

3507

Studies in Experimental Thrombosis.

TAKUJI SHIONOYA,* W. R. JOHNSON AND L. G. ROWNTREE.

(Introduced by A. J. Goldforb.)

From the Division of Medicine, Mayo Clinic and the Mayo Foundation.

Pulmonary embolism is responsible for many postoperative deaths in almost every extensive surgical practice. As yet no adequate means of combating this menace has been devised and the present study was undertaken in the hope that new leads in the direction of its prevention might be forthcoming.

The apparatus used is composed of an arterial and a venous cannula connected peripherally by a transparent, semipermeable colloid tube, the whole forming a U-shaped system. The cannulas are inserted into the carotid artery and jugular vein of a rabbit after the apparatus is filled with physiologic sodium chloride solution, and the membrane portion rests in a solution of this saline. When circulation is established the blood flows through the system and back to the animal without contact with air.

The influence of many factors on the rate and type of thrombosis may be determined by means of this device. It makes it easy to vary, control, and assay mechanical, chemical, physical, pharmacologic, and pathologic factors. The process of thrombosis can be followed with the unaided eye; the membrane may be detached at any time and studied as fresh tissue or it may be embedded in paraffin and sectioned for microscopic study.

When the original technic (side tubes paraffined and cannulas with clean glass surfaces) is used with the normal animal, flow ceases through the apparatus in from 10 to 20 minutes, most often on account of obstruction of the venous cannula by white thrombi. The microscopic structure of these thrombi (and those on the membrane) is identical with that reported by Welch,¹ Aschoff,² and others. With circulatory and metabolic stimulants such as thyroxin and ephedrin, the flow was maintained as long as forty minutes. With single intravenous injections of heparin or hirudin, the flow persisted for from 2 to 4 hours and fibrin formation was minimal or lacking, although thrombosis proceeded through the first stages, white thrombi appearing in large quantities. These white thrombi were composed of disintegrated platelets and leukocytes only, no fibrin being recognized grossly or microscopically. Magnesium sul-

* Rockefeller student on the Mayo Foundation.

and probably in degree with the morphological evidence of involution of the hyperplasia; (6) Desiccated thyroid does not cause a rapid fall in metabolism even in cases with hyperplastic glands; (7) Cases with adenomatous hyperplasia which do not react to iodine with storage and involution do not show a lowering of metabolism.

Another explanation of the metabolism lowering effect of iodine in Graves' disease has been advanced by Plummer.² He assumes that in Graves' disease the thyroid may be secreting an abnormal product, possibly an incomplete thyroxine which iodine completes. This hypothesis is at present without supporting evidence.

With the above evidence in mind it seemed probable that the temporary fall in heat production following the administration of large doses of iodine was not specific for Graves' disease, and should occur in all animals and in all clinical associations in man, in which there is a deficient iodine store associated with thyroid hyperplasia.

As the proper human cases were not available, rabbits were used because we were equipped with the necessary apparatus and a large experience in this kind of work with this animal. The rabbit is not a very satisfactory animal, first, because it is not available for studies on basal metabolism and secondly, because marked hyperplasia of the thyroid is uncommon. Cats, likewise, are unsatisfactory because they do not develop sufficient thyroid hyperplasia. Goiterous dogs would be ideal for such studies where material is available.

With the exception of 7 rabbits which were purchased in the goiter district of northern Ohio on the chance that their thyroids might be hyperplastic, all rabbits used were reared in this laboratory. They were fed daily our regular diet of alfalfa hay and oats, with carrots or greens once a week.

The respiratory exchange measurements were begun about 15 hours after the last feeding. The standard test period was two hours, and was repeated three times each week during the control period. With the administration of iodine many of the animals were tested daily.

Eighteen received iodine either as Lugol's solution administered orally in doses of 0.075 cc. daily or as potassium iodide intraperitoneally in doses of 25 mg. daily. Three were given Lugol's solution alone (two received 8 and one 3 doses). Six were given Lugol's solution for 3 days, followed in about two weeks by potassium iodide for 3 days. This was done for the purpose of determining whether the second administration of iodine after thyroid involu-

tion had occurred would further change the metabolism. Nine were given potassium iodide alone for three days.

A summary of the results is given in the accompanying table.

After having determined the heat production for a control period of two or more weeks, a snip of the lower pole of the left thyroid lobe was removed to determine its histological condition. The iodine was then started and heat production measurements were made daily for the first few days and afterwards on alternate days for approximately two weeks. Six of the rabbits which had received Lugol's solution were given potassium iodide and their heat production measured for the next 10 days.

Results: A drop in heat production was observed in five rabbits (589b, 604, 605, 616, 622). Three of these received 0.225 cc. (about 28 mg. I) of Logul's solution and two, 75 mg. (about 57 mg. I) of potassium iodide. Two rabbits showed a slight rise in heat production. No significant change occurred in 11 rabbits, 4 of which received the above amount of Lugol's solution and 7, the above amount of potassium iodide. The drop was detectable about 24 hours after iodine administration, and lasted beyond the two weeks observation period, although tests made 2 months later showed that heat production had returned to its pre-iodine level.

As regards the relation of the thyroid condition present at the beginning of the iodine administration to the animal's reaction to iodine, nothing definitely suggestive of a relationship was found. This means very little, however, since no well marked hyperplasias occurred in any of the series. Of the five rabbits showing a decrease in metabolism the thyroids of three were classified as "early hyperplasia," while in one the thyroid was "normal". The thyroid of the fifth rabbit was not examined. Of the 11 rabbits that showed no significant change in metabolism following iodine administration, the thyroids of three were classified as "normal early," four as "early" hyperplasia, and four as "normal".

It is of interest to note that the two rabbits (581 and 589a) which received 8 daily doses of 0.075 cc. Lugol's solution showed a rise in heat production, beginning about the fifth day, and continuing until the Lugol's solution was stopped, after which it returned to normal in a few days.

It will be necessary to use rabbits with definitely hyperplastic thyroids before it can be stated that the metabolism lowering effect of large doses of iodine is or is not related to the histological condition of the gland. Martin⁴ has obtained evidence that Lugol's solution in large doses lowers the metabolism in conditions other

TABLE I.

Rabbit No. and Sex	Age	No. Doses		Metab. before iodine admin. Total cal. 2 hr. periods.			Metab. after iodine admin. Total cal. 2 hr. periods.											
		Lugol's 0.075 cc.	KI 0.025 gm.	No. Readings	Extremes	Mean	Average	1st day	2nd day	3rd day	4th day	7th day	8th day	9th day	10th day	11th day	13th day	
561 M	Adult	8		3	11.94 10.94	10.83	11.04	10.45		12.38		12.84			13.11		12.77	
589a F	284 ds.	8		4	14.89 14.50	14.54	14.62	12.81		12.56		14.34	16.27		15.71			
605 M	568 ds.	3		5	13.89 13.06	13.35	13.46		11.81		13.32	11.00					11.18	
589b F	574 ds.	3		5	13.62 12.81	12.90	13.04	10.43	10.28	10.21	11.05						12.37	12.88
597 M	558 ds.	3	3	5	11.93 10.96	11.45	11.49	11.00	11.76	12.31	12.43				10.50			
604 F	560 ds.	3	3	3	13.28 12.97	13.20	13.15	12.23	13.25	11.24	11.75						11.31	10.89
			3					11.94	10.53			10.63	11.70					

