within a period of 2 minutes. These were in the form of a sudden drop and restitution to former level. When the intravenous temperature began to rise these fluctuations became more frequent, occurring as often as every 10 minutes.

This chart also illustrates diagramatically the great increase in capillary activity with the production of fever. The lower blood temperature would incline us to believe that the purpose of this was not a direct increase of local heat but rather a means of supplying the cells, especially of the muscles, with an increased food supply for metabolic activity and associated heat generation.

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A Comparison of the Value of Ferrous Iodide Administered Directly and Indirectly.*

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Ferrous iodide has been administered orally as a tonic for many years in the practice of medicine without any evidence of toxicity when therapeutic doses are not exceeded. Recently, however, "toxicity" on direct oral administration has been ascribed to it in vitamin A deficient rats[1] in explanation of the negative results obtained by Mason,[2] Cameron,[3] and Mendel[4] when ferrous iodide was used as a substitute for vitamin A.

In all of these experiments, dilute ferrous iodide was given *by pipette or syringe* to rats depleted of vitamin A, a method which prompted the criticism of toxicity. In the following experiments, comparison is made of the effects of ferrous iodide when given by this method and when given as a part of the diet, thus avoiding any possible toxic effect of direct oral administration.

In these experiments dilute syrup of ferrous iodide alone or combined with linoleic acid has been given daily, mixed with a small

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[1] Chidester, F. E., *Collecting Net.*, 1932, **7**, 229.

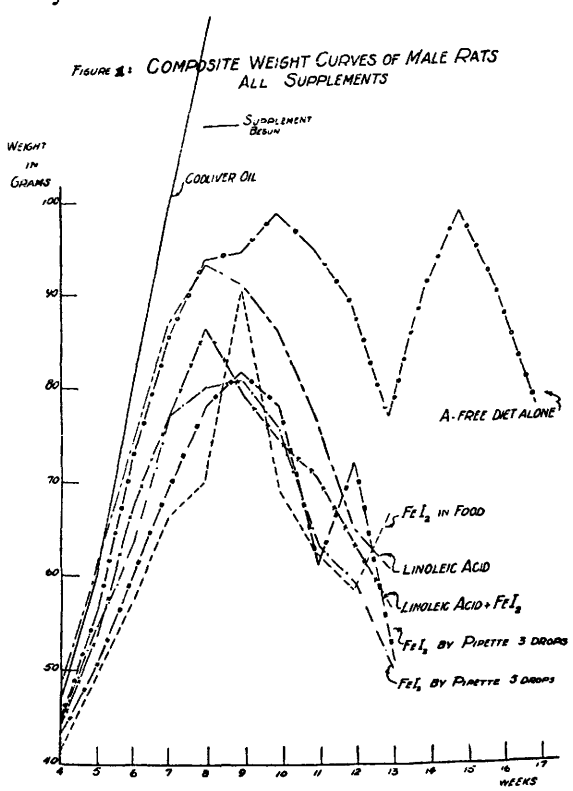
[2] Mason, Karl E., *Anat. Rec.*, 1931, **51**, Supplement 1, Abst. 91.

[3] Cameron, H. C., *Science*, 1932, **76**, 18.

[4] Reed, Lucille L., Mendel, Lafayette B., and Vickery, H. B., *Science*, 1932, **76**, 300.

amount of dry diet in a small glass dish left in the cage without other food until its contents was consumed. The results are compared with the earlier experiments in which direct oral administration was used. Standard vitamin A procedure was followed,[3] vitamin D being supplied throughout by the addition of 0.05 mg. of irradiated ergosterol per 1000 gm. of diet. At the first appearance of xerophthalmia, usually between the 8th and 9th weeks, administration of ferrous iodide or other supplement was begun and continued to the death of the animal when autopsy was done. Observations were made 3 times a week to detect improvement in the eyes. The following supplements were used: syrup of ferrous iodide diluted 1-350, 5 drops daily; linoleic acid, 4 to 6 drops; linoleic acid and dilute ferrous iodide mixed in equal amounts, 8 drops daily. The drops were measured from the same pipette in all cases.

Figure 1 shows the effect of the various supplements on growth. It is evident that death as represented by the end of the curve, comes at almost exactly the same time whether ferrous iodide is given by



pipette or mixed in the diet, alone or with linoleic acid. The break in the curve with an apparent gain in weight just before death, does not occur in the growth curves for individual rats, and seems to be caused in the composite curves by the diminishing numbers of rats toward the end of the experiment. The peak of growth occurs in most cases before any supplement is given and declines almost immediately thereafter to the death of the animal. The contour of the individual curves shows a striking similarity in both male and female rats. In all cases, the untreated vitamin A-free rats live longer than their supplemented litter mates. There is thus no evidence of any greater "toxicity" for ferrous iodide given by pipette than in the diet; and no evidence of growth promoting effect from any of the supplements. This is in striking contrast to codliver oil which maintains continuous growth. There was no evidence of improvement in xerophthalmia or of middle ear and tongue infections which occurred in all of the vitamin-free rats, treated or untreated.

The figures given in Table I, for the mean age at death of the animals in each group, bear out the observations made from the growth curves. In general, the females in all groups tended to live a few days longer than the males and to weigh a few grams less at death; but since the differences were small, figures for male and female rats have been combined. It is evident from these figures that neither ferrous iodide alone or combined with linoleic acid prolonged the life of vitamin A-free rats, since the unsupplemented rats of Group I—those on vitamin A-free diet alone—lived longer than any other lot. None of the differences are large in the life of a rat, but *all are in favor of the untreated rats.*

At first glance, it may be thought that ferrous iodide by mouth has hastened the death of the animals, since those receiving 3 drops by pipette died earlier than any other group. However, comparison of the figure for 23 rats given 5 *drops by pipette* with that for

TABLE I.
Comparison of Age at Death of Treated and Untreated Rats (Male plus Female)

Group	Treatment	No. Rats	Age at Death		Deviation from Group I		D / P.E.
			Mean	P.E.	Mean	P.E.	
I	Unsupplemented Rats	32	92.06	1.75	—	—	—
II	FeI_2 given by pipette (3 gtts.)	22	76.73	1.01	15.33	2.02	7.59(-)
III	FeI_2 given by pipette (5 gtts.)	23	85.57	1.98	6.49	2.64	2.45
IV	FeI_2 mixed in diet (5 gtts.)	37	87.84	1.13	4.22	2.08	2.03
V	FeI_2 plus Linoleic Acid in food	21	90.29	0.97	1.77	2.00	0.89
VI	Linoleic Acid alone in food	24	88.00	1.17	4.06	2.10	1.93

37 rats given 5 *drops in the diet* shows a difference of only 2 days, which is certainly not indicative of toxicity. The discrepancy in the 3-drop group must therefore be sought elsewhere.

Review of all the data from the statistical standpoint verifies these conclusions. Assuming that the individual figures are sufficiently uniform to make a smooth frequency curve, a mean difference between 2 groups that is 4 times its probable error offers odds of *142* to 1 that the difference is significant and could be obtained again under like conditions. In column 4, Table I, is given the difference, with its probable error, between the mean age of the untreated rats of Group I and that of each of the other groups. The last column gives the ratio of the mean difference to its probable error. It will be seen that only one difference is more than 4 times its probable error, and the difference in this case *is in favor of the untreated animals* (marked −). This is true in every instance in the figures for male and female rats considered separately (not shown here), and for weight at death as well as for age at death. Comparison of the age at death of all rats given ferrous iodide by pipette (5 drops) with those given ferrous iodide in the food (5 drops) reveals a mean difference of 2.27± P. E. of 2.28. There is thus no significant difference between the 2 methods of administering the ferrous iodide. With respect to weight at death, the mean difference between the 2 groups is 5.59± P. E. of 1.46, or a ratio of 3.82 to 1 *in favor of the animals fed by pipette.*

Conclusion. There is thus found to be no significant difference in response of animals to ferrous iodide fed by pipette or mixed in the diet, and no evidence of a "toxicity" factor from the former. Furthermore, no vitamin-A substituting effect is obtained with ferrous iodide alone or combined with linoleic acid given either by pipette or mixed in the food.