ANTITHYROID ACTIVITY OF N-PHTHALYL GLUTAMIC ACID IMIDE (K 17)

BY

J. McC. MURDOCH, F.R.F.P.S., M.R.C.P.Ed.
Senior Registrar

AND

G. D. CAMPBELL, M.B., M.R.C.P.Ed.
Research Fellow

From the Department of Therapeutics, University of
Edinburgh, and the Royal Infirmary, Edinburgh

N-phthalyl glutamic acid imide (K 17) was first synthesized in Germany by Kunz *et al.* (1956) while seeking to produce a drug combining the advantages of the barbiturates without their undesirable side-effects. This tasteless white crystalline substance is an imide of glutamic acid and a derivative of piperidine. It is reported to have a "calming psychological effect" and has been used extensively on the Continent in doses of 25 to 50 mg. two to four times daily, when it acts as a daytime sedative, while in doses of 50 to 100 mg. it acts as a night-time hypnotic (Esser and Heinzler, 1956; Jung, 1956). A toxic dose of this substance in experimental animals could not be ascertained (Kunz *et al.*, 1956): this is not only due to the fact that the compound is sparingly soluble in water, but also because of its extremely low toxicity. No side-effects were observed following the administration of K 17 to mice, rats, guinea-pigs, and rabbits (Kunz *et al.*, 1956).

In Germany clinical experience has already led to the suggestion that the drug is virtually non-toxic and will prove valuable in various psychological disturbances such as anxiety states, mild depression, excitability, and some vegetative dystonias (Esser and Heinzler, 1956; Jung, 1956; Stärk, 1956). These workers observed marked reduction of the raised basal metabolic rate in mild and moderately severe cases of hyperthyroidism as the result of K 17 therapy. No published work has so far established whether these effects are brought about by a direct action on the thyroid gland or by causing a general reduction in metabolism in some other way.

The antithyroid action of K 17 was therefore assayed by the method of Stanley and Astwood (1947) in order to determine whether the effects on the human basal metabolic rate, mentioned above, were in fact related to depression of thyroid function.

Method

In euthyroid patients, if thyroid activity—measured by standard counting techniques—after a tracer dose of ^{131}I is plotted against the square root of the time in minutes, the resultant curve is seen to be a straight line persisting for up to 10 hours after the administered dose: drugs exhibiting antithyroid effect can cause deviations from this straight line, and are grouped by Stanley and Astwood into the following grades: 0, no effect; 1, questionable or slight effect; 2, partial suppression of uptake; 3, complete inhibition for less than 4 hours; 4, complete inhibition for more than 4 to 24 hours; and 5, complete inhibition for more than 24 hours.

The effects on the accumulation gradient in the thyroid gland of varying doses of K 17 were studied in nine adult euthyroid patients, following tracer doses of 20 μC of ^{131}I .

Results

The drug was administered in doses varying from 50 to 400 mg., and the effects are shown in the accompanying Table and in three cases are represented graphically (Figs. 1–3).

Effects of N-phthalyl Glutamic Acid Imide on Thyroid Uptake

Case No.	Dosage (mg.)	Effect	"Grade" (Stanley and Astwood, 1947)
1	50	No effect	0
2	100	Partial suppression of uptake	2
3	150	Effect questionable or slight	1
4	150	Slight partial suppression	2
5	200	"	2
6	200	Effect "questionable" or slight	1
7	200	Slight partial suppression	2
8	200	Complete suppression for less than 4 hours	3
9	400	" " " " "	3

In Case 1 no effect was observed after a 50-mg. dose (Fig. 1); in Cases 3 and 6, given doses of 150 and 200 mg. respectively, the effects were questionable or slight; in Cases 2, 4, 5, and 7, after doses of 100, 150, 200, and 200 mg. respectively, there was obvious partial suppression of uptake (Fig. 2, Case 2). After 200-mg. and 400-mg. doses in Cases 8 and 9 (Fig. 3) complete inhibition was obtained, followed by release between 75 and 120 minutes later.

FIG. 1.—Case 1. Effect of 50 mg. K 17 on accumulation gradient of thyroid gland.

FIG. 2.—Case 2. Effect of 100 mg. K 17 on accumulation gradient of thyroid gland.

FIG. 3.—Case 9. Effect of 400 mg. K 17 on accumulation gradient of thyroid gland.

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.

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THE ENANTHEM OF GLANDULAR FEVER

BY

F. I. CAIRD, M.R.C.P.

Late Captain, R.A.M.C.; General Hospital, Birmingham

AND

P. R. HOLT, M.B., B.S.

Late Captain, R.A.M.C.; St. Luke's Hospital, New York

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-