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THE MOUSE THYROID AND RADIOACTIVE IODINE (I^{131})

II. The Excertion Rate of Radioactive Iodine Following Its Injection into the Adult Nursing and Non-Nursing Mouse, and Its Rate of Absorption by the Suckling Young

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THE MOUSE THYROID AND RADIOACTIVE IODINE (I^{131})

II. THE EXCRETION RATE OF RADIOACTIVE IODINE FOLLOWING ITS INJECTION INTO THE ADULT NURSING AND NON-NURSING MOUSE, AND ITS RATE OF ABSORPTION BY THE SUCKLING YOUNG

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ABSTRACT

This, the second in a series of papers on the mouse thyroid and carrier-free NaI^{131}, deals with the excretion of subcutaneously injected radioiodine as it is altered by lactation and nursing a litter. Excretion in the control is very rapid, so that by 4 hours post injection, 66% of the radioiodine is lost and by 48 hours only 8% remains. If, however, the mouse is nursing a litter the excretion rate is reduced to about 25% (as opposed to the 66% in the controls) within the first 4 hours. The bulk of the retained iodine is being transferred through the milk. Even by 48 hours the lactating mouse loses less iodine than does the control. There is no direct correlation between the concentration of injected radioiodine and the rate of its excretion.

In the suckling litter by 48 hours, regardless of its size, there was found more radioiodine than was retained by the mother. The dose, not the concentration, to any litter member never exceeded 5% of the total dose injected into the mother. The concentration (i.e., microcuries per gram of body weight) of radioiodine in the individual litter members varied considerably, and was somewhat correlated with the dose to the mother. In some extreme cases the concentration in a litter member at 48 hrs. was 50% of that found in the mother.

This is the second in the series of studies on the effect of radioactive iodine (I^{131}) on the lactating adult and the nursing young mice. In this study it was the purpose to determine the excretion rate of subcutaneously injected radioactive iodine and its concentration rate in the nursing litter.

Radioactive iodine is being used more and more extensively, not only in studying the various thyroid disturbances in clinical medicine, but in radiobiological research relating to the normal thyroid physiology. It seemed pertinent to determine the relation between the amount of injected radioiodine and its concentration in the adult, and the effect on this concentration when the adult is a lactating female with a newborn suckling litter. The approach to this analysis was by way of determining the excretion rate following injection into the mother of various doses of NaI^{131} and over varying periods.

MATERIALS AND METHOD

The mice used in these studies were of the Swiss albino stock, inbred in our laboratories for some months. The females were all adults of at least 4 months of age. The lactating females were injected with the carrier-free NaI^{131} on the third day following delivery of the litter, and the study was made during the following 48 hours.

Radioactive iodine (I^{131}) in the form of carrier-free sodium iodide was injected subcutaneously on the dorsal side of the mouse, without benefit of anesthesia. Since there was found to be a considerable weight difference between adults of the same age and healthy condition, the dose was determined in relation to the total body weight of the mouse concerned. This meant that the microcuries per gram of tissue was the same in all cases, except where the dose was intentionally varied. In the case of the lactating mice, there was naturally a larger total body dose since their weights ranged from 31 to 43 grams while the weight of non-lactating mice ranged from 27 to 34 grams.

The total doses used were interpolated from hospital practice with human patients with thyroid disorders, and were determined at the high tracer to high therapy levels. They were at 5, 10, and 20 microcuries per gram of total body weight. The maximum dose given to any individual adult female mouse was in the neighborhood of 800 microcuries of NaI^{131}.

Immediately following injection with a measured volume of carrier-free NaI^{131} of known radioactivity, the mouse as a whole was checked for radioactivity. This was determined for all such readings at the uniform distance of 16 cm. from the face of the counter tube. The activity of the mouse as a whole was then checked against a standard of NaI^{131} in a volume of agar essentially similar to the volume of the mouse, and at the same distance from the counter tube. It was possible, in this manner, to determine the actual amount of radioactive iodine contained in the injected mouse immediately after injection.

The Geiger-Müller counter reading of the intact, whole mouse, immediately after injection, was then taken as the base line for future comparisons with the amounts of radioactivity retained in the mouse. The subsequent readings were taken at 4, 24, and 48 hours, under identical physical (geometrical) conditions. The loss in radioactivity was then calculated, taking into account the natural decay rate of the radioiodine.

The excretion pathways of the mouse are probably the skin, urine, faeces, salivary glands and, in the case of the lactating mouse, the mammary glands. This is the case when the term excretion includes any and all means of eliminating the substance from the body. Slight variations in these readings between animals might be attributed to several factors, such as, for instance:

1. General metabolic activity and excitability of the mouse. Variations here might alter the uptake of I^{131} and its excretion. All animals were treated alike, with a minimum of handling. (Albert and Keating 1949, and Childs et al 1950).

2. Variables in food, water, and temperature. The food consisted of abundant Purina Laboratory Chow which is low in natural iodine content. The total iodine content of the mouse is itself low but adequate. The water was always in excess of the need and the temperature was the room temperature which which varied only slightly,

and equally for all animals studied, both controls and experimentals. (Leblond et al 1944).

3. Lactation. Subsequent reports will indicate that radioiodine readily passes through the milk to the nursing young. Lactation must therefore be considered as a pathway for excretion. When the litter numbers varied greatly, there was, in consequence, a variation in the drain on the milk supply by the suckling young. (Coarrier et al 1949, and Aten and Heyn 1950).

4. Oestrus. This would apply only to the non-lactating mouse. There have been no studies made on cyclic changes of iodine retention relating to oestrus. However, there is some evidence that the metabolic changes associated with oestrous (reflecting activity changes in the thyroid and the pituitary glands)may be considerable. The mouse has a 4 to 5 day oestrus cycle, and averages of data from various mice would tend to balance out any such variable.

5. Skin retention of I^{131}. It is known that animals with tumors have a higher-than-normal skin retention of radioiodine. ((Stevens et al 1949 and 1950). These experimental animals were tumor free. There were variations in the amount of radioactivity retained in the skin of different mice. Whether high skin retention of NaI^{131} may eventually prove to be an indication of subsequent skin tumor development, can only be

conjectured at this time. Variations might be due in part to the method of injection, but so far as possible this was identical for all mice. The skin is a known pathway for excretion.

OBSERVATIONS AND EXPERIMENTAL DATA

Taking into account the natural decay rate of I^{131} (the half life is 8 days), Geiger-Müller counter readings of whole and intact mice at 4, 24, and 48 hours showed a progressive iodine loss. The greatest loss from the injected adult was within the first 4 hours following injection. This was not true for the lactating and nursing adult mouse, where the excretion rate is considerably retarded.

In the non-nursing control mice at least 58% of the injected iodine was lost within 4 hours, by the various channels of escretion. In the nursing mouse with a suckling litter, however, as little as 25% of the injected iodine was excreted. The maximum excretion under these conditions was 39%. This high retention of I^{131} was, no doubt, associated with the passage through the milk to the nursing young.

By 48 hours there still existed a disparity between the nursing and the non-nursing mice, but in all cases there was a minimum excretion of 80% of all injected iodine. If the mouse was not nursing, however, it excreted at least 93% of the injected iodine within this period. This minimum difference, 13%, represents the average minimal retention effect due to lactation and nursing. The following table of data points up this

PERCENTAGE EXCRETION OF SUBCUTANEOUSLY INJECTED RADIOACTIVE IODINE (I^{131}) INTO THE FEMALE MOUSE*

	3 μc/gr. b.w.			10 μc/gr.b.w.			20 μc/gr.b.w.		
	HOURS POST INJECTION								
Female Mice	4	24	48	4	24	48	4	24	48
Non-Nursing	67	91	93	70	93	95	58	93	95
Nursing	39	81	88	25	78	81	29	71	80

*Each figure is an average of readings from a minimum of three mice, generally four. The Geiger-Müller counter readings were taken at uniform geometry and physical conditions, with the initial reading immediately after the subcutaneous injection of radioactive iodine into the adult female mouse.

Similar data were obtained by hydrolysis of animals at the various intervals following injection with radioactive iodine. The data compared very favorably with that presented above, particularly at 48 hours. However, since the hydrolysis terminated the observations and did not allow consecutive readings from the same animal, the above data alone are presented.

Table I

difference.

It was next of interest to determine the distribution of radioiodine between the mother and her litter. Here we found two natural variables. First, the number of mice constituting a single litter varied from 4 to 11. Second, there were variations among the suckling young as to their ability to attach themselves to the mother and to secure milk.

If we disregard these two variables, and simply consider the percentage of iodine in the mother and in the litter as a whole, we find that in general there is a gradual transfer of relative concentration from the nursing mother to her litter. This means, of course, that while the total retained radioiodine was being reduced rapidly, due to both excretion and decay, there is a constant shift in the relative amounts found in the mother and in the nursing young.

The following table is made up of percentages only, taking the total iodine in the mother and in the litter as 100% and disregarding the actual microcuries of radioactive iodine involved. The table demonstrates that whatever the amount of initially injected radioiodine into the mother, by 48 hours, and in the majority of cases, the litter as a whole contained more radioactivity than did the mother.

It was of further interest to determine the distribution of the radioactive iodine among the litter members. This

THE PERCENTAGE DISTRIBUTION OF RETAINED I^{131} IN THE MOUSE MOTHER AND THE SUCKLING YOUNG (LITTER AS A WHOLE) AT INTERVALS FOLLOWING THE INJECTION OF THE MOTHER. LITTER SIZES VARIED FROM FOUR TO ELEVEN.

μc/gr. body weight		INTERVALS FOLLOWING INJECTION 4 hours	24 hours	48 hours
3μc	MOTHER	79	35	44
	LITTER	21	65	56
10μc	MOTHER	47	35	40
	LITTER	53	65	60
20μc	MOTHER	59	31	36
	LITTER	41	69	64

TABLE II

interest was substantiated by the fact that there was found to be some variation in the histological damage among the young suckling mice nursing to an injected mother. The histological analysis will be reported in a subsequent paper. Counts were made of suckling young hydrolyzed in 5% NaOH, at various intervals following different doses to their mothers. Since the litter numbers varied from 4 to 11, the total radioactive iodine contained by the entire litter was taken as 100%. The estimates of the amount of radioactivity in each members of the various litters was determined with respect to the total value for the litter concerned, and is expressed as percentage of that total. The following table indicates that only when the litter numbers are small (e.g., 4) do the litter members get approximately the same concentration of radioiodine. When the litter number is as high as 10 or 11, there was often as much as 3x or 4 x disparity between the individuals of the litter.

In one exceptional instance, at 24 hours following injection of the mother with NaI^{131} in a concentration of 20 μc/gr. body weight, one individual in the litter of 8 obtained only 1.16% of the total litter concentration of iodine, while a litter mate received 22.24%. This disparity of 18x simply emphasizes the individual litter mate differences due to the relative avidity of the young for food and the availability of the food itself. The following table points up these variables. (See Table III).

DISTRIBUTION OF I^{131} AMONG SUCKLING LITTER MEMBERS, FOLLOWING INJECTION OF THE MOTHER AT VARIOUS INTERVALS. NUMBER OF MICE IN LITTER IN PARENTHESES

	PERCENTAGE OF LITTER TOTAL, IN INDIVIDUALS		
Injection of Mother μc/gr. Body Weight	4 hours	24 hours	48 hours
3 μc	9 - 13 (9) 21 - 28 (4)	6 - 16 (9) 21 - 30 (4)	9 - 18 (7) 6 - 17 (8)
10 μc	6 - 16 (10) 11 - 16 (7)	5 - 13 (11) 11 - 18 (7)	6 - 16 (10) 5 - 20 (8)
20 μc	5 - 19 (10) 9 - 19 (8)	1 - 22 (8) 7 - 19 (8)	9 - 21 (7) 8 - 23 (8)

TABLE III

The above table does not give data relative to the actual amount of I^{131} involved, but only to percentages of the total. It is obviously of interest, particularly in respect to any histopathological studies, to determine the exact amount of radioiodine associated with any deleterious effects on the thyroid or other organ systems. This is done in such studies, to be reported subsequently.

The table below gives the data from 18 litters, in which the litter members were weighed and their radioactivity per gram of total body weight was determined at three different intervals of 4, 24, and 48 hours, and following three different doses of NaI^{131} to the mother (3, 10, and 20 μc/gr. body weight). As one would expect it can be seen that the dose to the mother is, in general, reflected in the dose absorbed by the suckling litter members. The maximum absorption in a litter member was to the extent of 10.4 microcuries per gram of body weight (in litter No. 1023) when the mother received only twice this concentration. This occurred within 4 hours after the mother was injected, and in a litter of 10 members. This is an extremely high concentration for any ahimal and represents an ablation dose for the thyroid gland. In the same litter the minimum concentration for any individual was 3.1 μc/gr. body weight. This is still a therapy dose for retained radioiodine.

THE RADIOACTIVITY OF SUCKLING MOUSE LITTERS AT VARIOUS PERIODS FOLLOWING INJECTION OF VARIOUS CONCENTRATIONS OF NaI^{131} INTO THE MOTHER*

Dose	4 HRS. POST INJECTION				24 HRS. POST INJECTION				48 HRS. POST INJECTION			
		Aggreg. Wt.	Total uc.	uc/gm.		Aggreg. Wt.	Total uc.	uc/gm.		Aggreg. Wt.	Total uc.	uc/gm.
3 uc/gr.body wt.	Litter #883(9)	22.4	12.08	.54	#533(10)	41.7	11.36	.27	#1117(7)	14.9	2.24	.15
	Highest	2.6	1.6	.62	Highest	4.3	1.8	.43	Highest	2.4	.40	.17
	Lowest	2.5	1.1	.46	Lowest	3.8	.69	.18	Lowest	2.1	.21	.10
	Litter #1119(4)	4.5	6.3	.98	#807(4)	10.5	16.39	1.57	#775(8)	30.0	4.14	.14
	Highest	1.7	1.8	1.0	Highest	2.7	4.9	1.8	Highest	4.0	.71	.18
	Lowest	1.6	1.4	.86	Lowest	2.5	3.4	1.3	Lowest	3.8	.26	.07
10 uc/gr.body wt.	Litter #89(10)	36.5	53.3	1.5	#519(11)	20.0	25.5	1.3	#415(10)	26.8	35.5	1.3
	Highest	3.8	8.8	2.3	Highest	1.8	3.2	1.8	Highest	2.6	5.7	2.2
	Lowest	3.9	3.1	.8	Lowest	1.8	1.3	.8	Lowest	2.3	2.1	.9
	Litter #1313(7)	16.5	74.6	4.5	#507(7)	14.1	41.3	2.9	#709(8)	27.9	24.7	.89
	Highest	2.3	11.8	5.1	Highest	2.0	7.6	3.7	Highest	3.6	5.0	1.4
	Lowest	2.2	8.4	3.8	Lowest	2.0	4.7	2.3	Lowest	3.6	1.1	.3
20 uc/gr.body wt.	Litter #1023(10)	30.1	178.1	5.9	#585(8)	19.9	30.56	1.5	#971(7)	20.7	10.1	.49
	Highest	3.3	34.6	10.5	Highest	3.0	6.8	2.3	Highest	2.9	2.1	.76
	Lowest	3.0	9.2	3.1	Lowest	1.8	.36	.2	Lowest	2.9	.87	.3
	Litter #1029(8)	20.9	102.2	4.9	#985(8)	13.1	87.	6.6	#1251(8)	14.9	33.1	2.2
	Highest	2.9	19.6	6.8	Highest	1.8	16.7	9.2	Highest	2.1	7.5	3.6
	Lowest	2.9	9.1	3.1	Lowest	1.6	6.5	4.0	Lowest	1.8	2.8	1.6

*(Note: Figures in parentheses next to litter number represent the actual number of animals constituting the litter.)

TABLE IV

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After 48 hours, the maximum concentration in any litter member was 3.6 μc/gr. body weight. A high concentration of 2.2 μc/gr. body weight was found in a litter where the mother received only 10 μc/gr. body weight. A corresponding concentration in a man of 150 pounds would be about 147 millicuries - an enormous concentration.

DISCUSSION

The rate of thyroid uptake of radioiodine in human patients has been determined (Hertz et al '42, Keating et al '47, Skanse '48, Hamilton and Soley '39, McArthur et al '48, Chaikoff and Taurog '49) but the method used by many has been to make the determinations on the basis of the reciprocal value following calculations of excretion in the urine. (Edwards, Reilly, Holme '49, Mason and Oliver '49). This method has been questioned (quimby and McCune '47) because there has been found a considerable disparity between values for thyroid uptake determined by readings with the Geiger-Müller counter directly over the gland and the reciprocal value determined by urinary excretions. It is true that the concentration of iodine in the thyroid gland may be very great but it is not wise to assume that this is the only tissue concentration of the iodine. It has been shown for instance that skin tumors will also absorb radioiodine or alter its tissue distribution. The above authors did find that the total thyroid and urine content of iodine fell far short of the total amount injected. Nevertheless, when excretion rate alone was considered there was discovered some crude correlation between the several abnormal thyroid states so that, for instance, in thyrotoxicosis, there is always a low iodine excretion.

The excretion of radioiodine, or of labeled thyroxin, is extremely rapid in normal physiology but may be altered in abnormal thyroid states. The excretion rate may be taken therefore as a rather reliable criterion of normal or abnormal thyroid, or of certain cancerous states.

Stevens et al ('50) found that the metabolism of I^{131} is altered by the presence of cancer in rats with Walker tumor 256 (Stevens et al '49), and in mice with mammary carcinoma No. 1509-1a. The latter authors found that within 15 minutes following injection of radioiodine, 93% of it was found in 19 different parts of the body. When a tumor is present, the variations relate largely to thyroid and splenic concentration. The thyroids and spleens of tumor bearing mice, for instance, contained less I^{131} than did the thyroids of their controls. The authors claimed that the absorption of I^{131} injected intravenously into the tail was largely completed within 45 minutes.

The activity of the thyroid gland itself may therefore alter the rate of excretion (Beierwalter et al 1948, Stanley 1949, Williams et al 1949). Chaikoff and Taurog 1949, found that thyroidectomy in rats would depress the rate of incorporation of radioactive iodine into protein bound iodine fraction of plasma. Clarke, Moe, and Adams in 1949, studied the rate of conversion of orally administered radioactive iodine into the protein bound iodine of the plasma in patients with various thyroid states and in patients with hypertension and cardiac disease, accompanied by an elevated basal metabolic rate. A low excretion rate suggested hyperthyroidism (Fluharty et al '48, McArthur et al '48). The conversion rate in normal man ranged from 13 to 42%, and when the conversion rate was above 50% it was taken as evidence of hyperactivity of the thyroid gland. Patients who converted 10% or less were regarded as hypothyroid. "The results suggest that the rate of incorporation of radioactive iodine into protein bound iodine of the plasma may be a useful guide to thyroid activity". Excretion rates would bear a rough reciprocal relationship to the binding of iodine in the plasma.

Albert and Keating in '49 found that orally administered I^{131} to myxedematous patients was absorbed through the gastro-intestinal tract into the blood and distributed largely in extra-cellular fluid. The iodine in the blood appeared as iodide. It left the blood rapidly, appearing in the urine and in the thyroid gland. By the third day only a small amount of the iodine was found protein bound. From 85 to 95% was excreted through the urine as inorganic iodine, and 2% in the faeces, protein bound. At the end of the third day from 5 to 15% was found in the body tissues. Radiothyroxine was given intravenously. After one half-life of the iodine, 41% was excreted through the urine and 12%

through the faeces. Of the urinary excretion 85% was an inorganic iodide and 15% was organic iodine, consisting of both thyroxin and diiodotyrosine. Myant et al ('49) and Oddie and Scott ('50) found that the thyroid clearance rate is a sensitive test for the iodine collecting activity of the thyroid, and may be of great value in diagnosing thyrotoxic cases. Williams et al ('49) used the summation of urine and serum iodine as a reflection of thyroid states.

Schiff et al in '49 found that in intravenous injections of human patients with I^{131}, the salivary glands secreted a higher concentration than did the stomach. It was Davenport ('43) who described iodine secretion by way of the gastric mucosa.

Leblond and Gross in '50 found radioiodine in the thyroids of rats as soon as 2 minutes following injection and that "excretion of the thyroid hormone itself probably results from the proteolytic breakdown of thyroglobulin in the colloid and the diffusion of the resulting fragments through the epithelial wall of the follicle".

Gross and Leblond '47 found that 80% of labeled thyroxin was located in the faeces within 24 hours and was unchanged while 11% appeared as inorganic iodine. By this time from 80-95% of the injected iodine was excreted from the body, by the various channels.

Rutenberg et al '50 state that the total iodine content of the normal rat was very low, in the order of 0.1-0.2 mg. and that the administration of 2.4 mg. of NaI^{131} greatly exceeded the endogenous iodine content. They used this excess to determine the tissue turnover of iodine, and state "The thyroid specifically accumulated carrier free iodide. This function was depressed when carrier sodium iodide was added."

Baumann et al '49 found that Rhenium, also of the seventh periodic group as iodine, acted as does iodine when given to animals. Within 24 hours after injection as much as 90% was excreted.

In this paper we are dealing with normal mice, unless one must consider the condition of lactation and nursing as abnormal. In these latter cases, the mammary glands of the nursing mother within 4 hours of subcutaneous injection with radioiodine show a 6x concentration of radioactivity as compared with the controls (data to be reported in detail in a subsequent paper). Lactation witholds the iodine in the lactating mouse until it is drained by suckling young. The flow of radioiodine through the mother milk to the suckling young is therefore very rapid, much more so than has been demonstrated to be for strontium and plutonium (Finkel '47). It has been detected by Geiger-Müller counter in the nursing young within 8 minutes after subcutaneous injection of the mother. The lactating and nursing adult mouse is therefore rapidly drained of imposed radioactivity, and such activity is concentrated in the suckling young. However, the amount excreted by the mother through her skin, urine, faeces, and possibly the salivary glands, and the natural decay of iodine, together explain why the actual concentration of radioiodine in the members of the suckling litter is relatively low, as compared with the dose injected into the mother. There were exceptions. In some cases there appeared in the suckling young, within 4 hours after the mother was treated, approximately a 50% concentration (not dose) of the original injected concentration into the mother. This simply means that there are a number of variables which alter the rate and the pathway of elimination of radioiodine from a lactating female, and that under certain conditions the nursing you can get a concentration as high as 50% of that of the mother, which might be extremely deleterious.

It must be pointed out, however, that the litter member concentration of radioiodine, obtained from the milk, does not mean concentration within its thyroid, nor even within its tissues. A good portion of this iodine may be contained within the gut, and might never be absorbed by the tissues of the young. However, we know so little about the excretory efficiency of the suckling young that in determining the toxic levels to the young when the mother is treated we must take this calculated total concentration within the suckling litter members as the maximum probability.

SUMMARY AND CONCLUSIONS

1. Radioiodine injected into an adult mouse as carrier-free NaI^{131} is excreted at a very rapid rate so that at least 66% is lost within the first 4 hours, 90% within 24 hours, and 92% within 48 hours.
2. If the mouse is lactating and nursing a litter, the excretion rate is reduced to about 25% in the same interval of 4 hours. The bulk of the radioiodine is being transferred, at this time,

through the milk to the nursing young.

3. By 48 hours after subcutaneous injection with radioiodine, from 80 - 93% may be lost from the adult female mouse by excretion. The lower of these figures represents the condition in the lactating and nursing mouse, some of the iodine being retained in the milk.

4. The rate of radioiodine excretion was not directly correlated with the concentration used. The concentrations were high tracer to high therapy doses, as interpolated from human studies. They ranged from 2 to 20 microcuries per gram of body weight of the adults, whose weights ranged from 27 to 43 grams.

5. By 48 hours after injection the concentration of retained radioiodine in the litter, regardless of its size, exceeded that retained by the mother. The dose (not concentration) to any litter member never exceeded 5% of the total dose injected into the mother.

6. When the litter number was small (e.g. 4) the concentration per litter member tended to be rather the same but when the litter number was great (10 - 11)then there appeared a great disparity between litter mates with respect to the concentration per unit weight of tissue of radioiodine.

7. The concentration of radioiodine per individual litter member was variable as compared with the dose originally injected into the mother. In some extreme cases the concentration

(i.e., μc/gram body wt) in the young attained a value of 50% that found in the mother. But considering the relative total body weights of mother and suckling young, and the excretion factor, it can be stated that no more than 5% of the total radioactive iodine injected into the mother will reach a suckling young of 3 days of age.

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