THE COMBINED ACTIVITY OF THE SPLEEN AND OTHER ORGANS

COMMUNICATION I. THE EFFECT OF EXPERIMENTAL SPLENOPATHY ON THE FUNCTIONAL STATE OF THE THYROID GLAND AND OVARIES

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Little is known of the functions of the spleen and its effect on the activity of other organs under physiologic and pathologic conditions. Relevant experimental studies and clinical observations are in many respects contradictory [2, 3, 7]. The method of organ extirpation which has yielded so much information on the function of a number of organs has not proved entirely successful with regard to the spleen; the method of administration of spleen extracts, whose specificity is yet to be proved, also has its drawbacks.

Clinical practice affords encounters both with sequelae of loss of spleen functions following splenectomy and with the influence of pathologically changed spleen on the activity of other organs and systems. It is just this latter aspect of the problem, which is of considerable practical interest, which is particularly poorly represented and developed in experimental studies owing to the lack of a suitable model of experimental splenopathy. In recent years methyl cellulose-induced splenomegaly in white rats [9, 11] has been introduced and approved as a technique which reproduces the clinical picture of Banti's syndrome in man to a satisfactory degree.

The aim of the present work has been an attempt to elucidate under experimental conditions the effect of pathologically altered spleen on the functions of other organs.

In the first series of experiments a study was made of the functional state of the thyroid in rats with experimentally induced splenomegaly. The question of correlation of thyroid function and spleen has been subjected to repeated investigation. It was noted that mice fed on thyroid gland preparations showed enlargement of the spleen. In a series of studies carried out by L. Asher et al. [4-6] antagonism between the activity of the spleen and the thyroid has been demonstrated. At the same time other authors could find no signs of increased thyroid function on morphological examination of the gland in rabbits subjected to splenectomy [8].

The present experiments were carried out on white rats weighing 110-160 g. The animals were maintained on a full diet. Splenomegaly was induced by intraperitoneal administration of 2 ml of a 2.5% solution of methyl cellulose given twice a week for 15 weeks. A noticeably enlarged spleen could be palpated in all the animals at the time of termination of the injections.

The functional state of the thyroid gland was determined by the use of radioactive iodine I^{131} which was given subcutaneously in doses of 0.6-1 microcurie at different intervals of time after the start of methyl cellulose injections. Twenty-four hours after administration of I^{131} the animals were sacrificed by exsanguination, the thyroid was excised, weighed on a torsion balance, and its radioactivity determined on a Geiger-Müller counter as percentage of the injected dose of I^{131}.

In order to discover the possible effect of methyl cellulose itself (as against the splenomegaly induced by it) on the activity of the thyroid, a group of rats was given methyl cellulose 10 days after splenectomy; in order to prevent the development of bartonellosis, these rats were given a prophylactic dose of novarsenol

(0.3 mg per 100 g body weight) at the time of splenectomy. Further control was provided by pseudosplenectomy (laparotomy without removal of the spleen) in a group of animals who were also given the same dose of novarsenol and subsequent injections of methyl cellulose.

The experimental results are given in Table 1.

As can be seen from Table 1, experimentally reproduced splenomegaly in rats leads to considerable inhibition of thyroid function as shown by the I^{131} absorption test. This effect does not occur when methyl cellulose is given to splenectomized animals (I^{131} absorption in the animals in group 2 is even somewhat increased compared to the control), which indicates that splenomegaly and not methyl cellulose itself is the leading factor in the development of depression of thyroid function. It is also indicated by the fact that diminution of isotope absorption by the gland develops in parallel with enlargement of the spleen. The main conclusion to be drawn from this series of experiments is thus the occurrence of marked depression of thyroid function under conditions of experimentally reproduced splenopathy, viz. methyl cellulose-induced splenomegaly in white rats.

The second series of experiments was devoted to the study of the functional state of the ovaries in experimentally induced splenopathy. Speculation concerning a possible connection between the spleen and the gonads was encountered as early as S. P. Botkin's lectures [1] from which the following lines are taken: "The spleen is connected with other organs: this connection cannot be determined physiologically and even less so anatomically, but it nevertheless exists. I have in mind its connection with the reproductive system."

The association of splenomegaly with hypogenitalism is not infrequently seen in clinical practice. It has been demonstrated that administration of spleen extracts to sexually immature mice leads to delay in the initial onset of estrus [12].

The view has been put forward that splenectomy in man and animals enhances the production of gonadotropic hormone by the pituitary [13]. At the same time some authors carried out experiments with extirpation of the spleen and administration of spleen extracts and found no noticeable changes in the activity of the gonads [10].

In our investigation the experiments were performed on sexually mature female white rats weighing 120-150 g. The animals were kept in individual cages on a full diet. Each rat was subjected, prior to the experiment, to determination of the character of its estrus cycle using the generally accepted technique of

TABLE 1

Effect of Experimental Splenomegaly Induced by Methyl Cellulose on I^{131} Absorption by the Thyroid in White Rats

No. of animal group	Group characteristics	No. of animals	Weight of thyroid, mg	I^{131} absorption by thyroid after 24 hrs. %
1	Intact	15	19,2±1,6	22,4±2,8
2	Splenectomy + novarsenol + methyl cellulose (15 weeks)	15	21,2±2,3	27,8±4,3
3	Pseudosplenectomy (laparotomy) + novarsenol + methyl cellulose (15 weeks)	10	23,0±2,7	7,9±1,8
4	Methyl ellulose from beginning of administration after 3 weeks	10	20,6±2,1	22,7±3,6
5	The same after 6 weeks	10	21,5±2,9	21,8±2,8
6	" " 12 "	10	23,6±2,7	12,1±3,6
7	" " 15 "	15	24,5±1,9	6,4±2,2

Note: The table shows mean values and mean quadratic deviations for each group of animals.

TABLE 2

Effect of Methyl Cellulose-Induced Splenomegaly on the Estrus Cycle in White Rats

No. of animal group	Group characteristics	No. of animals	Character of estrus cycle		
			No deviation from the norm	Moderate upset of cycle (prolonged dys-estrus stage)	Cessation of estrus
1	Intact	15	15		
2	Splenectomy + novarsenol + methyl cellulose (15 weeks)	15	13	2	
3	Pseudosplenectomy + novarsenol + methyl cellulose (15 weeks)	10		1	9
4	Methyl cellulose from beginning of administration after 3 weeks	25	25		
5	The same after 6 wks.		22	3	
6	" " " 12 "			19	6
7	" " " 15 "			4	21

TABLE 3

Effect of Methyl Cellulose-Induced Splenomegaly on the Gonadotropic Hormone Content of the Hypophysis in White Rats

No. of rat group	Group characteristics	Dose of rat	Number of test mice	Reaction of mice		
				Enlargement of uterus and ovaries	Estrus	Corpora lutea
	Intact	4	6	2	1	1
		5	6	6	6	5
	Experimentally induced splenomegaly (methyl cellulose, 15 weeks)	3	6	-	-	-
		4	6	1	1	-
		5	6	6	6	6

vaginal smears; this was done over a period of 3 weeks. Then the experimental group of rats was given methyl cellulose as described above for a period of 15 weeks and the character of the estrus cycle was studied. In some rats the spleen was removed 10 days prior to beginning administration of methyl cellulose and a prophylactic injection of novarsenol was given; in another group of rats used as controls pseudosplenectomy (laparotomy), with novarsenol administration and subsequent injections of methyl cellulose was carried out.

The results of the experiments are presented in Table 2.

It follows from Table 2 that administration of methyl cellulose leads gradually to ever-more-noticeable disturbance of the estrus cycle up to complete cessation of estrus in an overwhelming majority of the animals 15 weeks after the beginning of injections. Methyl cellulose does not produce this effect in animals with removed spleen, which indicates that splenomegaly plays the leading role in the development of the phenomenon in question.

The third series of experiments was staged in order to discover more precisely the mechanism of the effect of methyl cellulose-induced splenopathy on the estrus cycle.

First of all a study was made of the reactivity of the vaginal mucosa to estrogenic influence in rats with splenomegaly. For this purpose 5 rats with splenomegaly produced by 15 weeks of methyl cellulose injections and cessation of estrus were given subcutaneously 10 international units folliculin each. After 72-96 hours cornification of the epithelial cells characteristic for the estrus phase was noted in all 5 rats.

Hence the reactivity of the vaginal mucosa is preserved in rats with splenomegaly.

A fourth series of experiments was then carried out to investigate the content of gonadotropic hormones in the hypophysis of rats with splenomegaly.

Hypophyseal hormone was tested on infantile mice weighing 6-8 g. The rat pituitaries were excised, weighed and triturated with physiologic solution until a fine suspension was formed; this was injected into infantile mice. After 100 hours the state of the reproductive apparatus was examined (the mice were given hypophyseal suspension five times in accordance with the accepted technique of gonadotropic hormone standardization).

The results are given in Table 3.

Table 3 shows that 1 international unit of gonadotropic hormones constitutes 5 mg hypophyseal substance both in the control animals and in rats with splenomegaly. (The criteria for judging the presence in the hypophyseal suspension of follicular stimulating hormone were the appearance of estrus in mice and increase in the weight of the uterus and ovaries, while the criterion for the presence of luteinizing hormone was demonstration of corpora lutea.) There is thus no change in the gonadotropic hormone content of the pituitary in rats with experimental splenopathy. Consequently, by the process of exclusion, it may be supposed that the cause of estrus cycle disturbance observed in rats with methyl cellulose-induced splenomegaly lies in ovarian dysfunction. In order to check this hypothesis we administered subcutaneously 20 international units of prolan to 8 rats with splenomegaly; not a single rat reacted to prolan injection by the appearance of estrus, signifying the loss of ovarian sensitivity to gonadotropic hormone. All these experiments indicate that experimentally induced (methyl cellulose) splenopathy is associated with definite depression of thyroid and ovarian activity.

SUMMARY

The author studied the effect of experimental splenomegaly (caused by the intraperitoneal injection of methyl cellulose to white rats) on the functional state of the thyroid gland (by the absorption of I^{131} by the gland) and of the ovaries (by studying the estrus cycle). It was established that splenopathy brought about pronounced depression of the functional activity of the thyroid gland and the ovaries. This phenomenon is caused by splenomegaly since the administration of methyl cellulose to splenectomized animals does not cause such changes in the thyroid gland and the ovaries. It was demonstrated that the changes in the estral cycle in splenopathy did not depend on disturbance of the gonadotropic activity of the hypophysis or on changes in the sensitivity of the vaginal mucosa to the estrogenic action.

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