The relation of tuberculous infection to erythema nodosum is summarized in Table III. No further investi-

TABLE III.—*Relation of Erythema Nodosum to Tuberculous Infection*

Tuberculin-positive children	88
With other evidence of active primary tuberculous infection	59
Without or with doubtful other evidence of active primary tuberculous infection	29
Tuberculin-negative children	12
Total:	100

gations were made in the 12 tuberculin-negative children. The eruption followed a sore throat in five of them and scarlet fever in one.

In none of the 100 children was there any evidence of rheumatic infection, and in the 80 who were observed for at least six months after the eruption there has been no sign of involvement of the heart.

Discussion

The high incidence (88%) of positive tuberculin reactions in the 100 children with erythema nodosum is comparable to the incidence found by many Continental workers and is even higher than that in the only other recent series from this country (Perry, 1944).

It cannot be stated with certainty that the erythema nodosum was due to tuberculosis in all the 88 tuberculin-positive children. It may be said, however, that at least in the 59 (67%) who at the time of the eruption had other evidence of active tuberculous infection there was a close relation between the eruption and the infection. In the remaining 29 children (33%) the same relation probably existed.

These results show that in this country, too, most of the children with erythema nodosum are passing through their primary tuberculous infection. Any child therefore with erythema nodosum should be considered to have been recently infected with tuberculosis unless carefully performed tuberculin tests are negative. Because of the high degree of sensitivity to tuberculin of the tuberculin-positive children with erythema nodosum a jelly test is usually sufficient to elicit a positive reaction. If intradermal tests are used, the amount of old tuberculin in the first injection should never exceed 0.01 mg.

Special investigations were not made in the 12 tuberculin-negative children, and there is therefore no direct evidence that a streptococcal infection was the main aetiological factor, though a sore throat or scarlet fever preceded the eruption in six.

The absence of any demonstrable relation between erythema nodosum and rheumatic fever in the present series is worthy of emphasis. Some doctors still consider that erythema nodosum is "rheumatic" in origin and fail therefore to carry out any further investigations. Out of 800 children with erythema nodosum Wallgren (1938b) saw only one in whom the eruption was related to rheumatic fever. Löfgren (1946), in his study of 184 cases of erythema nodosum in adults, found that there was no evidence that erythema nodosum is connected with rheumatic fever; and Skiöld found a probable connexion in only five (1.4%) out of 354 adults with erythema nodosum. It is clear, therefore, that erythema nodosum is very rarely due to rheumatic fever.

Summary

Out of 100 children with erythema nodosum 88 had positive tuberculin reactions. In 59 of these there was an active primary tuberculous lesion. In the remaining 29 tuberculosis was probably the aetiological factor. In none of the children was there any connexion between erythema nodosum and rheumatic fever.

I wish to thank Professor J. C. Spence, Professor E. J. Wayne, and Dr. T. Colver for their permission to make use of their cases, Professor R. S. Illingworth for his valuable advice, and Dr. D. Stone for his assistance. Part of the material was collected during the tenure of a Luccock Research Fellowship at the Medical School, King's College, University of Durham.

REFERENCES

- Begg, N. D. (1932). *Brit. J. Child. Dis.*, **29**, 193.
 Boganovitch, V. (1930). *Arch. Dis. Childh.*, **5**, 56.
 Brandon, K. F., Hardman, R. P., and Birke, W. H. (1938). *Canad. publ. Hlth J.*, **29**, 533.
 Collis, W. R. F. (1932). *Quart. J. Med.*, **1**, 141.
 — (1933). *British Medical Journal*, **2**, 1162.
 Debré, R., Saenz, A., Broca, R., and Mallet, R. (1938). *Rev. franç. Pédiat.*, **14**, 433.
 Dickey, L. B. (1932). *Amer. Rev. Tuberc.*, **26**, 614.
 Doxiadis, S. A., and McLean, D. (1948). *Arch. Dis. Childh.*, **23**, 273.
 Ernberg, H. (1921). *Jahrb. Kinderheilk.*, **45**, 1.
 — and Gabinus, O. (1939). *Amer. J. Dis. Child.*, **57**, 1012.
 Forman, L., and Whitwell, G. P. B. (1934). *Guy's Hosp. Rep.*, **84**, 213.
 Göbel, W. (1933). *Z. Kinderheilk.*, **55**, 30.
 Gray, W. D. (1945). *British Medical Journal*, **2**, 286.
 Landorf, N. (1935). *Acta paediatr., Stockh.*, **17**, suppl. 1, 180.
 Lincoln, E. M., Alterman, J., and Bakst, H. (1944). *J. Pediatr.*, **25**, 311.
 Löfgren, S. (1945). *Acta med. scand.*, **122**, 175.
 — (1946). *Ibid.*, suppl. 174.
 Mallet, R. (1938). *Erythème Nouveau et Infection Tuberculeuse*. Thèse No. 187. Paris.
 Miescher, G. (1948). *Schweiz. med. Wschr.*, **78**, 269.
 Moro, E. (1934). *Derm. Wschr.*, **98**, 633.
 Nobécourt, P., and Briskas, S. B. (1941). *Pr. méd.*, **49**, 713.
 Perry, C. B. (1944). *British Medical Journal*, **2**, 843.
 Roddy, R. L. (1949). *J. Pediatr.*, **34**, 338.
 Rötne, P. L. (1936). *Acta derm.-venereol., Stockh.*, **17**, suppl. 3.
 Skiöld, N. (1945). *Acta med. scand.*, suppl. 157.
 Smith, C. E., Beard, R. R., Whiting, E. G., and Rosenberger, H. G. (1946). *Amer. J. Publ. Hlth*, **36**, 1394.
 Spink, W. W. (1937). *Arch. intern. Med.*, **59**, 65.
 Thompson, B. C. (1939). *British Medical Journal*, **1**, 159.
 Uffelmann, J. (1872). *Dtsch. Arch. klin. Med.*, **10**, 454.
 Wallgren, A. (1927). *Z. Kinderheilk.*, **43**, 543.
 — (1928). *Amer. J. Dis. Child.*, **36**, 702.
 — (1930). In Engel and Pirquet's *Handbuch der Kindertuberkulose*, vol. 1, p. 809. Leipzig.
 — (1931). *Amer. J. Dis. Child.*, **41**, 816.
 — (1938a). *Lancet*, **1**, 359.
 — (1938b). *Amer. J. Dis. Child.*, **55**, 897.

POST-OPERATIVE THROMBOSIS*

INVESTIGATION OF A PROPOSED TEST FOR ITS PREDICTION

BY

G. W. VAUSE GREIG, M.B., F.R.C.S.

Surgical Registrar, the General Infirmary, Leeds

In a paper on intravascular thrombosis Cummine and Lyons (1948) claimed that by the examination of the post-operative coagulation time and estimation of the plasma fibrinogen-B they could foretell the onset of impending thrombosis. They further suggested that if the coagulation time as measured by the capillary tube method drops to four minutes, and if fibrinogen-B (an intermediate product in the change of fibrinogen into fibrin) can be demonstrated in the blood, then prophylactic anticoagulant therapy should be instituted.

In spite of the introduction of heparin and dicoumarol, thrombosis and embolism still contribute to the incidence of post-operative morbidity and mortality, and a simple test to determine which patients should be given anticoagulant drugs to prevent these complications is being widely sought. Investigation of a series of cases, using the proposed tests of Cummine and Lyons, was therefore undertaken.

*Being the subject of a short paper delivered before the Surgical Travellers Club at Leeds on January 21, 1949.

Method

It was decided to measure the coagulation time before operation and then daily after operation, but the fibrinogen-B test, which entails a venepuncture, was done pre-operatively, the day after operation, and then subsequently only when there was a fall in the coagulation time.

This regime was followed in 43 cases, and in a further eight acute cases the estimations were started the day after operation. All the patients investigated had undergone a major operation varying from a partial gastrectomy to a prostatectomy. Of the 51 patients 29 were over 55 years of age; only six were under 40, and of these one was a case of cholelithiasis for which a cholecystectomy had been performed, three had had partial gastrectomies for chronic duodenal ulceration, and one (the youngest of the series, aged 32) had had an abdomino-perineal resection for carcinoma of the rectum. Thus all were in the groups in which post-operative thrombosis is most common.

The estimations were discontinued when the patient was ambulant, as it was considered that by that time the danger of spontaneous intravascular clotting has generally passed. That this belief is erroneous was proved by the one case in the series which developed a thrombosis.

Results

The results may be divided into four groups.

Group 1.—In 12 cases the coagulation time throughout was above four minutes and no fibrinogen-B was found in their blood post-operatively (Fig. 1).

Group 2.—Ten patients had fibrinogen-B in their blood post-operatively, but their coagulation time remained higher than four minutes (Fig. 2).

Group 3.—Eleven cases showed a lowering of the coagulation time to four minutes or less but had no fibrinogen-B in their blood at the time of this fall (Fig. 3).

Group 4.—In 18 cases there was a fall of the coagulation time to four minutes or less associated with the finding of fibrinogen-B in the blood.

According to Cummine and Lyons there is no danger of thrombosis in the first three groups, and none of the cases in these groups showed clinical signs suggesting it.

The cases in Group 4, comprising more than one-third of the whole series, satisfied the criteria laid down by Cummine and Lyons for the prophylactic administration of heparin and dicoumarol. The first two cases showing this fall in coagulation time coincident with a positive fibrinogen-B test were given heparin and dicoumarol, and in both, as was to be expected, the result was a marked prolongation of the clotting time, but in one the plasma fibrinogen-B persisted (Fig. 4). However, as these two cases occurred

among the first five investigated, and as they displayed no evidence of thrombosis, it was decided to withhold anticoagulant drugs until the tests had been more certainly evaluated.

Out of the subsequent 16 cases in Group 4 only one developed a thrombosis, and this took place after the patient was ambulant and the daily coagulation time determination had been discontinued (Fig. 5): the day after the thrombosis her coagulation time was within normal limits and her blood free from fibrinogen-B. This woman, who had a deep femoral thrombosis, was not treated with heparin or dicoumarol, but was kept ambulant, with a firm crêpe bandage from toes to groin. She suffered no embolic phenomena or further spread of the thrombosis, and when seen three months later had only a slight residual swelling of the leg in the ankle region, with no incapacity.

FIG. 3.—Graph of case typical of Group 3 (man aged 58; carcinoma of rectum). Lowering of coagulation time to below four minutes, but not associated with fibrinogen-B in the blood.

FIG. 4.—Graph of case typical of Group 4 (man aged 57; partial gastrectomy for duodenal ulcer). Coagulation time below four minutes together with fibrinogen-B in the blood.

FIG. 5.—Carcinoma of caecum in a woman aged 64. The only case in Group 4 showing clinical signs of thrombosis—occurring after patient was fully ambulant.

Discussion

As this investigation progressed disappointment was felt because these proposed tests did not enable us to predict accurately the cases which would develop post-operative thrombosis: it is obviously not practicable to treat 35% of patients with heparin and dicoumarol. However, one point of interest did arise. This was that of the 43 cases examined both before and after operation 34 showed a fall in the coagulation time in the first twenty-four hours after operation and 21 of these had a fall to four minutes or less. Ten patients whose clotting times were measured at the end of operation before they left the operating theatre all showed a marked increase in rate of coagulation. These results suggest that what Bergquist (1940) called "the pre-thrombotic state" is not infrequently present within the first few hours after operation or even earlier, during operation, and this is the danger time when thrombosis in the leg veins is most likely to begin.

Summary

Investigations were carried out in 51 cases on a proposed method for the prediction of post-operative thrombosis. It was

FIG. 1.—Graph of case typical of Group 1 (woman aged 76; gallstone ileus). Coagulation time remaining above four minutes. No fibrinogen-B.

FIG. 2.—Graph of case typical of Group 2 (woman aged 51; portal hypertension). Fibrinogen-B present, but no lowering of coagulation time.

decided that the results were not accurate enough to warrant the use of heparin and dicoumarol in those cases in which the tests were positive.

It was found that there is commonly a fall in coagulation time during or immediately after operation, and it is suggested that thrombosis, if it does occur, probably starts during this period.

I am indebted to Professor Digby Chamberlain, who proposed and guided these investigations, and on whose cases they were carried out.

REFERENCES

- Bergquist, G. (1940). *Acta chir. scand.*, **83**, 415.
Cummine, H., and Lyons, R. N. (1948). *Brit. J. Surg.*, **35**, 337.

INCIDENCE OF SIGNS USUALLY CONNECTED WITH THYROTOXICOSIS WITH SPECIAL REFERENCE TO LID LAG*

BY

W. P. U. JACKSON, M.D., M.R.C.P., D.C.H.

Late Assistant Physician, Selly Oak Hospital, Birmingham

During recent observations on the coincidence of hyperthyroidism and peptic ulcer (Jackson and Pinkerton, 1949) it was noticed that a large proportion of patients with the latter complaint showed von Graefe's sign (lid lag), one of the characteristic ocular phenomena of thyrotoxicosis. This sign was first described in 1864 by von Graefe, who said: "... namentlich folgt bei Senkung der Cornea das obere Augenlid nicht." He remarked that it was not the result of exophthalmos, as it was present in early cases of thyroid disease which showed no proptosis. He considered it to be a sign pathognomonic of hyperthyroidism in the early stage: "... geringen Grade der Krankheit einen pathognomonischen Werth hat." It is now recognized that the sign is not peculiar to thyrotoxicosis (Eason, 1927) and that it may occur in normal people (Joll, 1932). Joll remarks that it also occurs in all forms of goitre, in myotonia congenita, and in all cases of proptosis.

Present Investigation

In order to determine the approximate incidence of lid lag in people without thyroid disease, and to see whether it was particularly common in cases of peptic ulcer, 600 people of all ages and approximately equal sex numbers who attended a general hospital were examined. All patients with dysthyroidism, severe illness, and prolonged pyrexia were excluded. Otherwise there was no selection, except that 38 extra cases of peptic ulcer were specially included. Other manifestations which occur in thyrotoxicosis were also looked for in this series. Preference for hot or cold weather was noted, and the subjects were questioned about excessive sweating. Lid lag, lid retraction, exophthalmos, enlargement of the thyroid gland, and tremor of the outstretched fingers were looked for. The heights and weights of all those over 18 were noted where practicable.

For present purposes lid lag is defined as occurring when a white band of sclera appears between the upper lid and the cornea on following a moving object downwards with the eyes. If lid retraction is present lid lag can be considered to exist only if there is a definite widening of the band of sclera already visible. This is the most objective way of defining lid lag, although in those whose lid is usually held at a low level there may be a degree of lagging

of the upper lid without any sclera coming into view. The results are shown in Table I.

TABLE I.—Results of Investigation

	Total No.	No. with Lid Lag
Whole series	600	85† (14%—or 10% of whole series excluding ulcer cases)
Patients with peptic ulcer	76	23 (33%)
" " lid retraction	14	8 (57%)
" " exophthalmos	3	3 (100%)
" " non-toxic goitre	35	5 (14%)
" " fine tremor	11	

† 58 males, 27 females.

Types of Eyelid Movement.—All cases of lagging of the upper eyelid were not alike. The band of sclera might appear during the whole movement of the eyeball or during any part of it. In other words, the lag might begin as soon as the eyeball started to descend, or the lid might move normally at first and lag later. The movement might be smooth or jerky. The lag in some cases was variable, at times being pronounced and at other times not being elicited at all. In five cases it was unilateral, and in two there was actually a reverse or upward movement of the eyelids as the eyeballs started downward. In one person the lid retraction was unilateral.

Lid Lag in Relation to Other Observations

The male sex predominated in the ratio of 2 to 1. All age groups produced subjects with lid lag, but it was more common in those over 40 (see Table II).

TABLE II.—Age Incidence of Lid Lag

Age	Total No. of Subjects	No. with Lid Lag
0-9 years	31	3 (9.7%)
10-19 "	50	2 (4%)
20-29 "	50	2 (4%)
30-39 "	72	8 (11%)
40-49 "	115	20 (17.4%)
50-59 "	132	22 (16.6%)
60-69 "	107	21 (19.6%)
70-79 "	43	7 (16%)

Eight of the 14 subjects with lid retraction also showed lid lag, as did all three with exophthalmos and five out of the 35 with simple goitres. Of the 76 cases of peptic ulcer 23 (33%) showed lid lag. This incidence is significantly higher than that of lid lag in the control series (10%). The impression was formed that lid lag was more common in thin people, and since peptic ulcer characteristically occurs in people with a low ponderal index (P.I.) (Draper, 1930; Robinson, 1938) this was suspected of being the explanation of the frequent occurrence of lid lag in peptic ulcer subjects. To test this hypothesis the P.I.† of all those over 18 was worked out, and all fell between 1.2 and 3.2. The number of subjects pertaining to each index was noted and expressed as a percentage of the whole. Thus three subjects (0.5% of the total) had a P.I. of 1.3. These percentages for each P.I. referring to (1) all the subjects, (2) the peptic ulcer subjects, and (3) those showing lid lag were plotted separately (see Chart). The mean P.I. in the full control series was 2.1 (slightly in excess of the mode), while in subjects with peptic ulcer and in those showing lid lag it was 1.9. The chart thus confirms the tendency for lid lag to occur in people of slim build, but it seems unlikely that this factor alone can explain its excessive appearance in peptic ulcer subjects. However, the male preponderance in both peptic ulcer—about 4 : 1 (Stewart, 1923; Ryle, 1932; Tidy, 1944 ;

†The ponderal index in this investigation was calculated by dividing the weight in pounds by the height in inches.

*Based on a paper read at the South African Medical Congress, Capetown, September, 1949.