CLINICAL RESEARCH PROTOCOLS TO ELUCIDATE
THE POSSIBLE HAZARDS OF INCREASED
IRON ENRICHMENT OF CEREAL PRODUCTS

JANUARY 1972

PREPARED FOR

DIVISION OF NUTRITION
BUREAU OF FOODS
FOOD AND DRUG ADMINISTRATION
WASHINGTON, D.C. 20204

CONTRACT NO. FDA 71-294

LIFE SCIENCES RESEARCH OFFICE
FEDERATION OF AMERICAN SOCIETIES
FOR EXPERIMENTAL BIOLOGY
9650 Rockville Pike
Bethesda, Maryland 20014
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by

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FOREWORD

The Life Sciences Research Office (LSRO), Federation of American Societies for Experimental Biology (FASEB), provides scientific assessments of topics in the biomedical sciences. These reports are based upon comprehensive literature reviews and the opinions of knowledgeable scientists engaged in work in the field. Although LSRO reports are recognized by FASEB as contributions to societal needs and most LSRO consultants are members of FASEB constituent societies, the reports do not reflect the views of the total FASEB membership or carry the endorsement of the six constituent societies of the Federation.

These clinical research protocols were prepared for the Division of Nutrition, Bureau of Foods, Food and Drug Administration (FDA) by the staff of the Life Sciences Research Office in accordance with the provisions of FDA Contract No. 71-294.

The recommendations embodied in these suggested clinical research protocols reflect the opinions of the participants in an ad hoc review group meeting at Beaumont House, FASEB, on October 5 and 6, 1971, and other consultants. The protocols have been reviewed by these experts. However, the authors accept responsibility for the contents of the report.

A separate report will be submitted based on a comprehensive review of the significance of dietary iron on iron overload syndromes and related iron storage phenomena undertaken concurrently with the preparation of these clinical research protocols.

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SUMMARY

This report includes two protocols of clinical research designed to elucidate the possible hazards of increasing the level of iron enrichment of cereal products as proposed by the Food and Drug Administration in the Federal Register, December 3, 1971, F.R. 23074. A selected group of internationally recognized hematologists and nutrition experts developed the specific recommendations for these clinical research studies. The report summarizes the recommendations of the consultants as interpreted and evaluated by the staff of the Life Sciences Research Office (LSRO), Federation of American Societies for Experimental Biology.

Protocol A is designed to study normal individuals and those with diagnosed diseases known to affect absorption and storage of iron, to test their absorption of iron from two breads with different amounts of iron and specific radioiron labels. Protocol B employs large groups of normal adult men subjected to phlebotomy to produce mild iron-deficiency anemia and then fed three levels of iron enrichment for a number of years. Periodic studies designed to test body iron stores and iron metabolism would be made.

A comprehensive appraisal of the protocols has been made by the consultants and the staff of the LSRO. It was concluded that neither experiment would provide a direct answer to the question. However, they will supply information that is a prerequisite to a further understanding of the mechanisms regulating iron absorption and storage.
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I. BACKGROUND

The Food and Drug Administration (FDA) has proposed (Federal Register, December 3, 1971; 36 F.R. 23074) that the iron content of enriched wheat flour be increased from the present 13.0-16.5 mg to 40 mg per pound; and that of enriched bread, buns and rolls be increased from the present 8.0-12.5 mg to 25 mg per pound. This increase in the iron content of enriched flour-containing dietary items has been proposed to prevent or reduce the prevalence of iron-deficiency anemia in the population of the United States. On the other hand, the question has been raised as to possible untoward effects of the additional iron enrichment on certain individuals.

It has been suggested by some that the increased iron intake may pose some hazard for those adults who do not require additional dietary iron. Concern has been expressed for the possibility of increasing the severity of iron overload in patients with diseases involving deranged iron metabolism. (In this report, conditions characterized by all degrees of recognizable excessive iron deposition in specific body tissues are referred to as "iron overload." ) In addition, there has been speculation that the increase in dietary iron may precipitate the symptoms of iron overload in persons with latent disease. Therefore, FDA requested that LSRO study the feasibility of designing clinical research investigations that might assess the importance of these concerns.

Preliminary planning meetings with outstanding authorities on iron metabolism and the clinical aspects of iron overload syndrome established an agenda for an ad hoc review group meeting. The review group considered the feasibility of developing protocols for promising clinical research. This report summarizes the recommendations of the consultants as interpreted by the LSRO staff.
II. SCOPE OF THE STUDY

A. PLAN OF THIS STUDY

Various approaches were considered as to how to assess the effects on segments of the U.S. population of the increased level of iron in enriched flour and related products such as enriched bread, buns and rolls. There are a number of long-term biomedical studies underway in the United States that include investigations of the influence of diet on the development of disease. However, the consultants could not identify any study that would provide information relevant to this LSRO review, nor was it considered feasible to attempt to include the measurement of iron intakes and the effect on iron stores in any of the ongoing biomedical studies of large population groups.

In discussing direct experimental approaches to the problem, consultants agreed that two segments of the population should be given special consideration in relation to increased dietary iron: those afflicted with various diseases of which iron overload is a clinical feature, and adult males who may not need additional iron in their diet. Two possible clinical experiments resulted from this discussion and were outlined in detail by two of the consultants reflecting the views of the others. These are discussed below as Protocols A and B. In essence, Protocol A is designed to measure any increase in the absorption of iron over a 10-day period by individuals with deranged iron metabolism. Protocol B is designed to measure the effect of extra dietary iron on iron stores in ostensibly normal males over a long period of time.

It is believed accurate to state that the main consideration of all of the consultants was a desire for more information as to how individuals in the groups under examination would react to the modest increase in the iron content of the diet furnished by the bread which each will consume. No one was able to equate any level of increased iron absorption or iron stores with the occurrence or severity of disease. The causal relationship between high iron stores and disease states is controversial. In hemochromatosis the two occur together but proof of cause and effect is lacking. The terms "hazard" and "overload" probably had different meanings for each consultant.
B. ADDITIONAL RELATED STUDY

A second study being conducted by LSRO for FDA is a comprehensive review of iron overload, *A Review of the Significance of Dietary Iron on Iron Storage Phenomena*. This review will discuss the role of iron intake in the development of hemosiderosis, hemochromatosis, other iron storage phenomena, and their clinical significance. Factors governing iron absorption, transport, utilization, storage, and excretion in man and experimental animals will be reviewed. The normal processes and ranges of variability in iron metabolism in children, adult women and men are a part of the comprehensive review; however, the medical and public health significance of iron deficiency anemia or its prevention and therapy is not part of either of these two LSRO reports.
III. PROTOCOL A

Absorption of Iron from Enriched Bread by Persons with Abnormal versus Normal Iron Metabolism

The details of this experiment are outlined in Table A.

The aim is to compare within each subject the amount of iron absorbed from each of two breads: the first containing the present level of iron enrichment (taken here as being 10 mg/pound of bread) and labeled with $^{59}$Fe, and the second containing the proposed higher level of iron enrichment (25 mg/pound) and labeled with $^{55}$Fe.

These breads will be fed on alternate days for 10 days as components of standard meals, and 14 days later the absorption of iron from each will be estimated by the ratio of the residual radioactivity from the two isotopes in red blood cell (RBC) hemoglobin. Each subject serves as his own control inasmuch as each isotope may be quantitatively determined in the presence of the other and each represents the residual radioactivity of the iron absorbed from one of the two breads. All feces will be collected during the 24-day experimental period as a check on absorption of the two isotopes.

Except for the normal subjects included for comparison, the experiment will be carried out on patients with diseases such as hemochromatosis, Laennec's cirrhosis or various hemolytic anemias, because these involve abnormalities of iron absorption, metabolism or distribution in the tissues.
Table A. ABSORPTION OF IRON FROM ENRICHED BREAD BY PERSONS WITH ABNORMAL VERSUS NORMAL IRON METABOLISM.

DURATION OF STUDY: Indefinite (as patients become available).

SUBJECTS: Males and females, to be screened for:
- Complete blood count, RBC indices, serum iron and TIBC, liver function, fecal and menstrual blood losses.

The following groups of subjects (1–3)* will be studied:
(a) Apparently healthy (controls),
(b) Hemochromatotics – (i) untreated, (ii) partly treated by phlebotomy, (iii) completely treated by phlebotomy,
(c) With sex-linked hemolytic anemia, pyridoxine-responsive anemia, or other sideroblastic anemias,
(d) With alpha-1 cirrhosis,
(e) With thalassemia minor or intermedia,
(f) With other hereditary hemolytic anemias, spherocytosis before splenectomy, or pyruvate kinase deficiency.

DESIGN: Double isotope study using breads enriched with high ($^{55}$Fe) and low ($^{59}$Fe) levels of iron, either reduced iron or ferrous sulfate.

DIETS: Standard meals to contribute an estimated 10–15 mg/day of iron.
In addition, 2 slices/meal of bread enriched
- either with 10 mg of $^{59}$Fe-labeled iron/lb (15 µCi/µg)(low level),
- or with 25 mg of $^{59}$Fe-labeled iron/lb (30 µCi/µg)(high level).
In each case the daily dose is about 5 µCi.
During 10 consecutive days the low-level bread will be given on odd days and the high-level on even days, for a total intake of 50 µCi (3).

TESTS OF ABSORPTION: On day 24 the $^{59}$Fe and $^{55}$Fe activities of the Hb are determined (4), assuming that RBC take up 90% of the absorbed iron and that the circulating RBC amount to 30 ml/kg of body weight.
As a precaution, all feces from days 0–24 are frozen and their accumulated $^{59}$Fe and $^{55}$Fe activities are determined (4).

PROCEDURES: Control subjects (a) will be tested as above.
(b)(i) subjects will be tested initially, phlebotomized until about 5 g of iron has been removed, and retested 2 months later, (ii) subjects will be tested initially 2 months after their most recent phlebotomy, (iii) subjects will be tested initially in a slightly iron deficient state, will have no more phlebotomy until the Hb is maximal and serum iron saturation is >70%, and then will be retested.
(c) subjects with high iron stores will be treated as (b) group subjects.
(d), (e), and (f) subjects will be treated as the controls (a).

INTERPRETATION: Combined isotope values reflect total level of absorption. The ratio of the $^{59}$Fe:$^{55}$Fe values will reflect influence of the enrichment level.

* Numbers in parenthesis refer to references, p 27.
IV. PROTOCOL B

Influence of Level of Cereal Iron Enrichment on Body Iron Stores of Normal Adult Males

The details of this experiment are outlined in Table B.

The basic objective is to obtain information on how normal adult males respond to different levels of dietary iron over relatively long periods of time. It is generally held that iron-replete individuals do not absorb iron from the diet beyond their daily needs. However, the effectiveness of the physiologic mechanisms that limit accumulation of unwanted iron stores is not thoroughly understood. This may be particularly important with respect to iron replete adult males. This experiment should indicate the effect on the level of body iron of three levels of iron intake administered for a sufficient time to insure that equilibrium between iron intake and iron stores has been reached.

Diets. Three groups of 100 healthy male penitentiary inmates would be supplied with diets identical except for the amount of iron contained in bread and bakery products. The three levels of iron enrichment would be (per pound of flour): 15 mg considered to be the present level; 40 mg as proposed in the new regulations; and 90 mg or three times the proposed increase.

Preparation. Initially, each prisoner would be subjected to a weekly phlebotomy of one pint of blood until his iron stores had been depleted as evidenced by a mild iron-deficiency anemia. This procedure would accomplish two things: each subject would start the experiment with the same baseline of iron stores, and it would give a measure of the range of iron stores occurring in a population of 300 ostensibly normal males of varying ages. The total iron removed by phlebotomy can be calculated from the amount of blood drawn and its Hb content. (The iron content of Hb is 0.35 per cent; in a normal male with 15 g Hb per 100 ml blood, 1 ml blood contains 0.5 mg iron.)

Efficacy of Iron Intakes. As the first measure of the efficacy of the three levels of iron enrichment, about 20 subjects from each of the three groups will be examined at monthly intervals to determine the rate of repair of the iron-deficiency anemia induced by the initial course of phlebotomies. Ten ml of heparinized blood would permit the determination of hematocrit, transferrin saturation, and RBC protoporphyrin.
The taking of these monthly samples would be discontinued when all three of these indices had returned to normal values in the subjects from the three groups.

**Measurement of Iron Stores.** The most important determination in this experiment is the build-up of iron stores as influenced by the different levels of iron enrichment. It is proposed that every 12 to 18 months during the study, 6 to 10 individuals be removed from each group (and from the experiment) and subjected to a repeat course of weekly phlebotomies as described above. This procedure would provide a direct measure of the iron stores which accumulated from the start of the experiment. Both the number of subjects and the intervals at which they are removed would be determined by the uniformity and rate of change in iron stores observed in preceding subgroups. The whole study could be terminated when the subjects on the highest level of iron intake showed no further increase in iron stores on three successive examinations, over a period of 24 to 36 months.

**Mechanism of the Regulation of Body Iron Stores.** Because it is reasonable to expect some degree of regulation of body iron stores with varying levels of dietary iron intake, it is suggested that useful information could be obtained from this experiment as to the mechanisms of this regulation. To determine to what extent this regulation is the result of variation in absorption and in excretion of iron, all subjects would be given an intravenous injection of 100 μCi of $^{55}$Fe as ferric citrate bound to 20 ml of homologous serum at the completion of the initial course of phlebotomies. The specific activity of the RBC would be determined at 4 month intervals on duplicate 10 ml samples of whole blood by a sensitive liquid scintillation technique (7). The rationale of this procedure is that, after an early rapid fall-off in the activity of the RBC due to the mixing of the $^{55}$Fe with the iron of the other body pools, subsequent values showing a much smaller decline fall on a straight line when plotted on semi-log graph paper. The slope of this line is the basis for calculating the loss of the label from the body (excretion). When the line is extrapolated back to zero time, its intercept on the ordinate (percent of total dose) permits an estimate of the total non-RBC body iron pool (stores). Details of the application of this method have been described earlier (8). It is believed that when applied to the three groups in this proposed experiment, differences in accumulation of stores and in excretion should be evident.
Additional Studies. In addition to the detailed observations on the 300 subjects, it is suggested that a larger number (500 to 1,000), who satisfy the health criteria for admission to the experiment, be added to each of the three experimental groups without initial phlebotomy or injection of $^{55}\text{Fe}$. Examination in these extra subjects would be limited to the determination of serum iron and transferrin saturation at 4-month intervals. Blood samples for these measurements are to be taken in late afternoon at the low point of the circadian cycle. The purpose in collecting these additional data would be to detect any upward trend in serum iron and transferrin saturation on the higher levels of iron intake which would be suggestive of increase in body iron.

Depending on the uniformity of results from the more intensive studies described above this larger group would be available for measurement of iron stores by means of phlebotomy.
Table B. INFLUENCE OF LEVEL OF CEREAL IRON ENRICHMENT ON BODY IRON STORES OF NORMAL ADULT MALES.

**DURATION OF STUDY:** At least 5 years.

**SUBJECTS:** Males, age 25-50, in prison ≥ 6 months, term remaining 2- ≥ 10 more years, no history of blood or liver disease and, on examination: no hepatomegaly or splenomegaly; microhematocrit > 42%; fasting transferrin saturation 20-50% (5); RBC protoporphyrin < 100 μg/100 ml RBC (6); normal reticulocyte count, serum bilirubin and SGOT; fully informed consent to participation.

**DESIGN:** Three diet groups in separate wings of a single penitentiary, starting with about 100/group; every 12-18 months, 6-10 subjects from each group will be withdrawn from the experiment and phlebotomized. Inducements: none, money, sentence remission, or privileges.

**DIETS:** Same for each group throughout the study, except for iron enrichment levels as follows:

<table>
<thead>
<tr>
<th></th>
<th>Added iron (mg Fe/lg)</th>
<th>Daily iron intake</th>
<th>Form of iron throughout, all groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bread</td>
<td>Flour</td>
<td>Enriched sources</td>
</tr>
<tr>
<td>Group I (present)</td>
<td>10</td>
<td>15</td>
<td>5</td>
</tr>
<tr>
<td>Group II (proposed)</td>
<td>25</td>
<td>40 (15+25)</td>
<td>13</td>
</tr>
<tr>
<td>Group III (increase x 3)</td>
<td>60</td>
<td>90 (15+75)</td>
<td>30</td>
</tr>
</tbody>
</table>

**SUPPLY OF DIETS:** It is hoped that the baking industry would make a long term commitment. Monitored by repeated Fe analyses of pooled 24-hour intakes removed by the double portions method for 7 consecutive days.

**DIET CONTROL:** Food consumption to be monitored by accepted nutritional survey techniques.

**PREPARATION OF SUBJECTS:** Weekly phlebotomy (1 unit, 475 ml whole blood) until two consecutive weekly tests without interim phlebotomy show hematocrit ≤ 35% and transferrin saturation ≤ 10%.
Table B. Continued.

<table>
<thead>
<tr>
<th>CALCULATION OF IRON STORES:</th>
<th>Difference between total iron removed (from volume and hematocrit of sample and known Fe content of Hb) and deficit in circulating rib (estimated by decrease of RBC resulting from phlebotomy).</th>
</tr>
</thead>
<tbody>
<tr>
<td>PERIODICAL STUDIES:</td>
<td>(a) Mechanism of regulating body iron stores - at end of preparation each subject will receive iv 100 μCi $^{55}$Fe as ferric citrate bound to 20 ml homologous serum; specific activity of circulating RBC will be determined in duplicate samples of 10 ml whole blood every 4 months (7, 8).</td>
</tr>
<tr>
<td></td>
<td>(b) Effect of enrichment - to observe rate of recovery from the induced anemia, monthly 10 ml samples of heparinized blood from 20 subjects/group will be analyzed for hematocrit, transferrin saturation and RBC protoporphyrin until all of these have returned to normal range in all selected subjects.</td>
</tr>
<tr>
<td>FINAL PROCEDURES:</td>
<td>Phlebotomy as at preparation. Iron stores will be calculated as before.</td>
</tr>
<tr>
<td>ORDER OF TERMINATION:</td>
<td>(a) of individuals - first, those with least time to do, at intervals judged according to uniformity and rate of observed changes in body iron stores.</td>
</tr>
<tr>
<td></td>
<td>(b) of study - when group III shows no increase in body iron stores on three consecutive examinations.</td>
</tr>
<tr>
<td>ADDITIONAL STUDIES:</td>
<td>To guard against unexpectedly high dropout rate or wide range of body iron stores, 500–1,000 subjects (same criteria) to join each group without preparative phlebotomy or $^{55}$Fe and to have serum Fe and transferrin saturation analyzed every 4 months on late-afternoon samples (trough of circadian curve). These subjects will be available for phlebotomy at the end of the experiment, if desired.</td>
</tr>
</tbody>
</table>

* Numbers in parenthesis refer to references, p 27.
V. EVALUATION OF PROTOCOL A

In concept and design this experiment is relatively simple and straightforward. Normal individuals and those with diagnosed diseases known to affect absorption and storage of iron are to be used to test the absorption of iron from two breads with different amounts of iron and specific radioiron labels. After the 10-day feeding experiment, an additional 14 days is allowed for the absorbed iron to be transported to the marrow and incorporated into the RBC. Because both isotopes will move in the body in the same manner, their measurement in the RBC of a blood sample should provide a good estimate of the proportion or ratio in which they were absorbed from the intestine.

However, estimation of the absolute amount of iron, represented by each isotope, absorbed into the body involves assumptions as to the distribution of the absorbed iron between the RBC and other body pools. In some of the diseases listed in Table A, it is known that on the first pass of absorbed iron through the liver more than normal amounts are sequestered (added to stores) and a lesser amount is passed on for RBC synthesis. In the outline as written, it is proposed that the feces of each subject be collected during the 24 days of the experiment to permit the calculation of the unabsorbed amount of each isotope. Among the consultants who commented on this procedure, all expressed the opinion that total body counting was more accurate and that it should be used in addition to, or in place of, fecal analysis. Heinrich (9) has discussed fully the various methods used for measuring iron absorption and the advantages of a whole body retention test.

Other comments and suggestions pertaining to this experiment are discussed briefly below.

Some of the clinical conditions listed in Table A are rare, and it may be impossible at one location to find enough patients in each category to provide meaningful data. Collaborative studies among several laboratories may be desirable.

Because the fully treated hemochromatotics are believed to absorb iron more avidly that other types of subjects, results from such patients should give an estimate of the upper limits of iron absorption.
The composition of the diet, e.g. the amount of meat versus the amount of cereal and vegetables, affects the availability of iron. Therefore, the meals which carry the different isotopes should be identical.

The chemical form of the two iron samples to be used has not been specified. Obviously both should be identical and, to the extent possible, should reflect what commercial millers or bakers are likely to employ.
VI. EVALUATION OF PROTOCOL B

There is reason to believe that the experiment outlined is the embodiment of what experts in the field of iron metabolism have wished, for years, to see done with normal adult males. In essence it represents a desire for information as to how such subjects respond to the intake of different amounts of dietary iron over a long time as reflected by their body iron stores. There was unanimous agreement that such a study would be extremely difficult to organize, control and supervise for the length of time indicated, and enormously costly. The consultants recognized that the conduct of such a study would be as demanding and perhaps as important as the long-term studies on large population groups attempting to relate lipid nutrition to cardiovascular disease.

Only two important suggestions were made for additional procedures to estimate body iron stores. These were made not for the purpose of displacing phlebotomy as the most accurate measure, but as ancillary tests in case phlebotomy could not be fully carried out. One suggestion was to measure the chemical concentration of non-heme iron in bone marrow specimens from the iliac crest, which should provide a measure of the amount of reticulo-endothelial stores. The other was to do ferrioxamine excretion tests at yearly intervals because these also provide a measure of iron stores, especially parenchymal stores.

The last-named procedure is based on the parenteral injection of desferrioxamine mesylate (deferoxamine mesylate, Desferal ® Mesylate-Ciba) (10), one of the iron chelating agents that have been used in the study of iron metabolism. Desferrioxamine is reputed to have a specific affinity for iron, greater than that of other available chelating compounds. It removes iron from ferritin, hemosiderin and probably transferrin but not from Hb. Both the desferri- and the ferri- compounds are water soluble and easily excreted in the urine. The red-colored ferrioxamine may be extracted from the urine and the amount of iron determined.
VII. LSRO STAFF CONCLUSIONS

The primary objective of this study was to determine the feasibility of developing protocols of clinical research which might answer the question: Will the proposed change in iron enrichment increase the prevalence or enhance the severity of iron storage disorders? We may now ask if the two experiments outlined in Protocols A and B are likely to answer that question. We conclude that neither will give a direct answer.

The experiment outlined in Protocol A is designed to permit the measurement of any difference in iron absorption, over a 10-day period, from two diets, identical except for the two breads with different levels of iron enrichment. The subjects will be mainly individuals with diagnosed diseases which are known, or believed, to have some derangement of iron metabolism. However, there is no factual information that iron per se is the basic cause of the diseases listed in Protocol A. It is only when body stores of iron become excessive that they influence the clinical management of patients with these diseases. Under present dietary conditions, clinicians manage this disorder by phlebotomy. We see no way of interpreting any increase in the absorption of iron over a 10-day period in terms of ultimate accumulation of iron stores.

The objective of the experiment outlined in Protocol B is to acquire information on the response of healthy, adult males over a long period of time to different levels of dietary iron provided in bread or other flour-containing items. The effects of this extra dietary iron on the accumulation of body stores will be of particular interest. The possibility that an iron storage disease, such as hemochromatosis, might be precipitated by any of the levels of iron intake is considered extremely remote. Finally, if it is possible to conduct the clinical studies outlined in Protocol B it is highly unlikely that the basic question will be answered.

However, these two proposed experiments have scientific merit. They will supply information that is a prerequisite to a further understanding of the mechanisms regulating iron absorption and storage.
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