, two of the nine L.K.M.-positive men had high titre antibodies compared to 10 out of 31 L.K.M.-negative male patients (N.S. $P = 0.28$).

Presumed Acute Viral Hepatitis

Of three patients (one man and two women) with presumed acute viral hepatitis two had had relapsing jaundice for over a year with consistently negative HBAg. Liver biopsy in the man showed resolving acute hepatitis. One of the women had a past history of thyrotoxicosis. There was no evidence of drug abuse or alcoholism and the hepatitis has since remitted in both cases. The third case was admitted with acute hepatic necrosis and died of liver failure, with a hepatic weight of 839 g. All three patients in this group had low titres of L.K.M. fluorescence (40-80) and two also had thyroid antibodies. In one patient tested repeatedly (case 16) the L.K.M. antibodies remained positive at the same titre throughout a two year follow-up period.

Drug-associated Hepatitis

Three women and one man had drug-associated hepatitis. The women all developed jaundice after a repeated halothane anaesthetic. In case 19 the patient died with acute necrosis within a month of onset (liver weight 580 g). In case 20 there was a non-icteric hepatitis (maximum bilirubin 1·3 mg/100 ml; aspartate aminotransferase (SGOT) 800 IU/l.) characterized on liver biopsy by centrizonal necrosis, a granulomatous reaction, and an eosinophil periportal infiltrate. Clinically, a high fever persisted for over a week. The patient made a full recovery within one month. In case 21 the patient developed hepatic necrosis and deep coma seven days after her second halothane anaesthetic for a submucous nasal resection, and at the time of writing she was recovering. The male patient had been taking methyldopa for mild hypertension for two weeks when he developed anorexia, high fever, and subsequent jaundice. His bilirubin rose to a maximum of 3·6 mg/100 ml and SGOT to 55 IU/l. There was a mild peripheral eosinophilia of 600/mm^3. Liver biopsy showed modest portal inflammation with mainly lymphocytic infiltrate and centrizonal swelling of liver cells. An oral cholecystogram gave normal results. The patient made a slow recovery and the results of liver function tests returned to normal on stopping methyldopa.

Serologically these four patients showed L.K.M. fluorescence to titres of 20-80, decreasing as the condition improved in two cases. Two of the female patients also had thyroid antibodies.

Subclinical Hepatitis

There were two cases of subclinical hepatitis. A 64-year-old woman wih a 22-year history of seropositive rheumatoid arthritis needing long-term steroid treatment was found to have hepatomegaly with a slight increase in serum alkaline phosphatase (16 K.A. units). She also had a non-toxic goitre and

was known to have had a false positive reaction for syphilis for some years. No biopsy was available. The second patient was a 57-year-old man who presented with peripheral neuropathy, papilloedema, and intermittent coma. Extensive investigations had shown raised cerebrospinal fluid pressure and protein content of 110 mg/100 ml, and air studies showed dilatation of lateral ventricles. There had been an episode of painless jaundice six years earlier. Liver biopsy showed expansion of portal tracts with mononuclear cells and there was patchy liver cell necrosis. No amyloid was seen in rectal and liver biopsy material. On the suspicion of collagenosis he was treated with corticosteroids but showed no response. He died after one and a half years of illness. No myeloma or other malignancy was found at necropsy and the central nervous system showed advanced atrophy of neurons with demyelination. On serum electrophoresis there was a monoclonal spike identified as IgG_3 kappa and this contained all the L.K.M. fluorescence activity, which could be shown to a titre of 600.

Primary Hepatocellular Carcinoma

The first of the two patients with primary hepatocellular carcinoma was a 75-year-old man who presented with haematemesis, preceded by nine months' vague ill-health. At necropsy a large hepatocellular carcinoma was found spreading into surrounding structures, the sections also showing an underlying micronodular cirrhosis. L.K.M. antibodies were found to a titre of 160 and the serum immunoglobulins showed raised IgA and IgM values. The second patient, a man aged 42, had an anaplastic liver cell cancer with no evidence of underlying cirrhosis at laparotomy. He showed L.K.M. fluorescence to 1/40 and thyroid to 1/20 repeatedly until shortly before he died one year after the onset of symptoms.

NON-HEPATIC DISEASE

In five of the seven patients whose liver function tests gave normal results the L.K.M. antibody was detected at intervals up to two years. One was a healthy girl with a biological false positive reaction for syphilis and a non-toxic goitre who had L.K.M. fluorescence to a titre of 320, the antibodies being of IgM class. Another was a 28-year-old woman with extensive chronic vitiligo; a palpable thyroid; longstanding history of allergy, including skin hypersensitivities; and hay fever. Her mother had myxoedema and three other relatives had vitiligo. Two patients with low-titre L.K.M. antibodies had polyarthritis and evidence of collagen disease and one man allegedly had carcinoma of the colon. In the remaining two patients, with longstanding Hashimoto's disease and polyarthralgia respectively, L.K.M. antibodies were found on one occasion only and specimens taken nine to 12 months later were negative.

Discussion

The separate identity of the L.K.M. antibody and its reaction with microsomal membranes of the rough endoplasmic reticulum can now be accepted on the basis of quantitative complement fixation, absorption of immunofluorescence with appropriate subcellular fractions, and immunoelectronmicroscopy findings with peroxidase-coupled antibodies. This autoantibody seems to be far less common than A.M.A. Whereas 158 A.M.A.-positive sera were detected among 7,500 new sera tested in 1973 only nine with L.K.M. were found on intensive search. It is striking that 26 out of the 33 sera containing these antibodies were derived from patients with overt liver disease, no less than 15 of whom had active chronic hepatitis.

Active chronic hepatitis may have several underlying causes, and though in most cases the aetiological or initiating factors have not been identified two subgroups of the syndrome have been defined. Persistent hepatitis B antigenaemia is associated with some cases of active chronic hepatitis in which there is a male predominance (Reed *et al.*, 1973), while certain drugs—for example, oxyphenisatin (Reynolds *et al*, 1971; Gjone *et al.*, 1972)—may produce a chronic hepatitis associated with the appearance of A.N.A. and S.M.A. in which both the disease and the antibodies regress when the drug is discontinued. A more permanent and intense autoimmunization may be observed in relation to "lupoid" hepatitis, where A.N.A. and S.M.A. are the conspicuous markers, and also in a small subgroup—mainly of middle-aged women showing high titres of A.M.A. with obstructive features and raised serum alkaline phosphatase values—which may overlap with the primary biliary cirrhosis group.

The finding of L.K.M. antibodies perhaps makes it possible to single out another subgroup of active chronic hepatitis cases which show some differences from the other groups. Striking features were the lower frequency of A.N.A. and S.M.A., the higher proportion of males, the younger age group with a relatively high incidence in children, and the defined icteric onset of the illness in nearly all of the cases studied so far. Comparison with a large group of patients with active chronic hepatitis without L.K.M. antibodies showed maximum serological differences in female patients, suggesting that our group was distinct from lupoid hepatitis. One other feature of uncertain significance was the finding of low IgA levels in three of the cases, though this high incidence does not provide statistical distinction from the L.K.M.-negative patients.

With regard to the difficulty in distinguishing between mitochondrial and L.K.M. fluorescence, previous series of active chronic hepatitis always contained a proportion of sera giving fluorescence patterns resembling A.M.A. which could not be interpreted in earlier studies. Conversely, it may be asked whether L.K.M. antibodies are present in some patients with primary biliary cirrhosis in addition to or instead of A.M.A. This is particularly relevant in view of the unexplained positive results of complement fixation studies with microsomal preparations observed in over 25% of primary biliary cirrhosis cases. (Doniach *et al.*, 1966). No firm answer can be given on this point. Mitochondrial antibodies react with all organs wheras L.K.M. staining is almost confined to liver and kidney. Despite looking very carefully for the two immunofluorescent patterns in 50 selected primary biliary cirrhosis sera it was impossible to see concomitant L.K.M. fluorescence. Furthermore, we have no doubt that many tissue antibodies have yet to be identified and are at present poorly understood.

The relation of L.K.M. antibodies to HBAg is at present difficult to define. We have failed to detect this autoantibody in many cases of viral hepatitis type B, though L.K.M. fluorescence was found in sera from three patients with active chronic hepatitis associated with HBAg. Prolonged follow-up with repeated antibody tests should be done in drug-induced hepatitis cases in order to ascertain whether the L.K.M. antibodies disappear with time, as this would be in favour of their stimulation by the drug hypersensitivity. The same applies to the occasional A.M.A. seen after halothane-associated jaudice (Rodriguez *et al.*, 1969; Simpson *et al.*, 1973). The two cases thought to have subclinical hepatitis were of special interest. The woman with chronic rheumatoid arthritis and biological false positive reaction was in some ways similar to the patients with A.M.A., "collagen" disorders, and subclinical liver disease studied earlier (Walker *et al.*, 1970; Whaley *et al.*, 1970). Some of these patients had fluorescence patterns which were atypical for A.M.A. Similar difficulties of interpretation were found in a series of patients with false positive reactions for syphilis (Doniach *et al.*, 1970). In the male patient with neurological disease and subclinical hepatitis the L.K.M. antibody was confined entirely to a monoclonal band (Florin-Christensen *et al.*, 1974) and the significance of this is unknown.

In seven patients low titre L.K.M. antibodies were found in the absence of any evidence of liver disease and in two of these their appearance was temporary. All but one of these patients suffered from collagenoses or thyroid autoimmunity. In this context it is interesting that in half of all patients having L.K.M. antibodies, irrespective of diagnosis, thyroid or gastric organ-specific antibodies also occurred. The identity of these antibodies could be shown by selective absorption of the thyroid or gastric immunofluoresence, leaving intact that due to the L.K.M. The L.K.M. antibody with its restricted organ reactivity may represent an intermediate form of autoimmunity between the strict organ specificity of the thyroiditis/gastritis/adrenalitis group of disorders and the complete non-organ specificity of such autoantibodies as A.M.A. and A.N.A.

Studies are in progress to attempt a separation of L.K.M.-associated active chronic hepatitis by tissue typing (Mackay and Morris, 1972) and the incidence of high titre viral antibodies, including rubella, measles, and herpes (Triger *et al.*, 1972), from the largest group of active chronic hepatitis patients who show no autoimmunity or HBAg and from the subgroups associated with high titres of A.N.A. and S.M.A. and those showing A.M.A. in the serum.

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ADDENDUM

Since this paper was submitted further information on the clinical significance of the L.K.M. antibody has come from Dr. J-C. Homberg, of Paris. He observed this immunofluorescence pattern independently and with other French immunopathologists collected 14 positive cases (11 F., 3 M.) over the past five years, representing about 0·1% of all sera tested. Ten were from patients with either active chronic hepatitis in young subjects or with unexplained cirrhosis (Homberg *et al.*, 1974).

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Haemolytic-Uraemic Syndrome in Typhoid Fever

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Summary

Among 48 patients with a typhoid infection 6 (12·5%) developed the haemolytic-uraemic syndrome. Neither glucose-6-phosphate dehydrogenase deficiency nor therapy with chloramphenicol could be incriminated as the causal factor. Evidence presented here suggests that the mechanism is localized intravascular coagulation.

The presence of leucocytosis in typhoid fever suggests a complication and should alert one to the possibility of the haemolytic-uraemic syndrome. Furthermore, in our area typhoid should be suspected as a cause in any patient presenting with acute renal failure.

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Introduction

Haemolysis and renal failure have been regarded as rare complications of typhoid fever. Retief and Hofmeyr (1965) found fewer than 40 cases of haemolytic anaemia associated with typhoid noted in the literature. Since then there have been further reports, usually of single cases. That this complication might be more common was suggested when Lwanga and Wing (1970), in a two-year retrospective study, found that of 130 patients with typhoid 7% had evidence of haemolysis, but that was in areas where glucose-6-phosphate dehydrogenase (G-6-PD) deficiency was common. Hersko and Vardy (1967) described haemolysis in five children, all with G-6-PD deficiency. Huckstep (1962) mentioned an incidence of haemolytic anaemia of 2% and of "nephrotyphoid" of 1%. Gulati *et al.* (1968) reported two cases of nephritis among 98 patients, and Wicks *et al.* (1971) reported renal complications in six out of 265 patients.

Lwanga and Wing (1970) claimed the first reported case of acute oliguric renal failure after intravascular haemolysis in typhoid fever. That was in a patient with G-6-PD deficiency. Though Allen (1969) reported one case with consumption co-