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THE INFLUENCE OF THE THYROID GLAND ON HYPERSENSITIVITY REACTIONS IN ANIMALS

*III. The influence of thyroidectomy on the precipitin
reaction, the Arthus phenomenon and the Schultz-Dale
reaction in guinea-pigs.*

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If in guinea-pigs or rabbits the thyroid gland is removed prior to sensitization with protein antigens, several anaphylactic *in-vivo* and *in-vitro* phenomena are precluded. This has been shown by a number of workers (1, 2, 3, 4, 5, 9). It has also been demonstrated that functional integrity of the thyroid gland is required for the development of histamine and acetylcholine reactions in guinea-pigs when these substances are introduced via the respiratory passages (6). On the other hand, the so-called allergic encephalitis can be provoked in guinea-pigs even after removal of the thyroid gland and epidermal sensitivity is not affected by thyroidectomy (7, 8). In what manner the thyroid interferes with the mechanism of sensitization, is completely obscure. As seems emerge from earlier investigations, antibody formation does not take place unless the thyroid gland is active, which might explain why in animals thyroidectomized and sensitized the administration of antigen fails to evoke signs of local or general anaphylaxis.

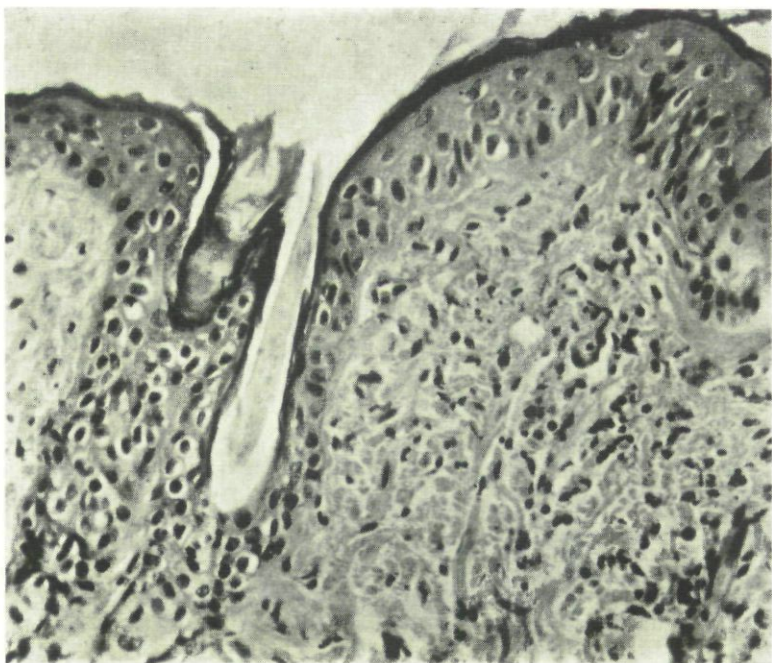


Fig. 1.

Skin specimen from animal 6, 48 hours after intracutaneous injection of the antigen.

However, as stated above, it has been demonstrated that biologically active substances such as acetylcholine and histamine when administered via the respiratory passages, do not give rise to reactions. From this observation it might be inferred that a system lacking thyroid activity is less capable of responding to substances which act on the unstriated musculature, so that antibody formation might be of secondary interest. Naturally, it is also conceivable that thyroidectomy does not prevent the formation of antibodies but merely their absorption by various organs; that, so to speak, the thyroid gland governs the distribution of antibodies within the system.

The chain of reasoning traced in the foregoing suggested an investigation as to the reaction of a given animal—thyroidectomized and sensitized—if one antigen was administered

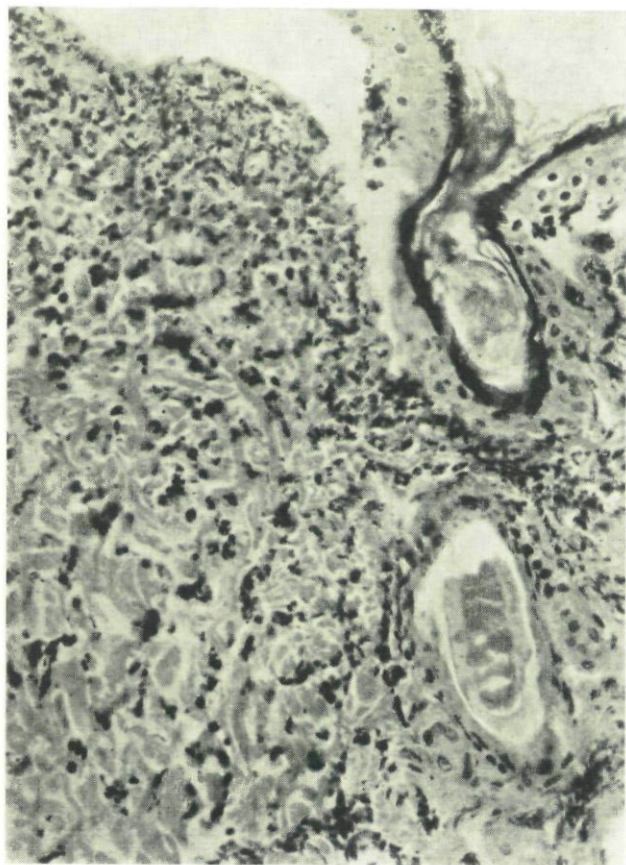


Fig. 2.

Skin specimen from control animal to animal 6, 48 hours after intracutaneous injection of the antigen.

(i) via the respiratory passages; (ii) into the skin by intracutaneous or superficial subcutaneous injection; (iii) *in vitro* to intestine and uterine musculature; and (iv) *in vitro* to serum.

MATERIALS AND METHODS

A number of male guinea-pigs weighing 300 to 400 g. were given 1 mC. of the isotope I^{131} by the intraperitoneal route. About 10 weeks later the thyroid activity was estimated

TABLE I

Animal no.	Date of inj. of I ₁₃₁	Date of inj. of tracer iodine	Bronchospasm	Arthus's phenomenon ¹	Precipitine reaction ²	Schultz-Dale reaction ³
5	March 11	May 22 no uptake		June 17 (+) Control +++	July 1 — Control +++	
6	June 6	September 6 no uptake		September 9 — Control no. 1 +++ Control no. 2 +++	September 13 — Control no. 1 +++ Control no. 2 +++	September 13 + Control no. 1 +++ Control no. 2 +++
12	March 12	May 22 no uptake		June 4 — Control ++		
13	March 12	May 22 slight uptake June 18 no uptake		September 1 — Control +++	September 7 — Control +	September 8 + Control +++

14	March 11	May 22 no uptake	June 17 (+) Control +++	July 1 — Control +++
15	March 11	May 22 slight uptake	September 1 (+)	September 7 — Control +++ + Control +++
20	March 6	April 14 no uptake	June 18 — Control +	June 16 — Control +++
20	March 6	April 14 no uptake	June 18 — Control +	June 16 — Control +++
54	May 6		September 1 — Control +++	September 7 — Control +++ + Control +++
1	— = no skin reaction (+) = slight skin reaction ++ = strong skin reaction with in- filtration +++ = strong skin reaction with necrosis	2 — = no visible precipitating anti- body + = precipitate in one test tube +++ = precipitate in at least 3 test tubes	3 + = slight but distinct contrac- tion +++ = maximum contraction	

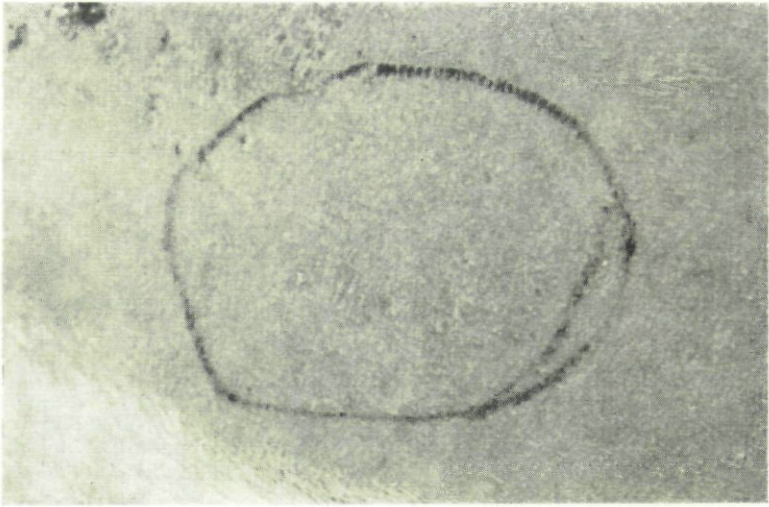


Fig. 3.

Arthus's phenomenon in animal 6 (thyroidectomized animal).

by means of a tracer dose of the same isotope. When the activity was to be considered low or absent, histamine was administered via the respiratory tract in order to test whether there was an increase in histamine resistance, which would seem to indicate a negligible thyroid activity. The animals were sensitized with 1 ml. 10 % egg-white solution. Roughly a fortnight after sensitization a precipitin estimation was carried out on serum collected by cardiac puncture. Quantitative determination being considered superfluous, only a so-called ring test was by gently pouring egg-white solutions of various concentrations (10 %, 1 %, 0.1 %, 0.01 %, 0.001 %, and 0.0001 %) over the antiserum. After a period of between 1 week and 2 months following cardiac puncture Arthus's phenomenon was produced by injecting 0.5 ml. 10 % egg-white solution into the skin. After a week the precipitin test was repeated, and then two of the animals were made to inhale egg-white solution in the form of an aerosol introduced into a glass cylinder. All animals were killed 1 week after the Arthus-phenomenon experiment and aerosol experiment respec-

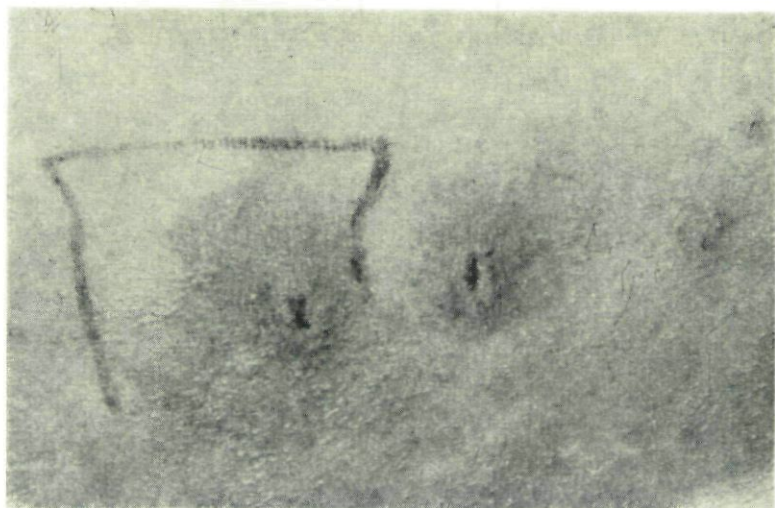


Fig. 4.

Arthus's phenomenon in the control animal to animal 6.

tively, and the Schultz-Dale reaction with conventional technique was performed in some of them on small intestine and uterine horn. For every animal a control animal was selected, which was treated in precisely the same manner except for the injection of I^{131} . Two controls were used for Animal 6. In guinea-pigs not sensitized, intracutaneous injection of egg-white was carried out to compare with the sensitized controls and thyroidectomized animals. In a number of normal animals the Schultz-Dale reaction was also performed.

RESULTS

As will be seen from Table 1, Arthus's phenomenon was negative in all thyroidectomized guinea-pigs. The reactions which in the table are indicated by (+) were slight reactions, i.e. not stronger than the cutaneous alterations that may be observed after egg-white injection in guinea-pigs not sensitized. Precipitin was not present in the serum of thyroidectomized guinea-pigs. In the two animals examined, bronchospasm

could not be produced. The corresponding controls showed mild bronchospasm, but there was a clear difference. The Schultz-Dale reaction was positive in all thyroidectomized guinea-pigs, likewise in the controls. There was a marked difference, however, viz. in the control animals contraction of the isolated muscular organs was stronger than in those thyroidectomized.

DISCUSSION

The present study seems to show that the sensitization mechanism is very strongly influenced by the thyroid gland. It has been demonstrated that anaphylactic reactions in the lungs and skin cannot be provoked in thyroidectomized guinea-pigs, and that no precipitin develops, but that the Schultz-Dale reaction none the less becomes positive. In normal, not sensitized, guinea-pigs no contraction of the small intestine was to be observed after addition of egg-white solution. The Schultz-Dale reaction can undoubtedly be considered to result from the biological activity produced by the antigen-antibody reaction, so that the conclusion can be drawn that antibodies have been formed in the thyroidectomized animals, though their demonstration in the lungs, skin, or serum is impossible with the methods used. It is further disclosed that the contraction of intestinal and uterine muscles respectively after addition of the antigen is weaker in the thyroidectomized than in the control animals, an observation that in co-operation with Ahlmark will be discussed in another paper.

As has emerged from histopathological study of skin specimens collected at the sites where Arthus's phenomenon was evoked, in the thyroidectomized animals there is a certain dilatation of the small blood vessels in the corium, slight perivascular aggregation of leucocytes, and some oedema of the epidermis. These changes occur also in skin specimens taken from unsensitized guinea-pigs 24 to 48 hours after injection of foreign protein. Biopsy in sensitized, not thyroidectomized guinea-pigs reveals massive leucocytic invasion of the corium, haemorrhage, and vascular dilatation. Frequently

the epidermis is separated from the subjacent tissues, and occasionally extensive areas of necrosis are noted.—However, owing to the difficulty of grading Arthus's phenomenon it cannot be ruled out that the slight changes histologically observed in thyroidectomized animals nevertheless are due to an antigen-antibody reaction of minor degree, though the difference between normal, unsensitized animals is not striking.

SUMMARY

The thyroid activity of guinea-pigs was abolished by the isotope I^{131} and egg-white solution injected to sensitize the animals. The anaphylactic reactions, which are provoked by antigen administration via the respiratory passages, were inhibited. When antiserum and antigen were combined in the so-called ring test, no precipitate developed. However, the Schultz-Dale reaction became positive in the same animals where no anaphylactic reaction was noted in e.g. the skin, and where the precipitin test was negative.

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