is too low to be generally useful. It appears at present, on the basis of the facts in the previous paper in this issue as well as in this report, that measles and distemper viruses are related antigenically but not to the extent where a distemper virus inoculation would give satisfactory protection against measles. Serologic studies in monkeys, as well as in these human volunteers, indicate that inoculation with measles virus results in the production of distemper antibody as well as measles antibody, while the distemper strain used gives rise to marked distemper antibodies but to only very low, or negative, measles antibody response. Further studies along these lines, with use of different distemper virus strains, might give more favorable results.

Summary

In 1959, a moderate measles epidemic occurred in the banana plantations of western Panama. During this epidemic, 453 persons were inoculated with a tissue culture measles vaccine, 356 others serving as controls. In addition, 388 persons were vaccinated with a tissue culture distemper vaccine, 414 others serving as controls.

It was concluded that, while the measles vaccine was effective, the high rate of reactions limits its usefulness. On the other hand, no reactions could be found due to the distemper vaccine, but the ability of this vaccine to protect against measles appeared to be limited.

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EXCRETION OF RADIOIODINE IN HUMAN MILK

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The possibility that I^{131} administered to a lactating woman might appear in the milk and might reach the nurseling in harmful amounts was studied in six nursing mothers. Most of them were already in the process of weaning their babies. The I^{131} was given by mouth to the mother in doses of either 10 or 30 μc just after the final breast feeding. The quantity of I^{131} that appeared in the milk secreted in 48 hours after administration was 1.4, 3.9, 0.14, 0.03, 6.2, and 26.8% of the total that had been administered, respectively, to the six mothers. Most of the I^{131} was secreted during the first 24 hours. It is recommended that candidates for diagnostic tests with I^{131} be questioned about lactation and that nursing should be interrupted for 24 hours, or, in the case of a large diagnostic or therapeutic dose, until measurements indicate that the I^{131} content of the milk is no longer significant.

It has been shown by several investigators that radioiodine (I^{131}) administered to lactating women will appear in the milk.[1] Since at times the amount of I^{131} appearing in the milk will be a hazard to the nursing infant, the lactating patient should always discontinue nursing during the course of the test. It should be a routine procedure to question female patients about lactation at the time I^{131} is administered. This precaution is not taken in some isotope laboratories, so it seems advisable to reemphasize that such a hazard exists.

We have been interested in determining how soon the patient might resume nursing after the administration of I^{131} and in correlating the milk excretion of I^{131} with plasma, urine, and thyroid content. We therefore obtained the cooperation of several nursing women who were willing to discontinue nursing for the period of the test.

Method

Studies were made of six nursing mothers. For the most part these women were already in the process of weaning their babies, but one patient (case 1) was feeding her baby only breast milk at the time the test was started. For this reason she had a considerably larger milk production during the course of the test.

Just before administration of I^{131} there was a final infant nursing. Thereafter every time the breasts became full they were manually stripped, and the total output was brought to the isotope laboratory. This was carried out for one week by patient 1 and for 48 hours by the others, with the exception of patient 6, by whom milk collections were discontinued after 24 hours.

Ten microcuries of I^{131} was administered by mouth to all patients with the exception of patient 1, who received 30 μc. Our routine dose for a simple 24-hour iodine uptake test is 5 μc or less. More was given to this group to insure adequate radioactivity for accurate measurement in the milk, plasma, and urine specimens.

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At intervals of 2, 6, 24, and 48 hours after I^{131} administration, measurement for radioactivity was also made (1) over the thyroid gland, (2) on a blood sample (for plasma level of radioactivity), (3) on all urine voided in each interval. In vivo measurements were made with the scintillation counter. In vitro measurements were made in a well scintillation counter.

TABLE 1.—*Percentage of Ingested I^{131} Present in Each Milk Collection*

Patient, No.	1		2		3		4		5		6	
	Cc. Milk	% of Administered Dose	Cc. Milk	% of Administered Dose	Cc. Milk	% of Administered Dose	Cc. Milk	% of Administered Dose	Cc. Milk	% of Administered Dose	Cc. Milk	% of Administered Dose
					1st 24 hours							
	120	5.5	79	0.24	20	0.35	...	...	...	...	58	0.19
	70	4.7	...	...	...	...	...	...	...	...	...	...
	152	7.1	61	0.63	22	0.75	8.0	0.11	10	0.03	94	1.55
	82	2.4	40	0.37	29	1.0	...	...	...	...	95	1.96
	218	3.6	...	...	39	0.7	...	...	...	...	98	1.83
					2nd 24 hours							
	183	1.9	...	...	38	0.50	...	...	...	...	50	0.68
	...	...	27	0.14	...	...	4.3	0.03	7.8	0.003	...	...
	135	0.87	...	...	32	0.46	...	...	...	...	...	...
	106	0.37	13	0.04	...	...	...	...	...	...	...	...
	200	0.37	...	...	58	0.20	...	...	...	...	...	...
Total.....	1,266	26.81	220	1.42	238	3.96	12.3	0.14	17.8	0.033	395	6.2

Results

Quantity of Milk Produced.—There was enormous variation, as would be expected (table 1), in the quantity of milk produced. The smallest milk production for the 48-hour period was only 12.3 cc. and the largest was 1,266 cc.

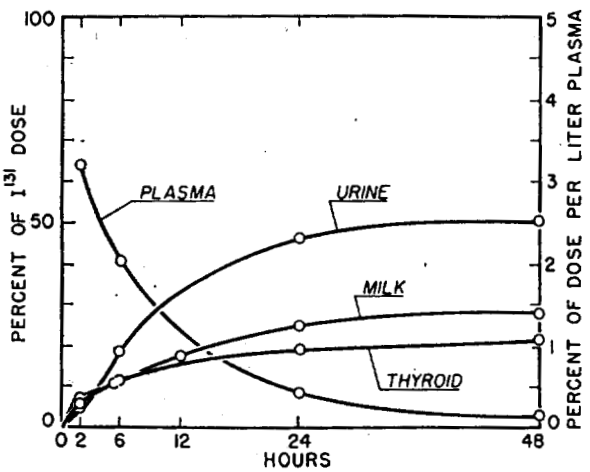

Fig. 1 (patient 1).—Curves of thyroidal uptake and cumulative milk and urine excretion expressed as percentage of ingested I^{131}. Plasma curve is expressed as percentage of ingested I^{131} per liter of plasma. Plasma and thyroid curves indicate low normal range of thyroid function. Forty-eight-hour total milk excretion of I^{131} is 26.8% of administered dose.

I^{131} Content of Milk.—The I^{131} content of the milk was roughly in proportion to the quantity of milk produced, as was previously demonstrated in I^{131} studies in cows.[2] In 48 hours the patient with the largest milk production excreted 26.8% of the administered dose of I^{131} in her milk. Figure 1 shows the cumulative curve of the milk excretion of I^{131} expressed in percentage of administered dose. It may be seen from this that most of this (23.3%) was excreted during the first 24 hours, so that there was a relatively small additional amount of I^{131} excreted in the milk during the second 24-hour period.

Plotted on semilog paper (fig. 2) the specific activity of the milk I^{131} content for a four-day period decreases exponentially. For patient 1 a minute trace of I^{131} was still found in the milk seven days after administration.

Thyroidal Uptake, Plasma Levels, and Urine Excretion of I^{131}.—All six patients were in the euthyroid range, although patient 1 was in the low normal range and has been given supplementary thyroid,

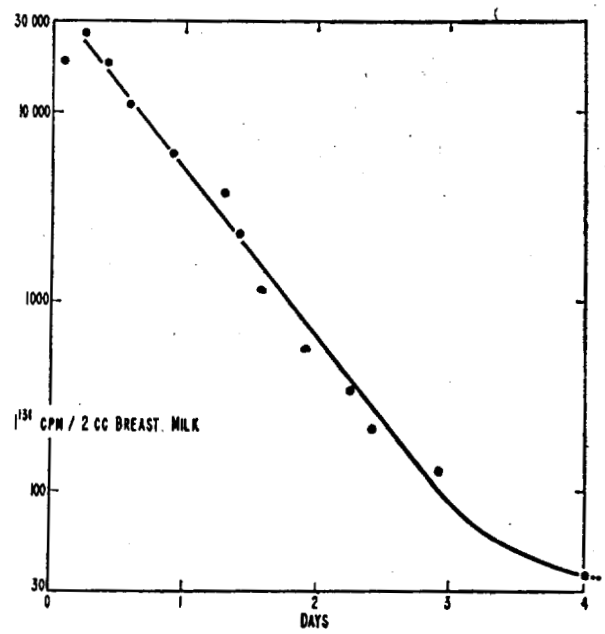

Fig. 2 (patient 1).—Curve on semilog paper showing decreasing concentration of I^{131} in breast milk.

with questionable benefit. The thyroid, plasma, and urine curves are produced here only for patient 1, (fig. 1), because this patient had the largest I^{131} milk excretion. For the six patients the 24-hour I^{131} thyroidal uptake ranged between 20 and 37% and the 24-hour urinary excretion of I^{131} between 46 and 65% of the dose administered. Balance calculations

at the end of 48 hours show the percentage of administered dose accounted for (thyroid, urine, and milk) to range between 90.0 and 100.4 (except for patient 6) (table 2). In all cases plasma levels of I^{131} at 48 hours were insignificant and did not amount to more than 1% of the total dose.

TABLE 2.—*Percentage of Administered Dose Excreted at End of 48 Hours*

Patient, No.	Thyroid Uptake, %	Cumulative Milk	Cumulative Urine	Total Accounted for, %
1.....	20	28.0	50	98.0
2.....	25	1.4	74	100.4
3.....	23	3.9	64	90.9
4.....	37	0.14	53	90.0
5.....	39	0.03	52	91.0
6.....	26	6.2	46	78.2*

* 24 hours only.

A comparison of the milk and urine content of I^{131} of patient 1 is of interest (fig. 1). For the first 24 hours the urine excretion was 46.0% of the ingested dose compared with a milk excretion of 23.3%. However, when based on percentage of ingested dose per liter of milk it is evident that roughly the same concentration was present in both (table 3).

In our patients with a small volume of milk production, the I^{131} concentration per liter was considerably less for milk than for urine. For example, patient 6 produced 0.395 liters of milk containing 6.2% of the administered dose of I^{131} (15% per liter) and 0.707 liters of urine containing 46% of the administered I^{131} (64% per liter).

Within 24 hours after I^{131} administration, most of the I^{131} that has not been concentrated in the thyroid gland has been excreted in the urine, leaving small amounts still in the blood stream. In addition, when there is a large milk production this becomes a major route of I^{131} exit from the body. When the milk production is small there is no increase in concentration of I^{131} in the milk, and perhaps a decrease, so the amount of I^{131} excreted in the milk is insignificant as compared with the urinary excretion.

Comment

A sizable percentage of orally administered I^{131} may be excreted in the milk. The quantity of milk produced is the important factor in determining the percentage of the administered dose that will be excreted by this route. If as much as 1 pt. is produced in 24 hours, the hazard to the infant might be considerable. Twenty-four hours after a tracer dose of I^{131} was given, Nurnberger and Lipscomb [1b] reported for one patient a thyroidal uptake of 34% and for her suckling infant a thyroidal uptake of 5%. For their second patient the uptake was 18% for the mother and 6% for the baby.

Miller and Weetch,[1d] on the basis of their calculations, concluded that a nursing infant might well receive a dose of 50 rep to the thyroid gland when the nursing mother had received 30 μc of I^{131}. We usually use a tracer dose of only 5 μc, and a dose to the infant thyroid gland of over 10 rep would be unlikely. Nevertheless, the inadvertent or thoughtless administration of radioactive material is not desirable, even though a dose of 10 rep would probably never seriously impair the function of the infant thyroid gland, nor does it seem likely that such a dose would be carcinogenic.

Since most of the milk excretion of I^{131} occurs in less than 12 hours, it would probably be safe for nursing to be resumed 12 hours after the dose is administered, but in order to allow for individual variation it would seem advisable to defer nursing until 24 hours after administration.

A small tracer dose administered to a nursing mother who is largely supplementing her infant's diet would probably be harmless for the infant. This would be particularly true of most of our group of patients, since the quantity of milk production was so small. For example, patient 5 produced only 17.8 cc. of milk during the 48-hour test period, and this contained only 0.033% of the administered dose. Since she was given 10 μc, the actual amount of I^{131} excreted was only 0.003 μc.

On the other hand, it is recognized that when hand stripping is substituted for infant nursing, the quantity of milk produced may be considerably diminished.[3] Since it is difficult to be certain that the milk production is actually small, it is certainly advisable to err on the side of conservatism and discontinue nursing during the test.

Since the plasma level curves are similar in all six patients, it seems evident that roughly the same amount of I^{131} was available for excretion into the milk for each patient for any given period of time. When there is a large milk output, carrying out considerable quantities of I^{131}, it is probable that some I^{131} is diverted from the thyroid gland, producing a lower gland uptake than that person would normally have. This possibility has been considered by Nurnberger and Lipscomb.[1b] Potter and Chaikoff [4] have presented experimental evidence for this lowering of thyroidal uptake by diversion of I^{131} into milk in their studies with lactating and nonlactating rats.

We have not analyzed the milk for hormonal I^{131}, but it has been shown that during the time of significant I^{131} milk content this iodine is not bound by protein.[1c] It may be that nursing mothers with hyperthyroidism might produce significant quantities of protein-bound I^{131} in the milk after treatment or a large tracer dose, but we have seen no data substantiating this.

TABLE 3.—*Comparison of I^{131} Excreted in Milk with That Excreted in Urine of Patient 1*

	Quantity of Urine, Liters	% of Administered Dose/Liter	Quantity of Milk, Liters	% of Administered Dose/Liter
1st 24 hr...	1.318	34.8	0.642	37.1

Summary and Conclusions

Milk excretion of orally administered I^{131} was measured in a group of six euthyroid lactating

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women. The concentration of I^{131} in the maternal milk will often be sufficiently high to be potentially hazardous to the child. The I^{131} appears in the milk within a short time after administration, and most of the I^{131} that is excreted in the milk appears during the first 12 hours, although small, continually diminishing amounts of I^{131} appear in the milk for many days. In none of these patients was the amount in the milk significant after 24 hours.

The specific activity of I^{131} in the milk (percentage of administered dose per liter of milk) showed a certain amount of variation for all these six patients, although the specific activity was less when the volume of milk production was small.

The percentage of administered dose of I^{131} excreted in the milk is roughly in proportion to the quantity of milk produced. The greatest hazard to the nursing infant will occur when the mother is supplementing little or not at all and because of this produces large quantities of milk. Therefore, technicians should routinely ask any woman of childbearing age whether she is lactating, and, if so, nursing should be discontinued for at least 12 and preferably 24 hours. If the tracer dose is over 30 μc, or if it should be necessary to administer a therapeutic dose of I^{131}, nursing should not be resumed until measurements indicate an insignificant milk content of I^{131}.

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Mrs. Gretchen Fox gave technical assistance in this study.

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ERYTHEMA NODOSUM IN PRIMARY HISTOPLASMOSIS

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Erythema nodosum was the primary complaint in two children (a girl aged 2 and a boy aged 2¾ years) and was found secondarily in connection with other problems in two other children (a girl aged 6½ and a boy aged 7½ years). In all four cases the skin tests for tuberculosis gave negative results but reactions to histoplasmin were strongly positive. In no case was there evidence of rheumatism. It seemed evident that the erythema nodosum was a manifestation of histoplasmosis. In regions known to harbor Histoplasma capsulatum this organism must be considered among the possible causes whenever the physician deals with a fever of undetermined origin.

Erythema nodosum is an allergic response clinically associated with certain disease states, of which tuberculosis, streptococcic infection, and rheumatic fever have been most often described. The earliest report was in 1808, by Willan, who noted the eruption in his book, "On Cutaneous Diseases." Its association with rheumatism was soon noted, then with tuberculosis. Other infections and drugs, notably sulfathiazole, have been reported as causing erythema nodosum.[1]

In 1932 Collis [2] described the clinical relationship between erythema nodosum and allergy to tuberculin or to a streptococcic "endotoxin." Shortly thereafter, Dickson [3] related the occurrence of this skin manifestation in patients with coccidioidomycosis to the time when their sensitivity to coccidioidin was at its greatest. Thus, bacterial, mycobacterial, and mycotic infections have variously been indicated as being related to erythema nodosum. It should be noted that geographical differences have been marked in the various series of cases reported.[1]

Although the occurrence of erythema nodosum in patients with primary histoplasmosis in geographical areas where this infection exists is not surprising, reports on it in the literature are scanty; we have noted this association since 1953. Dublin and associates [4] reported the case of an adult with proved histoplasmosis and with "bluish, erythematous-roughened, cutaneous areas of the knees," diagnosed as seborrheic dermatitis on the basis of a biopsy specimen. In 1950, Heilbrunn and Cain [5a] reported on a patient with pulmonary histoplasmo-

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