
Robert E. Shank Papers

Folder title:

Science reviews, 1970-1975.

Identifier:

FC034-S25-B109-F13

SCIENCE

SENT 7/1/75

BARAONA, E.; et al.

Alcoholic Hepatomegaly: Accumulation of Protein in the Liver

This paper provides evidence of accumulation of protein in the livers of alcohol fed rats. This is an important new concept.

The reader is presented with a difficult problem in assessing the data, however. The authors should indicate the values recorded ± after means. These could be standard deviations or standard errors. Moreover, the tests used for significance of differences should be stated.

XX

X

X

Although I hope that this paper will be published, the author should be asked to indicate the statistical expressions and terms used. If means are given with standard errors, the likelihood of significance at the 0.01 level are small for data as in line 9, page 5.

SCIENCE - Reviews

SCIENCE

Author HASUMURA, Y. ET.AL.

Title Acetaldehyde Oxidation by Hepatic Mitochondria: Its Decrease After Chronic Ethanol Consumption

Comments:

This is a paper of significant interest. It has been improved by the amendations suggested by the reviewers. The data provided concerning mean caloric intake could be more effectively interpreted by the reader if the age or body size of the rats had been given. To illustrate - the calorie requirement of the 44 day old female rat is of the order of 460 Kcal/Kg body weight daily, while that for the 96 day old female rat is 280 Kcal/Kg. body weight. The authors record intake of 299 Kcal/Kg.R Recording of weight gains of the two groups of animals would have been helpful.

(Continue on additional sheet if necessary)

Overall Evaluation

- ☐ Excellent, merits rapid publication
- ☒ Publish if space is available
- ☐ Belongs in a specialty journal
- ☐ Should not be published anywhere

If you recommend publication in Science, please check one or more of the following:

- ☐ Opens a new and significant area of research
- ☐ In an established field, rates in the upper tenth with respect to significance
- ☐ Has broad appeal to non-specialists
- ☒ Is important to specialists in three or more disciplines, namely

Biochemistry Nutrition Clinical Medicin

Confidential Comments:

This paper has been hurriedly prepared. It comes from a well established laboratory in this field and therefore ishhardly representative of the quality of investigation to be expected from this group.

Advisor's Name

Date MARCH 17, 1975

SCIENCE AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE
1515 MASSACHUSETTS AVENUE, NW, WASHINGTON, D C 20005 • 202-467 4440

INSTRUCTIONS FOR REVIEWERS - REPORTS

An unpublished manuscript is a privileged document. Protect it from any form of exploitation. It is unethical to use the information for the advancement of your own research. It is unethical to copy it or discuss it with others unless specific authorization has been obtained. Do not cite the manuscript or refer to the work it describes before it is published.

If you believe that you cannot judge a given paper impartially, please return it immediately to the editorial office with this explanation.

Criteria for judgment. We want to publish highly significant, technically sound papers. A paper should have news value for the scientific community, unusual interest to the specialist, or broad interest as an interdisciplinary problem.

Your recommendation. Because of space limitations, we can accept less than one-fifth of the papers submitted. Most of the papers meet the usual standards for specific experimentation. Hence we must be particularly selective. Since our rejection rate must be held at about 80%, many publishable papers must be declined. It is best if you do not make any specific statement about the acceptability of a paper in your comments for transmission to the author. To aid us in our selection, please indicate your overall evaluation in the appropriate space below.

____ Excellent and exciting, merits rapid publication.
XX Above average, publish if space is available.
____ Belongs in a more specialized journal.
____ Mediocre or poor, should not be published in Science.

If you recommend publication in Science, please check one or more of the following:

____ Opens a new and significant area of research.
XX In an established field, rates in the upper: ____ 1% ____ 5% ____ 10% X 20% with respect to significance. Evaluation based on a comparison with papers in first-rate primary journals, namely:

Proc.Soc. Exp.Biol.&Med. J.Clin.Invest. J.of Nutrition

____ Provides important information of broad interest to the scientific community.
____ Is important to specialists in three or more disciplines, namely:

Biochem. 1(2)3 Nutrition 1(2)3 Clin. Med. 1 2(3)

Indicate the breadth of interest within the discipline by circling the appropraite number. 1 = Nearly all workers will be interested. 2 = 25 to 75 percent will be interested. 3 = Just a few will be interested.

Organization and writing. Our audience consists of scientists in all fields, and all of them are busy. Papers should be organized so that the news comes first, supporting details second. They should be free of specialized jargon, shorthand expressions, and trivial details.

Significance. Has the author made the significance of his work obvious or is specialized knowledge required to understand the significance? One of the most useful functions a reviewer can serve is to suggest effective means of highlighting important ideas.

Report form. A report form is enclosed. Comments to be sent to the author should appear above the perforation; advice and confidential remarks addressed to the editor should appear below the perforation. Please retain the yellow copy for your files.

IT WOULD BE HELPFUL IF YOU CAN RETURN THE PAPER, ALONG WITH YOUR REVIEW AND THIS FORM. WITHIN 1 WEEK. IF YOU ARE UNABLE TO COMPLETE YOUR REVIEW IN THIS TIME, PLEASE TELEPHONE COLLECT. AREA CODE 202 467-4440.

Acetaldehyde Oxidation by Hepatic Mitochondria: Its Decrease After Chronic Ethanol Consumption

Abstract. Prolonged consumption of ethanol significantly reduces the capacity of rat liver mitochondria to oxidize acetaldehyde. This is associated with decreased mitochondrial respiration with acetaldehyde as substrate. The reduced ability of mitochondria to metabolize acetaldehyde may explain the high blood acetaldehyde levels in alcoholics which in turn could promote the perpetuation of liver injury.

Acetaldehyde, the first product of ethanol oxidation in the liver, has been incriminated in the development of ethanol dependence based on the findings that acetaldehyde competitively inhibits the oxidation of other aldehydes, resulting in the formation of biologically active alkaloid derivatives (1). Acetaldehyde is also considered a possible cause for the cardiotoxic (2) and hepatotoxic (3) complications of alcoholism. The significance of this mechanism has been recently enhanced by the observation that alcoholics display significantly higher blood levels of acetaldehyde than non-alcoholics given the same dose of ethanol (4), but the cause for this difference is unknown. Since acetaldehyde is metabolized by hepatic mitochondria in a nicotinamide adenine dinucleotide (NAD) dependent process (5), and since chronic ethanol consumption primarily impairs the ability of hepatic mitochondria to reoxidize NADH (3), we wondered whether the mitochondrial damage caused by prolonged intake of ethanol might result in a reduced capacity to metabolize acetaldehyde. It was reported, however, that chronic consumption of ethanol in animals did not change (6) or even increased (7) the activity of hepatic NAD-dependent aldehyde dehydrogenase. Therefore, we compared the effects of chronic ethanol feeding on both the capacity of intact mitochondria to oxidize acetaldehyde and the activity of aldehyde dehydrogenase in disrupted mitochondria.

Female Sprague-Dawley rat littermates were pair-fed nutritionally adequate liquid diets with 36 percent of the total calories as ethanol or isocaloric carbohydrates (8). After 4-5 weeks, liver mitochondria were obtained as described (3), and the capacity of mitochondria to oxidize acetaldehyde was determined by acetaldehyde disappearance as follows: intact mitochondria (0.5 mg protein per 25 ml flask) were incubated with 60 μM acetaldehyde in a buffer consisting of 0.3 M mannitol, 75 mM sucrose, 10 mM magnesium chloride, 10 mM potassium phosphate (pH 7.4), 0.5 mM

ethylenediaminetetraacetic acid and 10 mM potassium chloride, in a final incubation volume of 0. 5 ml. Following the addition of acetaldehyde to the system, the flask was closed and incubated with shaking (120 strokes per minute) for 0, 3 and 6 minutes at 37°C. The reaction was stopped by the addition of 0. 1 ml of perchloric acid in a final concentration of 0. 3 M. Acetaldehyde was measured with a Perkin-Elmer F-40 Gas-Liquid Chromatography (4). Mitochondrial respiration was assayed polarographically by determining oxygen consumption with a Clark oxygen electrode. The reaction was initiated at 30°C by the addition of acetaldehyde in a final concentration of 60 μM and 10μl of 0. 1M adenine 5'-diphosphate to a reaction mixture (2. 5 ml) containing intact mitochondria (equivalent to 3 mg protein) and the buffer described above. Mitochondrial NAD-dependent aldehyde dehydrogenase was assayed in a system containing an excess of NAD (0. 5 mM) and sodium deoxycholate for disruption of mitochondrial membranes (9). Mitochondrial glutamate dehydrogenase was also measured (9). Each measurement was carried out at least in duplicate. The results were compared to the corresponding values obtained in the pair-fed control littermates, the means (±SEM) and individual differences were calculated, and their significances were assessed by the paired Student t test.

As shown in Table 1, chronic ethanol consumption resulted in a significant reduction of the rate of acetaldehyde metabolism by intact rat liver mitochondria. This was associated with decreased mitochondrial respiration with acetaldehyde as substrate (11. 7 ±1. 2 nanoatoms O_2 consumed per minute per mg of mitochondrial protein in controls vs 8. 1±0. 5 in ethanol-treated animals, six pairs, $p<0.02$). The observed reduction of acetaldehyde metabolism can be ascribed, at least in part, to the decreased ability of NADH reoxidation in mitochondria of ethanol-fed animals, since prolonged intake of ethanol causes an impairment of the energy coupling site I of the

mitochondrial respiratory chain (3), the level of NAD-linked dehydrogenases. Indeed, the addition of fatty acids and other substrates for NAD-linked dehydrogenases in mitochondrial respiration did decrease the rate of acetaldehyde oxidation (Table 1), probably by competing with the substrates for NAD. It is noteworthy, however, that even in the presence of those substrates, acetaldehyde was again less metabolized in the mitochondria of ethanol-treated rats than in the controls (Table 1). By contrast, in disrupted mitochondria supplied with NAD, the activity of NAD-dependent aldehyde dehydrogenase (expressed as nanomoles NADH produced per minute per mg of mitochondrial protein) was found to be higher in ethanol-fed rats (37. 1 ± 1. 7) than in controls(32. 4±1. 6) (eight pairs, $p<0.02$). Conversely, the activity of glutamate dehydrogenase remained unchanged (1. 63±0. 07 micromoles NADH oxidized per minute per mg of mitochondrial protein in controls vs 1. 76±0. 07 in ethanol-treated animals, eleven pairs). The discrepancy between the rate of acetaldehyde oxidation in intact mitochondria and the enzyme activity in disrupted organelles suggests that the rate-limiting step of acetaldehyde metabolism is the ability of mitochondria to reoxidize NADH rather than the activity of aldehyde dehydrogenase. The recent observation that 2, 4-dinitrophenol, an uncoupler of oxidative phosphorylation in mitochondria, accelerated acetaldehyde metabolism in the perfused rat liver (10) supports the proposed mechanism.

The reduction of acetaldehyde metabolism observed in rats fed ethanol chronically might result in the accumulation of acetaldehyde in the liver as well as in the blood if the production rate of acetaldehyde is unchanged or increased. Indeed, recent human studies revealed that acetaldehyde levels in blood after the same dose of ethanol were significantly higher in alcoholics than in non-alcoholics, although there was

no difference in ethanol disappearance rates between these two groups (4). Since acetaldehyde itself has an inhibitory effect on mitochondrial respiration, especially in the segment of the electron transport chain prior to the NADH-ubiquinone oxidoreductase (11), it is possible that the enhanced acetaldehyde levels observed in alcoholics may contribute to the mitochondrial damage commonly found after chronic ethanol consumption. Indeed, it was reported that there are similarities between the effects of prolonged ethanol intake on liver mitochondria and the effects of acetaldehyde (3).

These results suggest the existence of a "vicious cycle" shown in Fig. 1: Elevated blood acetaldehyde resulting from enhanced ethanol metabolism (12) and/or decreased disposition (Table 1) may impair mitochondrial functions including the capacity of mitochondria to oxidize acetaldehyde. This in turn will elevate acetaldehyde blood levels even further, which may then perpetuate injury not only in the liver, but possibly also in the heart and brain.

Yasushi Hasumura
Rolf Teschke
Charles S. Lieber
Section of Liver Disease and Nutrition,
Veterans Administration Hospital
Bronx, New York, 10468 and
Department of Medicine,
Mount Sinai School of Medicine
of City University of New York, New York

References and Notes

1. V. E. Davis, M. J. Walsh, Y. Yamanaka, J. Pharmacol. Exp. Ther. 174, 401 (1970).

2. S. S. Schreiber, M. Oratz, M. A. Rothschild, F. Reff, C. Evans, J. Molec. Cell Cardiol. 6, 207 (1974).

3. A. I. Cederbaum, C. S. Lieber, E. Rubin, Arch. Biochem. Biophys. 165, 560 (1974).

4. M. A. Korsten, S. Matsuzaki, L. Feinman, C. S. Lieber, New Eng. J. Med. 292, 386 (1975).

5. L. Marjanen, Biochem, J. 127, 633 (1972);N. Grunnet, Eur. J. Biochem. 35, 236 (1973); R. Parrilla, K. Ohkawa, K. O. Lindros, U. P. Zimmerman, K. Kobayashi, J. R. Williamson, J. Biol. Chem. 249, 15 (1974).

6. G. Redmond, and G. Cohen, Science, 171, 387 (1971); N. H. Raskin, and L. Sokoloff, Nature, 236, 138 (1972).

7. R. M. Dajani, J. Danielski, J. M. Orten, J. Nutr. 80, 196 (1963); A. A. Horton, Biochim. Biophys. Acta, 253, 514 (1971).

8. The technique of pair-feeding described by L. M. DeCarli and C. S. Lieber, J. Nutr. 91, 331 (1967) was used in the present study. The composition of the ethanol and control diets was as follows: casein (supplemented with methionine 0. 3 mg/kcal, and cystine 0. 5 mg/kcal), 18 % of the total calories; fat, 35% of total calories; adequate vitamins and minerals; and in the control diet, carbohydrate, 47% of the total calories. In the ethanol formula, carbohydrate was isocalorically replaced to the extent of 36% of the total calories. The daily food intake (expressed as calories per kg of body weight) was same in controls (299±7) and in ethanol-treated animals (299±9)(eleven pairs).

9. The methods of S. O. C. Tottmar, H. Pettersson, K. -H. Kiessling, Biochem. J. 135, 577 (1973), were used for assays of the enzyme activity. To solubilize NAD-dependent aldehyde dehydrogenase from mitochondria, sonication, freezing and thawing and treatment with detergent (sodium deoxycholate) were found to be equally effective. In the present study, sodium deoxycholate was chosen because it gave clear solutions for spectrophotometric assay.

10. C. J. P. Eriksson, K. O. Lindros, O. A. Forsander, Biochem. Pharmacol. 23, 2193 (1974).

11. A. I. Cederbaum, C. S. Lieber, E. Rubin, Arch. Biochem. Biophys. 161, 26 (1974).

12. P. S. Misra, A. Lefevre, H. Ishii, E. Rubin, C. S. Lieber, Amer. J. Med. 51, 346 (1971).

13. We thank Miss G. Marcus for her excellent technical assistance. This work was supported in part by USPHS grants AA 00224, AM 12511 and the Veterans Administration (Project No. 5251-02).

Fig. 1 Possible relationship between ethanol consumption, altered acetaldehyde levels and mitochondrial impairment.

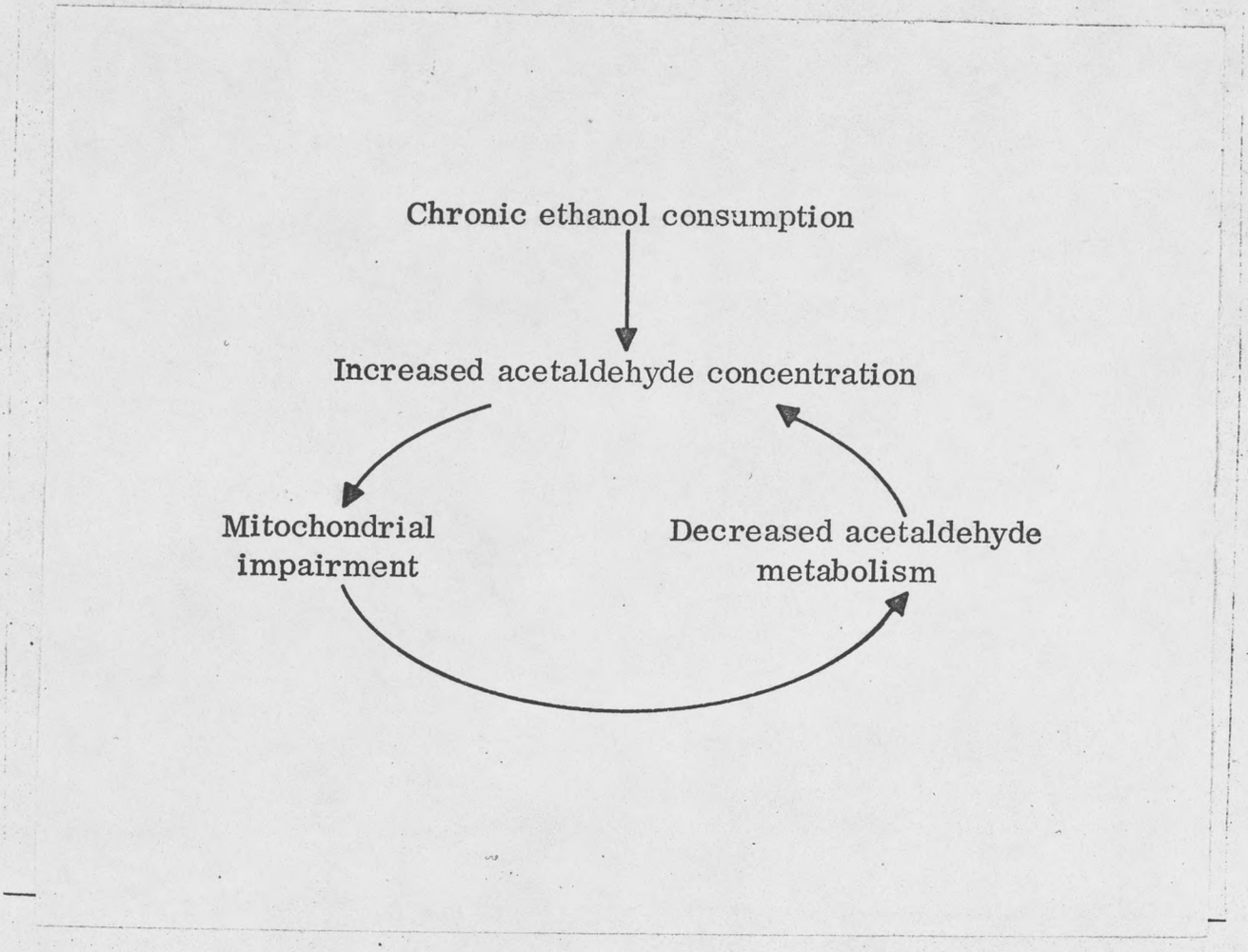
Chronic ethanol consumption
Increased acetaldehyde concentration
Mitochondrial impairment
Decreased acetaldehyde metabolism

Figure 1.

Table 1. Effect of chronic ethanol feeding on acetaldehyde oxidation.

Isolated liver mitochondria obtained from 11 pairs of rats fed ethanol (36% of total calories) or isocaloric carbohydrate were incubated with various substrates. The rate of acetaldehyde disappearance was measured by gas-liquid chromatography and expressed as nmoles acetaldehyde oxidized per minute per mg protein (± standard error of the means).

Substrate	Control	Ethanol	P
Acetaldehyde (60 μM)	14.6±0.7	11.8±0.8	<0.02
" + α-Ketoglutarate (10mM)	5.5±0.9	4.2 ±0.8	<0.01
" + β-Hydroxybutyrate (10mM)	10.2±1.3	7.1±0.8	<0.02
" + Palmytoyl CoA (15μM) + Carnitine (3mM)	8.8±0.5	7.6±0.4	<0.01

SCIENCE AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE
1515 MASSACHUSETTS AVENUE, NW, WASHINGTON, D.C. 20005 • 202—467-4350

11 March 1975

Dr. Robert E. Shank
Department of Preventive Medicine
Washington University Medical School
4566 Scott Avenue
St. Louis, Missouri 63110

Dear Dr. Shank:

Recently you were kind enough to referee an earlier draft of the enclosed paper by Dr. Hasumura ET.AL. on "Acetaldehyde Oxidation by Hepatic Mitochondria: Its Decrease After Chronic Ethanol Consumption." Will you please let me know whether the substance of your criticism has now been met?

Also enclosed are a new set of referee forms, a copy of the author's letter of transmittal, and a copy of your own earlier comments.

Sincerely,

John E. Ringle
Assistant Editor

JER/tt
Encls.

MOUNT SINAI SCHOOL OF MEDICINE
of The City University of New York
FIFTH AVENUE AND 100TH STREET · NEW YORK, N.Y. 10029

Please address reply to:
VETERANS ADMINISTRATION HOSPITAL
130 West Kingsbridge Road
Bronx, New York 10468

Section of Liver Disease
and Nutrition

March 5, 1975

REV: 10 MAR 75

Dr. John E. Ringle
Assistant Editor of Science
1515 Massachusetts Ave., NW.
Washington, DC 20005

Dear Dr. Ringle:

Thank you very much for your letter of February 12, 1975 and the comments concerning the paper by Drs. Hasumura, Teschke and myself entitled "Acetaldehyde oxidation by hepatic mitochondria: Its decrease after chronic ethanol consumption". Enclosed, I am returning the manuscript which has been revised to take into account all the suggestions made by reviewers, as indicated in the point by point reply. We hope that the paper is now acceptable for publication.

Sincerely yours,

C. S. Lieber

Charles S. Lieber, M. D.
Professor of Medicine

Enc. : Revised manuscript
Point by point reply to the reviewers' comments
CSL:nh

5 1/2 pp.
1 tbl.
1 fig.
2 x each.

Answer to Reviewer II

1) In the first version of the paper, it was stated that we used nutritionally adequate liquid diets (p. 3, line 19-21). In the revised version, we now give details of the composition of diets (reference 8). In addition, we have added the data of daily caloric intake in each group; these clearly show that ethanol-treated animals were not subjected to nutrient deficiency.

2) We now give the data of mitochondrial respiration assayed polarographically in a system containing 0. 4 mM ADP with acetaldehyde as substrate. In this stimulated state of mitochondrial respiration, again significantly less oxygen consumption was observed in the mitochondria of ethanol-fed rats than in controls.

3) To solubilize mitochondrial NAD-dependent aldehyde dehydrogenase, sodium deoxycholate was found to be as effective as sonication and freezing and thawing. This was also reported by Tottmar et al. (Biochem. J. 135; 577, 1973). We have incorporated these results in reference 9 of the revised version.

SCIENCE

Author HASUMURA, Y.; et al

Title Acetaldehyde Oxidation by Hepatic Mitochondria: Its Decrease After Chronic Ethanol Consumption

Comments:

This paper purports to demonstrate that chronic consumption of ethanol by rats reduces the capacity of rat liver mitochondria to oxidize acetaldehyde. This would be an important addition to the knowledge of the metabolic effects of alcohol. Unfortunately the data provided are not convincing or sufficient to establish the validity of the claimed effect. The paper provides no information concerning food consumption or weight gain of ethanol consuming rats as compared to control animals. Therefore, the question can be asked if the deficiencies noted in mitochondrial oxidation of acetaldehyde could be due to inanition or mutrient deficit? Secondly, the incubation medium is not adequate to assure maximum oxidative capacity. Specifically, there is no addition of CoA, ATP or ADP. Any one or all of these could be rate limiting. The relatively small differences noted in oxygen consumption and in aldehyde oxidation may result from varying concentrations of these cofactors in the mitochondrial preparations from the two groups of animals.

It also would be helpful in evaluating these findings to know if the procedure of Na deoxycholate disruption of mitochondria is as effective as alternate procedures such as sonication or freezing and thawing.

(Continue on additional sheet if necessary)

Overall Evaluation

- ☐ Excellent, merits rapid publication
- ☐ Publish if space is available
- ☐ Belongs in a specialty journal
- ☒ Should not be published anywhere

If you recommend publication in Science, please check one or more of the following:

- ☐ Opens a new and significant area of research
- ☐ In an established field, rates in the upper tenth with respect to significance
- ☐ Has broad appeal to non-specialists
- ☐ Is important to specialists in three or more disciplines, namely

Confidential Comments:

The deficits described above are serious in my view. Therefore, my opinion must be that the paper should not be published in its present form. The authors should certainly, however, have opportunity to respond to the specific criticisms.

2-12-3-

E. E. B. JAN 30 1975

Advisor's Name Robert E. Shank Dr. Robert E. Shank

Date 1/28/75

Answer to Reviewer I

In keeping with the suggestion of the reviewer, we have now included the data of mitochondrial glutamate dehydrogenase activity; they were not significantly different in ethanol-treated rats and controls. These results now clearly show that "we do not have less enzymically active protein/mg protein" in mitochondria of ethanol-treated rats compared to controls.

SCIENCE

Author HASUMURA, Y.; et al

Title Acetaldehyde Oxidation by Hepatic Mitochondria: Its Decrease After Chronic Ethanol Consumption

Comments:

This paper purports to demonstrate that chronic consumption of ethanol by rats reduces the capacity of rat liver mitochondria to oxidize acetaldehyde. This would be an important addition to the knowledge of the metabolic effects of alcohol. Unfortunately the data provided are not convincing or sufficient to establish the validity of the claimed effect. The paper provides no information concerning food consumption or weight gain of ethanol consuming rats as compared to control animals. Therefore, the question can be asked if the deficiencies noted in mitochondrial oxidation of acetaldehyde could be due to inanition or nutrient deficit? Secondly, the incubation medium is not adequate to assure maximum oxidative capacity. Specifically, there is no addition of CoA, ATP or ADP. Any one or all of these could be rate limiting. The relatively small differences noted in oxygen consumption and in aldehyde oxidation may result from varying concentrations of these cofactors in the mitochondrial preparations from the two groups of animals.

It also would be helpful in evaluating these findings to know if the procedure of Na deoxycholate disruption of mitochondria is as effective as alternate procedures such as sonication or freezing and thawing.

(Continue on additional sheet if necessary)

Overall Evaluation

- ☐ Excellent, merits rapid publication
- ☐ Publish if space is available
- ☐ Belongs in a specialty journal
- ☒ Should not be published anywhere

If you recommend publication in Science, please check one or more of the following:

- ☐ Opens a new and significant area of research
- ☐ In an established field, rates in the upper tenth with respect to significance
- ☐ Has broad appeal to non-specialists
- ☐ Is important to specialists in three or more disciplines, namely

Confidential Comments:

The deficits deecribed above are serious in my view. Therefore, my opinion must be that the paper should not be published in its present form. The authors should certainly, however, have opportunity to respond to the specific criticisms.

Robert S Thanks

Advisor's Name

Jan or early Feb. 1975.

Date

SCIENCE

Author VIVIAN, T. N.; et al.

Title Liver Alcohol Dehydrogenase Activity After Stress in Rats

Comments: The investigators utilizing electroshock of rats in an acute experiment report an increase in adrenal weight, a marked decrease in liver protein content, a decrease in ADH activity of liver, and the demonstration of stomach ulcers. These are interesting observations and in large measure have not been previously reported. From the information provided, however, the validity of the data are not fully established. Important omissions are more complete description of the procedure of shocking the animals, the molar concentration of pyrophosphate buffer, NAD and ETOH utilized (p.5-second paragraph), and the units of measurement in Table I for animal weight, liver weight, adrenal weight, protein "count", ADH activity and ADH/Protein.

(Continue on additional sheet if necessary)

Overall Evaluation

- ☐ Excellent, merits rapid publication
- ☐ Publish if space is available
- ☐ Belongs in a specialty journal
- ☒ Should not be published anywhere

If you recommend publication in Science, please check one or more of the following:

- ☐ Opens a new and significant area of research
- ☐ In an established field, rates in the upper tenth with respect to significance
- ☐ Has broad appeal to non-specialists
- ☐ Is important to specialists in three or more disciplines, namely

Confidential Comments: This paper is of poor scientific quality because of the omissions listed above. To refer to "protein count" represents naivete. To record standard deviation and standard error for ADN/Protein as 0.000 is not correct and indefensible. The fact that liver protein is reduced in these experiments by more than 40% is beyond credence of this reviewer.

December 16, 1974

Advisor's Name Date

SCIENCE AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE
1515 MASSACHUSETTS AVENUE, NW, WASHINGTON, D C 20005 • 202-467 4440

INSTRUCTIONS FOR REVIEWERS - REPORTS

An unpublished manuscript is a privileged document. Protect it from any form of exploitation. It is unethical to use the information for the advancement of your own research. It is unethical to copy it or discuss it with others unless specific authorization has been obtained. Do not cite the manuscript or refer to the work it describes before it is published.

If you believe that you cannot judge a given paper impartially, please return it immediately to the editorial office with this explanation.

Criteria for judgment. We want to publish highly significant, technically sound papers. A paper should have news value for the scientific community, unusual interest to the specialist, or broad interest as an interdisciplinary problem.

Your recommendation. Because of space limitations, we can accept less than one-fifth of the papers submitted. Most of the papers meet the usual standards for specific experimentation. Hence we must be particularly selective. Since our rejection rate must be held at about 80%, many publishable papers must be declined. It is best if you do not make any specific statement about the acceptability of a paper in your comments for transmission to the author. To aid us in our selection, please indicate your overall evaluation in the appropriate space below.

_____ Excellent and exciting, merits rapid publication.
_____ Above average, publish if space is available.
_____ Belongs in a more specialized journal.
__X__ Mediocre or poor, should not be published in Science.

If you recommend publication in Science, please check one or more of the following:

_____ Opens a new and significant area of research.
_____ In an established field, rates in the upper: ____ 1% ____ 5% ____ 10% ____ 20% with respect to significance. Evaluation based on a comparison with papers in first-rate primary journals, namely:

_____ _____ _____

_____ Provides important information of broad interest to the scientific community.
_____ Is important to specialists in three or more disciplines, namely:

_____ 1 2 3 _____ 1 2 3 _____ 1 2 3

Indicate the breadth of interest within the discipline by circling the appropraite number. 1 = Nearly all workers will be interested. 2 = 25 to 75 percent will be interested. 3 = Just a few will be interested.

Organization and writing. Our audience consists of scientists in all fields, and all of them are busy. Papers should be organized so that the news comes first, supporting details second. They should be free of specialized jargon, shorthand expressions, and trivial details.

Significance. Has the author made the significance of his work obvious or is specialized knowledge required to understand the significance? One of the most useful functions a reviewer can serve is to suggest effective means of highlighting important ideas.

Report form. A report form is enclosed. Comments to be sent to the author should appear above the perforation; advice and confidential remarks addressed to the editor should appear below the perforation. Please retain the yellow copy for your files.

IT WOULD BE HELPFUL IF YOU CAN RETURN THE PAPER, ALONG WITH YOUR REVIEW AND THIS FORM, WITHIN 1 WEEK. IF YOU ARE UNABLE TO COMPLETE YOUR REVIEW IN THIS TIME, PLEASE TELEPHONE COLLECT. AREA CODE 202 467-4440.

Science

AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE

1515 MASSACHUSETTS AVENUE, NW, WASHINGTON, D. C. 20005 • 467-4400

Sent 10/16/74

October, 1974

Dear Member:

As you renew your membership in AAAS, we'd like to enlist your help in extending membership to others. Do you have friends or colleagues whom you would like to introduce to AAAS, its programs, and publications? Do you know of young faculty members or young researchers who have mastered their specialties and whose interests are beginning to broaden? If so, please take a few moments to fill out and return the membership nomination form provided on the back of this letter.

We hope that your own membership in AAAS will be rewarding in the coming year. You may wish to attend the annual meeting, scheduled for January 26-31, 1975, in New York City. Also you will soon be hearing about some new and exciting AAAS audiotape programs, available to members at substantial discounts. And, of course, your weekly issues of SCIENCE will continue to bring you the kind of in-depth treatment of major policy issues that SCIENCE is uniquely capable of providing, along with technical research reports and articles in many scientific disciplines.

A return envelope is enclosed. Why not send your renewal notice today? We thank you for your continuing interest in AAAS.

Sincerely,

Margaret Mead
President-Elect

MM:hh
Enclosure

1974 Anniversaries:

126 Years—AAAS

91 Years—Science

AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE
1515 Massachusetts Avenue, N.W.
Washington, D.C., 20005

I would like to nominate the following for membership in the AAAS:
(Please print or type)

Name_____

Address_____

_____

Nominated by_____

* * * * * * * *

Name_____

Address_____

_____

Nominated by_____

* * * * * * * *

Name_____

Address_____

_____

Nominated by_____

* * * * * * * *

Name_____

Address_____

_____

Nominated by_____

* * * * * * * *

File

SCIENCE

Author: EWING, J. A.; et al.

Title: Alcohol Susceptibility and Plasma Dopamine B-Hydroxylase Levels

Comments:

This paper concludes that DBH activity in plasma of young normal human subjects may predict the person's propensity to drink more or less of alcoholic beverages by influenceng subjective responses to alcohol. The data presented is very limited and compares responses in two groups of nine subjects with highest and lowest DBH activity in one of three trials. It is stated that the subjects performed a variety of tests of performance and subjective state during an evening of drinking. The results of one such test are described. It is based on the patient's evaluation of his feelings on a visual analogue scale. It is reported that inthree of eight parameters in the test (felt better, less sick and less drunk) persons with highest values for DBH activity felt significantly better than those with lowest values. It is then deduced that these patients would drink more. No evidence is given for this. Actually mean blood alcohol values were slightly lower in this group. Moreover, the same test of subjective feelings was not done prior to drinking. Perhaps the same differences in the groups would have existed without the influence of alcohol.

(Continue on additional sheet if necessary)

Overall Evaluation

- ☐ Excellent, merits rapid publication
- ☐ Publish if space is available
- ☐ Belongs in a specialty journal
- ☒ Should not be published anywhere

If you recommend publication in Science, please check one or more of the following:

- ☐ Opens a new and significant area of research
- ☐ In an established field, rates in the upper tenth with respect to significance
- ☐ Has broad appeal to non-specialists
- ☐ Is important to specialists in three or more disciplines, namely

_____ _____ _____

Confidential Comments:

The paper does not afford sufficient scientific data to support the conclusion or hypothesis offered. It does not merit publication, in my opinion.

Advisor's Name

Date May 3, 1974

SCIENCE

(1)

Author **JOHNSON, H. A.**

Title **Regulation of Liver Growth**

Comments: The author in his comment on the paper of Fisher et al offers an alternative explanation of the mechanism involved in stimulation of hepatic DNA synthesis. Rather than imputing humoral factors, he would simply involve work load producing cytoplasmic hypertrophy and cell division. He offers support for his point of view in the references cited.

A consideration which he avoided or did not include was the discrepant result in the liver remnant in the animal with 86% hepatectomy. The question is"why does the 14% remnant fail to respond in DNA synthesis as does the 30% remnant?" This may not be easily or fully explained but I would look upon the comment and its publication more favorably if the issue were not avoided.

(Continue on additional sheet if necessary)

Overall Evaluation

- [XX] Excellent, merits rapid publication
- [ ] Publish if space is available
- [ ] Belongs in a specialty journal
- [ ] Should not be published anywhere

If you recommend publication in Science, please check one or more of the following:

- [ ] Opens a new and significant area of research
- [XX] In an established field, rates in the upper tenth with respect to significance
- [ ] Has broad appeal to non-specialists
- [ ] Is important to specialists in three or more disciplines, namely

Confidential Comments: Although I am quite in favor of publication, I would ask the author if he would be willing to include some comment on the application of his explanation of mechanisms relative to the results recorded with 86% hepatectomy.

Robert E. Shank, M.D.

Advisor's Name

April 16, 1971

Date

SCIENCE AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE
1515 MASSACHUSETTS AVENUE, NW, WASHINGTON, D.C. 20005 • 387-7171

INSTRUCTIONS TO REVIEWERS - REPORTS

Enclosed is the paper which you agreed to review during our telephone conversation today.

Criteria for judgment. We want to publish significant, technically sound papers. A paper should have news value for the scientific community, unusual interest to the specialist, or broad interest as an interdisciplinary problem.

Organization and writing. Our audience consists of scientists in all fields, and all of them are busy. Papers should be organized so that the news comes first, supporting details second. They should be free of specialized jargon, shorthand expressions, and trivial details.

Significance. Has the author made the significance of his work obvious or is specialized knowledge required to understand the significance? One of the most useful functions a reviewer can serve is to suggest effective means of highlighting important ideas.

Length. Specific suggestions for shortening will be appreciated. The preferred length is 1 to 6 manuscript pages, with up to 2 figures and tables (roughly 1 for each 3 manuscript pages).

// Paper is longer than we prefer. Suggestions for shortening are especially appropriate.

// Paper has more tables and figures than we can handle with maximum efficiency. Which 2 are most important to the argument? Can any of the others be omitted?

Report form. A report form is enclosed. Comments to be sent to the author should appear above the perforation, confidential remarks below. Please retain the yellow copy for your files.

Your recommendation. Because of space limitations we can accept less than one-third of the papers submitted. Most of the papers meet the usual standards for scientific experimentation. Hence we must be particularly selective. To aid us in our selection please indicate your overall evaluation in the appropriate box below the perforated line on the report form.

It will be helpful if you can return the paper, along with your review, within 1 week. If you are unable to complete your review in this time, please telephone collect. Area code 202, 387-7726.

SCIENCE
1515 MASSACHUSETTS AVENUE, NW, WASHINGTON, D. C. 20005

OCT 12 1970

Thank you for your helpful comments about the paper we recently sent to you. Your cooperation is much appreciated.

Sincerely,

John E. Ringle

John E. Ringle
Assistant Editor

137th MEETING
AAAS
CHICAGO, ILLINOIS
DEC 26-31st, 1970

Dr. Robert E. Shank
Department of Preventive Medicine
Washington University Medical School
4550 Scott Avenue
St. Louis, Missouri 63110

SCIENCE

Author FISHER, B. & FISHER, E. R.

Title Evidence for a Portal Blood Factor (PBF) as the Humoral Agent in Liver Regeneration

Comments:

This is a paper of significant interest, providing evidence of a humoral factor which has a role in increasing the rate of DNA synthesis in liver after partial hepatectomy. Evidence is also brought that the origin is extra hepatic and probably from sources in the abdomen.

The paper is well organized and carefully prepared. The research design is well described and appropriate for this study.

Some question remains in this reviewer's mind about the adequacy or pertinence of a statement on page six, third paragraph, third sentence, which reads "Cross circulation of rats with intact livers slightly but significantly altered hepatic DNA activity from that observed in single normal animals." The problem is that the change is very small and is in the direction of decreased activity in the recipient rat liver. I believe that this fact should be noted by the authors. It is difficult to propose a mechanism which might account for reduction. I also wonder how "significant" this change is in biologic terms even though the Wilcoxon statistical test assigns significance.

Only one numerical value for specific activity is given in the text (first line, page 7). It cannot, therefore, be related to other values. It may, therefore, not be necessary or helpful and could be deleted.

In Figure 1 the vertical axis should indicate a break in continuous values between 20 and 50.

(Continue on additional sheet if necessary)

Overall Evaluation

- [X] Excellent, merits rapid publication
- [ ] Publish if space is available
- [ ] Belongs in a specialty journal
- [ ] Should not be published anywhere

If you recommend publication in Science, please check one or more of the following:

- [ ] Opens a new and significant area of research
- [X] In an established field, rates in the upper tenth with respect to significance
- [ ] Has broad appeal to non-specialists
- [ ] Is important to specialists in three or more disciplines, namely

_____ _____ _____

Confidential Comments:

Advisor's Name

Date September 10, 1970

June 1970

2

10M 1069 - SULLIVAN

SCIENCE

Author MALACARNE, P. & DALLAPICCOLA, B.:

Title Infectious Hepatitis: A Possible Mitogenic Factor.

Comments: This is a short and succinct paper claiming that infectious hepatitis stimulates mitosis in lymphocytes, a finding which may or may not be at variance with the paper of Mella and Long (Science 155, 80, 1967). The latter records findings in leucocytes and indicates that in the white blood cells of normal subjects 8 - 20% are found to be in metaphase. The present report records metaphase at a rate of 0.03 per million lymphocytes. These are large differences in the two cell types. The authors indicate that they have counted or scored from nine million to 62 million lymphocytes per subject. They should be asked to provide additional description of the scoring procedure. Did they in fact count and score these large numbers?

In the discussion there is reference to the fact that others have determined that the response to PHA by lymphocytes is inhibited by several viral diseases. It is not apparent that this fact is in any way related or pertinent to the observations which they describe.

(Continue on additional sheet if necessary)

Overall Evaluation

- [ ] Excellent, merits rapid publication
- [ ] Publish if space is available
- [ ] Belongs in a specialty journal
- [x] Should not be published anywhere

If you recommend publication in Science, please check one or more of the following:

- [ ] Opens a new and significant area of research
- [ ] In an established field, rates in the upper tenth with respect to significance
- [ ] Has broad appeal to non-specialists
- [ ] Is important to specialists in three or more disciplines, namely

Confidential Comments: If additional description of the methods of counting is given and cognizance is taken of possible variance with other reports, the paper may be worthy of publication.

It might be helpful to refer the paper for other evaluation to someone experienced in the methodology - possibly R. A. Good, B. Mella or D. J. Long.

Reprinted from
SCIENCE

11 February 1966, Volume 151, Number 3711

EDITORIAL CORRESPONDENCE: 1515 Massachusetts Ave., NW, Washington, D.C. 20005. Phone: 202-387-7171. Cable: Advancesci, Washington. Copies of "Instructions for Contributors" can be obtained from the editorial office. ADVERTISING CORRESPONDENCE: Rm. 1740, 11 W. 42 St., New York, N.Y. 10036. Phone: 212-PE 6-1858.

Letters to Congressmen

Congressmen have well-established methods for learning both the public reaction and the attitudes of specially interested groups on matters with which Congress and the nation have had long experience—for example, taxes, public works, and foreign affairs. They receive the recommendations of the Executive Branch and the advice of staff members and other trusted counselors; they are waylaid by lobbyists; they listen to witnesses at committee hearings; and they read newspapers and the daily mail.

Communication with Congress on scientific and technical issues must follow established patterns, for the legislative process is the same whether Congress is considering a new dam or a new accelerator, the Post Office budget or the budget of the Atomic Energy Commission. Thus on issues involving science and technology Congress gets advice through all the usual means. All, however, have their shortcomings. Sometimes, it is charged, the selection of witnesses to appear at committee hearings is biased. Congress always wants an independent appraisal of Executive recommendations. Lobbysts, almost by definition, are special pleaders. The mail may give a distorted representation of informed judgment. For example, antivivisectionists and persons who believe that research animals are often mistreated have written many letters in support of current proposals to establish federal controls over the use of animals in research and teaching, but there have been few letters about these proposals from biologists and medical researchers.

Congressmen are aware of these difficulties and recognize the need for a wide basis of advice. In order to have a source of information that is independent of the Executive Branch, Congress established the Science Policy Research Division of the Library of Congress. To supplement its other resources, Congress sometimes asks the National Academy of Sciences or other scientific bodies for advice or special studies. But the paucity of letters from scientists on matters about which they are concerned and well informed often puzzles congressmen; they ask, "Why don't we hear from the scientists on this? Aren't they interested?"

Is it worth while to write a letter to a congressman? Not always. The letter may go to a congressman who is not interested, or it may arrive at a time when there is nothing he can do about it, or it may be forgotten in the welter of other mail and other business. Congressmen get junk mail, requests for favors, and much other mail that is not germane to pending legislation. Sometimes they are flooded by letters so nearly identical as to be the obvious result of an organized campaign.

Congressmen get few letters, however, that present a carefully reasoned analysis of why a decision one way or the other would be desirable. The rarity of such letters makes them stand out from the pile of other correspondence. Letters of this kind are particularly likely to be influential if they come from someone the congressman knows, or come with an introduction by a mutual acquaintance; if they come at the time legislation is being drafted, hearings are being held, or a vote is pending; or if they go to a congressman who is serving on the appropriate committee or who has shown a personal interest in the matter at issue.

There can be no guarantee that every letter will result in the desired action. Nevertheless, it is worth while for one who has well-formulated views which he can explain clearly to write to appropriate members of Congress. This is a recognized channel of communication that congressmen understand and use. At the lowest level, the volume of mail is interpreted as a measure of interest. At a higher level, the thoughtful, cogent analysis of an issue may help to achieve a sound decision.

—DAEL WOLFLE