matter had best await the outcome of further investigations. It is of interest to note that under anaerobic conditions the equivalent of 4–5 μmoles of glucose is metabolized during a comparable period.

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Deoxyribonucleic Acid in Mitochondria and Its Role in Protein Synthesis*

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This paper reports the detection of small amounts of DNA ranging between 340 and 560 μg/100 mg protein in lamb heart mitochondria. This material, which appears to be highly polymerized, was identified as DNA by its deoxyribose content, acid-precipitability, and selective sensitivity to pancreatic DNAase. Experimental evidence indicates that the DNA is not merely a contaminant arising from the breakage of nuclei during the preparation of the mitochondria. A biological role for DNA in heart mitochondria was established when the presence of a DNA-dependent RNA polymerase was observed. The ability of intact mitochondria to effect the incorporation of labeled amino acids was found to be sensitive to actinomycin D, but not to DNAase or RNAase. Inhibition by the antibiotic was partially reversed by the addition of excess DNA. The incorporating activity of a supernatant system derived from sonically disrupted mitochondria by centrifugation at 105,000 × *g* for 2–4 hours is reduced by DNAase or RNAase. In this case the addition of excess DNA reverses the inhibition of actinomycin D. Furthermore, actinomycin D is capable of inhibiting the incorporation of [8-^{14}C]-ATP by intact mitochondria.

The nucleus has been considered to be the exclusive site of DNA and hence of genetic information (Allfrey, 1959). However, reports from a number of laboratories on the presence of fibers or barlike structures with characteristics of bacterial nucleoplasm and of chemical analyses of DNA in chloroplasts (Ris and Plaut, 1962; Iwamura, 1962; Gibor and Izawa, 1963), kinetoplasts (Pitelka, 1961; Steinert, 1960; Steinert *et al.*, 1958), and the kappa particles of paramecia (Dippel, 1958; Hamilton and Gettner, 1958; Ris, 1961) speak in favor of the view that cytoplasmic particles which have been presumed or suggested to be "self-duplicating" contain DNA. This view is further strengthened by the demonstration (Nass and Nass, 1963a,b) that chick embryo mitochondria studied with the electron microscope show christae-free areas of low electron opacity which contain rodlike fibrous components with characteristic Feulgen-staining properties. These mitochondrial fibers were shown to be specifically digested with DNAase. In control incubations, RNAase and pepsin did not act upon the structures, although RNAase digested the cytoplasmic ribosomes and some nucleolar material and pepsin digested all of the mitochondrial structure except the fibers. These mitochondrial fibers appear to contain DNA.

While our studies were in progress, Schatz *et al.* (1964) observed that preparations of mitochondria from bakers' yeast which were purified by flotation in density gradients contain a significant quantity of DNA.

This report is concerned with experiments which indicate the presence of DNA in heart mitochondria and presents evidence that this DNA is not merely a contaminant but fulfills a biologically active role in mitochondrial protein synthesis.

EXPERIMENTAL PROCEDURE

Biological Material.—Lamb hearts weighing approximately 100 g were obtained from a local abattoir immediately after the animals were killed.[1] The hearts were cut into small pieces and packed in ice for the trip back to the laboratory.

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[1] We wish to thank the Charles Miller Company for their kindness in providing us with the fresh hearts.

Chemicals.—The following products were purchased: Puromycin and α-ketoglutaric acid (Nutritional Biochemicals Corp.); calf thymus DNA, liver-soluble RNA, ADP, and AMP (Sigma Chemical Co.); chloramphenicol (Parke-Davis Co.); crystalline RNAase and DNAase (Worthington Biochemical Corp.). DL-[1-^{14}C]Leucine (5μc/μmole), DL-[1-^{14}C]valine (0.5μc/μmole), and uniformly labeled L-[^{14}C]phenylalanine (300 μc/μmole) were obtained from the New England Nuclear Corp. DL-[1-^{14}C]Proline (4μc/μmole) was purchased from the Volk Radiochemical Co., and [8-^{14}C]ATP Na_2 (6.4 μc/μmole) was obtained from Schwarz BioResearch, Inc. Actinomycin D was the gift of Dr. Louis H. Sarett of Merck, Sharp, and Dohme Research Laboratories. All other chemicals were of reagent grade.

Assays.—RNAase and DNAase were assayed spectrophotometrically for nuclease activity (Kunitz, 1946). DNAase was assayed for proteolytic activity by the method of Kunitz (1947). DNAase was found to be without RNAase or proteolytic activity even when tested in amounts 100 times that used in the incorporation experiments.

Preparation of Mitochondria.—Heart mitochondria were prepared in the cold by the method of Slater and Cleland (1953) with the following modifications. After removal of the great vessels and fat, the heart tissue was minced with a scissors, passed through an ice-cold meat grinder, and homogenized in 30- to 50-g portions in a Waring Blendor for 9 seconds in 7 volumes of a solution of 0.30 M sucrose–0.005 M EDTA, *p*H 7.4. After an initial centrifugation at 1000 × *g* for 5 minutes in the GSA rotor of the Sorvall RC-2 refrigerated centrifuge, the supernatant fluid was strained through a double layer of washed gauze. The mitochondria were then isolated and washed five times in the sucrose-EDTA solution.

The washed mitochondria were taken up in the sucrose-EDTA solution which was 0.01 M in $MgCl_2$ to a final concentration of 20 mg of mitochondrial protein per ml as determined by the biuret method. This mitochondrial suspension was frozen overnight at −20° and was allowed to slowly thaw at 4° before treatment in the sonic oscillator.

Treatment of Mitochondria in the Sonic Oscillator and Preparation of the 105,000 × g Supernatant Fraction.—The mitochondrial suspension was then placed in the treatment unit of a 10KC Raytheon sonic oscillator previously chilled to 0° and the preparation was subjected to sonic vibration for 2.5 minutes at full power (generally 1.10 amp on our instrument when using 25 ml of suspension). After allowing 5 minutes for the oscillator to chill down again, the treatment was continued for an additional 2.5 minutes. The 3-hour 105,000 × *g* supernatant fluid used to study incorporation was obtained from the sonically disrupted mitochondrial preparation as previously described (Kalf and Simpson, 1959).

Treatment of the Protein.—At the termination of the incubation period, trichloroacetic acid was added to the incubation vessel to a final concentration of 5%, and the precipitated proteins were washed and plated as described (McLean *et al.*, 1958). Radioactivity of the samples was estimated with a windowless gas-flow low-background Geiger counter with an efficiency of 30%. Corrections were made for background counts (4–5 cpm) and for self-absorption.

Isolation and Determination of DNA.—DNA was isolated from 5-times-washed mitochondria according to the procedure of Schmidt-Thannhauser as modified by Fleck and Munro (1962). Sodium chloride extraction of DNA was accomplished by the method of Gibor and Izawa (1963) for DNA extraction from chloroplasts. Extractions of the KOH-digested mitochondria with sodium chloride were carried out until the extracts showed essentially no absorbance at 260 mμ. Generally, three extractions were required. The DNA was precipitated from the combined extracts with 2 volumes cold absolute alcohol overnight at −20°. The amount of DNA isolated was quantitatively determined by the method of Burton (1956) using calf thymus DNA as the reference.

TABLE I
DNA CONTENT OF WASHED LAMB HEART MITOCHONDRIA

Expt	No. of Washes	Mitochondrial Protein Obtained (mg)	DNA Content[a] (μg/100 mg mitochondrial protein)
1	5	1380	343
2	5	1641	341
3	3	3000	505
4	3	3000	440
5	5	420	450
6	5	438	338
7	5	1200	558
8	5	1200	525[b]
9 (liver mitochondria)	5	840	242

[a] Determined by Burton's method. [b] $HClO_4$ extraction of DNA after KOH digestion.

RESULTS

DNA Content of Mitochondria.—In a series of seven experiments (Table I), the DNA content of washed lamb heart mitochondria ranged between 340 and 560 μg/100 mg mitochondrial protein; protein was determined by the biuret method (Robinson and Hogden, 1940). With a few exceptions, the mitochondria were generally isolated from approximately 500 g tissue, representing 5–6 lamb hearts.

To test the completeness of the NaCl extraction and alcohol precipitation of DNA, an experiment was carried out (Table I, expt 8) in which DNA was extracted with hot 0.5 N $HClO_4$ from the material precipitated from a KOH digest of a portion of the mitochondria from experiment 7. Comparable values were noted (Table I) between the DNA content obtained in experiment 7 with that obtained in experiment 8 ($HClO_4$ extraction).

An experiment was performed to compare the DNA content of liver and heart mitochondria. DNA was extracted from rat liver mitochondria (containing 840 mg protein) obtained from 100 g tissue. Table I presents data in experiment 9 which demonstrate that one preparation of rat liver mitochondria showed a DNA content of 242 μg/100 mg mitochondrial protein. The ability of the isolated material to be precipitated with acid and to be selectively digested with pancreatic DNAase provides additional evidence that it is DNA. Brief exposure of a portion of the KOH-digested material used in experiment 8 (Table I) to crystalline pancreatic DNAase reduced its DNA content by 80%.

The polymerized nature of the DNA isolated from mitochondria by sodium chloride extraction and alcohol precipitation was demonstrated in the following manner: (1) It was nondialyzable; (2) centrifugation in a linear gradient (20–40% sucrose) showed a distribution for mitochondrial DNA which paralleled the distribution of highly polymerized calf thymus DNA run as a reference (Fig. 1).

TABLE II
EFFECT OF INHIBITORS ON [^{14}C]PHENYLALANINE INCORPORATION IN INTACT AND SONICALLY DISRUPTED MITOCHONDRIAL SYSTEMS[a]

System	Conditions		Specific Activity (c.p.m./mg protein) Experiment I	Experiment II
Intact mitochondria	Complete system		248	321
	+ Actinomycin D	(20 μg)	146	133
	+ RNAase	(10 μg)	239	301
	+ DNAase	(10 μg)	302	321
	+ DNA	(100 μg)	281	308
	+ DNA (100 μg) + actinomycin D	(20 μg)	170	
	+ Chloramphenicol	(10 μg)		138
3-hour 105,000 × *g* supernatant fluid	Complete		393	
	+ Actinomycin D	(20 μg)	297	
	+ RNAase	(10 μg)	254	
	+ DNAase	(10 μg)	253	
	+ Puromycin	(10 μg)	294	
	− s-RNA		267	
	+ DNA (100 μg) + actinomycin D	(20 μg)	381	

[a] The reaction mixture consisted of the following additions: liver s-RNA (100 μg), α-ketoglutaric acid (5.0 μmoles), ADP (0.6 μmole), AMP (0.6 μmole), KH_2PO_4 (15 μmoles), $MgCl_2$ (final concentration in all samples, 0.01 M), EDTA (final concentration in samples, 0.008 M), KCl (50 μmoles), Tris buffer, *p*H 7.4 (45 μmoles), uniformly labeled L-[^{14}C]phenylalanine (0.04 μmole containing 1.5 × 10^5 cpm), and either 0.1 ml intact mitochondria (containing 2 mg protein) or 0.5 ml supernatant fluid (containing approximately 0.5 mg protein) in a final volume of 1.0 ml, *p*H 7.4. Incubated 1 hour at 37°.

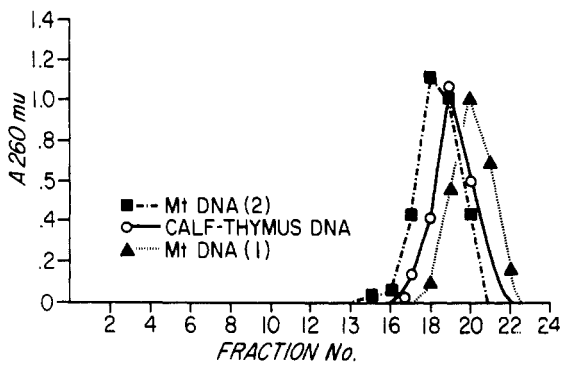

FIG. 1.—Sucrose-density-gradient centrifugation of mitochondrial and calf thymus DNA. DNA (100 μg), isolated from heart mitochondria, was layered on a linear sucrose gradient (20–40%) and was centrifuged in the Spinco SW-39 rotor at 39,000 rpm for 4 hours and the brake was not applied. A similar amount of highly polymerized calf thymus DNA was run as a reference. Fractions (6-drop) from the gradient were collected by hand by puncturing the bottom of the centrifuge tube. Before determining the extinction of the fractions each was made up to a final volume of 1 ml. Absorbance at 260 mμ was measured using a Zeiss PMQII spectrophotometer.

Role of DNA in Mitochondrial Protein Synthesis.—The ability of intact mitochondria from plants, microorganisms, and a variety of animal tissues to carry out the energy-dependent *in vitro* incorporation of radioactive amino acids has been well documented (consult the review article by Simpson (1962) for references to the many excellent papers on amino acid incorporation in mitochondria). In every case, the incorporating activity of intact mitochondria was found to be insensitive to RNAase. In 1959, Kalf and Simpson presented evidence which indicated that the ability of intact calf heart mitochondria to incorporate labeled amino acids was not impaired by treatment with sonic vibration for short periods of time in the presence of Mg^{2+}; the incorporating activity was found to be the property of a supernatant system derived from disrupted mitochondria by centrifugation at 105,000 × *g* for 4–8 hours. The incorporating activity of this sytem is energy-dependent, heat-labile, and inhibited by the usual inhibitors of protein synthesis. Furthermore, the labeled amino acid has been found to be in peptide linkage (Kalf and Simpson, 1959). In contrast to intact mitochondria, it was noted that the 105,000 × *g* incorporating system was inhibited 76% by low levels of RNAase in a system that was not preincubated with the enzyme. Data obtained in subsequent experiments and presented in Table II demonstrate that *DNAase* also inhibits incorporation by the 105,000 × *g* system, but is ineffective in the case of intact mitochondria. Figure 2 presents the relationship between incorporation in the 105,000 × *g* system and the concentration of these nucleases and shows increased reduction of incorporation with increasing concentration of enzyme.

The ability of DNAase and RNAase to suppress mitochondrial incorporation suggested that a DNA-dependent RNA polymerase might possibly be functioning in mitochondria. To test this hypothesis, the effect of a specific inhibitor of DNA-dependent RNA polymerases, actinomycin D (Reich *et al.*, 1961; Hurwitz and August, 1963), on mitochondrial incorporation was studied. It is apparent from Figure 3 that actinomycin D penetrates the mitochondrion and suppresses the incorporation of several amino acids. For example, increased amounts of actinomycin D showed increased reduction of incorporation of [^{14}C]leucine and at a concentration of 10^{-4} M incorporation was suppressed 87%. The relative lack of inhibition of phenylalanine incorporation by actinomycin D in contrast to the strong effect on leucine and proline (Fig. 3) might be explained by the fact that the phenylalanine samples were inadvertently not preincubated with the antibiotic before the addition of the isotope. Subsequent experiments in which preincubation was carried out show inhibitory effects more closely related to those observed for leucine or proline. The control samples in this experiment showed an incorporation of 0.1 mμmole [^{14}C]leucine/mg protein. Actinomycin D also inhibited the incorporating activity of the 105,000 × *g* supernatant system (Table II). It is also evident from Table II that the addition of a 5-fold excess of calf thymus DNA to a sample simultaneously treated with actinomycin caused a partial reversal of the inhibition

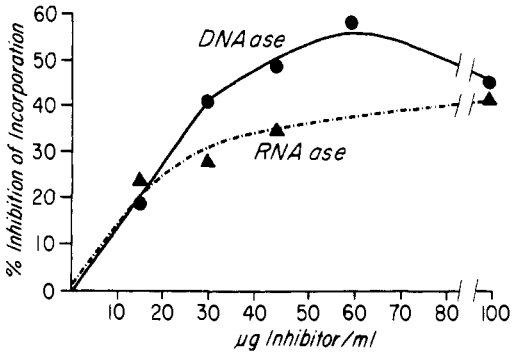

FIG. 2.—Inhibition of incorporation in the 105,000 g supernatant system by DNAse and RNAase. The reaction mixture is as described in the legend to Table II.

TABLE III
EFFECT OF ACTINOMYCIN D ON [^{14}C]-ATP INCORPORATION BY LAMB HEART MITOCHONDRIA[a]

System	Specific Activity (cpm/mg protein + nucleic acid)
Complete system	188
+ actinomycin D (20 µg)	34

[a] The reaction mixture was as described in the legend to Table II. The disodium salt of crystalline [8-^{14}C]-ATP was added in a concentration of 0.05 µmole containing 237,000 cpm. At the termination of the incubation the protein was treated as before, except that the extraction with trichloroacetic acid at 90° for 15 minutes was omitted.

of incorporation in the case of intact mitochondria and a virtually complete reversal in the 105,000 × g supernatant system.

More direct evidence for the presence of RNA polymerase was obtained from experiments in which [8-^{14}C]-ATP was incubated with intact mitochondria in the presence and absence of 10^{-3} M actinomycin D. The results of a typical experiment are presented in Table III and demonstrate that intact mitochondria have the capacity to incorporate [^{14}C]-ATP and that this incorporation is suppressed 82% by actinomycin D.

DISCUSSION

The results of these studies provide evidence for the presence of DNA in lamb heart mitochondria and for its role in protein synthesis. The hazards of contamination of mitochondrial preparations with nuclear DNA when gross cell homogenates are being fractionated is recognized. However, this DNA does not appear to be merely the result of absorption of nuclear material to the mitochondria since: (1) Repeated washing did not appear to decrease the DNA content appreciably. For example, in one such preliminary experiment three-times-washed mitochondria showed a DNA content of 480 µg/100 mg of mitochondrial protein, whereas a portion of these mitochondria carried through two additional washes showed a DNA content of 450 µg/mg of mitochondrial protein (expt 5, Table I) at each of the washing steps. (2) No release of material absorbing at 260 mµ was noted when washed mitochondria, isolated from a homogenate to which a large excess of highly polymerized calf thymus DNA had been added, were incubated with pancreatic DNAase under optimal conditions. In one such experiment 223 mg of mitochondrial protein was isolated from a homogenate to which 1.5 mg DNA had been added, and was

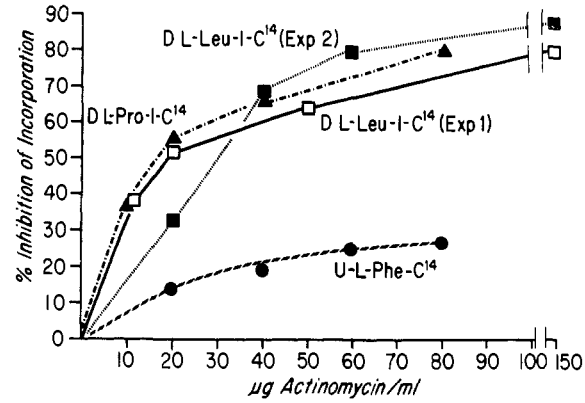

FIG. 3.—The effect of actinomycin D concentration on amino acid incorporation by intact mitochondria. The reaction mixture was as described in the legend to Table II. The concentration of radioactive amino acid added was calculated on the basis of the L isomer and was added in a concentration of 0.04 µmole, each L-amino acid containing approximately 150,000 cpm. In all but the phenylalanine experiment the system was preincubated with the antibiotic for 10 minutes before the addition of the labeled amino acid.

washed three times. After the third wash the mitochondria were drained well, homogenized in the sucrose-Versene medium, and made up to a final volume of 15 ml. Mitochondrial suspension containing 5 mg protein was incubated in Tris buffer with pancreatic DNAase under optimal conditions at 37° for 1 hour in a total volume of 1 ml. The reaction was stopped with $HClO_4$, and after chilling for 15 minutes the tubes were centrifuged and the absorbance of the supernatant fluid was measured at 260 mµ. The supernatant fluid obtained from the incubation in the absence of DNAase showed an absorbance of 0.31, whereas that incubated in the presence of DNAase (50 µg/ml) showed an absorbance of 0.34. A control sample to which 5 µg of calf thymus DNA had been added in addition to DNAase showed an absorbance of 0.45.

The results stated above *do not* eliminate the possibility that nuclear DNA might have penetrated inside the mitochondria during the blending procedure. However, a role for such DNA in mitochondrial protein synthesis might not be anticipated. A different type of evidence to support the view that the DNA is actually contained within the mitochondria per se is available from data pertaining to actinomycin inhibition of incorporation of labeled amino acids into protein and of [^{14}C]ATP into RNA by both intact and disrupted mitochondria; more important is the fact that DNAase suppressed incorporation *only* after the mitochondria were disrupted (Table II). Furthermore, contamination by nuclei can be ruled out since contaminating nuclei could reasonably be expected to incorporate amino acids to some extent under these incubation conditions. The incorporation, however, should show an inhibition in the presence of DNAase which inhibits nuclear incorporation (Allfrey *et al.*, 1957). No such inhibition is evident from the data in Table II.

As observed in the electron microscope the quantity of mitochondrial fibers with DNA characteristics appears to vary with different tissues (Nass and Nass, 1963a,b). By way of confirmation, we have found the amount of DNA in rat liver mitochondria (expt 9, Table I) to be somewhat lower than heart mitochondria (Table I). The DNA content of yeast mitochondria, 155–400 µg/100 mg protein (Schatz *et al.*, 1964), is comparable to heart and liver in experiments reported here (Table I).

The inhibitory effect of both DNAase and RNAase on amino acid incorporation by the 105,000 × *g* supernatant system suggested the possibility that the synthesis of messenger RNA which is mediated by a DNA-dependent RNA polymerase (Weiss, 1960; Stevens, 1960; Hurwitz *et al.*, 1961) might be occurring in this system. RNA polymerase is selectively inhibited by the polypeptide antibiotic, actinomycin D (Reich *et al.*, 1961; Hurwitz and August, 1963) as a result of the ability of the drug to bind DNA (Nakata *et al.*, 1961; Goldberg and Rabinowitz, 1962). Therefore it was of interest that actinomycin D suppressed incorporation in both intact and disrupted mitochondria (Fig. 3 and Table II). In our experiments, the addition of a 5-fold excess of calf thymus DNA simultaneously with actinomycin D partially reversed the inhibition in intact mitochondria and completely reversed it in the disrupted system (Table II). As a more direct test for the presence of RNA polymerase, [^{14}C]-ATP was incubated under optimal conditions for amino acid incorporation; Table III shows that the ATP was incorporated and that this incorporation was virtually completely inhibited by actinomycin D.

Although the extent of the inhibition by DNAase and actinomycin D is not large (Table II), Figures 2 and 3 show that much higher inhibition can be obtained using higher levels of the inhibitors. These facts might be explained on the basis of the stability of the m-RNA in the mitochondria. Work on systems obtained from bacteria has indicated that the m-RNA turns over very rapidly (Levinthal *et al.*, 1962) and that in these systems preincubation with inhibitors from 30–40 minutes results in a good inhibitory effect. On the other hand, Guidice and Novelli (1963) found that actinomycin D had little effect on total amino acid incorporation into regenerating liver, although the antibiotic interfered with the synthesis of a new enzyme. Similarly, messenger RNA in the reticulocyte appears to be stable throughout the entire protein-synthesizing period of the cell (Nathans *et al.*, 1962; Marks *et al.*, 1962). More recently, Revel and Hiatt (1964) have demonstrated that levels of actinomycin D which inhibit labeling of rat liver RNA have no effect on cytoplasmic amino acid incorporation *in vivo* or *in vitro*, or on the stimulatory activity of purified microsomal RNA in an *in vitro* amino acid–incorporating system. The data in Tables II and III demonstrate that actinomycin D, at a concentration of 20 μg/ml, inhibited amino acid incorporation only on the average of 40% (Table I, expt 1). The same amount of antibiotic was capable of inhibiting ATP incorporation into RNA by 82% (Table III). These facts suggest that the high amounts of inhibitors required for substantial inhibition might reflect the stability of mitochondrial m-RNA.

The involvement of soluble RNA, also believed to be synthesized by RNA polymerase (Franklin, 1963), in amino acid incorporation in mitochondria can be seen from the decreased incorporation when s-RNA is omitted from the 105,000 × *g* supernatant system (Table II).

The detection of a small amount of DNA in mitochondria attests to the fact that extranuclear DNA appears to be in all those cytoplasmic particles which have been suggested to be capable of "self-duplication" (see Nass and Nass, 1963b for references on "self-duplication" of cytoplasmic particles). In this connection, the presence of a DNA polymerase in mitochondria would be of considerable interest and an answer to this question awaits the results of experiments now in progress.

Acknowledgment

The excellent technical assistance of Mary Ann Gréce and Kathleen Ruf is gratefully acknowledged.

Added in Proof

Since the submission of this manuscript, Wintersberger (DNA-abhängige RNA-Synthese in Rattenleber-Mitochondrien, *Z. Physiol. Chem. 336*, 285 [1964]) has demonstrated an inhibition of incorporation of labeled uridine into the RNA of rat liver mitochondria by actinomycin D.

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