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A year later he returned because of pallor, irritability and loss of appetite. At this time he was definitely known to chew paint off objects, though his family tried to prevent him. The weakness of the leg had not recurred.

Physical examination disclosed nothing remarkable except pallor, which was confirmed by a hemoglobin content of 50 per cent, a red cell count of 2,600,000 and a smear showing moderate achromia but no stippled cells. Roentgenograms of the long bones again showed dense bands at the growing ends of the shafts. He was discharged on a high calcium diet with iron and ammonium citrate and cod liver oil (3 drachms [11.7 Gm.] daily). In a month his hemoglobin content was 80 per cent and his red cell count 4,000,000.

At 12 years he returned to the outpatient department because of enuresis. He gave a general impression of being dull. His mother gave the following report of his school progress: "He started to school at the age of 5 years. He spent two years in the first grade. The next year he had a teacher at home. The following year he spent in the second grade. He will start the fifth grade in the fall." Psychologic tests have not been given.

CASE 20.—A girl of 3 years was admitted to the hospital because of vomiting and abdominal pain of three months' duration. Her father and mother were separated at the time. Her birth and early development had been normal. She walked at 13 months and talked at 14 or 15 months. From the time she began to move about she chewed anything and everything, including paint from her crib and from window sills. About three months before her admission to the hospital she began to vomit, and the vomiting increased in frequency. A month later abdominal pain, irritability and pallor supervened. One month before admission strabismus was noted. During this period a gradual loss of weight occurred. She had complained of headache during the few days before admission.

On physical examination she was dull and drowsy. Her optic disks were noticeably choked, and her skull was hyperresonant on percussion. Her tendon reflexes were everywhere hyperactive, and Babinski signs were elicited on both sides.

Her hemoglobin level was 50 per cent; her red blood cell count was 2,600,000, and her blood smear showed achromia and 8 to 10 stippled cells per high power field. Her spinal fluid was under increased pressure and contained 18 cells per cubic millimeter and 108 mg. of total protein per hundred cubic centimeters.

Roentgen examination showed heavy bands at the growing ends of the long bones, consistent with lead poisoning, over a long period of time, with an especially heavy recent deposit.

Increasing drowsiness and vomiting continued in spite of treatment with hypertonic solution of dextrose (20 per cent) and dibasic sodium phosphate, and on her fifth hospital day bitemporal decompression was performed.

Frequent lumbar punctures were performed, with the removal of large amounts of spinal fluid (up to 200 cc. on one day), during the next four weeks. After that the patient gradually became interested in her surroundings, her vomiting stopped and she made a rapid recovery during the last two weeks of her stay. Six weeks after admission she was playing "normally" in bed, but psychometric examination showed a general level of intelligence around 3 rather than approaching 4 years, with special disabilities in the field of spatial relationship. She was discharged on the fifty-first day in the hospital, weak and underweight but able to walk and showing an active interest in life.

In spite of her mother's efforts she continued to eat paint at home, stripping all the paint off the porch railing before she was caught. A year later she was again admitted because of vomiting and abdominal pain. Her decompression wounds were bulging, but her optic disks were normal. Her gums showed a lead line. Her hemoglobin content was 53 per cent and her red blood cell count 3,900,000, with marked achromia and many stippled cells on smear. Spectroscopic examination of the blood showed a level "very much above anything found in normal controls." Roentgenograms of her long bones showed wide bands of lead deposit with recent accentuation at the growing ends. Roentgenograms of her skull showed no evidence of pressure. A lumbar puncture showed fluid under apparently increased pressure, with 6 monocytes per cubic millimeter and a total protein content of 46 mg. per hundred cubic centimeters. She was discharged on a high calcium diet and 18 drops of combined fish liver oils daily, and with assurance that she would be protected from paint in the future.

She was next seen when she was 9 years and 6 months of age, in response to a follow-up letter. Although she was friendly and outgoing, she was doing badly in school in the third grade, had a mental age of 7 9/12 years and an intelligence quotient of 80, with special defects in spatial orientation. Her score on the Ellis visual designs test was 1.5, which was below the calibrated level for her age.

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RADIOACTIVE IODINE STUDIES IN CHILDHOOD HYPOTHYROIDISM

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The usefulness of radioactive isotopes of iodine in the study of iodine metabolism has been demonstrated by several groups of workers.[1] They are of particular value in measuring the gross iodine metabolism of the thyroid in situ[1b] in normal persons and in patients whose thyroids need not be removed surgically. The studies reported in this paper, which were carried out with the cooperation of the department of pediatrics of the University of California Medical School, show that by the use of radioactive iodine certain aspects of the iodine metabolism in children with hypothyroidism can be examined.

Ordinary, or stable, iodine and radioactive iodine are chemically and physiologically the same as long as the amount of radioiodine is less than that which produces physiologic changes by the action of its radiation. In these experiments, less than one-fiftieth the amount of radioiodine necessary to produce biologic changes was used. The radioactivity of a single dose of radioiodine enables one to follow its metabolic fate and to distinguish it from the iodine already present in the body. The radioiodine concentrated in the thyroid may be determined quantitatively without surgical removal of the gland, since the gamma rays emitted by it penetrate the overlying tissues and can be measured with a suitable detecting device, such as the Geiger-Müller counter.[1b] Thus, the addition of a trace of radioiodine to ordinary iodine serves to label all the iodine atoms in an administered sample.

The 10 children included in these studies had severe hypothyroidism as indicated by careful histories, physical examinations and pertinent laboratory tests (table 1). Three of them were less than 1 year old, and the remaining 7 ranged in age from

The radioactive iodine was prepared through the cooperation of the radiation laboratory of the University of California.

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3½ to 19 years. None had received iodine or thyroid substance for six weeks or longer prior to the tests.

In the first experiment, iodine as sodium iodide containing a known amount of radioiodine, was administered orally in a dose of 14 mg. to each of the 8 older children and in a dose of 3.5 mg. to each of the 2 younger children. None of the patients had eaten for several hours prior to the ingestion of the experimental iodine. The counter tube of the Geiger-Müller counter was placed over the isthmus of the thyroid, and the uptake of iodine was measured as described in an earlier

TABLE 1.—*Data Concerning the Subjects*

Patient	Chronologic Age, Yr.	Age at Onset of Symptoms	I. Q. or M. A.	Epiphysial Age by Roentgenogram: O. A.	Epiphysial Age by Roentgenogram: B. A.	Basal Metabolic Rate, %	Plasma Cholesterol, Mg. per 100 Cc.	Plasma Carotene, Mg.	Blood: Hemoglobin: %	Blood: Hemoglobin: Gm.	Blood: Red Cells
	5 ± mo.	3 ± mo.	53	3 mo.	0.5 mo.	—	253	—	70	10	4,200,000
	Birth	Birth		6 mo.	3-5 mo.	—	264	—	98(Hel.)		4,000,000
	Birth	9.5 mo. (O.A. 17 mo.)		9 mo.	4.5 mo.	−45	256	—	67	8.5	3,900,000
	Birth	.....		4 yr.	1-2 yr.	—	252	—	90	—	4,000,000
	Birth	78		4½ yr.	3½ yr.	Unsatisfactory	298	0.23	84(Hel.)		4,000,000
	Birth	60		4½ yr.	2 yr.	−37(av)	270	0.00	86	9.8	3,800,000
	Birth	16 (O.A. 10 wk.) very retarded)		7 wk.	Newborn	−33	300	—	65(Hel.) (O.A. 7 wk.)		2,720,000
	1 ± yr.	72		5 yr.	2 yr.	−15	246	0.15	65 (O.A. 8 yr.)	—	4,100,000
	2 ± yr.	48		12 yr.	6 yr.	−50	282	0.30	58 (O.A. 12 yr.)	—	3,100,000
	1 to 2 yr.	80		12 yr.	2-6 yr.	−41	550	0.20	96	—	3,700,000

I.Q. indicates intelligence quotient; M.A., mental age; O.A., chronologic age; B.A., bone age.
Chronologic age at the time various tests were performed is that given in column 2 unless otherwise indicated.

TABLE 2.—*Uptake of Iodine by the Thyroids of Hypothyroid Children After Ingestion of Two Doses of Radioactive Iodine (With and Without Carrier Iodine)*

Patient	Age, Years	Uptake of Iodine Five Days After Ingestion of 14 mg. (or 3.5 mg.), Percentage	Uptake of Iodine Five Days After Ingestion of About 1 Microgram, Percentage
G. B.	½	0.08	...
D. B.	1½	0.02	3.5
M. M.	11/12	0.50	...
G. W.	3½	0.05	...
P. H.	4½	2.20	52.0
E. Z.	7	0.10	4.5
R. O.	8	0.02	...
D. M.	10	0.10	3.5
E. P.	16	0.03	1.9
A. D.	19	0.65	30.8

report.[1b] Except in the 2 patients who had goiters (P. H. and A. D., table 1), the thyroid tissue took up so little of the labeled iodine that accurate measurements were impossible until the end of the fifth day after the iodine had been administered. At that time, nearly all the labeled iodine that had not been concentrated in the thyroids had been excreted, and hence did not interfere with determination of the radioiodine in the thyroids. In column 3 of table 2 are given the amounts of labeled iodine in the thyroids at the end of the fifth day, calculated as the percentage of the dose originally ingested. Only three of the thyroids accumulated 0.5 per cent or more, while two accumulated 0.1 per cent and the

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remainder 0.05 per cent or less. In contrast, the thyroids of 5 normal adults five days after the oral ingestion of 14 mg. of iodine contained 4 per cent, and those of 3 normal children (4 to 10 years of age) retained 2 per cent of radioiodine.

The 3 children whose uptake was 0.5 per cent or more had palpable glands; 1 of them had a goiter which weighed approximately 50 Gm. as estimated by palpation. For patients A. D. and P. H., both of whom had goiters, reasonably accurate measurements could be obtained over the five days following the administration of a single dose of iodine (fig. 1). We were surprised to note that the type of curve was similar to that found in patients with hyperthyroidism.[1b] The uptake of iodine was rapid and was complete by the fourth hour. In the next twenty-four hours there was a rapid loss of about three fifths of the accumulated iodine, and during

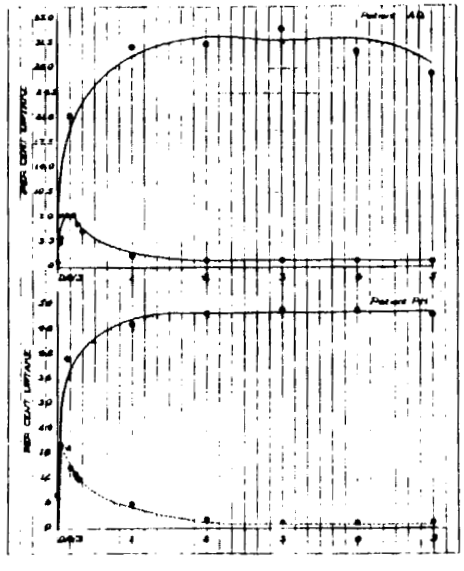

Fig. 1.—Uptake of radioactive iodine by the thyroids as measured in situ in patients A. D. and P. H. The abscissas indicate the time in days and the ordinates the percentage of the total dose of ingested iodine concentrated in the thyroids. In each curve the circles containing a dot indicate observations on a dose of 0.1 microgram of radioactive iodine administered on Feb. 5, 1940 and the circles containing a cross indicate observations on a dose of 14 mg. of radioactive iodine administered on April 21, 1941.

the succeeding four days a gradual loss of small amounts occurred. These 2 patients fall into a special group, since patients with goiter and severe hypothyroidism are rare in all regions except those in which goiter has been endemic for generations. Although the curves simulated those of hyperthyroidism, the character of the labeled iodine lost from the thyroids was not determined. If it were in the form of an active thyroid hormone, then such patients should be able to maintain themselves in a normal state of thyroid function provided sufficient iodine is absorbed. However, in neither of these patients has a sufficient trial of iodine

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therapy alone been conducted. In the other patients, the thyroids apparently were incapable of accumulating enough iodine to maintain a normal balance.

A few months later, 6 of these patients, including the 2 with goiters, received a second oral dose of radioiodine in the form of sodium iodide without carrier

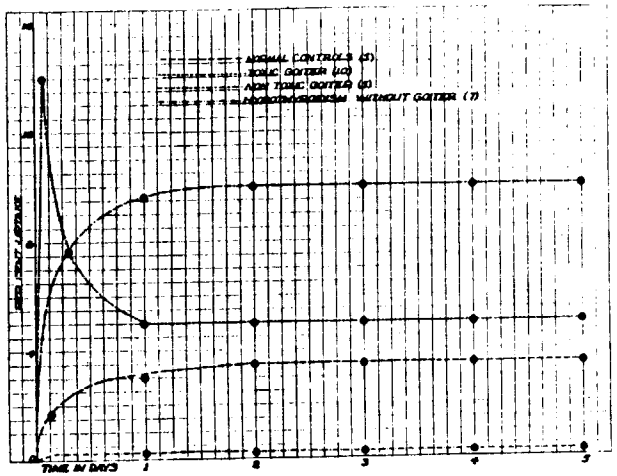

Fig. 2.—Uptake curves of iodine in the thyroids of patients measured in situ. The ordinate represents the percentage of a single dose of radioactive iodine taken up by the thyroids. The abscissa gives the time in days. Each subject received 14 mg. of labeled iodine.

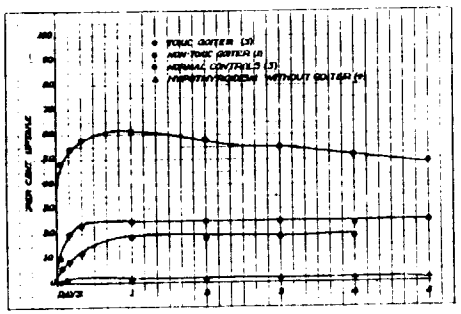

Fig. 3.—Uptake of radioactive iodine, given orally in a single dose of 0.1 microgram, in the thyroids of normal persons and of patients with various types of goiters.

iodine, so that the total for each patient was approximately 0.1 microgram of labeled iodine. In the 4 patients without goiters, the thyroids accumulated from 1.9 to 4.5 per cent of the labeled iodine by the end of the fifth day after its ingestion (table 2, column 4). It is apparent that thyroid tissue will take up a greater proportion of a small dose than of a large dose of iodine. The importance of this

fact is that by the use of extremely small amounts of radioiodine the presence of thyroid tissue may be detected in patients with hypothyroidism or myxedema. This test should demonstrate the presence of any thyroid tissue capable of concentrating iodine. We have not studied the effects of similar small doses of radioiodine on normal children. However, in 3 normal adults the average uptake of labeled iodine administered in a dose of approximately 0.0000002 Gm. was about 20 per cent, or

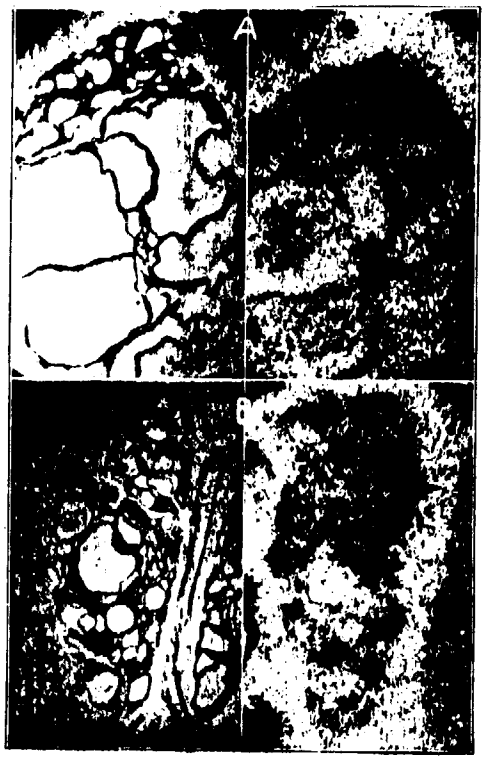

Fig. 4.—Sections of thyroid tissue from patient A. D. with their radioautograph. Note that most of the iodine is deposited in the cells of the acini rather than in the colloid.

from 4.5 to 10 times the uptake observed when a test dose of 14 mg. of labeled iodine was employed.

After retest with a dose of approximately 0.1 microgram of labeled iodine, the uptake curves of the 2 patients with goiter and hypothyroidism were similar to those of patients with toxic goiter (compare the curves of figures 1 with curves of patients with other thyroid diseases, figures 2 and 3). The maximum uptake in patient P. H., the child with a goiter weighing about 50 Gm., was about 53 per cent, while in patient A. D., the child with a slightly enlarged thyroid, the uptake was

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about 33 per cent. Specimens of the thyroids of both patients were taken for biopsy, and radioautographs were made according to the technic reported elsewhere[14] (figs. 4 and 5). The specimen from patient P. H., taken from the isthmus of the thyroid (to relieve pressure symptoms), showed atrophy with incomplete formation or rupture of many of the acini, little colloid, which stained poorly with hematoxylin and eosin, and acinal cells which varied in size and usually

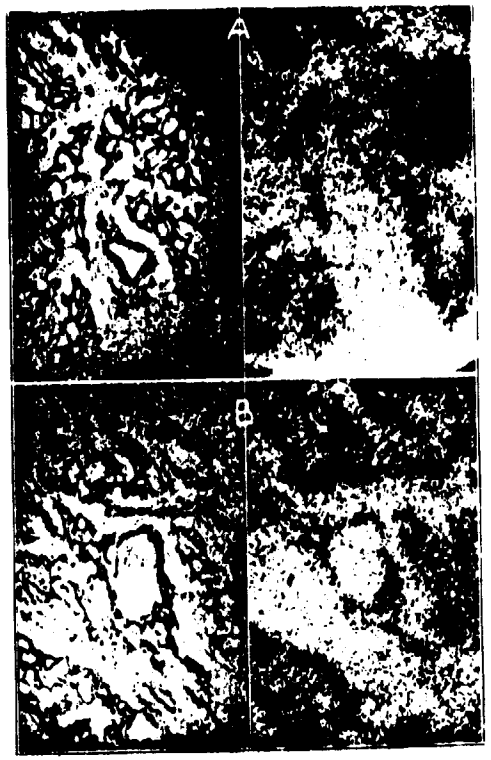

Fig. 5.—Sections of thyroid tissue from patient P. H. with their radioautographs. Note the "feathery" appearance of the acini and the relatively large amounts of iodine in the cells rather than in the colloid.

were pale and flattened. No lymphocytes, nodules or appreciable fibrosis were noted. The blood vessels were thin walled and contained no blood. The sections from the thyroid of patient A. D. showed a somewhat similar histologic picture but had more the appearance of an involuted gland. The radioautographs demonstrated that in both subjects most of the iodine was deposited in the cells of the acini rather than in the colloid and that surprisingly large amounts of iodine were concentrated in the thyroid. One must assume that some fault prevents the release

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of an active thyroid hormone from the accumulated iodine; otherwise, these patients should not have had the severe degree of hypothyroidism which was obvious even on casual clinical examination. The accompanying photograph of patient A. D. (fig. 6) shows his characteristic cretinoid appearance.

Some of the thyroid tissue from patients A. D. and P. H. was analyzed in order to determine the amount of radioactive iodine in the form of thyroxine, diiodotyrosine and inorganic iodine. These goiters had been removed forty-eight hours after the administration of radioactive iodine. Iodine fractionations were done by Dr. I. Perlman,[2] following technics employed in studying sheep's thyroids. Table 3 shows that about one fifth of the iodine was in the form of thyroxine.

Fig. 6.—Patient [redacted] at the age of [redacted] years. His appearance is characteristic of childhood myxedema.

TABLE 3.—*Results of Iodine Fractionations*

Subject	Sample	Amount of Thyroid Tissue Analyzed, Gm.	Thyroxine Iodine, Percentage	Diiodotyrosine Iodine, Percentage	Inorganic Iodine, Percentage
A. D.	First	0.185	12.1	60.8	18.2
	Second	0.176	11.4	57.9	18.5
P. H.	First	1.047	16.4	52.3	22.1
	Second	1.382	18.1	53.0	20.0

The thyroxine fraction probably was retained in the gland; otherwise these children would have maintained themselves in normal thyroid balance.

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COMMENT

Many of the assumed fundamental changes in the patients we have studied are a matter of speculation. Although we have no final pathologic description of the thyroids of the hypothyroid children (without goiter), the function of the glands, as measured by their inability to maintain a normal thyroid balance and to take up more than a fraction of the normal amount of iodine, apparently is as inefficient as in spontaneous myxedema of adults. It is known that the thyroids of patients with adult myxedema are fibrosed, atrophied and nonfunctioning. In other words, the results are what might have been predicted from previous knowledge.

In the 2 goitrous children, a state of hypothyroidism existed even though the thyroids of both accumulated more than the normal amount of iodine. One control study should be carried out in order to determine with certainty the failure of the thyroids of patients like A. D. and P. H. to release hormone into the circulation. This, of course, is the measurement of circulating thyroxine. To date, such studies have not been made because of technical difficulties in separation and measurement of radioactive iodine in the blood, although such measurements are possible if methods devised by Salter, Bassett and Sappington[3] are modified. If the circulating thyroxine is extremely low or even absent in such patients, the metabolic fault must lie in the inability of the thyroid to release, rather than in its inability to produce, this hormone.

It is strange, indeed, that the metabolism in respect to uptake curves and deposition of iodine within the gland is similar to that in the hyperplastic thyroids of patients with toxic goiters. Thus, that the extremes of thyroid function exhibit certain similarities is a fact susceptible to no further interpretation today than when it was first pointed out many years ago by David Marine.

SUMMARY

Labeled (radioactive) iodine has been employed to determine the ability of the thyroids in two groups of hypothyroid children to concentrate iodine.

The thyroids of children with hypothyroidsm and without goiters are able to concentrate only small amounts of orally administered iodine, as compared with the thyroids of normal children or adults. In these hypothyroid children, the remaining thyroid tissue concentrated a larger precentage of a dose of 0.1 microgram than of a dose of 14 mg. of iodine.

The thyroids of 2 children with goiters and with severe hypothyroidism took up relatively large amounts of iodine and by chemical analysis contained both thyroxin and diiodotyrosine in considerable quantities. The uptake curves of the thyroids as measured in situ were similar to those seen in hyperthyroidism in adults. Radioautographs made from sections of the thyroids of both of these children indicate that by the fifth day after the oral administration more of the iodine was in the cells than in the colloid.

University of California Medical School.

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REGULATION OF LEVEL OF VITAMIN A IN BLOOD OF NEWBORN INFANTS

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PART I

In previous communications[1] we reported that the concentration of vitamin A in the blood gave some indication of the degree of vitamin A storage in the body. Thus, low blood levels were usually associated with little or no storage in the liver of the rat, whereas high blood levels were accompanied by large stores; intermediate blood levels were of less significance, inasmuch as they were found to be associated with both large and small amounts of vitamin A in the liver.

The results of studies which we carried out on infants coincided, in general, with those obtained in studies on rats and indicated the practical importance of the blood level of vitamin A in the estimation of the vitamin A status of a subject. In febrile conditions, however, there is a rapid lowering of the vitamin A concentration in the blood, which is not necessarily accompanied by poor storage of the vitamin in the liver. It is not definitely known whether high temperature brings about destruction of the vitamin in the blood; whether, as a result of fever, there is an increased demand by the tissues for the vitamin, or whether there is an interference in the mobilization of vitamin A from the liver.

In the present communication it will be demonstrated that the generalization "abnormally low levels of vitamin A in the blood indicate poor storage" does not hold during the newborn period. The results of experiments bearing on the causation of the diminished concentration of vitamin A in the blood of newborn infants will also be reported.

Determinations of vitamin A (and carotene) were carried out on the blood of 108 normal newborn infants. The blood was obtained throughout the newborn period from the superior sagittal sinus except at birth, when cord blood was used for determination of the vitamin A and carotene levels. The method employed for these analyses has been fully described elsewhere.[1b]

The results of the determinations of vitamin A are plotted in the chart. It will be noted that there was a sharp drop in the concentration of the vitamin in the blood during the first two days of life, from an average value of 76 U. S. P. units per hundred cubic centimeters of plasma at birth to 37 units at the end of

From the Department of Pediatrics, New York University College of Medicine, and the Departments of Pediatrics and Obstetrics, Beth Israel Hospital.

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