goat's milk is consumed by the majority (Rutishauser, 1963), whereas in certain other tribes in Uganda in which milk is consumed in large quantities no case of ulcerative colitis has yet been reported. Of the two patients in our series who were asked about consumption of milk and its products, the more severely affected took them only occasionally. The effects on our patients of withholding and then reintroducing milk and its products were not observed. The likelihood that any of our patients would have been reared on cow's milk in infancy is extremely remote, considering the local conditions then.

Finally there is the psychogenic hypothesis. The patient may have a susceptible temperament, being over-conscientious, over-dependent on the approval of others, subject to inner conflict, hostility, anxiety, rebelliousness, and guilt, and likely to have a history of psychosomatic or psychiatric illnesses; psychotherapy alone may benefit his ulcerative colitis (Paulley, 1950; Grace and Wolff, 1951; Fullerton *et al.*, 1962). An emotional crisis may itself precipitate the onset or a relapse (Brown, 1963). In our series Cases 1, 2, and 3 had at least some of the personality traits, and Case 1 (but not the others) admitted an association between mental stress and bowel symptoms.

No single hypothesis can claim to explain all cases of ulcerative colitis. The very severe forms of the disease seem to be genuinely rare in Africans, while the milder forms, if occurring, may be "buried" beneath the great mass of infective diarrhoeas and may thus remain undetected. The explanation could lie in the rarity of early weaning, high milk consumption, or the predisposing personality type. Among the sophisticated groups in African society, however, where a more European type of diet is taken, where attendance at a specialist centre for special investigations is easier, and where exposure to new mental strains is commoner it may be that this disease will turn out to be not so rare. It will not be the first of the so-called diseases of Western civilization where this has proved to be the case.

Summary

So far as can be ascertained, no detailed reports have previously been made of ulcerative colitis developing in an African in tropical Africa. Four cases are recorded in whom the history and investigations were typical of this disorder. Three patients showed some of the personality traits said to be typical, and in one the onset of the disorder was related to psychological stress. Relevant psycho-social data are mentioned and the aetiology is discussed. Causes are suggested for the present apparent rarity of the disease in Africans in tropical Africa, where, however, it conforms to the world pattern of being relatively uncommon in less sophisticated communities. It is postulated that with increasing sophistication the disease may be seen more frequently in the future in tropical Africa.

Our thanks are due to our colleagues for allowing us access to their patients, and particularly to Dr. F. J. Bennett, reader in preventive medicine at Makerere Medical School, for interviewing all the patients in connexion with their psycho-social background. Dr. J. H. Roberts carried out the barium-enema examination and made the report on Case 4.

References

Acheson, E. D., and Truelove, S. C. (1961). *Brit. med. J.*, **2**, 929.
Birnbaum, D., Groen, J. J., and Kallner, G. (1960). *Arch. intern. Med.*, **105**, 843.
Brit. med. J., 1962, **2**, 36.
Ibid., 1964, **2**, 117.
Broberger, O., and Perlmann, P. (1959). *J. exp. Med.*, **110**, 657.
—— —— (1962). Ibid., **115**, 13.
Brown, C. H. (1963). *Amer. J. dig. Dis.*, **8** (N.S.), 525.
Brown, P. W., and Bargen, J. A. (1938). Ibid., **5**, 562.
Davis, F. W. (1949). *Amer. J. med. Sci.*, **217**, 505.
Fullerton, D. T., Kollar, E. J., and Caldwell, A. B. (1962). *J. Amer. med. Ass.*, **181**, 463.
Grace, W. J., and Wolff, H. G. (1951). Ibid., **146**, 981.
Hijmans, J. C., and Enzer, N. B. (1962). *Pediatrics*, **29**, 389.
Klavins, J. V. (1963). *J. Amer. med. Ass.*, **183**, 547.
Paulley, J. W. (1950). *Gastroenterology*, **16**, 566.
Pillay, V. K. G. (1964). *Brit. med. J.*, **2**, 689.
Reinhart, J. B. (1961). *Amer. J. Dis. Child.*, **101**, 401.
Rutishauser, I. H. E. (1963). *Trop. geogr. Med.*, **15**, 138.
Shaper, A. G., and Shaper, L. (1958). *East Afr. med. J.*, **35**, 647.
Stewart, G. T. (1950). *Brit. med. J.*, **1**, 405.
Taylor, K. B., Truelove, S. C., and Wright, R. (1964). *Gastroenterology*, **46**, 99.
Trowell, H. C. (1960). *Non-Infective Disease in Africa.* Arnold, London.
Truelove, S. C. (1961). *Brit. med. J.*, **1**, 154.
Weiner, H. A., and Lewis, C. M. (1960). *Amer. J. dig. Dis.*, **5** (N.S.), 406.
Wigley, R. D., and Maclaurin, B. P. (1962). *Brit. med. J.*, **2**, 228.

Preliminary Communications

Dose of Anti-D Gamma-globulin in Prevention of Rh-haemolytic Disease of the Newborn

Brit. med. J., 1966, **1**, 213–214

Recent work by ourselves (Clarke and Sheppard, 1965; Woodrow *et al.*, 1965) and others (Preisler and Schneider, 1964; Freda *et al.*, 1965; *Medical World News*, 1965) has shown that Rh-negative women can be prevented from being immunized by their Rh-positive foetuses. The method used has been the intramuscular injection of 5 ml. of high-titre incomplete anti-D gamma-globulin given shortly after delivery. This eliminates any Rh-positive foetal cells which may have leaked across the placenta at delivery or before. Evidence for protection is the absence of immune antibodies six months after delivery among the treated women and their presence in a proportion of the control groups. So far, in all the clinical trials reported, 21 out of 94 untreated controls have produced immune antibodies, whereas none out of 78 treated with anti-D gamma-globulin has done so (*Medical World News*, 1965).* It must be emphasized, however, that the effects of second Rh-positive pregnancies in the group of treated mothers will have to be observed before one can be sure that protection is complete. If it is, the prophylactic treatment of women at risk will necessitate large supplies of gamma-globulin, which is expensive to make and will require many volunteers to produce. It is therefore, as pointed out by Gorman *et al.* (1965), very appropriate at the present time to find out the minimum dose of gamma-globulin which is effective, and this communication presents some evidence on the matter.

Present Experiment

In a recent experiment we obtained 12 Rh-negative male volunteers and injected intravenously 5 ml. of Rh-positive ABO compatible foetal blood into six of them and 1 ml. into the remainder. Half an hour later two individuals in each of the two groups were given intramuscularly 0.5 ml., 1.5 ml., or 3 ml. respectively of our high-titre anti-D gamma-globulin (titre in albumin 1:2,560) prepared by Dr. W. d'A. Maycock

* These overall figures were given in October 1965. We have no later data from all the centres, but in those using our criteria for the trial (Woodrow *et al.*, 1965) the results at present (January 1966) are that one out of 40 of those treated and 12 out of 42 controls have produced immune anti-D six months after delivery.

and Mr. L. Vallet, of the Lister Institute of Preventive Medicine. Blood was taken just before the gamma-globulin injection and again 48 hours later to detect the number of foetal cells present. From each sample of blood, five slides were made and the foetal cells counted on each slide independently and blindly by two of us (R. F. and J. C.W.), for method see Woodrow *et al.* (1965). The basic data are set out in Table I and the results of the statistical analysis of foetal cell scores before and after treatment are given in Tables II and III.

It will be seen that (1) there is a very great difference ($P<0.001$) in the number of foetal cells, depending on the volume of blood given, the mean score for 5 ml. being 77.8 and that for 1 ml. 14.8; (2) there is a small but significant difference ($P<0.01$) in the scores before treatment by the two observers, showing how carefully experiments of this sort must be controlled to take into account observer bias; (3) there is a significant difference ($P<0.001$) in the clearance between the volunteers (largely due to No. 4), but this is unrelated to the volume of the gamma-globulin or to the volume of the foetal blood given; (4) statistical analysis of the scores 48 hours after treatment shows no significant difference with respect either to the volume of blood given or to the volume of gamma-globulin injected. All volumes of gamma-globulin were equally effective in removing the foetal cells from the circulation, even 0.5 ml. clearing 5 ml. of foetal blood.

These results suggest that a dose of 0.5 ml. of anti-D gamma-globulin should protect against Rh immunization by 5 ml. (or less) of foetal blood as effectively as the dose of 5 ml. of gamma-globulin used in the present clinical trials. To be certain about this matter, however, it will be necessary to continue experiments in our volunteers. We think a dose of 0.5 ml. will be effective, because we already have some information about dosage in relation to protection from another experiment carried out a year ago.

Each of 22 Rh-negative male volunteers was injected with 10 ml. of ABO Rh-positive foetal blood, and this gave a mean baseline foetal cell score of 188.5. Half an hour later 11 of the volunteers were given 10 ml. of pooled anti-D serum obtained from 14 Rh-negative men previously hyperimmunized with Rh-positive blood. The anti-D titre of the serum was 1:512 in albumin and 1:8 in saline. After 48 hours the foetal-cell scores were repeated and virtually complete clearance of the foetal cells was observed (Table IV). Moreover, four months later three out of 10 controls had developed immune anti-D while none of the 10 who had received the serum had become immunized. Since 10 ml. of this particular anti-D serum is equivalent to approximately 0.6 ml. of anti-D gamma-globulin, these results suggest that this small volume can not only clear 10 ml. of foetal blood but also protect against immunization.

TABLE I.—*Results of Experiments in which 12 Rh-negative Volunteers were Given Varying Amounts of Rh-positive Foetal Blood and Different Amounts of Gamma-globulin*

Subject	Volume of Blood Injected (ml.)	Volume of Gamma-globulin Given (ml.)	Foetal-cell Scores: Scored by R. F. — Before Gamma-globulin. Slides 1–5	Scored by R. F. — 48 Hours after Gamma-globulin. Slides 1–5	Scored by J. C. W. — Before Gamma-globulin. Slides 1–5	Scored by J. C. W. — 48 Hours after Gamma-globulin. Slides 1–5
1	5	0·5	52 61 92 63 70	0 0 0 0 1	60 60 80 81 88	0 0 0 0 0
2	5	0·5	97 76 67 59 100	0 0 0 0 1	90 95 68 69 98	0 0 0 0 0
3	5	1·5	87 60 72 70 71	0 0 0 0 0	80 93 77 80 89	0 0 0 0 0
4	5	1·5	78 66 71 78 78	2 3 4 1 2	72 82 84 86 85	3 2 0 1 0
5	5	3·0	96 49 81 93 101	0 0 0 0 1	91 64 82 89 72	0 0 0 0 0
6	5	3·0	104 71 64 63 66	0 0 0 1 1	90 83 72 64 89	0 0 0 0 0
7	1	0·5	8 16 7 7 16	0 0 0 0 1	19 14 10 17 12	0 0 0 0 0
8	1	0·5	14 14 16 14 10	0 0 1 1 1	15 13 18 13 16	0 0 0 0 1
9	1	1·5	11 11 11 10 13	0 0 0 0 2	18 18 26 13 11	0 1 0 0 0
10	1	1·5	12 21 14 18 15	0 0 0 0 1	17 24 21 18 22	0 0 0 0 0
11	1	3·0	11 13 11 8 8	0 0 0 0 0	18 19 12 10 15	0 0 0 0 0
12	1	3·0	12 21 17 10 14	1 1 1 2 2	25 16 20 18 18	0 0 0 0 0

TABLE II.—*Statistical Analysis of Foetal-cell Scores Before Gamma-globulin Treatment*

Comparisons	Analysis of Variance: D.F.	SS	MS	P
Volumes blood injected	1	119,070·00	119,070·00	<0·001
Observers	1	653·33	653·33	<0·01
Volumes blood injected × observers	1	9·63	9·63	N.S.
Volunteers	10	1,122·97	112·30	,,
Observers × volunteers	10	389·63	38·96	,,
Within volunteers	96	9,120·40	95·00	
Total	119	130,366·00		

D.F. = Degrees of freedom. SS = Sum of squares. MS = Mean square. N.S. = Not significant.

TABLE III.—*Statistical Analysis of Foetal-cell Scores After Gamma-globulin Treatment*

Comparisons	Analysis of Variance: D.F.	SS	MS	P
Volumes blood injected	1	0·4083	0·4083	N.S.
Gamma-globulin volumes	2	3·1500	1·5750	,,
Observers	1	4·4083	4·4083	,,
Volumes blood injected × gamma-globulin volumes	2	5·1167	2·5584	
Observers × volumes blood injected	1	0·0084	0·0084	
Observers × gamma-globulin volumes	2	0·3167	0·1584	
Volumes blood injected × observers × gamma-globulin volumes	2	0·8166	0·4083	,,
Volunteers	6	19·3500	3·2250	<0·001
Observers × volunteers	6	4·3500	0·7250	N.S.
Within volunteers	96	24·4000	0·2542	
Total	119	62·3250		

TABLE IV.—*Results of an Experiment in which 22 Rh-negative Male Volunteers Received 10 ml. of Rh-positive Foetal Blood, and 11 of Them were Then Given 10 ml. of Pooled Anti-D Serum*

Volunteer No.	1	2	3	4	5	6	7	8	9	10	11
Results in 11 Men Not Receiving Antiserum											
Initial foetal-cell count	186	163	228	172	92	170	186	116	165	184	286
48-hour foetal-cell count	197	137	184	132	135	170	98	154	131	146	N.T.
Immune anti-D formation—4 months later	—	A	—	A	—	—	—	N.T.	—	—	A
Results in 11 Men Receiving Antiserum											
Initial foetal-cell count	218	286	202	192	116	224	176	238	160	184	234
48-hour foetal-cell count	0	8	1	1	1	0	1	5	0	9	0
Immune anti-D production	—	—	—	—	—	—	N.T.	—	—	—	—

A = Immune anti-D appeared. N.T. = Not tested.

There is rapidly accumulating evidence that protection against Rh immunization is possible. The results of our two experiments suggest that doses as small as 0.5 to 1 ml. of anti-D gamma-globulin, prepared from hyperimmunized volunteers, are likely to be effective in most cases, thus making the large-scale prevention of such immunization a less difficult proposition.

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REFERENCES

Clarke, C. A., and Sheppard, P. M. (1965). *Lancet*, **2**, 343.
Freda, V. J., Gorman, J. G., and Pollack, W. (1965). Ibid., **2**, 690.
Gorman, J. G., Freda, V. J., and Pollack, W. (1965). Ibid., **2**, 181.
Med. Wld News, 1965, **6**, No. 36, p. 31.
Preisler, O., and Schneider, J. (1964). *Geburtsh. u. Frauenheilk.*, **24**, 124.
Woodrow, J. C., Clarke, C. A., Donohoe, W. T. A., Finn, R., McConnell, R. B., Sheppard, P. M., Lehane, D., Russell, Shona H., Kulke, W., and Durkin, Catherine M. (1965). *Brit. med. J.*, **1**, 279.