Summary

Analyses of human body fat obtained from 131 necropsies performed in Southern England have shown that D.D.T.-derived material and 1,2,3,4,10,10-hexachloro-6,7-epoxy-1,4,4a,5,6,7,8,8a-octahydro-exo-1,4-endo-5,8-dimethanonaphthalene (H.E.O.D.) are present. The mean content in the fat of the general population is 2.21 p.p.m. equivalent-D.D.T. and 0.21 p.p.m. H.E.O.D.

The results compare favourably, as regards amounts of insecticidal material present, with those found in the general population in West Germany, and more than favourably with those found in the general population of the United States. There are indications that equi-

librium levels in the fat have been reached, reflecting the current exposures to these materials.

We express our gratitude to Dr. Francis Camps and Dr. G. B. Forbes for their interest and assistance in this survey.

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A CLINICAL TRIAL OF IRON-FORTIFIED BREAD

BY

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Recent surveys of population groups (Kilpatrick, 1961; Kilpatrick and Hardisty, 1961) and reports from general practice (French, 1955; Fry, 1961) have revealed high prevalence rates of hypochromic anaemia. This might be reduced and new cases be prevented by an increase in the dietary iron in some universally consumed food. This report describes an experiment designed to assess the utilization of iron, from bread made with flour enriched with a high ferrum redactum content, by a group of adult women over a fairly long period of time.

In great Britain since 1953 all flour with an extraction rate of 80% or less has had iron added to ensure a minimum content of 1.65 mg. of iron per 100 g. of flour (Flour Order, 1953; Flour (Composition) Regulations, 1956). Iron, vitamin B₁, and nicotinic acid are added by millers to white flour. Iron may be ferrum redactum (very finely divided metallic iron) or ferric ammonium citrate (Flour (Composition) Regulations, 1956), but only ferrum redactum is known to be used at present (E. M. Laing, personal communication, 1961).

The absorption of iron from bread made with fortified flour was examined by Steinkamp, Dubach, and Moore (1955), who incorporated radio-iron (⁵⁹Fe) into the iron compounds most commonly used in the U.S.A. A single meal of approximately 100 g. of fortified bread, containing a total of about 3 mg. of iron, was given to 26 male and six female "normal" adult students, and radio-iron was estimated daily in the faeces and later in a blood specimen. Seven of the 32 subjects received ferrum redactum—five absorbed 10% or less, and the other two absorbed 26% and 38%, but both these may have had low iron stores. A vitamin C supplement considerably increased the absorption of each compound, but only one subject receiving ferrum redactum was so treated.

Harrill, Hoene, and Johnston (1957) made iron-balance studies of nine healthy young women with "normal" haemoglobin levels who were maintained on controlled diets for four-week periods. Iron compounds were added to the flour used to bake the bread for the diets so that each subject received just over 7 mg. of iron per day in addition to 5.5 mg. in the basic diet. Three iron compounds were studied in this way, including ferrum redactum, and all were found to be

poorly absorbed; the mean absorption of ferrum redactum was 2%.

Widdowson and McCance (1954) found that children who had been undernourished grew and improved equally well when given unlimited quantities of bread, whether made from wholemeal flour, unenriched 70% extraction flour, or 70% extraction flour fortified with iron and B group vitamins to wholemeal standard. All diets consisted of about 75% bread and contained little milk, meat, fish, or cheese. After one year no significant change in haemoglobin or haematocrit level was found in the children on any of the diets.

Method

Preliminary test bakes showed that the content of reduced iron in flour could be increased to about 100 mg./100 g. of flour before changes occurred in the resulting loaf. At this level the crumb colour changed to greyish white although the quality and flavour were unaltered. At 200 mg./100 g. of flour the colour and flavour were altered but not unpleasantly. For the present experiment the bread was made from flour fortified with reduced iron at 60 mg./100 g. of flour, so that the bread was indistinguishable in every way from a normal white loaf.

The subjects studied were 299 adult female patients living in four long-stay units of a mental hospital. The patients were divided into four groups.

Group I (63 patients) received bread made from flour fortified with ferrum redactum for six months. It was assumed that the average consumption of bread per patient was 8 oz. (225 g.) per day, so that approximately 80 mg. of elemental iron per patient per day was supplied in the bread. During the six months of the trial each patient in this group received on average a total of about 14.4 g. of elemental iron.

Group II (61 patients) received the same bread as Group I for six months, but in addition, for the last two months, each patient was also given 50 mg. of ascorbic acid immediately after breakfast and tea, when bread was the main item of the meal. Each patient in this group also received on average a total of about 14.4 g. of elemental iron during the trial.

Group III (67 patients) received tablets of ferrous gluconate which supplied 110 mg. of elemental iron per patient

per day for three months. Then after an interval of one month they were given compound tablets of ferrous gluconate (70 mg. of elemental iron per patient per day) and ascorbic acid (100 mg. per patient per day) for two months. During the six months of the trial patients in this group therefore received a total of about 14 g. of elemental iron.

Group IV (108 patients) formed a control group and received no iron therapy during the trial.

The trial began in August, 1961, and continued for six calendar months, during which time, apart from the bread described, all the patients received the normal hospital diet. To facilitate the daily issue of bread within the hospital each group was a complete long-stay unit.

Haemoglobin estimations were made on oxyhaemoglobin with an E.E.L. photoelectric colorimeter, using finger-prick samples of blood, before the trial commenced, at the end of three months, and at the end of six months. A blood film was made on every patient with an initial haemoglobin of 12.5 g./100 ml. (86%) or less. Preliminary work showed that a group of normal males showed a significant mean fall in haemoglobin during the day of about 0.3 g./100 ml. (Elwood, 1962), so to avoid possible bias from this source all samples were taken between 6 and 10 p.m.

Samples of normal and fortified bread were analysed for iron on five occasions during the trial and found to contain amounts of iron consistent with the level of fortification of the flour.

Haemoglobin levels were estimated as grammes per 100 ml. of blood. Standard errors of differences between means are shown where relevant; the criterion of significance adopted is $P < 0.05$ throughout.

Results

The number of patients in each group who started and dropped out of the trial is shown in Table I. Losses were higher in Group III, as the complete unit was rehoused during the trial. Such losses were unavoidable in a trial lasting six months, but so far as is known none were associated with low haemoglobin levels. Consequently subsequent tables and discussion relate only to 259 patients who completed the trial.

The age distributions of patients within each group are shown in Table II. These distributions do not differ

TABLE I.—Number of Patients in Each Group and Number who Dropped Out During the Trial

Group	No. at Start of Trial	No. who Dropped Out during Trial				No. at End of Trial
		Discharged	Transferred	Died	Total Lost	
I	63	2	7	1	10	53
II	61	4	2	—	6	55
III	67	1	12	2	15	52
IV	108	3	3	3	9	99
Total	299	10	24	6	40	259

TABLE II.—Age Distributions of Patients

Age in Years	Group				Total	
	I	II	III	IV	No.	%
16–	2	3	0	1	6	2.3
35–	6	7	4	10	27	10.4
45–	11	10	12	7	40	15.4
55–	15	12	15	25	67	25.9
65–	13	15	16	31	75	29.0
75+	6	8	5	25	44	17.0
All ages	53	55	52	99	259	100

Total $\chi^2 = 18.60$. D.F. = 12. $0.1 > P > 0.05$. Patients under 45 are grouped together for χ^2 .

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significantly. Table III shows that there was no significant difference between the four groups in the distributions of initial haemoglobin levels of the patients.

The changes in mean haemoglobin level of the patients in each group during the two three-month periods and over the total six months of the trial are shown in Table IV. All the changes are small except for a significant rise (0.53 ± 0.16 g./100 ml.) over the six months in the mean of Group III, which received iron tablets, and this was mainly due to the rise during the last three months (0.34 ± 0.12 g.). The only other significant change was a small fall over the six months (0.24 ± 0.11 g.) in the mean of Group I, which received fortified bread, and this was largely due to a fall in the first three months (0.23 ± 0.11).

Patients who had an initial level of less than 12.5 g./100 ml. (86%) were examined separately. The age distributions of these patients in each group were similar except that those in Group II were on the whole younger (mean age 50 years) than those in Groups I, III, and IV (mean ages 59, 61, and 62 years respectively). Changes in their mean haemoglobin levels are shown in Table V. During the first three months a significant mean rise occurred in the controls (Group IV) (0.47 ± 0.14 g.) and in Group III, who received iron tablets (1.02 ± 0.23 g.).

TABLE III.—Distribution of Initial Haemoglobin Levels

Initial Haemoglobin (g./100 ml.)	Group				Total	
	I	II	III	IV	No.	%
Below 12.0	6	6	8	15	35	13.5
12.0 (82%)–	5	7	5	10	27	10.4
12.5 (86%)–	4	8	8	10	30	11.6
13.0 (89%)–	10	6	11	13	40	15.4
13.5 (92%)–	11	8	9	19	47	18.2
14.0 (96%)–	10	11	3	15	39	15.1
14.5 (99%)–	7	9	8	17	41	15.8
Totals	53	55	52	99	259	100

Total $\chi^2 = 11.15$. D.F. = 18. $0.9 > P > 0.8$.

TABLE IV.—Changes in Mean Haemoglobin Level During Trial in All Patients

Group	No. of Patients	Changes in Mean Haemoglobin (g./100 ml.)		
		First 3 Months	Second 3 Months	Total 6 Months
I	53	$-0.23 \pm 0.11^*$	-0.01 ± 0.09	$-0.24 \pm 0.11^*$
II	55	-0.16 ± 0.08	$+0.15 \pm 0.11$	-0.02 ± 0.12
III	52	$+0.20 \pm 0.13$	$+0.34 \pm 0.12^*$	$+0.53 \pm 0.16^*$
IV	99	$+0.08 \pm 0.07$	-0.14 ± 0.08	-0.05 ± 0.14

* Significant.

TABLE V.—Changes in Mean Haemoglobin Level During Trial in Patients with an Initial Level of Less than 12.5 g./100 ml.

Group	No. of Patients	Changes in Mean Haemoglobin (g./100 ml.)		
		First 3 Months	Second 3 Months	Total 6 Months
I	11	$+0.41 \pm 0.19$	$+0.09 \pm 0.16$	$+0.50 \pm 0.21^*$
II	13	-0.02 ± 0.18	$+0.27 \pm 0.28$	$+0.25 \pm 0.31$
III	13	$+1.02 \pm 0.23^*$	$+0.58 \pm 0.27$	$+1.60 \pm 0.30^*$
IV	25	$+0.47 \pm 0.14^*$	$+0.04 \pm 0.12$	$+0.51 \pm 0.14^*$

* Significant.

In Group IV this largely accounted for a significant increase over the whole six months (0.51 ± 0.14 g.), but in Group III there was in addition an almost significant increase during the last three months (0.58 ± 0.27 g.). The two groups who were given fortified bread had no significant changes during either three-month period, though Group I did have a rise (0.50 ± 0.21 g.) over the total six months, which is just significant and is probably attributable to an almost significant increase during the first three months (0.41 ± 0.19 g.). Changes in these patients in the treated groups were compared with those shown by the control group during the same period.

Only the rise during the first three months and the overall rise shown by Group III were significantly greater than the corresponding changes shown by the control group.

Neither group which received fortified bread showed changes in these patients which differed significantly from those of the control group. Changes in Group I were very similar to those of the control group, but Group II showed changes during each period of the trial which differed, though not significantly, from those of both Groups I and IV. It was thought that this might have been due to the younger age distribution of these patients in Group II, so those between 45 and 74 years of age with an initial haemoglobin below 12.5 g./100 ml. were examined alone. In these patients changes in Group II during the first three months (0.13 ± 0.21 g.) were smaller, and in the second three months (0.25 ± 0.43 g.) larger than in either Group I or IV, though neither is significant, and the differences between the groups are on the whole smaller, though in a similar direction, than when patients of all ages are considered. It appears, therefore, that the difference in response of these patients with lower initial haemoglobin levels in Groups I and II is unlikely to be a reflection of a difference in age distribution within the groups.

The effect of the vitamin C supplement during the last two months is shown by a comparison of the changes in Groups I and II during the second three months of the trial. Group II, which received the supplement, showed a larger mean rise than Group I, who received fortified bread alone (Table IV), though the difference (0.14 ± 0.14 g.) is not significant. Patients with initial levels below 12.5 g./100 ml. in these two groups whose ages were between 45 and 75 years showed a difference in the same direction, but the excess rise in Group II (0.12 ± 0.46 g.) is not significant.

It is relevant to the assessment of the clinical importance of the significant changes noted in these results that any change in the mean haemoglobin within a group of about 0.25 g. or more, and any change of about 0.5 g. or more within a group limited to patients with initial levels of less than 12.5 g. was likely to be detected as significant.

Discussion

The National Food Survey in 1959 showed that over one-third of the daily requirements of iron are provided by bread and flour (Ministry of Agriculture, 1961). As about 90% of all bread consumed in Great Britain is white (Ministry of Agriculture, 1960) a considerable proportion of the daily intake of iron in this country has been added as ferrum redactum to the diet. However, little work seems to have been done in this country to investigate the absorption of this form of iron from bread (Widdowson, 1961).

The long-term effect of food additives is obviously of importance both to the general population and to those deficient, or liable to become deficient, in any particular nutrient. It seemed expedient, therefore, to conduct this trial in a relatively stable and easily accessible population with as broad a distribution of haemoglobin levels as possible. Preliminary investigation showed that long-stay female patients in a mental hospital were a satisfactory group for such a trial. While such a group may not represent the community

it is of interest that 44 (17%) of those included in this trial had an initial haemoglobin level of 12 g./100 ml. (82%) or less. This is similar to the prevalence of "anaemia" (12 g. or less) in women aged 55-64 years in the Rhondda Fach (Kilpatrick and Hardisty, 1961) and aged 15 and over in Wensleydale (Kilpatrick, 1961) —14% and 21% respectively. No patient with a megaloblastic anaemia was detected in any group.

The results of the trial show that the bread fortified with ferrum redactum at a level sufficient to give about 80 mg. of elemental iron per patient per day did not produce a significant rise in the haemoglobin level of women over a period of six months. Indeed, one group which received fortified bread (Group I) showed an unexpected fall (0.24 ± 0.11 g.) during the six months, which was significant. Women with lower initial levels (less than 12.5 g.) in the control group showed a significant mean rise (0.51 ± 0.14 g.), and those with similar initial levels in Groups I and II showed rises over the six months which did not differ significantly from that of the control group, though in only Group I was the rise (0.50 ± 0.21 g.) significant. The addition of vitamin C (50 mg. twice daily) to the diet of Group II did not appear to affect the changes significantly.

The amount of elemental iron each woman received daily in the fortified bread was lower than conventional therapeutic doses of iron, which are usually over 120 mg. per day (Hayhoe, 1960). However, over the six months each woman who had fortified bread received on average a total of about 14.4 g. of elemental iron, and so it is relevant that the woman who received iron tablets (Group III) and who each received the same total quantity of elemental iron during the trial (14 g. approximately) showed a significant rise in mean haemoglobin. This difference in response between patients on fortified bread and those on iron tablets was shown to a more marked degree by patients with lower initial haemoglobin levels.

It appears, therefore, that the iron used for fortification of the bread was not utilized to any appreciable extent, while iron given in conventional tablet form to a comparable group of patients was reasonably well utilized. The reason for this difference may lie either in the mode of administration or in the iron compound itself, or both these may have played a part.

It has been shown that bread or some component in it inhibits the absorption of iron (Steinkamp *et al.*, 1955), as does any increase in bulk in the diet (Sharpe, Peacock, Cooke, and Harris, 1950). However, in this trial these factors are not likely to have played a very important part, because, although ferrum redactum was given in bread which formed the main bulk of two meals, the iron tablets were given immediately after meals, and Steinkamp *et al.* (1955) have shown that the absorption of iron is similar whether it has been baked in bread or is ingested with the same quantity of ordinary bread.

It would seem, therefore, that the lack of response shown by the group which was given fortified bread might be due to the iron having been in a form which was poorly absorbed. Ferrum redactum, which is probably unchanged in the baking process (Laing, personal communication, 1961), disappeared from the *British Pharmacopoeia* as a treatment of hypochromic anaemia around 1910 (Widdowson, 1961), and no recent study of its absorption seems to have been made in this country. The conclusions of Steinkamp *et al.* (1955) are not fully relevant to the present work

as they were based on the results of a single meal of iron-fortified bread given to normal subjects.

The results of the experiment reported here give no evidence that additional fortification of flour is of therapeutic value; they also raise doubts about the value of the present level of fortification with ferrum redactum in this country.

Summary

Bread made from flour fortified with 60 mg. of ferrum redactum per 100 g. of flour was given for six months to two groups of 53 and 55 female patients in long-stay units of a mental hospital. Each patient received about 80 mg. of elemental iron per day. One group was given a vitamin C supplement twice a day for the last two months of the trial. A further group of 52 patients received the same total amount of elemental iron in tablet form as ferrous gluconate, and another group of 99 patients received no iron therapy. All groups were comparable with regard to age and haemoglobin level at the commencement of the trial.

No significant (at $P < 0.05$) increase in mean haemoglobin level was experienced by either group given fortified bread, but the group given tablets of ferrous gluconate did experience a significant mean increase. Patients with an initial haemoglobin level of less than 12.5 g./100 ml. in the group given fortified bread but no vitamin C experienced a significant increase in mean haemoglobin, but this increase was almost identical with that experienced by comparable patients in the control group. The patients with lower initial haemoglobin levels who received ferrous gluconate showed a significant mean increase of 1.60 ± 0.30 g. over the six months, which was significantly in excess of corresponding changes in all other similar patients.

These results are discussed and the therapeutic value of fortification of flour with ferrum redactum at a high level is considered; the relevance of the findings to the present statutory fortification of flour is indicated.

I would like to thank Professor J. Pemberton, who initiated this study, for advice, and Dr. C. B. Robinson and the nursing staff for the hospital for their willing co-operation. I am indebted to the directors of Messrs. Inglis and Co. Ltd., and to their chemist, Mr. J. E. C. Bell, for supplying the bread used in this trial. Thanks are also due to Dr. T. Moran, of the cereal research station, and Mr. J. E. C. Bell for preliminary test bakes; to Professor C. L. Wilson for analysing the bread; to Roche Products Ltd., who supplied the "redoxon" vitamin C tablets; and to John Wyeth and Brother Ltd., for "gluferate" tablets (ferrous gluconate and vitamin C).

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CLOSURE OF THE INGUINAL CANAL IN TREATMENT OF HERNIA

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Removal of the hernial sac up to its neck, and closure of the opening or defect in the parietes, constitute the twin prongs of surgical attack on abdominal hernia. It appears surprising, therefore, that surgeons have preferred to compromise these basic principles in the treatment of inguinal hernia. The majority of procedures in current use leave room for the emergence of the cord, and, by not closing the inguinal canal, permit the risk of recurrence. The review below is a clinical study of 103 cases of inguinal hernia treated by closure of the inguinal canal, and is a resurrection of an earlier and less successful experiment carried out in America by Burdick and Higinbotham (1935). The stimulus to reassessment came from a limited reappraisal made by Bodhe (1959), in India, and the present study, while confirming many of his clinical findings, also attempts to explain some of the factors which contribute to a satisfactory result.

Selection of Cases

Of the 103 cases, three required orchidectomy for abdominal testis, haematocele, and testicular tumour respectively; in these, closure of the canal was employed incidentally in the repair of associated inguinal hernia. Deliberate closure of the inguinal canal after excision of the cord was performed in 100 cases of inguinal hernia. Unless a subject was already a parent, with one or more children, he was not thought suitable for this procedure. In a country where marriage is early and the reproductive rate high, the possibility of reduced fertility was regarded by many patients as an inducement to co-operate in this experiment. With very few exceptions those selected for this procedure were over 35 years old, the large majority being well over 50. Table I shows the age distribution, in decades. (The two patients below 30 were operated upon for large recurrent hernia. In the third decade, only four patients were less than 35 years old.)

The hernias chosen for this procedure were those generally regarded as unfavourable—large indirect hernias of long standing, recurrent hernias, sliding hernias, and combined (pantaloon) hernias. Large direct hernias were also included where it was thought that a more effective repair could be obtained by this method. Table II shows the relative incidence of the various types. During the period in question 297 cases of inguinal hernia were seen, including 37 bilateral cases.

TABLE I.—Distribution of Cases According to Age

Age	Below 30	30–39	40–49	50–59	60+
No. of cases	2	23	10	20	45

TABLE II.—Incidence of Various Types of Hernia

Indirect, including scrotal	51
Direct	33
Pantaloon	5
Sliding	4
Recurrent	7

Surgical Technique

The incision is made in the line of the skin crease, and the inguinal canal is entered by division of the