Side-effects.—In doses of 200 mg. or more the drug caused drowsiness and a tendency to sleep in five patients. The sleep so induced was apparently deep, but a slight stimulus produced an immediate awakening without obvious mental "cloudiness." In fact, one patient, when awakened, denied ever having been asleep at all. Complaints of excessive thirst and hunger may have been related to the comparatively lower intake of food and fluid necessitated by the technique of the test. There were no complaints of "hang-over" or drowsiness on the morning after the test.

Summary and Conclusion

The effects of N-phthalyl glutamic acid imide (K 17) on thyroid uptake of radioactive iodine have been assessed in nine euthyroid patients.

From the results obtained it appears that N-phthalyl glutamic acid imide has a mild but definite antithyroid activity when given in doses of 200 mg. or more. At present the mode of its action is unknown. In the meantime, therefore, it would seem unjustifiable to use the drug for long-term sedative or hypnotic therapy, pending the results of a more detailed study of its long-term effects in a larger series of patients, and notably those suffering from mild or moderately severe hyperthyroidism.

We should like to thank Professor D. M. Dunlop and Dr. A. G. Macgregor for helpful advice in the preparation of this paper and for allowing us to study patients under their care. The work was made possible through an expense grant to Dr. A. G. Macgregor from the Secretary of State for Scotland through the Advisory Committee on Medical Research. We also wish to thank Miss Beatrice Jardine for technical assistance. The K 17 was supplied for this investigation by courtesy of the Distillers Company (Biochemicals) Limited).

REFERENCES

- Esser, H., and Heinzler, F. (1956). *Ther. d. Gegenw.*, 95, 374.
Jung, H. (1956). *Arzneimittel-Forsch.*, 6, 430.
Kunz, W., Keller, H., and Mückter, H. (1956). *Ibid.*, 6, 426.
Stanley, M. M., and Astwood, E. B. (1947). *Endocrinology*, 41, 66.
Stärk, G. (1956). *Praxis*, 45, 966.

THE ENANTHEM OF GLANDULAR FEVER

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The manifestations of glandular fever are well known to be very varied, and the diagnosis is usually made only after laboratory investigation. Any clinical aid to diagnosis is therefore of value.

Many major reviews of the disease do not mention the occurrence of an enanthem (Tidy, 1934; Contratto, 1944; Press *et al.*, 1945; Gardner and Paul, 1946; Tidy, 1950; Stevens *et al.*, 1951). However, Downey and McKinlay (1923), in their classical paper describing the characteristic atypical monocyte, state that two of their nine cases had haemorrhagic lesions on the palate. Glanzmann (1930) described papular and petechial lesions on the palate in glandular fever and discussed their differential diagnosis with respect to acute leukaemia and thrombocytopenic purpura. Kilham and Steigman (1942) described petechiae in the mouth of 8 of their 20 cases. One other patient had irregular red papules on the palate. Milne (1945), Read and

Helwig (1945), Wechsler *et al.* (1946), and Müller (1950) noted petechiae in the oral cavity in a few of their cases.

Berberich and Thomas (1949) and Hoagland (1952) drew attention to the diagnostic value of palatal lesions. They described groups of petechiae on the hard and soft palate, 5 to 20 in number. Bender (1954), Holzel (1954), and Shiver *et al.* (1956) independently gave more detailed descriptions of the enanthem. It consists of 10 to 100 small petechiae, usually at the junction of the hard and the soft palate, appearing from the third to the seventh day and disappearing after three to four days. They stress the absence of cutaneous purpura and the normal platelet count in those cases investigated.

Leibowitz (1953) described another lesion in 4 of his 25 cases: an irregular white macule about 2 mm. in diameter, surrounded by an erythematous base, persisting 24 hours or so, and occurring on the soft palate, tonsillar pillars, and tonsils.

The purpose of this communication is to confirm the diagnostic value of the enanthem and to discuss other similar lesions.

Material and Methods

At least 200 patients with acute febrile illnesses, with lymphadenopathy, or with jaundice, in whom glandular fever was a diagnostic possibility, were seen in five military hospitals between September, 1955, and May, 1957. Nearly all were males in the Service age group, but a few were females and children. Of 51 who had palatal lesions, 45 had at least one blood film examined and one Paul-Bunnell test performed. Four of the remaining six were young children, and are excluded from further consideration. The criteria used for the diagnosis of atypical mononuclear cells approximate to those of Downey and McKinlay (1923), although exact classification was not attempted.

The Paul-Bunnell reaction was not considered positive unless a titre of 1 in 80 or more was found after absorption with guinea-pig kidney and no significant titre after absorption with ox cells, according to the technique of Davidsohn (1937). Heterophil antibodies of this titre and pattern are generally regarded as occurring only in glandular fever (Leibowitz, 1953).

Results

The 45 patients investigated can be divided into four groups (see Table).

	Group A	Group B	Group C	Group D	Total
Glandular fever	Proved	Proved	Possible	No evidence	—
Atypical mononuclear cells ..	Seen	Not seen	Seen	Not seen	—
Paul-Bunnell test	Pos.	Pos.	Neg.	Neg.	—
Total No. of cases	23	5	7	10	45
Petechiae alone. More than 5 ..	12	2	1	3	18
" " Less than 5	6	3	4	2	15
Red macules. Alone	—	—	—	2	2
" " With petechiae	3	—	—	1	4
Linear macules. Alone	—	—	1	—	1
" " With petechiae	1	—	—	—	1
" " With red macules	—	—	—	1	1
White macules (with petechiae) ..	1	—	1	—	2
Vesicles (with petechiae)	—	—	—	1	1

Two patients not investigated had vesicular lesions alone.

Group A comprised 23 patients with positive haematological and serological evidence of glandular fever as defined.

Group B consisted of five patients serologically positive but without atypical mononuclear cells. Two had only one blood film examined, on the second and fourth days. The blood in these two cases may well have been examined too early, for by the eighth day Stevens *et al.* (1952) found that only 50% of 210 cases had developed atypical cells. In view of the diagnostic significance of the differential Paul-

Bunnell reaction in the titre used, these five patients are considered with the 23 in group A as having "proved glandular fever."

Group C comprised seven patients in whom atypical mononuclear cells were found but the serology was negative. In two cases the titre in the Paul-Bunnell test rose between the first and second tests. In two more no Paul-Bunnell test was carried out after the 11th day. At this stage of the illness the test is often negative (Gardner and Paul, 1946). Further, a varying proportion of cases in different series have persistently negative Paul-Bunnell reactions. Thus, despite the known frequent occurrence of atypical mononuclear cells in other conditions (Shubert *et al.*, 1954), these patients are considered to have "possible glandular fever."

Group D consisted of 10 patients in whom there was neither haematological nor serological evidence of glandular fever. Only three had the blood examined after the ninth day. These patients are considered as having "no evidence of glandular fever."

Types of Palatal Lesion

Five types of lesion were seen:

1. **Petechiae.**—These are 1–2 mm. across, irregular in outline, and purple in colour. They usually occur at the junction of the soft and the hard palate, but may be seen anywhere on the palate. They may number from 1 to 50 or so. If infrequent they tend to be smaller, angular in shape, and somewhat redder. If numerous they may coalesce, but there are always a few small and clearly petechial lesions to indicate the nature of the eruption. Neither the symmetrical distribution nor the crescentic grouping described by Holzel (1954) is often seen. The petechiae first appeared 30 hours after the first symptom, but often developed on the third day. Each lesion lasted three to four days. Several crops may occur. In one case they were seen as late as the 26th day of illness. Petechiae occurred in all clinical varieties of glandular fever and bore no relation to the type of sore throat observed, the height of fever, the degree of adenopathy, or the presence of splenomegaly or exanthem. In most cases they disappeared within 48 hours of the fever settling. A second crop was occasionally associated with a second rise in temperature. Eighteen patients had more than five petechiae and no other palatal lesions: 14 had proved and 1 had possible glandular fever; three had undoubtedly rubella. Fifteen had fewer than 5 petechiae and no other lesions: of these, 9 had proved and 4 possible glandular fever, and 2 no evidence of it. Two patients, both with proved glandular fever, had petechiae on the buccal mucosa; one of these developed transient skin purpura and microscopic haematuria, but no thrombocytopenia.

2. **Red Macules.**—These are 3–4 mm. across, roughly circular, and deep red in colour. They occur anywhere on the palate, number up to three, and were seen from the 1st to the 14th day of illness. Two patients had these lesions alone: neither had evidence of glandular fever. Four had red macules and petechiae; three of them had proved glandular fever and one no evidence of it.

3. **Linear Macules.**—These are pinkish macular lesions 1 mm. across and 6–8 mm. long on the soft palate, sometimes arranged in a radial fashion; they were seen in three cases from the 7th to the 18th day of illness. Two had no evidence of glandular fever (one with these lesions alone and one with linear and red macules), while one patient with linear macules and petechiae had proved glandular fever.

4. **White Macules.**—Two patients had the lesion described by Leibowitz (1953); both had petechiae—one had possible and one proved glandular fever.

5. **Vesicular Lesions.**—Obviously vesicular lesions with erythematous surround were seen in three patients. One had a transient urticaria of unknown cause, another chickenpox: neither had blood examinations. The third had petechiae around the palatal vesicles and no evidence of glandular fever; the clinical picture was that of herpangina (Zahorsky, 1924; Huebner *et al.*, 1951), but virological studies were not carried out.

Discussion

These results confirm the findings of Berberich and Thomas (1949) and subsequent authors concerning the positive value of multiple palatal petechiae in the clinical diagnosis of glandular fever. If fewer than five petechiae are present there is still a strong suspicion of the disease.

Haemorrhagic lesions in the palate are not, of course, confined to glandular fever. They may occur in leukaemia (Love, 1936) and in purpuric diseases, but in such conditions petechiae on the buccal mucosa, other lesions in the mouth, and cutaneous petechiae or purpura should be present (Glanzmann, 1930). They are described in meningococcal meningitis, in the exanthematic rickettsial illnesses, and in dengue (Stewart, 1944), but only as part of a profuse and usually diagnostic exanthem.

The enanthem of scarlet fever (Wiener, 1947), measles (Koplik, 1896; Wiener, 1947), and roseola infantum (Clemens, 1945) should be distinguishable. That of chickenpox and smallpox is clearly vesicular. Forchheimer (1898) described rose-red macules the size of a pinhead on the soft palate in rubella; a petechial eruption was seen in three of our cases in which the diagnosis was undoubtedly rubella. Glanzmann (1930) discussed the difficulties in distinguishing rubella and glandular fever. Petechiae may precede or accompany the vesicular lesions of herpangina (Huebner *et al.*, 1951; Kravis *et al.*, 1953) on the anterior tonsillar pillars and soft palate, as noted in our suggestive case.

Palatal lesions are not mentioned in clinical descriptions of a wide variety of illnesses which glandular fever may simulate: streptococcal and non-streptococcal tonsillitis, acute undifferentiated respiratory disease (Commission on Acute Respiratory Diseases, 1944, 1947), influenza (Horsfall, 1952), the typhoid group (Banks, 1949), brucellosis (Spink, 1956), infective hepatitis (Hoagland and Shank, 1946), lymphocytic choriomeningitis (Adair *et al.*, 1953), or any of the recently described benign meningitic or meningoencephalitic illnesses of viral origin (Acheson, 1954; Tyrrell and Snell, 1956; Lyle, 1956; Karzon *et al.*, 1965; Garnett *et al.*, 1957; Rotem, 1957).

More studies are needed to determine the frequency of the enanthem of glandular fever. Some find it in 5% of cases or less (Milne, 1945; Read and Helwig, 1945; Wechsler *et al.*, 1946; Hoagland, 1952), some in 25% (Stevenson and Brown, 1943; Berberich and Thomas, 1949), and Shiver *et al.* (1956) in 50% of sporadic cases. All our 28 patients with proved glandular fever had some palatal petechiae; 14 had more than five. In the same period the use of the screening procedure for heterophil antibodies, as described by Butt and Foord (1935), in at least 100 more of our patients revealed no other case in which subsequent investigation showed a diagnostic Paul-Bunnell reaction. The frequency of the enanthem in any given epidemic may well be misleading, as different epidemics are known to show different clinical (Tidy, 1934) and laboratory features. (Shubert *et al.*, 1954).

The other lesions described occur occasionally in glandular fever but also in other diseases, although Leibowitz's white macules may be specific. The occurrence of petechiae with red or linear macules is, however, significant.

In conclusion, there is little doubt that the finding of multiple pin-point palatal petechiae in the absence of petechiae elsewhere or other palatal lesions is strong clinical evidence of glandular fever if rubella can be excluded. This should be of value in the diagnosis of cases of sore throat, adenopathy, skin rash, jaundice, lymphocytic meningitis, and polyneuritis.

Summary

The characteristic enanthem of glandular fever is an eruption on the palate consisting of multiple pin-point petechiae. If petechiae are few the sign is suggestive only.

The petechiae may occur from the 2nd to as late as the 26th day of the illness. Their duration is related to the duration of fever.

Other similar palatal lesions are discussed.

Our thanks are due to numerous colleagues for their help, in particular to Captains J. H. Adams, A. Addison, H. Baron, and O. W. Samuels, R.A.M.C., and to Miss Carla Tophoff for assistance in translation.

ADDENDUM.—Kendall *et al.* (*Brit. med. J.*, 1957, 2, 131) describe petechiae on the soft palate and scanty atypical monocytes in pharyngo-conjunctival fever. It is possible that some of our cases with "no evidence of glandular fever" or "possible glandular fever" had this condition, though none had conjunctivitis.

REFERENCES

- Acheson, E. D. (1954). *Lancet*, 2, 1044.
 Adair, C. V., Gaud, R. L., and Smadel, J. E. (1953). *Ann. intern. Med.*, 39, 675.
 Banks, H. S. (1949). *The Common Infectious Diseases*. Arnold, London.
 Bender, C. E. (1954). *J. Lancet*, 74, 7.
 Berberich, W. F., and Thomas, F. H. (1949). *U.S. nav. med. Bull.*, 49, 271.
 Butt, E. M., and Foord, A. G. (1935). *J. Lab. clin. Med.*, 20, 538.
 Clemens, H. H. (1945). *J. Pediatr.*, 26, 66.
 Commission on Acute Respiratory Diseases (1944). *J. Amer. med. Ass.*, 125, 1163.
 — (1947). *Medicine (Baltimore)*, 26, 441.
 Contratto, A. W. (1944). *Arch. intern. Med.*, 73, 449.
 Davidson, I. (1937). *J. Amer. med. Ass.*, 108, 289.
 Downey, H., and McKinlay, C. A. (1923). *Arch. intern. Med.*, 32, 82.
 Forchheimer, F. (1898). *Philad. med. J.*, 2, 15.
 Gardner, H. T., and Paul, J. R. (1946). *Yale J. Biol. Med.*, 19, 839.
 Garnett, D. G., Burlingham, A., and van Zwabenberg, D. (1957). *Lancet*, 1, 500.
 Glanzmann, E. (1930). *Das lymphoide Drüsenfieber*. Karger, Berlin.
 Hoagland, C. L., and Shank, R. E. (1946). *J. Amer. med. Ass.*, 130, 615.
 Hoagland, R. J. (1952). *Amer. J. Med.*, 13, 158.
 Holzel, A. (1954). *Lancet*, 2, 1054.
 Horsfall, F. L. (1952). In *Viral and Rickettsial Infections of Man*, 2nd ed., edited by T. M. Rivers. Lippincott, Philadelphia.
 Huebner, R. J., Cole, R. M., Beeman, E. A., Bell, J. A., and Peers, J. H. (1951). *J. Amer. med. Ass.*, 145, 628.
 Karzon, D. T., Barron, A. L., Winkelstein, W., jun., and Cohen, S. (1956). *Ibid.*, 162, 1298.
 Kilham, L., and Steigman, A. J. (1942). *Lancet*, 2, 452.
 Koplik, H. (1896). *Arch. Pediatr.*, 13, 918.
 Kravis, L. P., Hummeler, K., Sigel, M. M., and Lecks, H. I. (1953). *Pediatrics*, 11, 113.
 Leibowitz, S. (1953). *Infectious Mononucleosis*. Grune and Stratton, New York.
 Love, A. A. (1936). *Arch. Otolaryng. (Chicago)*, 23, 173.
 Lyle, W. H. (1956). *Lancet*, 2, 1042.
 Milne, J. (1945). *New Engl. J. Med.*, 233, 727.
 Müller, G. (1950). *Z. klin. Med.*, 146, 1.
 Press, J. H., Shlevin, E. L., and Rosen, A. P. (1945). *Ann. intern. Med.*, 22, 546.
 Read, J. T., and Helwig, F. C. (1945). *Arch. intern. Med.*, 75, 376.
 Rotem, C. E. (1957). *Lancet*, 1, 502.
 Shiver, C. B., Berg, P., and Frenkel, E. P. (1956). *J. Amer. med. Ass.*, 161, 592.
 Shubert, S., Collee, J. G., and Smith, B. J. (1954). *Brit. med. J.*, 1, 671.
 Splink, W. W. (1956). *The Nature of Brucellosis*. University of Minnesota Press, Minneapolis.
 Stevens, J. E., Bayrd, E. D., and Heck, F. J. (1951). *Amer. J. Med.*, 11, 202.
 — (1952). *Blood*, 7, 31.
 Stevenson, E. M. K., and Brown, T. G. (1943). *Glasg. med. J.*, 140, 139.
 Stewart, F. H. (1944). *U.S. nav. med. Bull.*, 42, 1233.
 Tidy, H. L. (1934). *Lancet*, 2, 180, 236.
 — (1950). *Postgrad. med. J.*, 26, 9.
 Tyrrell, D. A. J., and Snell, B. (1956). *Lancet*, 2, 1028.
 Wechsler, H. F., Rosenblum, A. H., and Sills, C. T. (1946). *Ann. intern. Med.*, 25, 113, 236.
 Wiener, K. (1947). *Skin Manifestations of Internal Disorders*. Kimpton, London.
 Zahorsky, J. (1924). *Arch. Pediatr.*, 41, 181.

At a recent joint meeting of the British Tuberculosis Association with the Society of Medical Officers of Health, Dr. H. D. CHALKE, president of the Society, spoke of the changed role of the M.O.H. in tuberculosis, and emphasized the educative role of health visitors. He himself preferred the general purposes health visitor, although he agreed that a few specialized tuberculosis health visitors were very valuable as a nucleus based on chest clinics. He also commented on the hazards of allowing uncontrolled immigration and vagrancy, especially since for the first time within statistical record more people were coming into Britain than were leaving it. Dr. K. NEVILLE IRVINE discussed the value of B.C.G. vaccination and the useful ages at which this could be given. Although ideally the newborn child should be vaccinated, Dr. Irvine felt this was not practical and agreed with the present principle of vaccination before leaving school. He looked forward to the wider use of freeze-dried vaccine.

SERUM PROTEIN CHANGES FOLLOWING B.C.G. VACCINATION

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A previous communication (Gilliland *et al.*, 1956) presented the results obtained by studying the serum protein of patients with pulmonary tuberculosis by the method of electrophoresis on paper. This study showed that the degree of change in the serum proteins was a measure of the severity of the systemic illness, and that the changes reverted to normal with recovery from the disease. This has since been confirmed by Leggat (1957).

Because of the difficulty in establishing the time of onset of tuberculous infections it was found possible to classify as "recent" only those in whom the infection was thought to be of less than six months' duration. The infections were usually severe enough to cause the patients to seek medical advice, so that minor degrees were seen infrequently.

B.C.G. vaccination, however, provides both a known time of onset of the infection and a course which is considerably less virulent than clinical tuberculosis. It was therefore thought to be of interest to investigate serially the serum protein in a group of nurses receiving B.C.G. vaccination.

Method and Results

A total of 17 student nurses whose tuberculin tests were negative by the Heaf multiple puncture method volunteered to act as subjects for this investigation. Samples of blood were obtained before B.C.G. vaccination and at three-weekly intervals thereafter to 18 weeks. The site of vaccination was inspected on each occasion and a note made of any constitutional disturbance or intercurrent illness. The biochemical methods used were those detailed in the previous communication (Gilliland *et al.*, 1956).

All vaccinations took a normal course and the girls remained fit throughout.

The results are shown in the Table (overleaf), including the mean albumin/ α_2 ratios and the standard errors of these means. The albumin/ α_2 ratios are plotted in the

Serum protein changes following B.C.G. vaccination. Shaded area shows normal values.

Chart, and it will be seen that there is a decrease during the first eight to nine weeks followed by an increase back into the normal range. These changes are significant, being several times the standard error of the mean. Although the changes are not of great magnitude, they consistently affect