drug supplement one another, the ideal procedure for general use should include oth. In special hospitals, however, where large numbers of casualties are seen, it would be desirable to build up three series of cases—treated respectively with drug, with serum, and with neither (controls)—so that the clinical assessment on these procedures (discussed above) could eventually be made.

Summary

Experimental wounds (with crushed muscle and the presence of a foreign body) were made in guinea-pigs, and large numbers of gas-gangrene organisms were inserted; untreated animals died within twenty-four hours.

Application of sulphonamide compounds to the wounds at the same time as insertion of the organisms saved a large proportion of the animals infected with *Cl. welchii* and with *Cl. septicus*, but it had only slight influence upon infections with *Cl. oedematiens*. Sulphathiazole was the most effective compound to use in all cases; sulphanilamide was superior to sulphapyridine in preventing infection with *Cl. welchii*, but it had practically no activity against *Cl. septicus*.

Local application of sulphathiazole to the wound was more effective in preventing infection than systemic administration by intraperitoneal injection. Delay of two hours in applying the treatment greatly reduced its effectiveness.

Sulphanilamide is absorbed from wounds very quickly (in less than twenty-four hours), giving a high but transitory concentration in the fluids of the wound (1,500 mg. per 100 c.cm.); sulphapyridine is absorbed slowly from the wound (seven to ten days) and its concentration in the wound is low (42 mg.) but prolonged; sulphathiazole occupies an intermediate position, being absorbed in about five to six days and producing a concentration of about 104 mg.

The development of the infection in these wounds could also be prevented by administration of sera (antitoxin). Monovalent sera specific for *Cl. welchii*, *Cl. septicus*, or *Cl. oedematiens* protected the guinea-pigs against these organisms respectively. A commercial polyvalent serum gave protection against *Cl. welchii* (most strains) and *Cl. oedematiens*, but not against *Cl. septicus*.

It is recommended that war wounds should be protected against the development of gas gangrene by the local application of sulphonamide compounds together with injection of antitoxin.

Grateful acknowledgments are due to Dr. R. Cruickshank, Prof. A. A. Miles, and Dr. H. J. Parish for kindly supplying the strains; to Messrs. Bayer Products, Ltd., Burroughs Wellcome and Co., and May and Baker Ltd. for kindly providing the compounds; to Col. L. Colebrook, Dr. A. J. Ewins, Dr. A. T. Fuller, Dr. D. W. Henderson, and Miss D. Stephenson for much helpful advice and information; and to Miss M. Kuck for technical assistance and co-operation.

REFERENCES

- Bohman, H. R. (1937). *J. Amer. med. Ass.*, **109**, 254.
 Bosse, P., and Bosse, G. (1939). *Fortschr. Ther.*, **15**, 202.
 Brown, J. L. (1937). *British Medical Journal*, **1**, 1157.
 Burton, H., McLeod, J. W., McLeod, T. S., and Mayr-Harting, A. (1940). *Brit. J. exp. Path.*, **21**, 288.
 Buxton, St. J. D. (1940). *British Medical Journal*, **2**, 802.
 Childrey, J. H. (1939). *Arch. Otolaryng.*, **29**, 986.
 Chorine, V. (1940). *Bull. Acad. Méd., Paris*, **123**, 323.
 Colebrook, L. (1940a). *Lancet*, **2**, 113.
 — (1940b). *British Medical Journal*, **2**, 682.
 Domagk, G. (1937). *Klin. Wschr.*, **16**, 1412.
 Eisenhammer, S. (1940). *Lancet*, **2**, 760.
 Henderson, D. W., and Gorer, P. A. (1940). *J. Hyg., Camb.*, **40**, 345.
 Herrell, W. E., and Brown, A. E. (1940). *Proc. Mayo Clin.*, **15**, 611.
 Jaeger, K. H. (1936). *Disch. med. Wschr.*, **62**, 1831.
 Jeffrey, J. S. (1940). *Edinb. med. J.*, **47**, 727.
 Jensen, N. K., Johnsrud, L. W., and Nelson, M. C. (1939). *Surgery*, **6**, 1.
 Key, J. A., and Burford, T. H. (1940). *Sth. med. J., Nashville*, **33**, 449.
 Legroux, R. (1940). *Mém. Acad. Chir.*, **66**, 415.
 Levaditi, M. C., Bréchet, H., Gérard-Moissonier, and Tournay, R. (1940). *Bull. Acad. Méd., Paris*, **123**, 39.
 Long, P. H., and Bliss, E. A. (1937). *Canad. med. Ass. J.*, **37**, 457.
 Marshall, E. K., jun., and Litchfield, J. T. (1938). *Science*, **88**, 85.
 Mayo, C. W., and Miller, J. M. (1940). *Proc. Mayo Clin.*, **15**, 609.
 Merz, H. (1937). *Schweiz. med. Wschr.*, **67**, 342.
 Nicholson, W. F. (1938). *British Medical Journal*, **1**, 115.
 Nititi, F. (1939). *Bull. Acad. Méd., Paris*, **122**, 432.
 Riou, M. (1939). *Rev. méd. franc. Extrême-Orient*, **17**, 1091.
 Russell, D. S., and Falconer, M. A. (1940a). *Proc. roy. Soc. Med.*, **33**, 494.
 — (1940b). *Lancet*, **2**, 100.
 Sézary, A. (1939). *Presse méd.*, **47**, 1408.
 Smith, J. A. (1940). *British Medical Journal*, **1**, 1016.
 Stephenson, D., and Ross, H. E. (1940). *Ibid.*, **1**, 471.
 Tilling (1936). *Munch. med. Wschr.*, **83**, 952.
 Wardle, E. N. (1940). *British Medical Journal*, **2**, 743.

ACTIVATION OF THROMBOPLASTIN PREPARATIONS BY HAEMOLYSIS AND BY LECITHIN

BY

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During an investigation into the effect of storage on the prothrombin index of blood (Crosbie, Scarborough, and Thompson, 1941) one of us (A. C.) observed that the presence of haemolysis in the plasma was often associated with a decreased coagulation time as determined by Quick's technique. This acceleration was more pronounced when Russell-viper venom was used instead of brain extract as the source of thromboplastin as recommended by Fullerton (1940). While seeking an explanation for this phenomenon we read the letter of Hobson and Witts (1940) stating that they had confirmed the original observation of Trevan and Macfarlane (1936-7) that the coagulant action of Russell-viper venom was potentiated by the addition of lecithin. It occurred to us that the accelerating effect of haemolysis might be due to the liberation of lecithin into the plasma from the ruptured envelopes of erythrocytes. In this paper, a summary of which has already appeared (Crosbie and Scarborough, 1941), we give an account of our results. While the paper was being prepared for the press Witts and Hobson (1940) published their own observations, which demonstrated that lecithin used in association with Russell-viper venom produces an acceleration of the coagulation time as determined by Quick's method, and suggest that the adjuvant action of lecithin may be used in the elucidation of three types of haemorrhagic tendency.

Material and Methods

None of the subjects from whom blood was taken for this investigation had any form of haemorrhagic disease. Apart from a few patients with jaundice, to whom specific reference is made, the subjects either attended the out-patient department for minor complaints or were normal healthy adults. All coagulation times were determined by the method of Quick (1936), except that snake venom or venom plus lecithin replaced brain extract as the source of thromboplastin.

4.5 c.cm. of venous blood withdrawn with the minimum of trauma was added to 0.5 c.cm. of M/10 potassium oxalate or, in some cases, to 0.5 c.cm. of 3.8% sodium citrate. In order to reduce cell damage to the minimum, centrifugalization was avoided and plasma was obtained by allowing the specimens to stand overnight in a refrigerator at 2° to 5° C. This treatment does not affect the coagulation time as determined by Quick's original method with brain extract as the source of thromboplastin. 0.1 c.cm. of plasma was pipetted into a clean dry test-tube (7 × 70 mm.) in a water bath at 37° C. and mixed with 0.1 c.cm. of thromboplastin preparation. Immediately 0.1 c.cm. of M/40 calcium chloride was added and the coagulation time at 37° C. was determined in seconds.

Three sources of thromboplastin were used:

1. Brain Extract.—This was prepared according to the method of Quick, but from human instead of from rabbit brain as originally recommended.
2. Russell-viper Venom (stypven, B. W. and Co.).—Two different batches of material were used. They did not differ appreciably in activity. A dilution of 1 in 10,000

(0.1 mg. in 1 c.cm.) proved satisfactory: higher dilutions were found to give increased coagulation times.

3. Russell-viper Venom plus Lecithin.—The preparation of lecithin used was a 10% alcoholic solution of ovolectithin (B.P.C.). This substance is by no means pure. It is prepared from dried egg-yolk by extraction with alcohol and precipitation by acetone. According to the 1934 *Codex*, "when so prepared the product consists of a mixture of true lecithin and a similar compound, kephalin." A large number of different lecithins occur naturally, and lecithins are present in the membrane of human erythrocytes to the extent of 3.25 to 5.75 mg. per c.cm. of cells (Ponder, 1934). The particular preparation of ovolectithin used by us was equally active over a wide range of dilutions, and we accordingly adopted the dilution previously suggested by Hobson and Witts (1940).

Haemolysis was produced mechanically — "slight" haemolysis by gentle shaking for one minute, and "marked" haemolysis by vigorous shaking for two minutes. Haemolysed plasma was then obtained by centrifuging.

Results

The following points emerge from a consideration of Table I, which illustrates the effect of haemolysis on the coagulation time of both oxalated and citrated plasma with either brain extract or 1 in 10,000 Russell-viper venom as the source of thromboplastin:

1. The coagulation time is reduced by haemolysis, the reduction being greater with "marked" than with "slight" haemolysis.

2. The acceleration of the coagulation time is more pronounced when venom instead of brain extract is the source of thromboplastin. It is indeed possible that the differences obtained with brain extract are without significance.

3. In the absence of haemolysis the observations show a fairly wide scatter. This scatter is reduced by "slight" haemolysis. After "marked" haemolysis there is extraordinary uniformity throughout the series, especially when venom is the source of thromboplastin. Associated with this regularity of the final result there is wide variation in the extent to which the coagulation time is reduced by haemolysis.

4. Viper venom, in the absence of haemolysis and without lecithin, is a more potent source of thromboplastin than is brain extract. It should be pointed out, however, that Quick regularly obtains coagulation times of 11 to 15 seconds using brain extract.

With a view to determining whether the acceleration of the coagulation time found in association with haemolysis was due to the liberation of haemoglobin into the plasma or to some other substance freed at the same time, the following series of experiments was designed.

A solution of "crystalline ox haemoglobin" was prepared containing 250 mg. in 2 c.cm. 0.9% sodium chloride (12.5 grammes haemoglobin per 100 c.cm.). This was added to plasma free from haemolysis in the proportion of 0.1 c.cm. of haemoglobin solution to 1 c.cm. plasma. We have unfortunately been unable to trace the source of the preparation of haemoglobin used. It was contaminated with methaemoglobin. To an equal amount of the same plasma was added 0.1 c.cm. of freshly withdrawn human blood (14 grammes of haemoglobin per 100 c.cm.) completely haemolysed by saponin. The coagulation times of the specimens of plasma so treated were then determined with venom and brain extract (Table II). It is evident from Table II that the acceleration of the coagulation time produced by the addition of blood haemolysed by saponin exceeds that produced by the addition of haemoglobin, which is slight and may not be significant. This result suggests that the factor responsible for the acceleration may not be haemoglobin. Leathes and Mellanby

TABLE I.—Effect of Haemolysis on Coagulation Time of Plasma (41 Cases)

No Haemo-lysis	Slight Haemolysis			Marked Haemolysis		
Time (sec.)	Time (sec.)	Reduction		Time (sec.)	Reduction	
		Sec.	%		Sec.	%
A. With viper venom and oxalated blood :						
15	13	2	13	10	5	33
15	11	4	27	9	6	40
15	15	0	0	9	6	40
15	13	2	13	9	6	40
18	13	5	28	9	9	50
20	11	9	45	9	11	55
20	15	5	25	10	10	50
22	15	7	32	11	11	50
22	13	9	41	10	12	55
22	16	6	27	9	13	59
25	15	9	38	10	14	53
25	14	11	44	11	14	56
25	19	6	24	11	14	56
B. With viper venom and citrated blood :						
13	10	3	23	8	5	39
13	11	2	15	10	3	23
14	11	3	21	10	4	29
15	13	2	13	8	7	47
15	12	3	20	11	4	27
17	19	2	0	9	8	47
17	15	2	12	11	6	35
20	15	5	25	9	11	55
20	15	5	25	11	9	45
26	12	14	54	10	16	62
29	12	17	59	10	19	66
30	12	18	60	11	19	63
30	16	14	47	11	19	63
30	17	13	43	11	19	63
C. With brain extract and oxalated blood :						
21	21	0	0	21	0	0
25	27	2	0	25	0	0
29	27	2	7	26	3	10
30	34	4	0	33	3	0
33	26	7	21	25	8	24
34	36	2	0	32	2	6
38	39	1	0	37	1	3
38	38	0	0	37	1	3
40	32	8	20	31	9	22
D. With brain extract and citrated blood :						
25	25	0	0	25	0	0
26	25	1	4	25	1	4
26	24	2	8	25	1	4
30	28	2	7	25	5	17
33	30	3	9	22	11	33

TABLE II.—Effect of "Haemoglobin" and of Haemolysed Blood on Coagulation Time of Plasma (17 Cases)

Plasma (No Hae- molysis)	Plasma plus " Ox Haemoglobin "			Plasma plus Haemolysed Blood		
Time (sec.)	Time (sec.)	Reduction		Time (sec.)	Reduction	
		Sec.	%		Sec.	%
A. With viper venom and oxalated blood :						
13	15	2	0	10	3	23
14	14	0	0	12	2	14
15	20	5	0	15	0	0
15	13	2	13	10	5	33
15	14	1	7	10	5	33
16	13	3	19	13	3	19
20	18	2	10	10	10	50
22	16	6	27	12	10	46
24	20	4	17	10	14	58
25	25	0	0	9	16	64
B. With brain extract and oxalated blood :						
20	23	3	0	23	3	0
24	23	1	4	22	2	8
24	27	3	0	20	4	17
28	25	3	11	26	2	7
34	28	6	18	24	10	29
35	29	6	17	23	12	34
35	35	0	0	26	9	26

(1939) had already reported to the Physiological Society the potentiating effect of lecithin on the thrombokinase of daboia venom, and we accordingly determined to try the effect of lecithin. Lecithin was added to the venom as already described: we have also added it to the plasma in the proportion of 0.1 c.cm. ovolectithin to 1 c.cm. plasma.

The results of the third series of experiments are given in Table III, which shows that the acceleration of the coagulation time produced by lecithin is of the same order as that produced by "slight" haemolysis. Under the conditions of the experiment the addition of lecithin to the

TABLE III.—*Effect of Haemolysis and of Lecithin on Coagulation Time of Plasma (21 Cases)*

No Haemolysis	Slight Haemolysis		Lecithin					
			Added to Plasma			Added to Venom		
	Time (sec.)	Reduction	Time (sec.)	Reduction	Time (sec.)	Time (sec.)	Reduction	Time (sec.)
		Sec.	%	Sec.	%	Sec.	Sec.	%
A. With viper venom and oxalated blood :								
14	8	6	43	12	2	14	3	21
15	15	0	0	15	0	15	0	0
15	10	5	33	10	5	33	10	5
15	9	6	40	11	4	27	10	5
20	12	8	40	15	5	25	16	4
20	9	11	55	14	6	30	30	6
23	9	14	61	14	9	39	9	14
24	11	13	54	14	10	42	15	9
24	12	12	50	20	4	17	17	7
28	14	14	50	25	3	11	15	13
28	12	16	57	25	3	11	17	11
30	20	10	33	20	10	33	18	12
B. With brain extract and oxalated blood :								
20	20	0	0	18	2	10		
21	18	3	14	18	3	14		
21	20	1	5	21	0	0		
22	20	2	9	21	1	5		
25	27	-2	0	22	3	12		
28	27	1	4	24	4	14		
29	27	2	7	25	4	14		
31	31	0	0	31	0	0		
35	36	-1	0	26	9	26		

venom was more efficient than its addition to the plasma. The adjuvant effect of lecithin, like that of haemolysis (Table I), is more apparent when venom is the source of thromboplastin. Again little significance attaches to the differences observed with brain extract.

The effect of haemolysis and of lecithin in accelerating the coagulation time as determined by Quick's method on plasma, in which the prothrombin content is reduced, is shown in Table IV, which gives the results obtained in nine

TABLE IV.—*Effect of Haemolysis and of Lecithin on Coagulation Time of Plasma in Jaundice (Low Plasma Prothrombin) (9 Cases)*

No Haemolysis	Marked Haemolysis		Lecithin added to Venom		
			Reduction		
	Time (sec.)	Reduction	Time (sec.)	Reduction	Time (sec.)
		Sec.	%	Sec.	%
A. With viper venom and oxalated blood :					
40	19	21	52	30	10
55	14	41	75	25	30
60	23	37	62	40	20
80	68	12	15	60	20
120	115	5	4	130	-10
B. With brain extract and citrated blood :					
44	30	14	32	30	14
44	34	10	23	40	4
46	26	20	43	38	8
65	30	35	54	52	13

cases of jaundice. Both "marked" haemolysis and the addition of lecithin shorten the coagulation time when either venom or brain extract is the source of thromboplastin. The effect is greater with haemolysis. Even the shortened coagulation times are, however, still grossly in excess of those obtained with apparently normal blood (Table I).

The results of our investigations have been summarized in the accompanying distribution diagram. This shows the wide range of variation obtained when venom is used as the source of thromboplastin. The distribution curve is bimodal, with peaks at 15 and 20 seconds. Diluted venom tends to give times rather longer than those with the more concentrated preparation. When lecithin is added to the venom the coagulation times are shorter and the scatter appears to be reduced. In view, however, of the smaller number of observations it is impossible to be definite on this point. In the presence of haemolysis the

coagulation time is further reduced and the distribution curve now shows a single peak at 9 to 10 seconds with a relatively small scatter. This appears to be the best curve of the series. The addition of venom and lecithin to

Diagram showing the variation in coagulation time obtained when venom is used as the source of thromboplastin.

haemolysed plasma produces coagulation times which tend to be shorter still, but the data are not sufficient to warrant a definite statement.

Conclusions

The results here set forth would appear to indicate that Russell-viper venom alone is unsatisfactory as a source of thromboplastin. Its action can be potentiated by one or more of the products of haemolysis or by one or more of the constituents of ovoid lecithin, but it is not possible to say, as Witts and Hobson have done, that the adjuvant effect is due to lecithin. In nine cases of jaundice the effect produced by haemolysis was the greater. A preparation of haemoglobin was also found slightly effective. Acceleration of the coagulation time was greater with venom, but in the jaundiced cases occurred also with brain extract as the source of thromboplastin. In conditions of reduced plasma prothrombin the adjuvant effect of haemolysis and of lecithin can be demonstrated, but the reduced coagulation time still exceeds that of apparently normal blood. The influence of phospholipoids in the coagulation mechanism has been recognized for many years since Howell's original work on the subject, but the effect of haemolysis in accelerating the coagulation time has not been reported hitherto. It is this aspect which we particularly wish to stress. Plasma free from haemolysis contains phospholipins, and the presence of haemolysis adds to their amount to an immeasurably small extent. It would appear, therefore, that some highly active substance is liberated from the red cells. Our results suggest that this may be a phospholipoid. On more mature reflection we wish to retract the last statement in our letter (Crosbie and Scarborough, 1941): we have not been able to decide whether there is any advantage in determining this reduced coagulation time when investigating the presence of low plasma prothrombin. Our results support the valuable suggestion made by Witts and Hobson

that a new technique is available for the study of haemorrhagic diseases in the determination of coagulation time (Quick) with Russell-viper venom before and after the potentiating effect of ovolecithin, but we feel that work of a more specific nature is required before ascribing this effect to lecithin. Special precautions will, however, be necessary to avoid even a trace of haemolysis.

Summary

The effect of haemolysis in accelerating the coagulation time of plasma is recorded.

Experiments dealing with the influence on the coagulation time of the addition of venom and lecithin to haemolysed plasma are described.

The conclusions derived from the investigation are given.

Acknowledgment is made to the Moray Fund of Edinburgh University for a grant towards the expenses of this investigation.

REFERENCES

- Crosbie, A., and Scarborough, H. (1941). *British Medical Journal*, 1, 31.
and Thompson, J. C. (1941). *Edinb. med. J.*, 48, 41.
Fullerton, H. W. (1940). *Lancet*, 2, 195.
Hobson, F. C. G., and Witts, L. J. (1940). *Ibid.*, 2, 247.
Leathes, J. B., and Mellanby, J. (1939). *J. Physiol.*, 95, 39 P.
Ponder, E. (1934). *Mammalian Red Cell*, Borntraeger, Berlin.
Quick, A. J. (1936). *Amer. J. Physiol.*, 114, 282.
Trevan, J. W., and Macfarlane, R. G. (1936-7). Report of Medical Research Council, p. 143.
Witts, L. J., and Hobson, F. C. G. (1940). *British Medical Journal*, 2, 862.

CYCLICAL MUCOSAL ULCERATION

BY

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Recurrent buccal and genital ulceration is a syndrome which has attracted but scant attention. Recurring ulceration of the mouth is a common condition, described in textbooks under varying titles—ulcerative stomatitis, dyspeptic ulcers, aphthous ulcers, periadenitis mucosa necrotica recurrens (Sutton and Sutton, 1935), and stomatitis neurotica chronica (Sibley, 1899 and 1914). Recurring ulceration of the vulva was first described by Lipschütz (1913). He called the condition "ulcus vulvae acutum," by which name it is usually known, and in a second paper, in 1923, he reported 51 cases, but only 1 of these also had buccal ulceration.

The coexistence in the same patient of both conditions—namely, non-venereal ulcerative lesions of the mouth and genitalia—was originally described by Neumann (1895); and Wien and Perlstein (1932) in a comprehensive review of the subject could find reports of such a combination in only 30 cases and themselves described a single case. Since then Ravell (1932), Gray (1932), Thompson (1932), Talalov (1934), Hunt (1934), Ziserman (1935), Deuell and Landon (1936), Behcet (1937), Michaëlis (1937), and Tagami (1937) have reported between them 19 cases. In only 9 of the total of 50 cases is there any mention of the effect of menstruation on the ulcers, and in only 6 of these had the ulcers a regular time relation to the menstrual cycle—three cases of McDonagh (1924) and those of Talalov (1934), Ziserman (1935), and Michaëlis (1937). In 5 of the 8 cases recorded below the ulcers bore a constant time relation to menstruation, and it is this association of the ulcers with menstruation that I particularly wish to emphasize.

In all the patients whom I have seen with this condition the stomal and the genital ulcers have always had the same general characteristics. They vary in size from a pin-head to about one centimetre in diameter, and their appearance is preceded by and associated with pain at the site of ulceration, often malaise and depression, and occasionally dyspeptic symptoms. They are superficial, often appear-

ing to start as small papules or vesicles; they are surrounded by an inflammatory halo, their bases covered with a yellow slough, and they heal without scars. I have seen them on the inside of the cheeks, lips, tongue, tonsillar region, and pharynx, and also the labia, vagina, and cervix uteri. The number of ulcers present at one time varies from one to about twelve. They are unassociated with an adenitis.

Of the 8 cases reported below the most interesting is a group of 6 patients, all of whom are near relatives. Mrs. A. died, aged 55, from cancer of the uterus. There is no history that she or her only sister had complained of either buccal or vulvar ulceration. But Mrs. A. had three daughters—Mrs. B., Mrs. C., and Mrs. D.—of whom the first and the last both suffer from recurrent ulceration, as do also three of Mrs. B.'s four daughters, one of Mrs. C.'s four daughters, and the only daughter of Mrs. D. All the male members are healthy.

The following diagram illustrates the position more clearly. Ages are given in brackets and the initials of those who have buccal and/or genital ulceration are printed in *italics*.

Case Records

Case 1.—Mrs. B., aged 53, has had buccal and vaginal ulcers for twenty years. The stomal ulcers occur on the inner aspect of the lower lip and at the side of the tongue. There is usually only one mouth ulcer present at a time. The vaginal ulcers always occur at the same time as the buccal and are accompanied by a great deal of soreness. All the ulcers appeared two to three days before the onset of menstruation and disappeared during actual menstruation, but they always reappeared for two or three days after the period had ceased. Her menstrual cycle was always regular 3/28 until the menopause, but the flow was scanty and she had severe premenstrual and intramenstrual dysmenorrhoea. Since the menopause the ulcers have still regularly recurred every four weeks. During her four pregnancies the ulceration was always very much worse, but it improved following delivery. The only investigation has been a blood Wassermann, and this was negative. She has had no treatment whatsoever for the condition. Mrs. B. has four daughters, and three of these have ulcers. The eldest, Mrs. E. F., has genital and mouth ulcers, but further details about her are not available.

Case 2.—Miss B. B., aged 17, the third daughter of Mrs. B., has had mouth ulcers for eighteen months but no genital ulcers. The ulcers have occurred regularly every four weeks, and last for one or two days. Although she is nearly 18 she has never yet menstruated, and secondary sexual characteristics have not appeared. Her general nutrition is poor and she is pale. Apart from these facts there are no other positive findings, and no investigations have been undertaken. She has not had any special treatment.

Case 3.—Miss C. B., aged 10, the fourth daughter of Mrs. B., has been troubled with ulcers on the side of her tongue at irregular intervals for the last eighteen months. Recently they have been very large and painful, previously having been only small and causing little inconvenience. She is a well-built, healthy-looking child, and there is no evidence of infection of her teeth, tonsils, or sinuses. No investigations or special treatment have been undertaken.

Case 4.—Mrs. D., sister of Case 1, is aged 36, and has had ulceration of the mouth and vulva since the age of 12—two