Patient's serum was also tested against tissues obtained from kidney and the thyroid in order to test the specificity of the auto-antibodies.

RESULTS

Before studying the cases of infantile cirrhosis we studied the sera of 15 normal controls for the presence of auto-antibodies against tissue extracts of liver, kidney, and thyroid. T.R.C. tests in the 15 normal controls were negative against all the tissue extracts tried.

Results of T.R.C. test in the cases of infantile cirrhosis are given in the Table. It will be seen that specific antibodies against liver tissue were present in 10 (83%) out of the 12 cases.

Results of T.R.C. Test in 12 Cases of Infantile Cirrhosis

Case No.	Age in Years	Sex	T.R.C. Test Results Against Various Tissues (Titre)			
			Liver	Kidney	Thyroid	Remarks
1	2	M	1,2,500	×	×	Specific antibodies
2	3	M	1/25,000	×	×	"
3	5½	F	1/25	1/5	1/25	Non-specific antibodies
4	2	M	1/2,500	×	×	Specific antibodies
5	4	M	1/250	×	×	"
6	3½	M	1/250	×	×	"
7	3½	M	1/250	×	×	"
8	4	M	1/25,000	×	×	"
9	2	F	1/2,500	×	×	"
10	1½	M	1/250	×	×	"
11	1	M	1/250	×	×	"
12	1½	M	×	×	×	No antibodies against any tissue

× = No agglutination.

DISCUSSION

The role of auto-antibodies in liver cells was perhaps first stressed by Mackay (1958), who postulated that in cases of "lupoid hepatitis" hepatic cell components might become antigenic and that the antibodies called forth in response to this antigen might react damagingly with liver and perpetuate the condition. Gajdusek (1958) reported circulating complement-fixing (homologous) antibodies in cases of viral hepatitis, lupoid hepatitis, biliary cirrhosis, and nutritional hepatitis. Mackay (1958) was able to demonstrate high antibody titre in the serum of a patient with primary biliary cirrhosis.

In the present work auto-antibodies against liver tissue were demonstrated in cases of infantile cirrhosis. The antibodies were specific in 10 out of the 12 cases studied. We are trying to observe more cases of infantile cirrhosis, but from these preliminary observations it can be postulated that infantile cirrhosis results from formation of antibodies against the liver cells. These antibodies might attack and damage the liver cells, resulting in their death and fibrosis.

It may be argued that the circulating antibodies are merely a reflection of the pathological process in the liver, and are not implicated in its causation. While this possibility cannot be ruled out at the present stage of our work, it may be of interest to quote instances of tissue damage resulting from experimental auto-immunization. Lesions have been obtained by immunizing with adrenal (Colover and Glynn, 1958), testis (Freund *et al.*, 1953), brain (Kabat *et al.*, 1947), eye antigens (Collins, 1953), peripheral nerve (Waksman and Adams, 1955), and thyroid (Witebsky *et al.*, 1957) tissue extracts. Skin reactions of the delayed hypersensitivity type have been obtained in autoimmunized animals as well as in those sensitized by skin homograft (Brent *et al.*, 1958).

So far we have not been able to find out the exact serum fraction with which these antibodies are asso-

ciated, but we are working in that direction. An attempt is also being made to induce cirrhosis in animals by inducing formation of liver antibodies in them.

SUMMARY

Antibodies against liver tissue were detected in 10 out of 12 cases of infantile cirrhosis by the method of tanned-cell agglutination test.

The possible role of antibodies in the production of infantile cirrhosis is discussed.

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REFERENCES

- Achar, S. T. (1955). *Child Hlth*, **4**, 291.
— and Raju, V. B. (1951). Report to the Research Committee, Madras State, India.
Bras, G., Jelliffe, D. B., and Stuart, K. L. (1954). *Arch. Path.*, **57**, 285.
Brent, L., Brown, J., and Medawar, P. B. (1958). *Lancet*, **2**, 561.
Collins, R. C. (1953). *Amer. J. Ophthalm.*, **36**, 150.
Colover, J., and Glynn, L. E. (1958). *Immunology*, **1**, 72.
Freund, J., Lipton, M. M., and Thompson, G. E. (1953). *J. exp. Med.*, **97**, 711.
Gajdusek, D. C. (1958). *Arch. intern. Med.*, **101**, 9.
Gibbons, J. B. (1890). *Indian med. Gaz.*, **25**, 119.
Green-Armytage, V. B. (1926). *Ibid.*, **61**, 44.
Kabat, E. A., Wolf, A., and Bezer, A. E. (1947). *J. exp. Med.*, **85**, 117.
Kutumbiah, P. (1956). *Antiseptic*, **53**, 643.
Lahiri, S. C. (1936). *Indian med. Gaz.*, **71**, 313.
Mackay, I. R. (1958). *New Engl. J. Med.*, **258**, 185.
Mukherjee, S. K. (1922). *Infantile Cirrhosis of the Liver*. Indian Medical Record Book Depot, Calcutta, India.
Narayanamurthi, K., Bahadur, R., and Tirunmurti, T. S. (1939). *Indian J. Paediat.*, **6**, 85.
Rao, R. M. V. (1934). *Ibid.*, **1**, 159.
— (1935). *Indian J. med. Res.*, **23**, 69.
Rao, P. K. (1950). *Indian med. Gaz.*, **85**, 150.
Roitt, I. M., and Doniach, D. (1958). *Lancet*, **2**, 1027.
Smetana, H. F., Hadley, G. G., and Sirsat, S. M. (1961). *Pediatrics*, **28**, 107.
Srivastava, J. R., and Aikat, B. K. (1954). *Indian J. med. Sci.*, **8**, 446.
Waksman, B. H., and Adams, R. D. (1955). *J. exp. Med.*, **102**, 213.
Witebsky, E., Terplan, K., Paine, J. R., and Egan, R. W. (1957). *J. Amer. med. Ass.*, **164**, 1339.

Medical Memoranda

A Fatal Case of Phenindione Sensitivity

In 1947 Soulier and Gueguen first used phenindione as an anticoagulant in clinical medicine. They reported scarlatiniform rashes, polydipsia, and polyuria as side-effects.

CLINICAL DESCRIPTION

A 49-year-old oil company foreman presented on May 19 with a three-day history of intermittent pain in the left side of his chest which radiated to the left arm. There was no past history of allergy or drug sensitivity.

He was admitted to hospital and examination revealed no abnormal physical signs. The E.C.G. was normal and the white blood count was 7,200/c.mm. (50% neutrophils, 42% lymphocytes). Phenindione was started with an initial dose of 200 mg. While in hospital he also received chloral and glyceryl trinitrate. Ten days later a second E.C.G. showed ST elevation and T-wave inversion in aV1. He went home on June 2, having been stabilized on a daily dose of 100 mg. of phenindione. On June 14, 25 days after starting phenindione, he was readmitted. He complained of fever, a petechial rash over the legs, and urticaria on the forearms which he had noticed for three days. Treatment with promethazine and diphenhydramine was started immediately, and on the following day phenindione was stopped. His

white-cell count on admission was 5,000/c.mm. (50% polymorphs), but 48 hours later it had fallen to 4,000/c.mm. (12% polymorphs). The urine contained a small amount of protein. A daily dose of 40 mg. of prednisone was begun on June 16. At this time he had a generalized lymphadenopathy; the liver was enlarged but not tender, and there were crepitations in the right lung. The rash on his face, shoulders, and arms was now desquamating.

The polymorph count continued to fall, and by June 21 had dropped to 3% of a white blood count of 3,000. Many atypical mononuclear cells, resembling those seen in glandular fever, were present. Paul-Bunnell tests were repeatedly negative and at no time were L.E. cells seen in the peripheral blood. Blood for culture was taken on June 21 and coagulase-positive staphylococci were grown. The patient was treated with methicillin, and within four hours was afebrile for the first time since his admission. Two days after isolating the staphylococci the white-cell count had risen to 16,600/c.mm. (75% polymorphs). His general condition improved and the dose of prednisone was decreased. On July 1 his fading yet extensive erythematous rash became intensely pruritic. An increase in the prednisone dosage produced transitory benefit, but during a period of four hours on July 4 he developed a generalized purpura which became confluent over the extremities. The white-cell count was 17,000/c.mm., platelets 200,000/c.mm., and the Hess test was positive. The bleeding and clotting times were normal. Examination of the urine showed numerous granular casts, a small amount of protein, but no red blood cells. Occult blood was found in the stools.

From July 4 to his death eight days later his condition gradually deteriorated. Large bullae formed in the skin and serosanguineous fluid oozed from raw areas on his hands. Later the skin on his back and shoulders broke down and from these areas he lost large quantities of fluid. Parenteral therapy with M/6 lactate, saline, plasma, and whole blood failed fully to correct his dehydration. Four days before his death the white-cell count had again fallen, this time to 4,000/c.mm., 32% being polymorphs, some of which showed toxic granulation. At the time of death the superficial layers of approximately 90% of his skin had been lost. During the last 48 hours the blood urea rose to 312 mg./100 ml. and the blood-pressure fell despite the use of pressor agents. On the day of his death the white blood count fell to 2,000/c.mm.

Post-mortem Findings (Dr. Donald Teare). — An exfoliative form of purpura covered almost the entire surface of the body, only small patches of skin on the front of the thighs, lower abdomen, and scalp escaping. Most of the superficial epidermis of the trunk had peeled off. The heart was generally dilated but otherwise normal. The left ventricular wall showed no hypertrophy, and the valves appeared normal. An atheromatous plaque was found at the bifurcation of the left coronary artery but there was no evidence of coronary occlusion. A recent pleurisy covered the lower lobes of both lungs and three small lung abscesses were present in the left lower lobe. There was recent bronchopneumonia in both lower lobes. The liver was congested and fatty (weight 2,380 g.). The intestines were rather oedematous but otherwise normal. The kidneys were slightly swollen and very congested. The spleen was firm and congested. The bone-marrow appeared active. The brain was oedematous. The cause of death was thought to be bronchopneumonia and exfoliative dermatitis due to phenindione therapy.

Histological examination confirmed the presence of a severe dermatitis with collections of inflammatory cells in the superficial dermis, mainly perivascular in distribution. In the myocardium were scattered foci of necrotic muscle surrounded by lymphocytes and occasional plasma cells. In these foci there was loss of sarcoplasm, but many muscle nuclei remained. The kidneys showed swelling and cellular proliferation in many glomeruli; occasional casts were present in the tubules, which looked normal. There were several subcapsular areas of fibrosis and lymphocyte infiltration. Areas of extramedullary haemopoiesis were

found in the pulp of the spleen, the adrenals, and kidneys. Small foci of extramedullary haemopoiesis were also found in connective tissue around the kidneys, and very occasional collections of similar cells were present in the liver.

DISCUSSION

Six other fatal cases with phenindione sensitivity have been reported (Kirkeby, 1954; Brown and MacMillan, 1954; Burns and Desmond 1958; Barritt and Jordan, 1960; Postgraduate Medical School of London, 1960) (see Table).

Fatal Cases of Phenindione Sensitivity

	MacMillan and Brown (1954)	Kirkeby (1954)	Burns and Desmond (1958)	Perry Smith (1959)	Barritt and Jordan (1960)	Postgrad. Med. School (1960)	Present Case
Fever		+	+		+	+	+
Rash		+	+		+	+	+
Adenopathy ..		+	+		+	+	+
Agranulocytosis ..	+	+	+	+		+	+
Eosinophilia ..		+	+			+	
Atypical mononuclear cells			+				+
Increased erythropoiesis				+			+
Skin sloughing ..	+	+	+				+
Jaundice		+					
Renal failure ..		+			+	+	+

The case described above differs from others in that extensive skin loss followed a severe purpuric dermatitis. A large volume of fluid was lost from the skin, and the terminal renal failure and hypotension could be attributed in part to this. Renal failure due to hypersensitivity reactions has been reported in other cases, but in the present case tubular necrosis was not found. Extramedullary erythropoiesis was a notable feature in our patient and was observed in the spleen, the adrenals, the kidneys, the perirenal connective tissue, and to a less extent in the liver. Perry C. Smith (1959) reported one other case in which increased erythropoietic activity was noted.

As in the case described by Brown and MacMillan corticosteroids did not prevent a fatal outcome in our patient.

The not infrequent cases of phenindione sensitivity together with the occasional fatality suggest that in long-term anticoagulant therapy phenindione is no longer the drug of choice.

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REFERENCES

- Barritt, D. W., and Jordan, S. C. (1960). *Lancet*, **1**, 1309.
Brown, K. W. G., and MacMillan, R. L. (1954). *Amer. J. med. Sci.*, **227**, 526.
Burns, C., and Desmond, F. B. (1958). *N.Z. med. J.*, **57**, 283.
Kirkeby, K. (1954). *Lancet*, **2**, 580.
Postgraduate Medical School of London (1960). *Brit. med. J.*, **2**, 1219.
Smith, Perry C. (1959). *Arch. intern. Med.*, **51**, 617.
Soulier, J. P., and Gueguen, J. (1947). *C.R. Soc. Biol. (Paris)*, **141**, 1007.