The effects of a restricted diet and of various diets upon the resistance of animals to certain poisons / by Reid Hunt.

TREASURY DEPARTMENT
ıblic Health and Marine-Hospital Service of the United States

HYGIENIC LABORATORY.—BULLETIN No. 69
JUNE, 1910

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SYNOPSIS AND TABLE OF CONTENTS.

There are, further, a number of clinical observations indicating that certain foods have important specific effects. Thus certain cases of diabetes mellitus are much benefited by oatmeal; the attempts to explain this action on the supposition that the starch of oats is different from that of other cereals are unsatisfactory. There can be little doubt that some specific action (i. e., an action independent of its fuel value) should be attributed to the oatmeal.

Several writers have called attention to differences in the susceptibility of different races of mice and rats to transplantable tumors. In a few cases these differences seem to have been traced to the influences of heredity.[a] In others they were attributed to differences in diet, [b] but whereas in Haaland's experiments the most susceptible mice (to a certain sarcoma) were those which had received a diet of hempseed, bread, milk, and some oats, and the least susceptible those which had received bread and oats, in Stahr's experiments mice which had received a diet of hempseed and milk were less susceptible than those which had had a diet of bread and water. Careful studies on this subject with especial reference to changes in weight and rate of growth (factors which seem, according to Mareschi[c] to be very important and which also seem important in my experiments upon the influence of diet upon the resistance to certain poisons) may lead to important results. Jensen [d] has suggested that it may be possible to influence favorably, by diet, metastases and recurrences.

Certain diseases (beriberi and pellagra) seem to be closely associated with and perhaps dependent upon the use of certain articles of diet (rice and maize); the latter may be "spoiled," but nevertheless the effects may properly be called specific, since other "spoiled" food does not have a similar effect.

Wherry[e] found guinea pigs made scorbutic by an exclusive diet of barley and water to show a greater degree of hemorrhagic extravasation when inoculated with plague than is usually seen.

In the course of numerous experiments performed, for the most part, for other purposes, I have observed some very striking alterations in the resistance of animals to certain poisons produced entirely by changes in diet. Thus of animals kept upon diets such as are in daily use by man some were able to resist many (up to 40) times the amount of certain poisons fatal to animals kept upon other diets. Although the results with certain of these poisons probably have no

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[a] Tyzzer. Jour. of Med. Res., 1909, 21, p. 519.

[b] Haaland. Berl. kl. Wochenschr., 1907, 44, p. 713; Stahr, Centrbl. f. Allgem. Path. und pathol. Anat., 1909, 20, p. 628.

[c] Mareschi. Zeitsch. f. Immunitätsforsch. u. exp. Ther., 1909, 2, (1), p. 651. Cf. also Bashford and Russell, Lancet, 1910, 1, p. 782.

[d] Jensen. Zeitsch. f. Krebsforsch., 1909, 7, p. 284.

[e] Wherry. Jour. Infectious Diseases, 1909, 6, p. 564.

ation to man, yet they show that man is doubtless daily producing
ofound effects upon his resisting power to poisons and diseases, a
owledge of some of which may be of much practical importance.
nd it seems certain that by the use of some of these reactions changes
metabolism, which are not recognized by the methods ordinarily
nployed, may be detected.

Although the experiments are very incomplete, they may have
lue in suggesting new lines of research and new points of view for
alyzing some of the problems now vaguely referred to as "the
sisting power of the individual," "constitution," "diathesis," etc.

THE EFFECTS OF A RESTRICTED DIET AND OF VARIOUS DIETS UPON THE RESISTANCE OF ANIMALS TO CERTAIN POISONS.[a]

By Reid Hunt,

Professor of Pharmacology, U. S. Public Health and Marine-Hospital Service.

Part I.

THE EFFECT OF A RESTRICTED DIET UPON THE RESISTANCE OF ANIMALS TO CERTAIN POISONS.

A. HISTORICAL.

The great practical value of an intimate knowledge of the metabolic processes which occur in partial inanition is obvious; as von Noorden [b] has remarked, no one not familiar with these processes can form a correct judgment as to which of the alterations in metabolism in a given disease are to be attributed to the latter and which to simple inanition.

As is well known, however, some fundamental problems in this connection are still in dispute. Thus the question whether the body in inanition can learn to use less material and work more economically is not definitely settled. It seemed probable that a study of the resistance to poisons of animals in a condition of partial inanition would throw some light upon some of these problems.

The literature bearing directly upon this subject is very small; Mansfeld [c] has recently summarized the greater part of it as follows: Delafoy found that starving frogs are much more sensitive to strychnine than are normal frogs. Lewin stated that starving animals are more resistant to quinine, atropine, and nicotine than are well nourished ones. Roger found the same when quinine and atropine were

[a] Manuscript submitted for publication June 3, 1910.

[b] von Noorden. Handbuch der Pathologie des Stoffwechsels, 2d ed., 1906, vol. 1, p. 480.

[c] Mansfeld. Archives internat. de Pharmacodynamie et de Thérapie, 1905, 15, p. 467; Mansfeld and Fejes, ibid., 1907, 17, p. 347.

injected into a peripheral vein but found the reverse to hold when the drugs were injected into the portal vein. Jordan found digitalin to be more toxic to starving dogs. Adducco reported that cocaine, strychnine, and phenol are much more poisonous to starving than to well nourished dogs.

Mansfeld himself found that starving rabbits are much more susceptible to chloral hydrate, paraldehyde, and morphine than were well nourished ones. Starvation did not cause an increased susceptibility to ethyl alcohol, amylene hydrate, and ethyl urethane. Mansfeld explained this difference in terms of the Meyer-Overton hypothesis.

Lo Monaco and Trambusti [a] reported that well nourished animals are less resistant to phosphorus than are poorly nourished ones.

Salant and Rieger [b] found the resistance of rabbits to caffeine to be diminished when the animals were starved for four or five days; the fatal dose was about 30 per cent less than in well fed rabbits.

B. EXPERIMENTAL.

I. Experiments with Acetonitrile.

The poison with which the most striking results were obtained was acetonitrile (CH_3CN). A consideration of the pharmacological action of this poison led to the belief that a study of the influences affecting its toxicity would be more suggestive than that with many other and better known poisons. The chief of these considerations was this: Most of the ordinary poisons undergo no marked chemical changes before exerting their toxic effects although the changes which they may subsequently undergo are often of much interest and their study has thrown important light on problems of metabolism. Acetonitrile, however, according to the generally accepted view of Heymans and Masoin, is poisonous only, or largely, as a result of the formation from it of hydrocyanic acid.[c] I have given arguments in earlier papers for the view that the formation of hydrocyanic acid is due to certain processes of metabolism which may be modified by drugs and diet. Thus, from a study of the toxicity of a number of nitriles of both the aliphatic and aromatic series, I was led to the view that, in the formation of hydrocyanic acid from acetonitrile, processes of oxidation (by which the methyl group is oxidized to formic acid) are probably involved. Believing that the tolerance for alcohol is probably due to the body's acquiring an increased power to oxidize the

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[a] Centralbl. f. innere Medizin, 1894, 15, p. 701.

[b] Proceedings of Amer. Soc. for Pharmacol. and Exp. Therapeutics, Jour. of Pharmacol. and Exp. Therapeutics, 1910, vol. 1, p. 572.

[c] The literature on this subject is given in Archives internationales de Pharmacodynamie et de Thérapie, 1904, 12, p. 447, and Bulletins 33 and 47, of the Hygienic Laboratory, U. S. Public Health and Marine-Hospital Service.

hyl group of this substance,[a] I was led to the hypothesis that ani-
als which had received alcohol for some time would be able to oxi-
ize the methyl group of acetonitrile more rapidly, thus freeing a
rger amount of hydrocyanic acid, and that such animals would there-
re be more susceptible to acetonitrile than would normal ones.
xperiments showed that animals which had received alcohol for
me time were more susceptible to acetronitrile, and also that they
ecomposed a larger proportion of this substance than did the
ntrols.

Similar reasoning led to experiments with this nitrile in partial
anition. It was thought probable that in this condition the
tensity of certain processes of oxidation may be lowered and that
onsequently animals on a restricted diet would decompose less
cetonitrile than do normal animals and consequently be more
esistant to the poison. It was thought that a positive result would
e of special interest for it would probably be an example of specific
owering of metabolism,[b] for there is little evidence that general
etabolism is lowered in inanition.[c] As will be shown, the results
upport the hypothesis.

(*a*) EXPERIMENTS ON MICE.

Most of the mice used were bred in the laboratory; they were care-
fully weighed and the acetonitrile (dissolved in water) injected sub-
cutaneously in proportion to body weight.

In the first group of experiments the food consisted of oats; some
of the mice were given all they would eat, whereas others were given
but a very small amount daily. Only a few experiments, viz, those
in which the dose of acetonitrile was near the fatal dose, are cited.

Series 1.

A. CONTROLS. (v, 68.)

Date.	Weight of mouse.	Remarks.
1905.	*Grams.*	
Feb. 16	20.46	Oats and water.
Feb. 24	18.12	
Feb. 27	17.45	Acetonitrile, 8.73 mgms., i. e., 0.5 mgm. per gm. mouse; survived.
Feb. 16	24.82	Oats and water begun.
Feb. 24	21.52	
Feb. 27	21.57	Acetonitrile, 14.02 mgms., i. e., 0.65 mgm. per gm. mouse; died, 4½ hours.

[a] The correctness of this hypothesis has recently been proved by Pringsheim (Biochem. Zeitschr., 1906, 12, p. 143), who found that animals accustomed to alcohol oxidized a given amount in two-thirds the time required by those unaccustomed to it.

[b] Brugsch and Hirsch (Zeitschf. für exp. Pathol., 1907, 4, p. 947) found the assimilation limit for d-l-alanin to be much lower in hunger than normally.

[c] von Noorden. Handbuch der Pathologie des Stoffwechsels, 2d ed., 1906, vol. 1, p. 480; cf. Staehelin, Deutsche med. Wochenschr., 1909, 35, p. 609.

B. RESTRICTED FOOD. (v, 44–45.)

Date.	Weight of mouse.	Remarks.
1905.	*Grams.*	
Feb. 16	23.16	Limited diet commenced.
Feb. 21	18.85	
Feb. 27	18.25	Acetonitrile, 20.08 mgms., i. e., 1.1 mgms. per gm. mouse; survived.
Feb. 16	19.11	Diet as above.
Feb. 21	16.02	
Feb. 27	14.02	Acetonitrile, 22.4 mgms., i. e., 1.6 mgms. per gm. mouse; survived.
Feb. 16	18.15	Diet as above.
Feb. 21	15.35	
Feb. 27	13.25	
Feb. 28	13.57	Acetonitrile 27.14 mgms., i. e., 2 mgms. per gm. mouse; survived.

The first and third of the mice of "B" were placed on a diet of oats soaked in ethyl alcohol the strength of which was gradually increased to 45 per cent; their weights increased in the course of 5 weeks to 19.02 and 19.31 grams, respectively, but they died from 0.3 and 0.35 mgm. acetonitrile per gm. mouse. Other mice which had received the full diet of oats and water for the same period recovered from 0.55 and 0.6 mgm. per gm. mouse.

Series 2.

A. CONTROL. (v, 82.)

Date.	Weight of mouse.	Remarks.
1905.	*Grams.*	
June 7	24.85	Oats and water.
June 14	21.61	
June 19	21.72	Acetonitrile, 15.23 mgms., i. e., 0.7 mgm. per gm. mouse; died 2¾ hours.

B. RESTRICTED DIET.

1905.	*Grams.*	
June 7	29.61	Limited diet begun.
June 12	25.31	
June 16	21.21	
June 19	17.35	Acetonitrile, 20.82 mgm., i. e., 1.2 mgms. per gm. mouse; survived.
June 20	.....	Diet changed to ham and cheese.
June 30	20.01	
July 3	21.32	
July 11	25.12	Acetonitrile, 15.09 mgms., i. e., 0.6 mgm. per gm. mouse; died, 1½ to 2 hours.

Series 3.

A. CONTROL. (v, 84.)

1905.	*Grams.*	
June 7	20.85	Oats and water.
June 14	18.31	
June 25	18.26	Acetonitrile, 12.78 mgms., i. e., 0.7 mgm. per gm. mouse; died, 11 hours.

B. LIMITED DIET.

ate.	Weight of mouse.	Remarks.
05.	*Grams.*	
e 9	16.61	Limited diet commenced.
e 16	14.91	
e 24	14.12	
e 27	13.35	Acetonitrile, 13.55 mgms., i. e., 1 mgm. per gm. mouse; survived.
e 7	18.21	Diet as above.
e 16	16.51	
e 24	14.82	
e 26	14.45	Acetonitrile, 17.34 mgms., i. e., 1.2 mgm. per gm. mouse; survived.
e 7	24.55	Diet as above.
e 16	20.02	
e 25	16.60	Acetonitrile, 26.56 mgms., i. e., 1.6 mgm. per gm. mouse; died, 17 hours.

Series 4.

A. CONTROLS. (v, 85.)

905.	*Grams.*	
ɔt. 19	17.85	Oats and water.
ɔt. 25	18.31	
t. 1	17.13	Acetonitrile, 8.57 mgms., i. e., 0.5 mgm. per gm. mouse; survived.
ɔt. 19	15.80	Diet as above.
ɔt. 25	14.92	
t. 2	14.61	Acetonitrile, 8.04 mgms., i. e., 0.55 mgm. per gm. mouse; died, 3 hours.

B. RESTRICTED DIET. (v, 85.)

905.	*Grams.*	
ɔt. 19	16.20	Limited diet begun.
ɔt. 26	14.33	
t. 1	11.60	Acetonitrile, 9.33 mgms., i. e., 0.8 mgm. per gm. mouse; survived.
ɔt. 19	17.66	Diet as above.
ɔt. 26	14.03	
t. 2	12.85	Acetonitrile, 10.92 mgms., i. e., 0.85 mgm. per gm. mouse; survived.
ɔt. 19	18.12	Diet as above.
ɔt. 26	16.22	
t. 2	12.31	Acetonitrile, 12.31 mgms., i. e., 1 mgm. per gm. mouse; died, 1¼ hours.

In the following group of experiments the diet consisted of "cakes" ade from cracker dust and water; the controls received all they ould eat (between 3 and 4 gms. daily), whereas those on the limited et received but 1 gm. per day. The resistance to acetonitrile of ice which have received a diet of cakes is much less than that of ose which have had oats.

Series 5.

A. CONTROLS. (v, 87.)

Date.	Weight of mouse.	Remarks.
1905.	*Grams.*	
pt. 19	12.60	Cakes.
pt. 30	13.55	
ct. 2	12.71	Acetonitrile, 2.29 mgms., i. e., 0.18 mgm. per gm. mouse; survived.
pt. 19	16.80	Cakes.
pt. 30	15.45	
ct. 2	14.81	Acetonitrile, 2.96 mgms., i. e., 0.2 mgm. per gm. mouse; died 1 hour.

Other mice of this series died from 0.22 and 0.26 mgm. acetonitrile per gm. mouse.

B. RESTRICTED DIET.

Date.	Weight of mouse.	Remarks.
1905.	*Grams.*	
Sept. 19	18.87	Restricted diet begun.
Sept. 25	15.41	
Sept. 28	14.31	
Oct. 1	13.41	Acetonitrile, 6.03 mgms., i. e., 0.45 mgm. per gm. mouse; survived.
Sept. 19	23.55	Diet as above.
Sept. 25	18.51	
Sept. 28	18.05	
Oct. 1	16.71	Acetonitrile, 10.03 mgms., i. e., 0.6 mgm. per gm. mouse; survived.
Oct. 2	17.15	Cakes 4 gm.
Oct. 9	14.91	
Oct. 13	15.21	Acetonitrile, 9.13 mgms., i. e., 0.6 mgm. per gm. mouse; died 2½ hours.
Sept. 19	16.69	Restricted diet begun.
Sept. 25	13.65	
Sept. 28	12.41	
Oct. 2	12.58	Acetonitrile, 8.81 mgms., i. e., 0.7 mgm. per gm. mouse; died 3½ hours.

Series 6.

In this series the mice of one group were given alternately, for 4 or 5 days at a time, full and restricted diets. It has been stated that such a method of feeding leads to a greater increase in weight than does the use of a full diet continuously, the inference being that the body learned to be more "economical" with its food.[a]

A. CONTROLS. (v, 181.)

Date.	Weight of mouse.	Remarks.
1905.	*Grams.*	
Oct. 14	15.62	Oats and cakes.
Oct. 26	17.01	
Nov. 6	18.08	
Nov. 17	19.53	
Nov. 25	19.34	
Dec. 11	20.33	
Dec. 18	21.67	Acetonitrile, 11.92 mgms., i. e., 0.55 mgm. per gm. mouse; survived.
Oct. 14	18.22	Diet as above.
Oct. 26	17.62	
Nov. 6	17.92	
Nov. 15	17.58	
Dec. 11	19.93	
Dec. 17	21.16	Acetonitrile, 13.33 mgms., i. e., 0.63 mgm. per gm. mouse; survived.
Oct. 14	14.05	Diet as above.
Oct. 26	15.61	
Nov. 6	16.80	
Nov. 15	17.73	
Nov. 21	18.12	
Dec. 2	17.28	Acetonitrile, 10.87 mgms., i. e., 0.63 mgm. per gm. mouse; died 15 hours.
Oct. 14	18.43	Diet as above.
Oct. 26	22.31	
Nov. 6	23.53	
Nov. 15	23.20	
Nov. 21	23.71	
Dec. 11	24.48	
Dec. 16	24.61	Acetonitrile, 15.99 mgms., i. e., 0.65 mgm. per gm. mouse; died 2 hours.

[a] According to Michaud (Zeitschr. f. physiol. Chem., 1909, 59, p. 405), N-metabolism may be much lowered by alternate periods of hunger and feeding.

B. FULL AND RESTRICTED DIETS ALTERNATELY.

Date.	Weight of mouse.	Remarks.
1905.	*Grams.*	
t. 14	17.06	Diet begun.
t. 17	15.85	
t. 18	14.45	
t. 23	17.15	
t. 25	17.71	
t. 27	14.95	
ov. 3	13.85	
ov. 6	14.81	
ov. 10	17.45	
ov. 15	15.70	
ov. 21	16.66	
ov. 24	16.40	
ov. 28	14.35	
ec. 2	17.10	Acetonitrile, 10.26 mgms., i. e., 0.6 mgm. per gm. mouse; survived.
ec. 3	.....	Diet continued.
ec. 5	17.25	
ec. 11	16.75	
ec. 16	19.45	
ec. 17	18.84	Acetonitrile, 16.96 mgms., i. e., 0.9 mgm. per gm. mouse; died 2 to 3 hours.
ct. 14	16.76	Diet begun.
ct. 17	14.75	
ct. 18	13.35	
ct. 23	16.85	
ct. 25	17.85	
ct. 27	14.82	
ov. 3	12.75	
ov. 6	16.40	
ov. 10	14.51	
ov. 15	16.02	
ov. 21	12.63	
ov. 28	17.05	
ec. 2	17.35	
ec. 4	15.72	
ec. 11	15.75	
ec. 16	18.45	Acetonitrile, 14.76 mgms., i. e., 0.8 mgm. per gm. mouse; survived.
ct. 14	15.68	Diet begun.
ct. 17	11.65	
ct. 23	12.65	
ct. 25	13.83	
ct. 27	14.91	
ov. 3	16.65	
ov. 6	16.70	
ov. 10	16.65	
ov. 15	17.02	
ov. 21	17.46	
ov. 24	17.63	
ov. 28	16.11	
ec. 2	15.06	
ec. 3	14.54	Acetonitrile, 11.63 mgms., i. e., 0.8 mgm. per gm. mouse; died in about 15 hours.

The above experiments show that the mice which had received lternately full and restricted diets were somewhat more resistant to cetonitrile than were those which had received only the unrestricted iet. The difference was not as great as when a restricted diet alone vas fed. If the increase in weight of the mice in the two groups be alculated in percentage the following figures are obtained:

Unrestricted diet: 38 per cent, 16 per cent, 33 per cent, 28 per ent.

Full and restricted diets alternately: 14 per cent, 10 per cent, 12 per cent.

The mice on the unrestricted diet had increased in weight much more than those on the alternately full and restricted diet.

That the increased resistance to acetonitrile of the mice which had received the restricted diet was not due simply to a loss of weight is suggested by those experiments in which mice receiving a full diet also lost weight but did not show an increased resistance to the poison. Many experiments will be quoted in later parts of this paper in which a marked loss of weight occurred on various diets (cheese e. g.) without there being such an increased resistance. Moreover, the administration of ethyl alcohol frequently causes a loss of weight, but the resistance to acetonitrile is distinctly lowered.

Other illustrations of marked losses of weight without an increased resistance to acetonitrile are as follows:

Hydrated chloral.

Series 7.

A. CONTROLS. (IV, 171.)

Date.	Weight of mouse.	Remarks.
1905.	*Grams.*	
Jan. 9	18.21	Oats and water.
Jan. 13	17.02	
Jan. 21	18.41	Acetonitrile, 6.44 mgms., i. e., 0.35 mgm. per gm. mouse; survived.
Jan. 9	14.51	Oats and water.
Jan. 13	14.42	
Jan. 22	15.61	Acetonitrile, 6.24 mgms., i. e., 0.4 mgm. per gm. mouse; died in 17 hours.

B. HYDRATED CHLORAL.

1905.		
Jan. 9	17.92	Hydrated chloral, 5 per cent, on oats.
Jan. 13	15.45	
Jan. 16	14.13	
Jan. 22	13.71	Acetonitrile, 4.1 mgms., i. e., 0.3 mgm. per gm. mouse; survived.
Jan. 9	19.25	Hydrated chloral as above.
Jan. 13	17.01	
Jan. 16	16.61	
Jan. 23	15.55	Acetonitrile, 5.44 mgms., i. e., 0.35 mgm. per gm. mouse; died in 11 hours.

It is possible, however, that in certain cases of increased resistance to acetonitrile caused by the administration of other poisons the loss of weight caused by the latter may be a factor.

The above experiments show very clearly that mice which have received a restricted diet are more resistant to acetonitrile than are those which have received an unrestricted diet. This result might be due to either of two causes, (1) the processes by which acetonitrile is decomposed in the body with the formation of hydrocyanic acid may be less active in inanition, or (2) inanition may render the mice less susceptible to the hydrocyanic acid. The first and more probable suggestion will be discussed later; that the second suggestion is not applicable is shown by the following experiment with nitroprussiate of soda, a poison which very readily liberates hydrocyanic acid in the body:

Series 8.

A. CONTROL.

Date.	Weight of mouse.	Remarks.
1905.	*Grams.*	
Oct. 3	19.75	Cakes, all the mice would eat.
Oct. 9	18.62	
Oct. 14	18.45	Nitroprussiate of soda, 0.148 mgm., i. e., 0.008 mgm. per gm. mouse; survived.

B. RESTRICTED DIET.

1905.	*Grams.*	
Oct. 3	20.82	Cakes, 1 gm. daily.
Oct. 5	19.01	
Oct. 7	17.22	
Oct. 9	16.21	
Oct. 12	16.25	
Oct. 14	15.55	Nitroprussiate of soda, 0.14 mgm., i. e., 0.009 mgm. per gm. mouse; died, in 1½ hours.

(b) EXPERIMENTS WITH GUINEA PIGS.

These experiments were performed primarily to determine whether there was a difference in the amounts of sulphocyanate excreted, after the injection of acetonitrile, between normally fed guinea pigs and those which had received a restricted diet. An increased excretion of sulphocyanate probably means an increased breaking up of the acetonitrile molecule and it was hoped that in this way something could be learned concerning the processes of metabolism of animals kept upon a restricted diet. The diet was in all cases qualitatively the same, but less was given to those on the restricted diet; the animals were weighed every other day and only sufficient food given to prevent a marked loss of weight. As the animals were not full grown the controls increased considerably in weight. In the first experiment the sulphocyanate was not determined quantitatively, but an approximate estimation of the relative amounts excreted was obtained by comparing the intensity of the ferric chloride reaction.

Series 9.

A. CONTROL. (v, 152.) FULL, MIXED DIET (CARROTS AND CABBAGE).

Date.	Weight of guinea pig.	Remarks.
1905.	*Grams.*	
Feb. 23	490	
Mar. 9	565	
Mar. 20	675	Acetonitrile, 168.8 mgms., i. e., 0.25 mgm. per gm. guinea pig; survived.

The urine gave an intense reaction with ferric chloride on both the first and second days after the injection of the acetonitrile.

B. RESTRICTED DIET. (v, 116.)

Date.	Weight of guinea pig.	Remarks.
1905.	*Grams.*	
Feb. 21	382	
Mar. 3	430	Restricted diet begun.
Mar. 6	405	
Mar. 9	407	
Mar. 14	376	
Mar. 17	377	
Mar. 20	325	Acetonitrile, 81.25 mgms., i. e., 0.25 mgm. per gm. guinea pig; survived.

The urine excreted in the first 24 hours, although abundant, gave no reaction whatever with ferric chloride; that for the second 24 hours gave an intense reaction.

In the following experiments the sulphocyanate was determined by Lang's [a] method.

Series 10.

In this experiment, after the injection of the acetonitrile, the feeding was reversed; i. e., the guinea pig which had received an unrestricted diet was placed on a restricted diet, and vice versa. After about two weeks sodium sulphocyanate was administered to each in order to determine whether there was any difference in the ability of the animals to excrete preformed sulphocyanate.

A. CONTROL. UNRESTRICTED DIET. (v, 117.)

Date.	Weight of guinea pig.	Remarks.
1905.	*Grams.*	
Oct. 17	355	
Oct. 28	400	
Nov. 3	425	
Nov. 15	490	
Nov. 22	495	Acetonitrile, 99 mgms., i. e., 0.2 mgm. per gm. guinea pig; survived. In the first five days after the injection of the acetonitrile the urine contained 38.7 mgms. cyanogen (corresponding to about 62 mgms. acetonitrile., i. e., about 63 per cent of the cyanogen of the nitrile had appeared in the urine).
Nov. 27	.....	Restricted diet begun.
Dec. 4	475	
Dec. 9	475	
Dec. 11	450	Sodium sulphocyanate, 180 mgms., i. e., 0.4 mgm. per gm. animal, injected subcutaneously; survived. In the following three days 49 mgms. of cyanogen (= 151.9 mgms. NaCNS, or 84.4 per cent of the amount injected) was excreted in the urine.

[a] Lang, Archiv. für exper. Path. und Pharmakol, 1894, v. 34, p. 247.

B. RESTRICTED DIET. (v, 117.)

Date.	Weight of guinea pig.	Remarks.
1905.	*Grams.*	
ct. 21	385	Restricted diet begun.
ct. 30	400	
ov. 3	395	
ov. 8	390	
ov. 15	410	
ov. 22	410	Acetonitrile, 82 mgms., i. e., 0.2 mgm. per gm. guinea pig; survived. The urine of the five days following the injection of the nitrile contained 23.7 mgms. cyanogen; this corresponds to 38 mgms. of acetonitrile. Hence about 46 per cent of the cyanogen of the nitrile appeared in the urine as sulphocyanate.
ov. 27	.....	Unrestricted diet begun.
ec. 4	460	
ec. 9	500	
ec. 11	495	Sodium sulphocyanate, 198 mgms., i. e., 0.4 mgm. per gm. animal; survived. In the following three days 49 mgms. cyanogen (=151.9 mgms. NaCNS, or 77 per cent of the amount injected) was secreted in the urine.

These experiments show (1) that the guinea pig upon a restricted iet excreted in the urine less sulphocyanate, after the administra- ion of acetonitrile, than did the one upon an unrestricted diet, and 2) that there was not a distinct difference between the amounts of ulphocyanate excreted in the two cases after the administration of he sodium salt. Hence it may be concluded that the increased xcretion in the former case was due to an increased formation of the ulphocyanate and not to any differences in the rate of excretion or lestruction of the sulphocyanate which was formed.

Series 11.

A. CONTROL. UNRESTRICTED DIET. (v, 104.)

Date.	Weight of guinea pig.	Remarks.
1905.	*Grams.*	
eb. 14	380	Acetonitrile, 76 mgms., i. e., 0.2 mgm. per gm. animal; died in 13 hours.

B. LIMITED DIET. (v, 118.)

1905.	*Grams.*	
an. 30	415	Restricted diet begun.
eb. 2	401	
eb. 8	376	
eb. 14	327	Acetonitrile, 65.4 mgms., i. e., 0.2 mgm. per gm. animal; survived.

The urine of "B" for the first 24 hours gave but a faint reaction or sulphocyanate; with animals on an unrestricted diet the first 24 hours urine gave, as a rule, an intense reaction.

Series 12.

The following experiments were conducted as above, except that the resistance of the animals toward another cyanogen compound, viz., nitroprussiate of soda, was first tested. The dose of the nitroprussiate of soda was but slightly less than the one usually fatal to guinea pigs; if either guinea pig had had a markedly decreased resistance to this poison it would probably have died.

A. CONTROL. (v, 98.)

Date.	Weight of guinea pig.	Remarks.
1905.	*Grams.*	
Sept. 26	335	Unrestricted diet.
Oct. 2	362	
Oct. 13	360	
Oct. 23	430	
Oct. 28	480	
Nov. 3	490	
Nov. 6	495	Nitroprussiate of soda, 4.95 mgms., i. e., 0.01 mgm. per gm. animal; survived.
Nov. 7	.....	Unrestricted diet continued.
Nov. 8	465	
Nov. 15	500	
Nov. 21	520	Acetonitrile, 130 mgms., i. e., 0.25 mgm. per gm. animal; died in 13 hours.

B. RESTRICTED DIET. (v. 98.)

1905.	*Grams.*	
Sept. 26	358	Restricted diet begun.
Sept. 28	392	
Oct. 2	397	
Oct. 6	355	
Oct. 15	350	
Oct. 19	350	
Oct. 23	380	
Nov. 3	375	
Nov. 6	365	Nitroprussiate of soda, 3.65 mgms., i. e., 0.01 mgm. per gm. animal; survived.
Nov. 7	.....	Restricted diet continued.
Nov. 8	365	
Nov. 11	360	
Nov. 18	390	
Nov. 21	365	Acetonitrile, 91.25 mgms., i. e., 0.25 mgm. per gm. animal; survived. The urine for the 4 days following the injection of the acetonitrile contained 18 mgms. cyanogen, i. e., 31.5 per cent of the cyanogen of the nitrile was excreted as sulphocyanate.
Nov. 27	.....	Unrestricted diet begun.
Dec. 4	445	
Dec. 14	480	Acetonitrile, 91.25 mgms., i.e., 0.19 mgm. per gm. animal; died in 12 hours. The urine gave a strong reaction with ferric chloride.

Thus, with equal doses of acetonitrile the guinea pig on an unrestricted diet died while that on the restricted diet recovered. Later when the animal which had received the restricted diet was placed upon an unrestricted diet it died from a dose of acetonitrile smaller, per gm. body weight, than that from which it had recovered when it was receiving a limited diet.

The excretion of sulphocyanate after the injection of acetonitrile into the guinea pig which had received the limited diet was less (31.5 per cent of the cyanogen injected) than that which is usually found in the case of animals on an unrestricted diet.

Summary.—The above experiments show (1) that guinea pigs which have been kept upon a restricted diet are more resistant to acetonitrile than are those which have received an unrestricted diet, and (2) that in the former less of the cyanogen of the acetonitrile is execreted as sulphocyanate. The increased resistance to the poison and the diminished execretion of sulphocyanate are probably both dependent upon a lessened breaking up of the acetonitrile molecule and this again upon a diminution in the intensity of those processes of metabolism by which the acetonitrile molecule is decomposed. The body "spares" the acetonitrile molecule in hunger as it does the protein molecule and the fundamental processes may be the same in the two cases.[a]

[a] Experiments were made with acetonitrile under a number of other conditions and with a number of poisons which have at different times been supposed to alter some processes of physiological oxidation; the results were essentially negative. Thus chloroform water was fed or injected subcutaneously into mice and guinea pigs and their resistance to acetonitrile tested; no change was noted. Negative results were also obtained with quinine, sodium bicarbonate, and carbon monoxide, and with mice kept in pure oxygen or in a greatly rarefied atmosphere. Mice kept in a cage with a wheel upon which they exercised a great deal seemed to be slightly less resistant to acetonitrile than were those kept in jars where there was little opportunity of exercise.

The effects of inanition and several drugs were tested upon the action of another poison, methyl alcohol, the toxicity of which I have been led (Johns Hopkins Hosp. Bull., 1902, 13, p. 213) to believe is due in part to the formation in the body of secondary toxic substances; the results were negative.

Part II.

THE EFFECTS OF VARIOUS DIETS UPON THE RESISTANCE OF ANIMALS TO CERTAIN POISONS.

A. HISTORICAL.

Although much has been written on the effect of different diets upon some of the changes in metabolism caused by poisons, and there are a number of observations on the effect of diet upon the changes undergone by poisons in the body,[a] but little seems to have been done upon the resistance to poisons caused by different diets. In fact the only experiments bearing directly upon this subject with which I am acquainted are those of Foster[b] upon the resistance of dogs to ricin: Of three dogs which had been kept upon a high plane of protein nutrition all died from 1 mgm. ricin per kilo, whereas of 3 kept on medium or low planes of protein nutrition 2 survived this dose.[c]

B. EXPERIMENTAL.

1. Experiments with Acetonitrile.

Although I have found diet to produce marked changes in the resistance of animals to some of the better-known poisons (such as morphine, cocaine, atropine, etc.) the most striking and, from a theoretical standpoint, the most interesting results were obtained with acetonitrile. This was the result anticipated for the reasons given in Part I, viz, that the formation of hydrocyanic acid from acetonitrile is intimately connected with processes of metabolism and these again with the character of the diet. Moreover, I have shown in previous publications[d] that the toxicity of acetonitrile is closely related to one of the most important glands of internal secretion (the thyroid) and it was of especial interest to determine by means of the reactions based upon this relation whether it is possible to influence the activity of this gland by diet.

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[a] Abderhalden and Brahm (Zeit. f. physiol. Chem., 1909, 62, p. 133), for example, find that dogs which have received only milk secrete no methyl pyridine after the administration of pyridine, but that they rapidly acquire this power after the feeding of meat and retain it even when the milk diet is resumed.

[b] Foster. Proc. Soc. Exp. Biol. and Med., 1909, 6, p. 61

[c] But cf. Foster, Jour. of Biolog. chem., May, 1910, v. 7, p. 379.

[d] Bulletin 47, Hygienic Laboratory, 1909.

Before describing the experiments a few of the conditions which are known to influence the resistance of animals to acetonitrile may be referred to briefly. The more important of these are:

Thyroid.—Numerous experiments have shown that minute amounts of thyroid fed to mice for a short time markedly increase the resistance of these animals to acetonitrile. The opposite effect, viz, an increased susceptibility to this poison is produced when thyroid is fed to rats [a] and guinea pigs.

Iodine compounds.—The administration of iodine compounds to animals has an effect (if it has any at all) upon their resistance to acetonitrile similar to but far less marked than that of thyroid, i. e., it increases the resistance of mice but diminishes that of rats and guinea pigs. I have given reasons elsewhere for believing that the effect of iodine in these cases is exerted through the thyroid gland.[b]

Sulphur.—Lang [c] found sodium thiosulphate to protect animals, to a certain extent, against hydrocyanic acid; Heymans [d] and his co-workers found it to have a similar, but often more marked, action against a number of nitriles. I found thialdine, carbothialdine, and potassium xanthogenate to have an antagonistic action toward a number of nitriles; a number of other sulphur compounds had little or no such action.[e]

In most of these experiments the sulphur compounds were injected subcutaneously or intravenously, and there is nothing to suggest that the sulphur which is contained in so many articles of food would have a similar protective action; that this may be the case, however, is suggested by certain experiments to be described later.

Season has, as was pointed out in a previous publication, a marked effect upon the resistance of mice to acetonitrile. This question will be discussed in later parts of this paper.

(*a*) EXPERIMENTS ON MICE.

In order to make the conditions as uniform as possible and to eliminate differences in susceptibility which might result from differences in race, previous diets, etc., the experiments were performed,

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[a] It is a matter of some interest that animals which are supposed to be as closely related zoologically as are mice and rats should differ so markedly in some of their physiological reactions. Uhlenhuth and Weidanz (Arbeiten. aus dem kais. Ges.-Amte., 30, p. 434) and Trommsdorf (Ibid., 1909, 32, p. 560), as a result of a study of certain serum reactions, have recently reached the conclusion that these animals are not as closely related as is usually supposed.

[b] Jour. Amer. Med. Ass., 1907, 49, p. 1323.

[c] Lang. Archiv für exper. Path. u. Pharmakol., 1895, 36, p. 77.

[d] Heymans. Archives internat. de Pharmacodynamie et de Therapie, 3, pp. 77, 359; 7, p. 297; 8, p. 1.

[e] Hunt., ibid., 1904, 12, p. 447.

with few exceptions, upon mice which had been bred in the laboratory and which had lived under as nearly as possible identical conditions.

As the experiments were very numerous only the largest nonfatal and the smallest fatal doses are recorded in the tables. As a rule there is no difficulty in determining the fatal dose within 0.01 to 0.02 mgm. per gm. mouse; where, however, the fatal doses vary as widely as they did in these experiments many animals were used in determining the approximately fatal dose.

ACETONITRILE—MICE.

Series 13. (Jan., 1910.) (xii, 12.)

Groups of young, nearly grown mice (10 in each group) were kept upon the following diets for about 6 weeks (from December 3, 1909, to January 14, 1910). The milk and oatmeal, and the bread and oil were intimately mixed.

[Dose in mgm. per gm. mouse.]

Diet.	Change in weight (average).	Fatal dose of acetonitrile.	
		Recovered.	Died.
a. Milk, raw [a]	Increased 8.3 per cent (from 15 to 16.25 gms)	0.08	0.10
b Olive oil, 1 part; bread, 3 parts. [b]	Decreased 21 per cent (from 15 to 11.85 gms.)	.21	.25
c. Milk, boiled [c]	Decreased 2.7 per cent (from 15 to 14.66 gms.)	.25	.33
d. Cod liver oil, 1 part; bread, 3 parts. [d]	Increased 6.7 per cent (from 15 to 16 gms.)	.30	.50
e. Oatmeal, 1 part; boiled milk, 2 parts. [e]	Increased 38.4 per cent (from 15 to 20.22 gms.)	.45	.50
f. Oatmeal, 1 part; raw milk, 2 parts.	Increased 42.7 per cent (from 15 to 21.41 gms.)	1.30	1.40
g. Oatmeal, 1 part; water, 2 parts. [e]	Increased 16.3 per cent (from 15 to 17.44 gms.)	1.70	1.80
h. Bread (C) and water [b]	Increased 17.6 per cent (from 14.8 to 17.4 gms.)	2.70	3.00

[a] Two of the 10 had died before the acetonitrile was given. [b] Four had died.
[c] Seven had died. [d] Eight had died. [e] One had died.

The results of these experiments will be discussed in more detail later, but reference may be made in this connection to a few points. The result with group *b* shows that a marked loss of weight may occur without an increased resistance to acetonitrile (cf. results on inanition, Part I). The results with groups *b*, *d*, and *h* show how markedly a high degree of resistance caused by one diet may be lowered by the addition of another food (in these cases oils). The results also show that raw and boiled milk may have different effects under different conditions, although both lowered the resistance caused by oatmeal alone. There was no relation between the increase in weight and the susceptibility to the poison.

The mice of groups *e*, *f*, *g*, and *h* which had survived were, on January 15, placed on a diet of raw milk; after 3 weeks their resistance to acetonitrile was again tested. The fatal doses of the previous period are placed in parentheses for comparison:

[Dose in mgm. per gm. mouse.]

Previous diet.	Change in weight (average).	Fatal dose of acetonitrile.	
		Recovered.	Died.
e. Oatmeal, 1 part; boiled milk, 2 parts.	Increased 7.5 per cent (from 16.75 to 18 gms.)....	(0.45)	0.20(0.50)
f. Oatmeal, 1 part; raw milk, 2 parts.	Decreased 1.4 per cent (from 19 to 18.74 gms.)....	0.28(1.30)	.33(1.40)
g. Oatmeal, 1 part; water, 2 parts.	Increased 5.9 per cent (from 16.67 to 17.67 gms.) .	1.00(1.70)	(1.80)
h. Bread (C) and water.....	Increased 15.2 per cent (from 18.4 to 21.2 gms.)...	.13(2.70)	.15(3.00)

Thus the change to the raw milk diet very quickly and greatly reduced the resistance of all the groups except the one which had received, during the previous period, the diet of oatmeal and water. As will be shown later oatmeal usually leads to a long continued resistance. The reduction of resistance in the above experiment was especially striking in the case of the mice which had received bread in the previous period.

Series 14. (Feb., 1908.) (x, 104.)

Fifteen mice, not fully grown, were placed upon the following diets and their resistance to acetonitrile determined after about 8 weeks. The group "Oatmeal and milk" received at first no water; the milk (which had been boiled) was placed in a vessel separate from the oatmeal. Later a vessel containing water was also placed in the cage. The mice were not weighed until at the end of the experiment. The bread was from a different bakery than that used in the preceding series.

[Dose in mgm. per gm. mouse.]

Diet.	Weight (average).	Fatal dose of acetonitrile.	
		Recovered.	Died.
	Grams.		
a. Bread (S).....	19.70	0.65	0.70
b. Oatmeal.....	20.12	1.60	1.70
c. Oatmeal and milk (boiled).....	20.35	2.10	2.40

Series 15. (Mar., 1908.) (x, 108.)

Grown mice were placed upon the following diets for about 12 weeks:

[Dose in mgm. per gm. mouse.]

Diet.	Weight (average).	Fatal dose of acetonitrile.	
		Recovered.	Died.
	Grams.		
a. Bread (S)	19.56	.....	0.35
b. Oatmeal	22.27	2.10	2.30
c. Oatmeal and milk (boiled)	24.56	2.30	2.50

Series 16. (Mar., 1906.) (vi, 154.)

Mice were placed upon the following diets for about 4 weeks. They were weighed at frequent intervals:

[Dose in mgm. per gm. mouse.]

Diet.	Change in weight (average).	Fatal dose of acetonitrile.	
		Recovered.	Died.
a. Barley	Decreased 4.4 per cent (from 21 to 20 gms.)	0.46	0.48
b. Rye	Decreased 1 per cent (from 17.96 to 17.76 gms.)	.53	.55
c. Wheat	No change (19.7 gms.)	.55	.57
d. Oats	No change (17.9 gms.)	.75	.80

Series 17. (May, 1908.) (x, 172.)

Groups of young mice (15 in each) were fed as below for 8 to 9 weeks:

[Dose in mgm. per gm. mouse.]

Diet.	Change in weight (average).	Fatal dose of acetonitrile.	
		Recovered.	Died.
a. Egg yolk (boiled)	Increased 40 per cent (from 12.98 to 18.2 gms.)	0.12	0.15
b. Milk (boiled)	Increased 26 per cent (from 12.48 to 16.13 gms.)	.20	.21
c. Cheese	Increased 15 per cent (from 13.2 to 15.14 gms.)	.24	.25
d. Milk (raw)	Increased 13 per cent (from 12.84 to 14.55 gms.)	.28	.30
e. Ham (lean)	Increased 26 per cent (from 12.28 to 15.50 gms.)	.30	.31
f. Egg white (boiled) and bread (equal parts).	Increased 6.2 per cent (from 12.87 to 13.67 gms.)	.32	.35
g. Egg white (boiled) and oatmeal (equal parts).	Increased 13 per cent (from 13.25 to 15 gms.)	.50	.54
h. Bread (S)	Increased 16.4 per cent (from 12.67 to 14.75 gms.)	.80	1.00
i. Bread and oat ash [a]	Increased 5.8 per cent (from 12.67 to 13.4 gms.)	.80	.90
j. Oats	Increased 2 per cent (from 13.49 to 13.80 gms.)	1.50	1.80
k. Potatoes (boiled)	Decreased 7.6 per cent (from 12.67 to 11.67 gms.)	1.80	2.20
l. Liver hog (boiled)	Increased 10 per cent (from 13.49 to 14.91 gms.)	2.80	3.50

[a] The ash from 100 gms. oats was intimately mixed with the bread and fed daily.

There was, in this series, quite a close parallelism between the egree of resistance and the rate of growth; the more rapid the growth he less was the resistance.

Series 18. (July, 1908.) (xi, 2.)

These experiments were performed in July, a month in which the esistance of mice to acetonitrile is always low.

[Dose in mgm. per gm. mouse.]

Diet.	Change in weight (average).	Fatal dose of acetonitrile.	
		Recovered.	Died.
. Egg yolk (boiled)	Increased 24 per cent (from 15.3 to 19 gms.)	0.098	0.11
. Egg, entire (boiled)	Increased 22 per cent (from 14.2 to 17.4 gms.)	.095	.10
. Oats, extracted [a]	Decreased 16 per cent (from 15.5 to 13 gms.)	.190	.20
. Brain [b] (sheep) and oatmeal (equal parts).	Increased 15 per cent (from 17 to 19.5 gms.)	.210	.22
. Egg yolk and liver (equal parts).	Increased 23 per cent (from 15.1 to 18.6 gms.)	.290	.30
. Oatmeal	Increased 5.7 per cent (from 15.7 to 16.6 gms.)	.400	.45
. Kidney, sheep (boiled)	Increased 20 per cent (from 13.7 to 16.5 gms.)	.630	.64
. Egg white and oatmeal (equal parts).	Increased 10 per cent (from 15.7 to 17.3 gms.)	.750	.80
. Egg white and liver (equal parts).	Increased 2 per cent (from 15.1 to 15.4 gms.)	.870	.90
. Liver, hog (boiled)	Increased 1 per cent (from 15.3 to 15.5 gms.)	1.50	1.80

[a] Residue after extraction with 96 per cent alcohol.
[b] Mice die in a few days on an exclusive diet of brain.

The combinations of foods gave results of some interest. Thus a mixture of egg white and egg yolk did not have an effect different from that of egg yolk alone. A mixture of egg white and liver led to a condition in which the resistance to acetonitrile was but one-half as great as when liver alone was given. The effect of adding egg white to oatmeal was the reverse; the mice became twice as resistant as when oatmeal alone was given. Brain added to oatmeal and egg yolk added to liver caused a lower degree of resistance than when oatmeal or liver was given alone.

With two or three exceptions there was, in this series, a fairly close parallelism between the degree of resistance and the increase in weight; the greater the latter the lower was the former.

Series 19. (Aug., 1907.) (x, 102.)

A number of adult mice were fed upon the following diets for about 5 weeks:

[Dose in mgm. per gm. mouse.]

Diet.	Weight (average).	Fatal dose of acetonitrile.	
		Recovered.	Died.
	Grams.		
a. Bread (S)	19.71	0.47	0.49
b. Oats	21.42	.56	.60

Series 20. (Dec., 1907.) (x, 100.)

A number of adult mice were kept upon the following diets for a period of about 4½ months. Many young mice were born; a careful record was not kept, but those receiving the diet of hemp seed and milk seemed to be the most prolific.

[Dose in mgm. per gm. mouse.]

Diet.	Weight (average).	Fatal dose of acetonitrile.	
		Recovered.	Died.
	Grams.		
a. Bread (S)	25.19	0.56	0.58
b. Bread and milk (raw)	19.63	.58	.59
c. Oats and milk (raw)	23.61	.65	.75
d. Hemp seed and milk (raw)	19.94	.65	.....
e. Hemp seed	20.76	.68	.70
f. Oats	20.86	1.70	1.80

The milk very distinctly lowered the resistance caused by the oats.

Series 21. (Dec., 1909.) (xii, 2.)

Groups of mice, not fully grown, were fed as follows for about 6 weeks. The corn-meal mush was made by boiling a commercial white corn meal with water. Part of this mush was placed aside in a warm room and allowed to become sour before feeding. The bread was from a different bakery than that used in the immediately preceding series.

[Dose in mgm. per gm. mouse.]

Diet.	Change in weight (average).	Fatal dose of acetonitrile.	
		Recovered.	Died.
a. Corn-meal mush (fresh)	Decreased 3.8 per cent (from 13.80 to 13.28 gms.)	0.80	0.90
b. Corn-meal mush (sour)	Decreased 18.1 per cent (from 14.72 to 12.05 gms.)	.80	.90
c. Bread (C) and oats	Increased 26.2 per cent (from 13.8 to 17.42 gms.)	1.20	1.30

The resistance of other mice of these groups toward atropine sulphate and cocaine hydrochloride was tested; no difference was found between groups *a* and *c*, but those of group *b* were less resistant to both poisons.

Series 22. (Mar., 1908.) (x, 112.)

Mice, not fully grown, were fed as below for about 6 weeks.

[Dose in mgm. per gm. mouse.]

Diet.	Change in weight (average).	Fatal dose of acetonitrile.	
		Recovered.	Died.
Beans, "navy" (boiled)	Decreased 2.8 per cent (from 14 to 13.6 gms.)	0.95	1.00
Corn, whole grain	Decreased 11.4 per cent (from 14 to 12.4 gms.)	1.10	1.20
Peanuts (raw)	Decreased 7.1 per cent (from 14 to 13 gms.)	1.80	2.00
Beef (lean)	Increased 7 per cent (from 14 to 15 gms.)	1.80	2.00

Series 23. (Dec., 1909.) (xii, 11.)

Mice, not fully grown, were kept on the following diets for about weeks.

[Dose in mgm. per gm. mouse.]

Diet.	Change in weight (average).	Fatal dose of acetonitrile.	
		Recovered.	Died.
Cotton-seed oil, 1 part; bread (C), 2 parts.	Decreased 41.5 per cent (from 15.4 to 9 gms.)	0.50	0.70
Olive oil, 1 part; bread (C), 2 parts.	Decreased 24.7 per cent (from 15.4 to 11.6 gms.)	.65	.80
Bread (C)	Increased 1.6 per cent (from 15.9 to 16.16 gms.)	2.20	2.50

The addition of oil to the diet led to a marked loss of weight and o a low degree of resistance.

Series 24. (Dec., 1909.) (xii, 30.)

The mice were fed as below for about 5 weeks.

[Dose in mgm. per gm. mouse.]

Diet.	Change in weight (average).	Fatal dose of acetonitrile.	
		Recovered.	Died.
Egg, entire	Increased 10.7 per cent (from 16.33 to 18.08 gms.)	0.85	0.95
Mush from good corn meal.	Decreased 9.7 per cent (from 16.33 to 14.75 gms.)	1.40	1.70
Mush from moldy corn meal.	Decreased 15.8 per cent (from 16.33 to 13.75 gms.)	2.50	.....

The resistance of mice to acetonitrile is usually high in the winter. The mice on the egg diet had not increased in weight as much as they usually did on this diet; their resistance was also higher.

Series 25. (Feb., 1910.) (xii, 34.)

The mice were fed as below for nearly 6 weeks. The corn oil was extracted with cold ether from yellow corn meal prepared in the laboratory.[a] The egg oil was extracted from the yolk of eggs with ether and alcohol; most of the lecithin was afterwards removed.

[Dose in mgm. per gm. mouse.]

Diet.	Change in weight (average).	Fatal dose of acetonitrile.	
		Recovered.	Died.
a. Corn oil, 1 part; bread (C), 2 parts.	Decreased 15.3 per cent (from 15.83 to 13.4 gms.)....	0.17	0.20
b. Egg oil, 1 part; bread (C), 2 parts.	Decreased 22.8 per cent (from 15.85 to 12.33 gms.)....	.18	.23
c. Olive oil, 1 part; bread (C), 2 parts.	Decreased 5.36 per cent (from 15.85 to 15 gms.).....	.35	.....
d. Egg (whole).....	Increased 34.9 per cent (from 12.6 to 17 gms.).....	.35	.45
e. Bread (C).....	No change (12.33 gms.).....	4.30	4.40

The mice fed upon this particular kind of bread (C) had again a remarkably high degree of resistance. The addition to the bread of corn and egg oils lowered the resistance to about one-twentieth. The changes in weight caused by the egg diet and the bread and egg oil diet are interesting; the former caused a great increase in weight, whereas the latter caused a decrease. Both, however, caused a low degree of resistance. These results suggest that it is not the oil in the egg which causes the increase in weight (it is probably the lecithin); the oil may, however, be largely responsible for the lowered resistance in both cases.

Series 26. (Feb., 1910.) (xii, 38.)

Young mice, 12 in each group, were fed as below for about 37 days. The two kinds of bread used (C and S) were those used in previous experiments. The "Oat extract" was prepared by extracting oats, ground in the laboratory, with three times its weight of distilled water; two parts of this extract was mixed with one part of corn meal.

[a] I am indebted to Dr. Norman Roberts for the preparation of this oil.

[Dose in mgm. per gm. mouse.]

Diet.	Change in weight (average.)	Fatal dose of acetonitrile.	
		Recovered.	Died.
Milk, raw [a]	Increased 3.16 per cent (from 12.33 to 12.72 gms.)	0.10	0.11
Milk, boiled [b]	Increased 4.65 per cent (from 12.33 to 12.9 gms.)	.15	.16
Corn meal, [b] 1 part; boiled milk, 2 parts.	Increased 27.33 per cent (from 12.33 to 15.7 gms.)	.50	.60
Bread (S) [c]	No change (12.24 gms.)	.....	1.00
Corn meal, 1 part; raw milk, 2 parts.	Increased 37.14 per cent (from 12.33 to 16.91 gms.)	1.00	1.10
Corn meal, 1 part; oat extract, 2 parts. [d]	Decreased 3.56 per cent (from 12.33 to 11.8 gms.)	2.40	2.50
Corn meal [d]	Decreased 7.54 per cent (from 12.33 to 11.4 gms.)	3.00	3.40
Bread (C) [e]	Increased 4.46 per cent (from 12.33 to 12.88 gms.)	4.00	4.10

[a] One mouse had died.
[b] Two mice had died.
[c] Five mice had died.
[d] Two mice died.
[e] Four mice died.

Thus the difference between the effects of the two brands of bread oted in preceding experiments is evident here also. The addition milk (raw or boiled) lowered the resistance caused by the corn eal, the boiled being more active in this respect than the raw ilk.

Series 27. (May, 1910.) (xii, 46.)

Young mice (10 in each group) were fed as below for about 5 weeks. wenty-five grams of corn meal were given daily; that fed to group *a* as mixed with 25 c. c. water, that to *b* with 5 c. c. of Armour's xtract of red bone marrow [a] plus 20 c. c. water, that to *c* with one-ourth of an egg yolk and 25 c. c. water, that to *d* with one-fourth of n egg white and 25 c. c. water, that to *e* with 25 c. c. 20 per cent lycerin, that to *f* with 5 c. c. of Fairchild Bros. and Foster's lecithin olution [b] and 20 c. c. water, that to *g* with the ash of 100 c. c. milk nd 25 c. c. water, and that to *h* with 25 c. c. 0.1 per cent solution of otassium iodide.

[Dose in mgm. per gm. mouse.]

Diet.	Change in weight (average).	Fatal dose of acetonitrile.	
		Recovered.	Died.
Corn meal [c]	Decreased 26.18 per cent (from 11.8 to 8.71 gms.)	1.80	2.00
Corn meal and bone marrow. [d]	Decreased 20 per cent (from 11.8 to 9.44 gms.)	1.10	1.20
Corn meal and egg yolk [e]	Decreased 11.01 per cent (from 11.8 to 10.5 gms.)	.....	.70
Corn meal and egg white	Increased 8.48 per cent (from 11.8 to 12.8 gms.)	1.20	1 20
Corn meal and glycerin [f]	Decreased 15.25 per cent (from 11.8 to 10 gms.)	.....	.70
Corn meal and lecithin [g]	Decreased 17.20 per cent (from 11.8 to 9.77 gms.)	1.30	1.40
Corn meal and milk ash [d]	Decreased 5.08 per cent (from 11.8 to 11.2 gms.)	1.40	[h] 1.00
Corn meal and potassium iodide. [g]	Decreased 24.83 per cent (from 11.8 to 8.87 gms.)	2.40	2.50

[a] See New and Non-Official Remedies, 1910, p. 144.
[b] Ibid., p. 117.
[c] Three mice had died.
[d] One mouse had died.
[e] Eight mice had died.
[f] Five mice had died.
[g] Two mice had died.
[h] Results irregular.

The mice which had lost the most weight were the most resistant to the poison.

The survivors from groups *b*, *d*, *f*, and *h* were placed upon a diet of eggs for about 13 days, when their resistance to acetonitrile was again determined; the fatal doses of the previous period are placed in brackets for comparison.

[Dose in mgm. per gm. mouse.]

Previous diet.	Change in weight (average).	Fatal dose of acetonitrile.	
		Recovered.	Died.
b. Corn meal and bone marrow.	Increased 68.31 per cent (from 9.5 to 16 gms.) . . .	0.15 (1.10)	0.20 (1.20)
d. Corn meal and egg white...	Increased 33.19 per cent (from 12.2 to 16.25 gms.)	.15 (1.20)	.25 (1.20)
f. Corn meal and lecithin.....	Increased 65.95 per cent (from 9.4 to 15.6 gms.)..	.35 (1.30)	.45 (1.40)
h. Corn meal and potassium iodide.	Increased 44.34 per cent (from 8.66 to 12.5 gms.)..	(2.40)	.90 (2.50)

Thus the diet of eggs had an effect similar to that of milk in other series; that is, it quickly lowered the resistance of the mice to acetonitrile.

A number of experiments were performed in which the mice were weighed separately, at short intervals; in many cases, after the resistance to acetonitrile had been determined, the diet was changed and later the resistance again determined.

Series 28.

A. INITIAL DIET: HAM AND AMERICAN CHEESE. (v, 158.)

Date.	Weight of mouse.	Remarks.
1905.	*Grams.*	
Apr. 3	14.42	Diet of ham and cheese begun.
Apr. 10	13.91	
Apr. 19	14.65	Acetonitrile, 2.93 mgms., i. e., 0.2 mgm. per gm. mouse; survived.
Apr. 20	.....	Diet changed to rice.
Apr. 26	15.25	
May 3	15.55	
May 4	15.22	Acetonitrile, 6.09 mgms., i. e., 0.4 mgm. per gm. mouse; survived.
Apr. 3	12.21	Ham and cheese diet begun.
Apr. 10	11.81	
Apr. 18	13.21	Acetonitrile, 3.96 mgms., i. e., 0.3 mgm. per gm. mouse; died, 2 hours.
Apr. 3	17.41	Ham and cheese.
Apr. 10	16.31	
Apr. 17	16.65	Acetonitrile, 6.66 mgms., i. e., 0.4 mgm. per gm. mouse; died, 2½ hours.

B. INITIAL DIET: RICE. (v, 162.)

1905.	*Grams.*	
Apr. 3	15.35	Diet of rice begun.
Apr. 10	13.31	
Apr. 17	12.05	Acetonitrile, 6.03 mgms., i. e., 0.5 mgm. per gm. mouse; survived.
Apr. 3	16.05	Diet of rice begun.
Apr. 10	14.25	
Apr. 17	11.81	
Apr. 18	11.31	Acetonitrile, 7.03 mgms., i. e., 0.6 mgm. per gm. mouse; survived.
Apr. 21	.....	Diet changed to ham and cheese.
Apr. 26	14.41	
May 3	17.25	
May 4	17.45	Acetonitrile, 6.98 mgms., i. e., 0.4 mgm. per gm. mouse; died, 5 hours. A few other mice of this group died after 14 to 17 days of the exclusive rice diet.

C. INITIAL DIET: OLIVE OIL ON OATS. (v, 160.)

Date.	Weight of mouse.	Remarks.
1905.	*Grams.*	
Apr. 3	14.21	Olive oil on oats.
Apr. 10	11.11	
Apr. 17	10.01	
Apr. 19	10.22	Acetonitrile, 2.04 mgms. i. e., 0.2 mgm. per gm. mouse; survived.
Apr. 21	.....	Diet changed to rice.
Apr. 26	10.75	
May 3	9.23	Acetonitrile, 5.54 mgms., i. e., 0.6 mgm. per gm. mouse; survived.
Apr. 3	12.55	Oil on oats.
Apr. 10	11.71	
Apr. 17	10.51	
Apr. 20	11.05	Acetonitrile, 2.76 mgms., i. e., 0.25 mgm. per gm. mouse; survived.
Apr. 21	.....	Diet changed to rice.
Apr. 26	12.55	
May 3	11.51	
May 4	10.72	Acetonitrile, 8.58 mgms., i. e., 0.8 mgm. per gm. mouse; survived.
May 5	.....	Diet changed to ham and cheese.
May 18	17.92	
June 3	17.82	
July 17	22.05	Acetonitrile, 11.03 mgms., i. e., 0.5 mgm. per gm. mouse; died, 2½ hours.
Apr. 3	16.26	Olive oil on oats.
Apr. 10	14.71	
Apr. 18	13.35	Acetonitrile, 4 mgms., i. e., 0.3 mgm. per gm. mouse; died, 4 to 6 hours.
Apr. 3	17.10	Olive oil on oats.
Apr. 10	15.85	
Apr. 17	13.75	Acetonitrile, 5.5 mgms., i. e., 0.4 mgm. per gm. mouse; died, 4½ hours.

D. INITIAL DIET: BREAD AND OATS. (v, 164.)

1905.	*Grams.*	
Apr. 3	14.56	Diet of bread and oats begun.
Apr. 10	14.30	
Apr. 19	15.31	Acetonitrile, 3.83 mgms., i. e., 0.25 mgm. per gm. mouse; survived.
Apr. 3	20.85	Bread and oats.
Apr. 10	19.82	
Apr. 17	19.81	
Apr. 20	20.06	Acetonitrile, 6.02 mgms., i. e., 0.3 mgm. per gm. mouse; died, 4 hours.
Apr. 3	12.50	Bread and oats.
Apr. 10	12.80	
Apr. 18	13.01	Acetonitrile, 4.55 mgms., i. e., 0.35 mgm. per gm. mouse; died, 3 hours.

SUMMARY OF SERIES 28.—The effects upon the resistance to acetonitrile of the initial diets in the above experiments may be summarized as follows:

[Dose in mgm. per gm. mouse.]

Diet.	Change in weight (average).	Fatal dose of acetonitrile.	
		Recovered.	Died.
L. Ham and cheese	Increase 1.1 per cent	0.20	0.30
R. Rice	Decrease 25 per cent	.60	.....
O. Oil and oats	Decrease 19 per cent	.25	.30
B. Bread (S) and oats	Increase 0.9 per cent	.25	.30

Thus the mice which had received the diet of rice were the most resistant; they also lost most in weight. The mice on the oil and oats diet lost almost as much in weight without any increase in their resistance. An examination of the above protocols show that the resistance to acetonitrile of mice which had been receiving a diet of ham and cheese or of olive oil and oats was increased when they were

placed on a diet of rice, and that the resistance of mice which had been increased by a diet of rice was lowered by a diet of ham and cheese; the latter also caused a rapid increase in weight. The bread used in the above experiments was from the same bakery as that used in the previously described experiments in which a low degree of resistance resulted from a bread diet.

Results similar to the above were obtained in the following experiments:

Series 29.

A. INITIAL DIET: HAM AND CHEESE. (v, 158–159.)

Date.	Weight of mouse.	Remarks.
1905.	*Grams.*	
May 27	15.61	Diet of ham and cheese begun.
June 10	15.55	
June 19	18.10	Acetonitrile, 3.8 mgms., i. e., 0.21 mgm. per gm. mouse; died, 1¾ hours.
May 5	15.25	Diet of ham and cheese begun.
May 19	16.05	
June 3	19.85	
June 19	18.72	Acetonitrile, 4.68 mgms., i. e., 0.25 mgm. per gm. mouse; died, 1½ hours.
May 26	18.15	Diet of ham and cheese begun.
June 3	19.05	
June 18	16.26	Acetonitrile, 4.88 mgms., i. e., 0.3 mgm. per gm. mouse; died, 1 hour.

B. INITIAL DIET: RICE. (v, 162.)

1905.	*Grams.*	
May 27	18.21	Diet of rice begun.
June 3	17.55	
June 14	14.91	
June 18	13.30	Acetonitrile, 9.31 mgms., i e., 0.7 mgm per gm. mouse; survived.
June 20	13.22	Diet changed to ham and cheese.
June 30	17.35	
July 3	19.22	Acetonitrile, 9.61 mgms., i. e., 0.5 mgm. per gm. mouse; died, 12 to 18 hours.

Series 30.

A. INITIAL DIET: RICE. (v, 166.)

1905.	*Grams.*	
June 21	20.15	Diet of rice begun.
June 30	18.95	
July 10	15.05	Acetonitrile, 10.54 mgms. i. e., 0. 7 mgm. per gm. mouse; survived.
June 21	21.35	Diet of rice begun.
June 30	18.35	
July 10	15.06	Acetonitrile, 12.05 mgms., i. e., 0.8 mgm. per gm. mouse; survived.
July 12	15.05	Diet changed to ham and cheese.
July 31	22.35	
Aug. 2	23.05	Acetonitrile, 11.53 mgms., i. e., 0.5 mgm. per gm. mouse; died, 2 hours.

B. INITIAL DIET: HAM AND CHEESE. (v, 165.)

1905.	*Grams.*	
June 21	19.15	Diet of ham and cheese begun.
July 6	18.05	
July 10	16.05	Acetonitrile, 3.21 mgms., i. e., 0.2 mgm. per gm. mouse; died, 2 hours.

These experiments also show that the change from a diet of rice to one of ham and cheese caused a marked increase in weight and a low resistance.

Series 31.

A. DIET: OATS AND WATER. (v, 30.)

Date.	Weight of mouse.	Remarks.
1904.	*Grams.*	
ov. 11	19.51	Diet of oats and water begun.
ov. 25	17.23	
ec. 11	19.35	Acetonitrile, 6.77 mgms., i. e., 0.35 mgm. per gm. mouse; survived.
ov. 8	21.86	Diet of oats and water begun.
ov. 25	19.36	
ec. 11	19.43	Acetonitrile, 7.38 mgms., i. e., 0.38 mgm. per gm. mouse; survived.
ov. 8	22.35	Diet of oats and water begun.
ov. 25	20.95	
ec. 10	19.11	Acetonitrile, 7.64 mgms., i. e., 0.4 mgm. per gm. mouse; died, 3 to 9 hours.

B. DIET: OATS IN 20 PER CENT DEXTROSE. (v, 30.)

1904.	*Grams.*	
ov. 8	21.56	Diet of oats and dextrose begun.
ov. 25	20.85	
ec. 10	20.02	Acetonitrile, 8 mgms., i. e., 0.4 mgm. per gm. mouse; survived.
ov. 8	18.31	Diet of oats and dextrose begun.
ov. 25	18.02	
ec. 11	18.85	Acetonitrile, 8.48 mgms., i. e., 0.45 mgm. per gm. mouse; survived.
ec. 12	.....	Diet of oats and dextrose continued.
ec. 25	17.71	Acetonitrile, 14.17 mgms., i. e., 0.8 mgm. per gm. mouse; survived.

C. DIET: AMERICAN CHEESE. (v, 31.)

1904.	*Grams.*	
ov. 8	24.45	Diet of cheese begun.
ov. 25	20.70	
ec. 11	16.31	Acetonitrile, 5.71 mgms., i. e., 0.35 mgm. per gm. mouse; survived.
ec. 12	.....	Diet of cheese continued.
ec. 23	13.31	Acetonitrile, 4.79 mgms., i. e., 0.36 mgm. per gm. mouse; died, 6 to 8 hours.
ov. 8	25.85	Diet of cheese begun.
ov. 25	24.35	
ec. 13	19.22	Acetonitrile, 7.3 mgms., i. e., 0.38 mgm. per gm. mouse; died, 3¾ hours.
ov. 8	23.45	Diet of cheese begun.
ov. 25	19.52	
ec. 10	17.10	Acetonitrile, 6.84 mgms., i. e., 0.4 mgm. per gm. mouse; died, 3 to 9 hours.

SUMMARY OF SERIES 31.—The above experiments may be summarized as follows:

[Dose in mgm. per gm. mouse.]

Diet.	Change in weight (average).	Fatal dose of acetonitrile.	
		Recovered.	Died.
. Oats and water	Decrease 9 per cent	0.38	0.40
. Oats and dextrose	No change	.55	.....
. Cheese	Decrease 24 per cent	.35	.38

Thus there was an increased resistance to acetonitrile without any increase in weight and a lowered resistance with a considerable loss of weight.

With a shorter period of feeding, the effect of dextrose in increasing the resistance of mice to acetonitrile was less marked, as is shown in the following:

Series 32.

A. DIET OF OATS AND WATER. (v, 170-171.)

[Dose in mgm. per gm. mouse.]

Date.	Weight of mouse.	Remarks.
1905.	*Grams.*	
Jan. 9	18.21	Diet of oats and water begun.
Jan. 13	17.02	
Jan. 21	18.41	Acetonitrile, 6.44 mgms., i. e., 0.35 mgm. per gm. mouse; survived.
Jan. 9	14.51	Diet of oats and water begun.
Jan. 22	15.61	Acetonitrile, 6.24 mgms., i. e., 0.4 mgm. per gm. mouse; died, 17 hours.

B. DIET OF OATS IN 20 PER CENT DEXTROSE. (v, 32.)

1905.	*Grams.*	
Jan. 9	17.85	Diet of oats and dextrose begun.
Jan. 23	18.15	Acetonitrile, 7.26 mgms., i. e., 0.4 mgm. per gm. mouse; survived.
Jan. 9	18.07	Diet of oats and dextrose begun.
Jan. 21	19.15	Acetonitrile, 9.58 mgms., i. e., 0.5 mgm. per gm. mouse; died, 8 hours.

Series 33. (Mar., 1906.) (v, 136.)

In the following experiments the effects of adding alcohol, dextrose and alcohol, and dextrose to the diet of oats and water was determined. A number of mice were placed upon these diets (with others on diets of oats and water and dried beef) and their resistance to acetonitrile tested after periods of 7, 11, and 14 weeks. As the experiments were numerous, only a summary of the results will be given:

A. AFTER 7 WEEKS.

[Dose in mgm. per gm. mouse.]

Diet.	Change in weight (average).	Fatal dose of acetonitrile.	
		Recovered.	Died.
A. Oats and water	Increased 6.7 per cent	0.58	0.62
B. Oats in alcohol gradually increased from 5 to 50 per cent.	Decreased 8.7 per cent	.60	.62
C. Oats in dextrose solution increased from 5 to 20 per cent.	Increased 16.7 per cent	.50	.55
D. Oats in dextrose solution (increased from 5 to 20 per cent) and alcohol (increased from 5 to 50 per cent.)	Increased 6 per cent	1.20	1.30
E. Dried beef in water	Decreased 8.8 per cent	1.00	.....

B. AFTER 11 WEEKS.

A. Oats and water	Increased 3.3 per cent	0.80	.....
B. Oats in alcohol	Decreased 5.6 per cent	.30	0.35
C. Oats and dextrose	Increased 7 per cent	.....	1.00
D. Oats and alcohol and dextrose	Decreased 2.7 per cent	.90	1.10
E. Dried beef in water	Decreased 6.5 per cent	1.20	.....

C. AFTER 14 WEEKS.

Date.	Change in weight (average).	Fatal dose of acetonitrile.	
		Recovered.	Died.
A. Oats and water	Decreased 3.3 per cent	0.90	1.10
B. Oats and alcohol	Decreased 20 per cent	.60	.....
C. Oats, alcohol, and dextrose	Increased 2 per cent	1.10	1.10
D. Dried beef in water	Increased 2 per cent	1.00	1.20

SUMMARY OF SERIES 33.—In the above experiments there were, after 7 weeks, no marked differences in the susceptibility to acetonitrile of the mice upon the different diets except that the mice which had received both alcohol and dextrose, and those which had received beef, were much more resistant to this poison than were the others. After 11 weeks the characteristic effects of alcohol in diminishing the resistance of animals to acetonitrile and of oats in increasing it were manifest. The change in weight of the mice in the above experiments was, in most cases, so slight that not much importance is to be attached to it as a cause of the differences in the susceptibility.

That an exclusive diet of lean dried beef will lead to an increased resistance to acetonitrile, and that alcohol added to such diet will diminish the effect of the beef, is shown by the following experiments; the alcohol was slowly increased from 5 to 50 per cent.

Series 34. (Feb., 1906.) (v, 132.)

A. AFTER 3 TO 4 WEEKS.

[Dose in mgm. per gm. mouse.]

Diet.	Change in weight (average).	Fatal dose of acetonitrile.	
		Recovered.	Died.
A. Oats and water	Decreased 2 per cent	0.50	0.60
B. Beef and water	Increased 15 per cent	.40	.....
C. Beef and alcohol	Decreased 10 per cent	.35	.....
B. AFTER 7 WEEKS.			
A. Oats and water	Increased 6.7 per cent	0.58	0.62
B. Beef and water	Decreased 8.8 per cent	1.00	.....
C. Beef and alcohol	Decreased 20 per cent	.50	.55
C. AFTER 11 WEEKS.			
A. Oats and water	Increased 3.3 per cent	0.80	.....
B. Beef and water	Increased 22 per cent	1.30	1.30
D. AFTER 14 WEEKS.			
A. Beef and water	Increased 25 per cent	1.10	.....

In the following experiments the diet consisted of "cakes" made by mixing varying amounts of other foodstuffs with ordinary "crackers" or "biscuits;" the controls were fed on "cakes" made from the latter only. The experiments, which were very numerous, are given in tabulated form. Only the largest nonfatal and the smallest fatal doses are recorded.

Series 35. (Oct., 1905.) (v, 176.)

The mice were fed on the diets named below for 12 days.

[Dose in mgm. per gm. mouse.]

Diet.	Change in weight (average).	Fatal dose of acetonitrile.	
		Recovered.	Died.
a. Cakes	Decreased 12 per cent	0.20	0.25
b. Lard, 1 part; cakes, 3 parts	Decreased 13 per cent	.15	.20
c. Corn starch, 1 part; cakes, 3 parts	Decreased 9 per cent	.15	.20
d. Casein, 1 part; cakes, 3 parts	Decreased 1 per cent	.18	.20
e. Dextrose, 1 part; cakes, 3 parts	Decreased 7 per cent	.25	.30

Series 36. (Oct., 1905.) (v, 178.)

The mice were fed on the diets named below for 13 days.

[Dose in mgm. per gm. mouse.]

Diet.	Change in weight (average).	Recovered	Died.
a. Cakes	Decreased 11 per cent	0.27	.....
b. Lard, 2 parts; cakes, 2 parts	Decreased 28 per cent	.....	0.15
c.[a] Casein, 2 parts; cakes, 2 parts	Decreased 18 per cent	.12	.15
d. Starch, 2 parts; cakes, 2 parts	Decreased 29 per cent	.20(?)	.30
e. Dextrose, 2 parts; cakes, 2 parts	Decreased 16 per cent	.35	.40

[a] Another mouse of this group died from 0.18 mgm. acetonitrile. A mouse which had recovered from 0.12 mgm. per gm. was placed for 2 weeks upon dextrose cakes; it recovered from 0.3 mgm. acetonitrile per gm., i. e., from a dose twice as large as the fatal dose for mice on casein.

Series 37. (Nov., 1905.) (v, 90.)

The mice were fed on the diets named below for 8 days.

[Dose in mgm. per gm. mouse.]

Diet.	Change in weight (average).	Recovered.	Died.
a. Cakes	Decreased 16 per cent	.....	0.30
b. Lard and cakes, equal parts	Decreased 31 per cent	.....	.12
c. Starch and cakes, equal parts	Decreased 31 per cent	.....	.25
d. Casein and cakes, equal parts	Decreased 27 per cent	0.25	.....
e. Dextrose and cakes, equal parts	Decreased 12 per cent	.35	.....
f. Ham and cheese, equal parts	Increased 3.5 per cent	.15	.....
g. Egg and cheese, equal parts	Decreased 1 per cent	.20	.30
h. Rice	Decreased 23 per cent	.65	.80

Some of the mice in this series which had acquired a high degree of resistance to acetonitrile as a result of the rice or dextrose diet were placed upon a diet of ham and cheese; after about 2 weeks they were again tested with acetonitrile. Their resistance was found to

be markedly diminished, although their weight had increased and their general condition had apparently improved.

SUMMARY OF SERIES 35–37.—The addition of lard, in comparatively large proportion, to the diet of mice reduces their resistance to acetonitrile markedly; it also causes a marked loss of weight. The effect of corn starch is apparently the same; casein in large amounts caused a marked loss of weight, but its effect upon the resistance to acetonitrile was variable. Dextrose, which in these experiments caused a loss of weight (which was, however, rather less than that caused by the exclusive diet of cakes alone) caused a decided increase in the resistance. Rice, as usual, caused a marked loss of weight and also a marked increase in the resistance. There were, however, in the above experiments several cases in which a marked loss of weight was not accompanied by an increased resistance.

Several extensive series of experiments were performed in which small amounts of various foods, blood, various organs of animals, and certain other substances which may, at times at least, have some interest in connection with dietetic studies, were added to cakes and fed to mice. Many of these experiments were performed as controls to other experiments, and in this respect the negative results often obtained have a certain interest. They will be reported in as brief a form as possible.

Series 38. (Aug., 1905.) (v, 30.)

The mice were fed on the diets named below for about 4 weeks. Such expressions as "casein 0.3+4" indicate that 0.3 gm. casein was made into a cake with 4 gms. cracker dust.

[Dose in mgm. per gm. mouse.]

Diet.	Change in weight (average).	Fatal dose of acetonitrile.	
		Recovered.	Died.
a. Cakes	Decreased 28 per cent	0.20	.....
b. Peptone, 0.3+4	Decreased 25 per cent	.20	0.30
c. Nutrose, 0.3+4	Decreased 5 per cent	.29	.30
d. Gelatine, 0.3+4	Decreased 32 per cent	.35	.45
e. Casein, 0.3+4	Decreased 25 per cent	.15	.....

Series 39. (Oct., 1905.) (v, 86–87.)

The mice were fed on the following diets for about 1 week.

[Dose in mgm. per gm. mouse.]

Diet.	Change in weight (average).	Recovered.	Died.
a. Cakes	Increased 0.8 per cent	0.20	0.25
b. Parathyroids (beef), 0.2+4	Increased 9 per cent	.16	.15
c. Casein, 0.2+4	Increased 6 per cent	.22	.28
d. Peptone, 0.2+4	Increased 9 per cent	.25	.....

Series 40. (July, 1905.) (v, 33.)

The mice were fed for about 1 week.

[Dose in mgm. per gm. mouse.]

Diet.	Change in weight (average).	Recovered.	Died.
a. Cakes	Decreased 9 per cent		0.15
b. Casein, 0.3+4	Increased 4 per cent	0.12	.15
c. Suprarenal, 0.3+4	Increased 21 per cent		.15
d. Thymus, 0.3+4	Increased 1 per cent	.18	.20
e. Nuclein (yeast), 0.3+4	Decreased 2 per cent	.20	.25
f. Gelatine, 0.3+4	Decreased 8.8 per cent	.23	.30

Series 41. (Dec., 1906.) (v, 130.)

The mice were fed for about 10 days.

[Dose in mgm. per gm. mouse.]

Diet.	Change in weight (average).	Recovered.	Died.
a. Cakes	Increased 0.5 per cent	0.55	0.55
b. Pancreas (desiccated), 0.3+4	Increased 13 per cent		.35
c. Spleen (desiccated), 0.3+4	Increased 9 per cent	.35	.50
d. Tartaric acid, 0.1+4	Decreased 4 per cent	.45	.65
e. Brain (desiccated), 0.3+4	Increased 6.8 per cent	.65	.80
f. Parotid (desiccated), 0.3+4	Decreased 0.9 per cent	.60	.80
g. Mammary gland (desiccated), 0.3+4	Increased 12 per cent	2.00	
h. Prostate (desiccated), 0.3+4	Increased 9 per cent	2.00	
i. Testes (desiccated), 0.3+4	Increased 8.5 per cent	2.00	

Some of the mice of the groups *g*, *h*, *i*, of the above table were placed upon plain cakes and their resistance to acetonitrile again tested after a week. Mice which had received the mammary gland (and which had recovered from 2 mgms. per gm.) now died from 0.4, 0.5, and 0.6 mgm. acetonitrile; of mice which had received the prostate, one recovered from 0.4 mgm. and one died from 0.6 mgm. per gm. mouse, whereas of those which had received the testes, two recovered from 0.7 and 0.9 mgm. These results show the brief duration of the increased resistance caused by prostate and mammary gland.

Series 42. (Sept., 1905.) (v, 78.)

The mice were fed on the following diets for 7 to 8 days.

[Dose in mgm. per gm. mouse.]

Diet.	Change in weight (average).	Recovered.	Died.
a. Cakes	Increased 7 per cent	0.23	0.25
b. Parathyroids (beef), 0.05+4	Increased 10 per cent	.10	.20
c. Ovaries, 0.3+4	Increased 3 per cent	.23	.30

Series 43. (Sept., 1905.) (vi, 86.)

The mice were fed as below for about 1 week.

[Dose in mgm. per gm. mouse.]

Diet.	Change in weight (average).	Recovered.	Died.
. Cakes	Decreased 10 per cent	0.20	0.22
. Parathyroids (beef) 0.2+4	Decreased 7 per cent	.08	.10

Series 44. (Dec., 1906.) (vii, 142.)

The mice were fed as below for 9 to 10 days.

[Dose in mgm. per gm. mouse.]

Diet.	Change in weight (average).	Recovered.	Diet.
. Cakes	Decreased 8 per cent	0.50	0.65
. Mammary gland, 0.1+4	Increased 1 per cent	1.30	1.40
. Testes, 0.1+4	Increased 2 per cent	1.40	1.50
. Prostate, 0.1+4	No change	3.00	.....

Three mice of group *d* were given a diet of plain cakes for a week nd again tested with acetonitrile; 1 recovered from 0.5 mgm., 1 lied from 0.7 mgm. and another from 0.8 mgm. per gm.; thus the igh resistance caused by the prostate was of short duration.

Series 45. (May, 1907.) (vii, 126.)

The mice were fed as below for 12 days.

[Dose in mgm. per gm. mouse.]

Diet.	Change in weight (average).	Recovered.	Died.
Cakes	Decreased 5.5 per cent	0.22	0.23
. Mammary gland, 0.05+4	Increased 3 per cent	.26	.30
Ovaries, 0.1+4	Increased 8 per cent	.35	.40
Corpus luteum (desiccated), 0.1+4	Decreased 3 per cent	.....	.28

Series 46. (Dec., 1906.) (vii, 144.)

The mice were fed as below for 10 days.

[Dose in mgm. per gm. mouse.]

Diet.	Change in weight (average).	Recovered.	Died.
Cakes	No change	.....	0.40
Pancreas, 0.1+4	Increased 10 per cent	0.44	.55
Tamarinds (pulp) 0.3+4	Increased 5 per cent	.70	.85
Ovaries, 0.3+4	Increased 10 per cent	1.10	1.60

Series 47. (May, 1907.) (vii, 122.)

The mice were fed as below for 18 days.

[Dose in mgm. per gm. mouse.]

Diet.	Change in weight (average).	Recovered.	Died.
a. Cakes	Decreased 7 per cent		0.28
b. Prostate, 0.05+4	Decreased 15 per cent	1.00	1.40

Series 48. (Jan., 1907.) (vii, 174.)

The mice were fed as below for 13 days.

[Dose in mgm. per gm. mouse.]

Diet.	Change in weight (average).	Recovered.	Died.
a. Cakes	Decreased 5 per cent	0.80	0.90
b. Guinea-pig embryos (desiccated), 0.3+4	Increased 4 per cent	.60	.70
c. Prostate, 0.01+4	Increased 3 per cent		.85

Series 49. (June, 1907.) (vii, 82.)

The mice were fed as below for 11 days.

[Dose in mgm. per gm. mouse.]

Diet.	Change in weight (average).	Recovered.	Died.
a. Cakes	Decreased 5 per cent	0.31	0.32
b. Milk sugar, 0.3+4	Decreased 12 per cent	.27	.30

Series 50. (Dec., 1906.) (vii, 140.)

The mice were fed as below for 12 days.

[Dose in mgm. per gm. mouse.]

Diet.	Change in weight (average).	Recovered.	Died.
a. Cakes	Decreased 2 per cent	0.70	0.75
b. Umbilical cord (desiccated), 0.1+4	No change		.90
c. Placenta (desiccated), 0.3+4	Increased 1.5 per cent	.70	.85

Series 51. (Dec., 1906.) (vii, 135.)

The mice were fed as below for 10 days.

[Dose in mgm. per gm. mouse.]

Diet.	Change in weight (average).	Recovered.	Died.
a. Cakes	Increased 1 per cent	0.45	0.48
b. Saccharin, 0.1+4	Decreased 0.5 per cent	.55	.48
c. Carcinoma of liver, 0.2+4	Decreased 2 per cent	.90	1.10
d. Egg albumen (dried), 0.4+4	Increased 3 per cent	.45	.60
e. Ox gall (purified), 0.2+4	Decreased 20 per cent	.60	.80

Series 52. (May, 1906.) (vi, 190.)

The mice were fed as below for 16 days.

[Dose in mgm. per gm. mouse.]

Diet.	Change in weight (average).	Recovered.	Died.
Oats and water	Increased 7 per cent	0.45	0.50
Oats and 5 per cent glycerin	Decreased 5.5 per cent	.37	.40

Series 53. (Nov., 1906.) (vi, 179.)

The mice were fed as below for 11 days.

[Dose in mgm. per gm. mouse.]

Diet.	Change in weight (average).	Recovered.	Died.
Cakes	No change	0.70	0.80
Kidney (dog), 0.2+4	Decreased 1.5 per cent	.90	1.00

Series 54. (Mar., 1906.) (vi, 180.)

The diet was continued for 23 days.

[Dose in mgm. per gm. mouse.]

Diet.	Change in weight (average).	Recovered.	Died.
Cakes	Decreased 17 per cent	0.21	0.25
Meat extract (Liebig) 0.2+4	Decreased 19 per cent	.27	.30

Series 55. (Nov., 1906.) (vi, 156.)

The mice were fed as below for 10 days.

[Dose in mgm. per gm. mouse.]

Diet.	Change in weight (average).	Recovered.	Died.
Cakes	Decreased 13 per cent	.....	0.50
Chocolate, 0.3+4	Decreased 5 per cent	0.40	1.00
Liver (human), 0.2+4	Decreased 11 per cent	.75	.80
Egg albumen (dry), 0.2+4	Decreased 9 per cent	1.00	1.30

Series 56. (Nov., 1906.) (vi, 194.)

The mice were fed as follows for 11 days.

[Dose in mgm. per gm. mouse.]

Diet.	Change in weight (average).	Recovered.	Died.
Cakes	Increased 1 per cent	0.15	0.20
Sodium salicylate, 0.02+4	Increased 4.6 per cent	.24	.25
Sodium benzoate, 0.02+4	Increased 4 per cent	.30	.40
Pepsin, 0.05+4	Increased 1 per cent	.30	.40
Pancreatin, 0.05+4	Increased 7 per cent	.30	.60

Series 57. (Nov., 1905.) (vi, 140.)

The mice were fed as below for 7 days.

[Dose in mgm. per gm. mouse.]

Diet.	Change in weight (average).	Recovered.	Died.
a. Cakes	Decreased 1 per cent	0.30	0.35
b. Pituitary body, 0.1+4	Increased 15 per cent	.20	.25

Series 58. (Nov., 1906.) (vi, 171.)

The mice were fed as below for 10 days.

[Dose in mgm. per gm. mouse.]

Diet.	Change in weight (average).	Recovered.	Died.
a. Cakes	Decreased 1 per cent	0.45	0.55
b. Prunes, 0.2+4	Increased 6 per cent	.30	.50
c. Tartaric acid, 0.2+4	Decreased 17 per cent	.75	.....

Series 59. (Feb., 1906.) (vi, 158.)

The mice were fed as below for 13 days.

[Dose in mgm. per gm. mouse.]

Diet.	Change in weight (average).	Recovered.	Died.
a. Cakes	Increased 2 per cent	.....	0.30
b. Submaxillary gland (ox), 0.5+4 (desiccated).	Increased 4 per cent	0.25	.33

Series 60. (Aug., 1905.) (vi, 36.)

The mice were fed as below for 13 days.

[Dose in mgm. per gm. mouse.]

Diet.	Change in weight (average).	Recovered.	Died.
a. Cakes	Not recorded	0.20	0.24
b. Suprarenal gland, 0.1+4	Decreased 3 per cent	.10	.15
c. Nuclein (yeast), 0.1+4	Decreased 13 per cent	.18	.20
d. Thymus, 0.1+4	Decreased 16 per cent	.18	.20

Series 61. (Aug., 1905.) (v, 81 and 49.)

The mice were fed as below for 29 days.

[Dose in mgm. per gm. mouse.]

Diet.	Change in weight (average).	Recovered.	Died.
a. Oats in water	Increased 7 per cent	0.50	0.65
b. Oats in 0.2 per cent hydrochloric acid	Decreased 10 per cent	.70	.90

Series 62. (Jan., 1905.) (iv, 170 and v, 50.)

The mice were fed as below for 2 weeks.

[Dose in mgm. per gm. mouse.]

Diet.	Change in weight (average).	Recovered.	Died.
Oats in water	Increased 3 per cent	0.35	0.40
Oats in 0.5 and then 0.25 per cent hydrochloric acid.	Decreased 12 per cent	.60	.....

Series 63. (Mar., 1908.) (x, 152.)

The mice were fed as below for 11 days.

[Dose in mgm. per gm. mouse.]

Diet.	Change in weight (average).	Recovered.	Died.
Cakes	Decreased 14 per cent	0.40	0.42
Ammonium acetate, 0.1+4	Decreased 12 per cent	.65	.75
Sulphur, 0.01+4	Decreased 9 per cent	3.90	4.00

Series 64. (Jan., 1908.) (x, 70.)

The mice were fed as below for 11 days.

[Dose in mgm. per gm. mouse.]

Diet.	Change in weight (average).	Recovered.	Died.
Cakes	Increased 3 per cent	0.37	0.38
Magnesium chloride, 0.05+4	Increased 6 per cent	.40	.50
Caffeine 0.03+4	Increased 1 per cent	.40	.60
Calcium chloride, 0.05+4	Increased 0.5 per cent	1.10	1.2

Series 65. (Oct., 1908.) (xi, 74.)

The mice were fed as below for 8 days.

[Dose in mgm. per gm. mouse.]

Diet.	Change in weight (average).	Recovered.	Died.
Cakes	Decreased 4 per cent	0.36	0.37
Cystin, 0.05+4	Decreased 6 per cent	.54	.60

Series 66. (Mar., 1908.) (x, 114.)

The mice were fed as below for 10 days.

[Dose in mgm. per gm. mouse.]

Diet.	Change in weight (average).	Recovered.	Died.
Cakes	Increased 2 per cent	0.48	0.50
Sulphur 0.05+4	Decreased 8 per cent	3.48	3.80

Series 67. (Jan., 1908.) (x, 74.)

The mice were fed as below for 10 days.

[Dose in mgm. per gm. mouse.]

Diet.	Change in weight (average).	Recovered.	Died.
a. Cakes	No change	0.70	0.80
b. Borax, 0.05+4	Decreased 7 per cent		.40
c. Saponin, 0.01+4	Decreased 4 per cent	.53	.60

Series 68. (Sept., 1905.) (vi, 29.)

The mice were fed as below for 18 days.

[Dose in mgm. per gm. mouse.]

Diet.	Change in weight (average).	Recovered.	Died.
a. Cakes	Decreased 8 per cent	0.3	0.33
b. Copper acetate, 0.0056+4	Decreased 7 per cent		.40

Series 69. (Dec., 1905. (vi, 90.)

The mice were fed as below for 10 days.

[Dose in mgm. per gm. mouse.]

Diet.	Change in weight (average).	Recovered.	Died.
a. Cakes	Decreased 13 per cent	0.35	0.40
b. Taurin, 0.3+4	Decreased 9 per cent	.50	.45
c. Cystin, 0.3+4	Decreased 30 per cent	.75	.80
d. Sulphur, 0.1+4	Decreased 23 per cent	2.00	3.00

Several mice of groups *c* and *d* were placed upon plain cakes; there as still an increased resistance to acetonitril three weeks later.

Series 70. (Nov., 1907.) (x, 78.)

A few c. c. of blood were obtained from a woman who had died after an operation for exophthalmic goitre; there was only enough for experiments upon two mice. Control experiments were made with normal human and rabbit blood.

The mice were fed as below for 11 days.

[Dose in mgm. per gm. mouse.]

Diet.	Change in weight (average).	Recovered.	Died.
a. Cakes	Decreased 2 per cent		0.25
b. Rabbit blood, 0.5 c. c.+4	Decreased 2 per cent	0.25	.30
c. Normal human blood, 0.5 c. c.+4	Decreased 4 per cent	.26	.30
d. Exophthalmic goitre blood 0.5 c. c.+4	Decreased 3 per cent		.35

Series 71. (May, 1908.) (x, 184.)

A small amount of blood was obtained from a mild case of exophthalmic goitre and fed as below for 9 days.

[Dose in mgm. per gm. mouse.]

Diet.	Change in weight (average).	Recovered.	Died.
Cakes	Decreased 1 per cent	0.25	0.30
Exophthalmic goitre blood, 1 c. c.+4	Decreased 8 per cent	.30	.33
Normal human blood, 1 c. c.+4	Decreased 12 per cent	.33	.35

Series 72. (June, 1907.) (vii, 34.)

The "exophthalmic goitre blood" of this and the next series was obtained at autopsy from a well-marked case of this disease. The results of these experiments have been described in more detail elsewhere.[a]

The mice were fed as below for 10 days.

[Dose in mgm. per gm. mouse.]

Diet.	Change in weight (average).	Recovered.	Died.
Cakes	Increased 3.5 per cent	0.38	0.39
Human blood (placenta), 1 c. c.+4	Increased 5.6 per cent	.37	.39
Exophthalmic goitre blood, 1 c. c.+4	Decreased 2.3 per cent	.70	.75

Series 73. (June, 1907.) (vii, 67.)

The mice were fed as below for 11 days.

[Dose in mgm. per gm. mouse.]

Diet.	Change in weight (average).	Recovered.	Died.
Cakes	Decreased 6.2 per cent	0.31	0 32
Exophthalmic goitre blood, 1 c. c.+4	Decreased 4.9 per cent	.45	.48

Series 74. (Jan., 1907.) (vii, 174.)

Two guinea pigs were fed for 5 days in succession 0.6 gm. desiccated thyroid; they were then bled to death and their blood used for the following experiments. Although these guinea pigs were deeply intoxicated with the thyroid, their blood gave no physiological test for thyroid.[b] (That blood does not interfere with the physiological test for thyroid is shown by experiments in which small amounts (0.1 mgm., for example) of thyroid were added to blood and fed to mice; the latter showed a markedly increased resistance to acetonitrile).

[a] The Probable Demonstration of Thyroid Secretion in the Blood in Exophthalmic Goitre, Journ. Amer. Med. Assoc., 1907, 49, p. 240.

[b] The possible bearing of this upon the relation of hyperthyroidism to exophthalmic goitre was discussed in the paper referred to above.

The mice were fed as below for 12 days.

[Dose in mgm. per gm. mouse.]

Diet.	Change in weight (average).	Recovered.	Died.
a. Cakes	Decreased 5.2 per cent	0.80	0.90
b. Blood (dried) from thyroid-fed guinea pigs, 0.3 gm.+4.	Increased 4.1 per cent	.60	.85
c. Normal guinea pig blood (dried), 0.3 gm. +4.	Increased 5 per cent		.85

Series 75. (July, 1905.) (vi, 48.)

The mice were fed as below for 7 days.

[Dose in mgm. per gm. mouse.]

Diet.	Change in weight (average).	Recovered.	Died.
a. Cakes	Decreased 5.4 per cent	0.24	0.30
b. Peptone, 0.2+4	Decreased 10.6 per cent	.15	.17
c. Sheeps' blood (dried), 0.2+4	Decreased 17 per cent	.17	.20
d. Thyreoidectin,[a] 0.2+4	Decreased 7.5 per cent		.20

[a] See New and Non-official Remedies, 1910, p. 32.

Series 76. (June, 1905.) (v, 128.)

The mice were fed as below for 12 days.

[Dose in mgm. per gm. mouse.]

Diet.	Change in weight (average).	Recovered.	Died.
a. Cakes	Increased 0.6 per cent	0.30	0.32
b. Thyreoidectin, 0.3+4	Decreased 13.7 per cent	.08	.15

Series 77. (Jan., 1907.) (vii, 193.)

The mice were fed as below for 10 days.

[Dose in mgm. per gm. mouse.]

Diet.	Change in weight (average).	Recovered.	Died.
a. Cakes	Increased 8.1 per cent	0.37	0.40
b. Normal horse serum (dry), 0.3+4	Increased 10 per cent	.32	.37
c. Yeast, 0.3+4	Increased 24 per cent		.35
d. Antidiphtheritic serum (dry), 0.3+4	Increased 10 per cent		.75
e. Caffeine	Decreased 2.4 per cent	.90	

Series 78. (July, 1905.) (vi, 34.)

The mice were fed as below for 12 days.

[Dose in mgm. per gm. mouse.]

Diet.	Change in weight (average).	Recovered.	Died.
a. Cakes	Decreased 19.5 per cent		0.30
b. Peptone, 0.3+4	Decreased 22 per cent	0.12	.15
c. Thyreoidectin, 0.3+4	Decreased 19 per cent	.20	.30

Series 79. (Feb., 1910.) (xii, 16.)

Many of the above experiments having shown that several fats and ils increase the susceptibility of mice to acetonitrile, the following xperiments were made with corn meal from which the oil had been xtracted by ether.

The mice were fed as below for about 7 weeks.

[Dose in mgm. per gm. mouse.]

Diet.	Change in weight (average).	Recovered.	Died.
orn meal	Increased 15.86 per cent (from 11.91 to 13.8 gms.)	1.40	1.50
xtracted corn meal	Increased 9.02 per cent (from 11.41 to 12.44 gms.)	2.00	2.10

Thus the resistance of the mice which had received the fat-free corn neal was distinctly greater than that of those which had received the at-containing meal.

SUMMARY OF ABOVE RESULTS.

In many cases the experiments of the above series were not suffiiently numerous to permit of definite conclusions being drawn. here was also no constant standard of comparison, but it is not ifficult in most cases to determine, in a general way, whether the esistance of mice to acetonitrile caused by a certain diet should be lassed as "high," or "low," or "medium."

Cakes.—A larger number of experiments were performed with akes than with any other single diet. An examination of the above ables shows clearly that the resistance of mice which had received an xclusive diet of cakes should be classed as "medium;" the fatal dose aried from about 0.22 mgm. to about 0.64 mgm. per gm. mouse. he most important factor in this variation is undoubtedly the season. his is clearly shown by the following table, which gives the average atal dose for several months; the fatal dose for mice which had eceived a diet of bread [a] and oats is given for comparison.

	Cakes.	Bread and oats.		Cakes.	Bread and oats.
anuary	0.64	0.56	July	0.25	0.31
ebruary	.30	.35	August	.22	.18
arch	.38	.58	September	.24	.25
pril	.....	.53	October	.27	.39
ay	.25	.30	November	.41	.45
ne	.33	.28	December	.52	.55

Inasmuch as in many cases the diet of cakes was continued for but short period and the mice had received previously various other

[a] The bread used in all of the experiments was of the brand described as "S;" it lways caused a relatively low degree of resistance.

diets, it is not improbable that the latter had in certain cases exerted an influence upon the effects of the former.

Oats and oatmeal.—Mice kept on a diet of oats and oatmeal were usually very resistant to acetonitrile; in most series of experiments they were more resistant than the mice upon any other diet. The length of time during which they received this diet was a very important factor in the degree of resistance attained; when transferred from a mixed diet to one of oats the increased resistance came slowly and, on the other hand, when mice which had become resistant on a diet of oats were placed on other diets the resistance disappeared slowly (cf. series 13).

With diets of barley, rye, and wheat the resistance was less (in the order named) than that with oats; hempseed also led to a low degree of resistance as compared with oats; thus in series 20 the fatal dose of acetonitrile was twice as large for the oats-fed as for the hempseed-fed mice. The effect of maize will be discussed later.

Bread.—Some of the most remarkable results obtained were with bread. The bread was obtained from two sources designated "C" and "S," respectively. In both cases it was sold as ordinary white wheat bread; the dealer supplying it considered the one the equivalent of the other. Yet mice receiving an exclusive diet of "C" were invariably much more (as much as four times as) resistant to acetonitrile than were those fed upon "S." This difference may have been due to the two brands containing different percentages of fat, or sugar, or milk, or salt, or to the kind of flour used, or to some special treatment of the latter.[a]

Whatever the explanation, it is evident that for careful dietary studies the exact composition of the bread should be known; it also seems desirable for the words "white wheat bread" to mean something more definite than they do at present. It is not entirely improbable that in certain cases of sickness different kinds of bread would have different effects analogous to those found in experiments on lower animals.

Maize.—An exclusive diet of corn meal usually caused a loss of weight and generally a high degree of resistance to acetonitrile. Corn starch added to cakes (1 or 2 to 2) caused a marked loss of weight and a low degree of resistance.

Milk.—An exclusive diet of milk led to a low degree of resistance; this was true both of raw and boiled milk. In two cases the resistance was less with the raw, in one with the boiled milk. In the latter case there had been a much more rapid increase in weight with the boiled than with raw milk. Series 13 shows how marked and rapid

[a] Doctor Hale found samples of the bread used to each contain "nitrite-reacting material" equivalent to about 0.3 per 1,000,000 sodium nitrite.

ıay be the lowering of resistance when mice are transferred from arious diets to one of milk.

Milk added to oatmeal or corn meal led to a lower degree of resistnce (with two exceptions) than did these alone; boiled milk seemed ıore effective than did raw milk. There was a greater increase in eight on the combined diet than on either alone. In two series 14 and 15) the resistance of mice was greater upon a diet of oatmeal nd boiled milk than upon a diet of oatmeal alone.

A combined diet of bread and milk did not have an effect different om that of bread alone.

These results show how many factors are involved and what great ariations in the resistance are caused by comparatively slight hanges in the diet. The fact that mice are so very sensitive to ıch changes, however, increases the probability that this method ıay at least suggest promising lines of investigation. Thus the ıct that at times boiled milk leads to a diminished resistance may e found to be due to a change in the sulphur content of such milk r to the sulphur compounds having undergone some change during ıe heating. It is well known that traces of sulphur are expelled from ıilk on boiling and it will be shown later that sulphur in some forms f combination is very effective in protecting animals against cetonitrile whereas in other forms it is inert in this regard. Differnces in sulphur content or changes in its form of combination too mall to be clearly detected by ordinary chemical means might be ıus detected physiologically; and if a certain form of sulphur is an mportant factor in the resistance of animals to acetonitrile it is robable that it is important in relation to growth or resistance to ther forms of intoxication. The fact that boiled milk, as compared ith raw milk, does not invariably cause a diminished resistance may e due to there being compensating factors involved. Thus it is tated that boiling leads to a partial decomposition of the lecithin ontained in milk. There are reasons for believing that lecithin, ither directly or indirectly, causes an increased susceptibility in mice o acetonitrile. If such a decomposition occurred it might offset ther effects of heat. However, the only value these results have at resent is that they are suggestive of new lines of work.

Cheese led to a distinctly low degree of resistance whether (as in eries 17) there was an increase in the weight of the mice or (as in eries 31) a marked decrease.

Casein fed in cakes in large amounts distinctly lowered the resistnce as compared with cakes.

Ham.—An exclusive diet of lean ham caused a low degree of esistance in the single experiment in which it was fed alone (17). A mixture of ham and cheese had a similar effect; this was true whether there had been a decrease or an increase in the weight of

the mice. The experiments of series 28, 29, and 30 afford some rather striking illustrations of how the resistance of mice could be varied by changing from a diet of rice (which causes a high degree of resistance) to one of ham and cheese and vice versa.

Beef.—A diet of lean dried beef led to a marked increase in the resistance to acetonitrile; the addition of alcohol to the beef led to the opposite result, i. e., it lowered the resistance by about one-half. The beef caused an increase in weight; beef and alcohol caused a decrease. This is another illustration of the frequent independence of change in weight and changes in susceptibility. *Witte's peptone* added to cakes increased the susceptibility very distinctly. *Liebig's Extract* added to cakes had no distinct effect in the single experiment in which this was tested. *Gelatin* increased the resistance in two cases.

Liver.—An exclusive diet of liver led to a very great increase in the resistance to acetonitrile; this was greater than was the case with any other article of food (series 17). The addition of comparatively small amounts of dried liver to cakes (0.2 gm. to 4 gms. cakes) also increased the resistance as compared with cakes alone. Egg yolk diminished the resistance to acetonitrile; this effect was largely counteracted by the addition of liver. The diet of egg yolk and liver caused a marked increase in weight, whereas that of liver alone has, as a rule, but a slight effect. *Carcinoma* of the liver caused in one case a marked increase in resistance. *Purified ox gall* (U. S. P.) added to cakes (0.2 gm. to 4 gms.) caused a marked loss of weight and a slight increase in resistance. *Taurin* (0.3+4) caused a slight loss of weight and a slight increase in resistance.

Kidney.—An exclusive diet of kidney led to an increase in weight and a marked increase in resistance. The addition of a small amount of dried kidney (0.2 gm. to 4 gms. cakes) caused a slight increase as compared with a diet of cakes alone.

Brain.—Mice died in a few days upon an exclusive diet of brain. When fed with oatmeal (equal parts by weight) the resistance was less than when oatmeal alone was fed; there was a greater increase in weight in the former case. When dessicated brain was added to cakes (0.3 gm. to 4 gms.) there was a greater increase in weight and a greater degree of resistance than when cakes alone were fed.

Egg.—*Egg yolk* caused a very great diminution of resistance and a marked increase in weight in series 17 and 18; the entire egg had an equally great effect in series 18. Young mice were used in both of these series. With somewhat older mice there was a less marked increase in weight and a rather high degree of resistance. A diet of equal parts of egg yolk and liver caused a marked increase in weight and a degree of resistance intermediate between that caused by liver

alone and egg yolk alone; it was nearer the latter than the former. Mice died in a very few days from an exclusive diet of egg white. Added to bread and liver in equal parts, it diminished the resistance as compared with bread or liver alone; in one case, when added to oatmeal, it seemed to increase the resistance as compared with oatmeal.

Olive oil.—Olive oil added to a diet of bread or of oats invariably caused a marked loss of weight and a diminution of resistance; the effect was more marked with bread than with oats, i. e., the latter seemed to counteract to some extent the effect of the oil. *Cotton-seed oil and corn oil* caused a still greater loss of weight and an equally great diminution of resistance. *Cod-liver oil* caused a less marked loss of weight and a less marked diminution of resistance. *Lard* had a similar effect. Glycerin caused a slight loss of weight and a slightly diminished resistance.

Dextrose.—Dextrose added to a diet of cakes or of oats caused an increased resistance; this developed rather slowly. It frequently caused an increase in weight, especially when fed with oats.

Rice invariably caused a marked loss of weight and a marked increase in resistance. In several experiments rice-fed mice which had recovered from a large dose of the nitrile were placed upon a diet of ham and cheese; their weight rapidly increased and they were also less resistant to the nitrile. Partial inanition may be in part responsible for the high degree of resistance, but corn starch added to cakes caused a loss of weight but lowered resistance.

Potatoes.—An exclusive diet of potatoes caused in the only experiment with it a loss of weight but a very high degree of resistance.

Beans ("navy," boiled) caused in one experiment a very slight loss of weight and comparatively low degree of resistance; an exclusive diet of *peanuts* in the same series caused a somewhat greater loss of weight and a high degree of resistance.

Tamarinds and *tartaric acid* added to cakes in small amounts increased the resistance somewhat; in one case the tartaric acid caused a marked loss of weight and a very considerable increase in resistance. *Prunes* in one experiment had no effect. *Hydrochloric acid* (0.2 per cent on oats) caused in two cases a loss of weight and increased resistance.

Blood.—Normal human and rabbit blood (fresh) increased the resistance slightly; dried sheep blood diminished it slightly. *Thyreoidectin* (the dried blood of sheep from which the thyroids had been removed) in two cases diminished the resistance; in one case the diminution was marked. Normal horse serum and antidiphtheritic and antitetanic sera had no distinct effect in the few experiments in which they were tried. Of more interest are the experiments in which the blood from cases of exophthalmic goiter was fed. In two series such blood (from a severe case) caused a marked degree of resistance; in

another series with blood from a mild case the effect was not greater than with normal human blood.

Prostate (desiccated) added in small amounts (0.05–0.3 to 4 gms.) caused a marked increase in the resistance;[a] *testes* had a similar effect; *ovaries* also had a similar but less marked effect; *mammary gland* also increased the resistance markedly.[b] *Thymus* and *submaxillary* had no distinct effect. *Pituitary suprarenal* and *spleen* each in one case seemed to diminish the resistance; *parathyroid* in the three cases in which it was fed distinctly diminished the resistance. *Placenta* and *umbilical cord* had no effect; guinea pig embryos seemed, in one experiment, to slightly diminish the resistance. *Pancreatin* and *pepsin* seemed to increase the resistance. *Yeast* (0.3 to 4 gms. cakes) caused a marked increase in weight and a slightly diminished resistance.

Sulphur even in small amounts invariably caused a marked increase in resistance.[c] *Cystin* caused a distinct but not very marked increase in the resistance; the effect of *taurin* was still less. *Caffeine* in two cases caused an increased resistance without change in weight. *Sodium salicylate, sodium benzoate,* and *ammonium acetate* each in one case increased the resistance slightly.

DISCUSSION.

The above experiments show that mice fed upon articles of food such as enter largely into the daily diet of man vary greatly in their resistance to a definite poison. In extreme cases mice after having been fed upon certain diets may recover from forty times the dose of acetonitrile fatal to mice kept upon other diets. It is, moreover, possible to alter the resistance of these animals at will and to overcome the effects of one diet by combining it with another. In some cases the changes may be brought about in a very short time, in others they are produced more slowly. Many questions are suggested by these results; an answer can be given to but a very few of them.

Does the diet influence the resistance to hydrocyanic acid? The increased resistance to acetonitrile caused by certain diets could be

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[a] The effect of prostate upon the resistance of mice to acetonitrile is the same as, but much less marked than, that of thyroid. Prostate increases the susceptibility of rats and guinea pigs to this poison; having the same effect upon these animals as thyroid.

[b] Several clinicians have called attention to a relation between the thyroid and mammary glands. Thus Sainton and Fernet (Progrès Médical, 1908, p. 279) state that the latter are often found hypertrophied in myxœdema and atrophied in Grave's disease; Afert (Sem. méd., 1908, p. 71) and others report myxœdema as occurring after removal of the breasts.

[c] Sulphur likewise increases the resistance of rats and guinea pigs to acetonitrile, the effect being due to the neutralization, through the formation of sulphocyanic acid, of the hydrocyanic acid formed from the nitrile.

attributed to one of two factors, (1) an increased resistance to the hydrocyanic acid liberated from the nitrile, or (2) a diminished formation of hydrocyanic acid. Some evidence for the second supposition will be presented later; the following experiments indicate that some of the diets which cause an increased resistance to acetonitrile do not cause a similar increased resistance to hydrocyanic acid. Experiments (series 8) have already been cited to show that a restricted diet does not cause an increased resistance to another cyanogen compound (nitroprussiate of soda).

It was shown above that a diet of ham and cheese diminishes the resistance of mice to acetonitrile, whereas a diet of rice increases such resistance. The following experiments show that a similar relation does not hold as regards hydrocyanic acid.

Series 80. (May, 1905.) (v, 190.)

A. HAM AND CHEESE.

Date.	Weight of mouse.	Remarks.
1905.	*Grams.*	
May 3	23.21	Diet of ham and cheese begun.
May 12	22.32	
May 19	23.45	
May 26	23.15	Hydrocyanic acid, 0.0695 mgm., i. e., 0.003 mgm. per gm. mouse; survived.
May 5	17.41	Diet of ham and cheese begun.
May 12	17.62	
May 19	16.85	
May 26	18.45	Hydrocyanic acid, 0.059 mgm., i. e., 0.0032 mgm. per gm. mouse; survived.
May 26	17.15	
May 27	.....	Diet of ham and cheese begun.
June 3	14.71	
June 10	14.12	
June 19	15.55	Hydrocyanic acid, 0.0498 mgm., i. e., 0.0032 mgm. per gm. mouse; survived.
May 5	14.81	Diet of ham and cheese begun.
May 12	13.52	
May 19	13.75	
May 26	12.25	Hydrocyanic acid, 0.0429 mgm., i. e., 0.0035 mgm. per gm. mouse; died, 15 minutes.

B. RICE.

1905.	*Grams.*	
May 5	20.51	Diet of rice begun.
May 12	18.92	
May 19	17.05	
May 26	14.31	Hydrocyanic acid, 0.0372 mgm., i. e., 0.0026 mgm. per gm. mouse; died, 1 hour 40 minutes.
May 5	15.41	Diet of rice begun.
May 12	12.65	
May 19	13.01	
May 26	11.41	Hydrocyanic acid, 0.0343 mgm., i. e., 0.003 mgm. per gm. mouse; died, 1 hour.
May 5	15.41	Diet of rice begun.
May 12	12.95	
May 19	12.25	
May 26	10.71	Hydrocyanic acid, 0.0375 mgm., i. e., 0.0035 mgm. per gm. mouse; died, 45 minutes.

Thus the mice which had been fed upon rice were more susceptible to hydrocyanic acid than were those which had had a diet of ham and cheese; i. e., the effect was just the opposite to that obtained with acetonitrile.

In previous experiments I found that whereas mice to which thyroid had been fed showed a very marked resistance to acetonitrile they were slightly more susceptible to hydrocyanic acid and nitroprussiate of soda.[a] The thyroid had caused in these experiments a loss of weight and I am inclined to attribute the increased susceptibility to these poisons to a lowering of "general resistance" rather than to any specific effect; the same probably holds true for the increased susceptibility to hydrocyanic acid which the mice which had been on a rice diet showed in these experiments.

These experiments afford support to the view that the protective action of a rice diet depends upon its preventing, in some way, the liberation of hydrocyanic acid from acetonitrile and not upon its exerting a favorable influence upon the neutralization of hydrocyanic acid; for in the latter case it would be expected that such a diet would reduce the susceptibility of mice to hydrocyanic acid itself, which is not the case.

Relation of changes of weight and rate of growth to resistance to acetonitrile.—It was shown in Part I that a restricted diet, which is accompanied by a marked loss of weight, increases the resistance of mice (and guinea pigs) to acetonitrile and the question was raised whether a marked loss of weight caused by other agencies might not be associated, causally, with an increased resistance to this poison. It also seemed probable, on theoretical grounds, that a diet which caused rapid growth and an increase in weight would, as a result of the increased metabolic activities, cause a more rapid decomposition of the acetonitrile molecule with a corresponding increase in the amount of hydrocyanic acid produced; hence mice (and other animals) receiving such a diet would be expected to be more susceptible to acetonitrile than those receiving diets which did not cause such a rapid growth. Several of the above experiments appear, at first sight, to support such a hypothesis. Thus the effect of an exclusive diet of rice was strikingly similar to that of a very restricted diet; there was a marked loss of weight and a high degree of resistance. When the rice diet was followed by one of ham and cheese there was, as a rule, an increase in weight and a marked diminution of the resistance to acetonitrile. In many other cases also the highest resistance occurred with the diets which caused but slight increases in weight and the lowest resistance with diets which caused the most rapid growth. The latter was especially marked in the case of a diet of eggs; the latter sometimes caused an increase of 40 per cent in weight in the course of a few weeks and the development of a very great susceptibility to acetonitrile. In certain cases in which the growth of the mice on this diet had been less marked, the susceptibility to the

[a] Jour. Biolog. Chem., 1905, i, p. 33.

poison was also less. Moreover, the more rapid growth caused by adding milk to oatmeal or corn meal was usually accompanied by an increased susceptibility as compared with the resistance caused by the oatmeal or corn meal alone. In two of the longer series of experiments described above (17 and 18) there was a close parallelism between the degree of susceptibility and the rate of growth; in another series (13), however, there seemed to be no relation between the two.[a]

On the other hand, there were many cases in which a loss of weight was not accompanied by an increase in resistance and others in which it was accompanied by a distinctly increased susceptibility. The latter was invariably the case, for example, when oils or fats were added to the diet. There were also many cases in which there was a rapid growth accompanied by an increased resistance. Thus although the addition of milk to oatmeal or corn meal increased the growth and lowered the resistance as compared with the effects of oatmeal or corn meal alone, it increased both the rate of growth and resistance as compared with an exclusive diet of milk. Similarly in series 18 a combination of egg yolk and liver led to as rapid a growth as did a diet of egg yolk alone, but the fatal dose of acetonitrile was three times as great in the former as in the latter case.

Notwithstanding these facts, I believe that in some cases there is a close, although perhaps indirect, relation between the influence of a diet upon growth and resistance to acetonitrile; this will be discussed in connection with the effect of diets upon the activity of the thyroid.

Relation to fats, proteins, and carbohydrates.—In order to determine whether there is a definite relation between resistance to acetonitrile and the proportion of fat, protein, and carbohydrates much greater attention to the composition of the diets would be necessary than was given to it in these experiments; the latter do, however, suggest certain general conclusions. Thus fats (lard, olive, cotton seed, corn, and cod liver oils) always led to a low degree of resistance; this was also the case in experiments upon rats. The effect of oil in corn meal is shown by the experiments in which extracted and unextracted meal was fed to mice; the latter caused a lower resistance than did the former. The low degree of resistance caused in mice by diets of milk, eggs, and cheese may also be connected in part with the large fat content of these diets; the same may also be true, to a less extent, for "cakes" which contain considerable (about 8 per cent) of fat.

Rice, which is very poor in fat, caused a high degree of resistance, but so did oats and oatmeal which are fairly rich in fats. Wheat and most kinds of wheat bread contain but little fat, but as a rule they cause a low degree of resistance.

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[a] Series 17 and 18 were performed in the summer, series 13 in the winter; whether season has an influence remains to be determined.

Dextrose increased the resistance of mice to acetonitrile.[a] Thus fats and at least some carbohydrates have opposite effects, thereby affording another illustration of the nonequivalence, in certain respects, of these food stuffs.[b]

Certain proteins (casein, peptones, and egg albumin) added to other foods lowered the resistance.

Before leaving this subject attention may be called to a parallelism between the effects of various foods upon the resistance of mice to acetonitrile and their efficiency in maintaining nitrogen equilibrium. Rubner [c] arranged a number of foods as follows with reference to the amount of protein in the food necessary to maintain nitrogen equilibrium and to yield 3,600 calories: Potatoes,[d] rice, maize, white bread, black bread, mother's milk, cow's milk, peas, eggs, meat.

Arranging the foods of the above experiments (Series 17 with the probable place of others in parentheses) in the order of their efficiency in protecting mice against acetonitrile, the following is obtained: Potatoes, (maize), (rice), (rye), bread (S), ham (lean), milk, eggs.

These diets stimulated growth in almost the reverse order.

It may be that this parallelism is only accidental, but it is suggestive of a deeper significance.

Sulphur, free and in certain forms of combination, increases the resistance of mice (and other animals) to acetonitrile; the question whether some of the results obtained in these experiments are due to this element in special forms of combination must be left to further

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[a] In this connection brief mention may be made of a series of experiments performed several years ago to determine whether dextrose and other carbohydrates exert a protective action against acetone, the problem being suggested by the well-known clinical observations that in many cases of severe diabetes the acetone excretion is diminished and the symptoms improved by the administration of small amounts of carbohydrates. The experiments were performed upon rabbits and guinea pigs. The results were somewhat irregular, but they showed clearly that whereas rabbits died in from 3 to 8 days from daily doses of 3.8 to 4.1 gm. acetone per kilo weight, they lived for from 6 to 22 days when large doses of dextrose, cane, or milk sugar were administered with the acetone. The results were sufficiently striking to lead me to suggest that the administration of dextrose before chloroform anæsthesia might diminish the acetone excretion which usually follows such anæsthesia; the observations performed on this suggestion gave negative results. Beddard (Lancet, 1908, I, p. 782) has recently made a similar suggestion (from an entirely different standpoint, however) and at least one case has been reported (Weir, Lancet, 1909, II, p. 710) in which the administration of dextrose to a patient suffering from delayed chloroform poisoning seemed to have had a remarkably favorable effect. I also found rabbits to withstand slightly larger doses of ethyl alcohol and for longer periods when dextrose was administered simultaneously.

[b] Cf., for example, Cathcart, Jour. of Physiol., 1909, 39, p. 311; Shaffer and Coleman, Arch. of Internal Med., 1909, 4, p. 543.

[c] Rubner, Volksernährungsfragen, 1908, p. 19

[d] The potatoes contained 42 gm. protein, the rice 69 gms., the bread 85 gms., etc.

studies. That sulphur can not be the determining factor in many cases, however, is shown by the fact that the same diet often affects mice on the one hand and rats and guinea pigs on the other in opposite ways, whereas sulphur has the same effect in all three cases.

The methods described in this paper will probably prove useful in investigating some of the physiological problems of sulphur metabolism and in throwing light upon the forms of combination in which this element occurs in foods and the effect upon them of cooking, etc.

Relation of diet to the thyroid.—In addition to the various possible explanations enumerated above of the effects of different diets upon the resistance of animals to acetonitrile there remains to be considered the possibility that some of the diets influence the resistance by exerting an influence primarily upon the thyroid, which in turn influences other organs. I have reported elsewhere experiments which show that the changes in the resistance of animals to acetonitrile caused by the administration of iodine compounds is due, at least largely, to the effect of the iodine upon the thyroid, and it is generally accepted in clinical medicine that some of the effects frequently called "iodism" should more properly be called "thyroidism."[a] The recognition of this fact has led to experiments in exophthalmic goiter with food free from or very poor in iodine.

The question at once arose if the marked resistance to acetonitrile caused by certain diets might not be attributed to the effects of the iodine, which, as is well known, is contained to some extent in most articles of food.[b] This question has not been thoroughly examined, but there are several reasons for supposing that this factor is comparatively unimportant. Thus the effect produced by certain diets was often far greater than the maximum effect obtainable with very large amounts of iodine (cf., for example, the experiments in Series 81 below). There was, moreover, no parallelism between the degree of change in resistance and the amount of iodine reported to be present in the food. Thus, as has been shown above, both the yolk of egg and milk cause a very marked diminution in the resistance of mice to acetonitrile; yet the former is comparatively rich in iodine, containing, according to some analyses, nearly thirty times as much iodine as the latter. Oats and oatmeal, on the contrary, ordinarily contain an unusually small amount of iodine, but they cause a high degree of resistance.

These considerations directed my attention to another possibility, viz, that perhaps some of the diets contained substances especially

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[a] Cf. Heubner, Therap. Monatshefte, October, 1909.

[b] Bourcet, De l'iode dans l'organisme, Thèse, Paris, 1900; Monéry, Recherches nouvelles sur le fonction iodée de la glande thyroide, Thèse, Lyon, 1903; Dochez, Johns Hopkins Hospital Bull., 1908, 19, p. 235.

adapted to building up the iodine free [a] part of the thyroid or stimulating in some way its growth; it is known from earlier experiments that such thyroid has a certain degree of physiological activity.

This was also suggested by the fact that I had found great differences between different groups of mice in the manner in which they reacted to the administration of iodine compounds; some groups of mice showed a greatly increased resistance to acetonitrile after the administration of potassium iodide or certain other iodine compounds, whereas other groups showed a much less or even no increased resistance after equal or larger doses of the same compound. There was, moreover, little relation between the amount of iodine fed and the degree of increased resistance attained. These facts suggested that the thyroid often varies in its ability to take up iodine or to make an active compound of it and that this is governed to some extent, at least, by the diet.

An examination of the literature showed that there is considerable evidence that the thyroids of both man and the lower animals vary much in different individuals in their ability to take up iodine. As is well known the administration of iodine compounds usually leads to an increase in the amount of iodine in the thyroid, but several writers have called attention to exceptions to this rule. Thus Neumeister [b] found no iodine in the thyroids of rabbits to which large doses of potassium iodide had been given daily for 14 days. Oswald [c] Monéry,[d] and Jolin [e] report cases in man in which large doses of potassium iodide administered shortly before death had not led to an increased amount of iodine in the thyroid; in some of these cases, however, the thyroids were probably very abnormal. Doctor Seidell and I also found that dogs varied much as to the amount of iodine their thyroids took up after the administration of iodoform and potassium iodide. Marine and Lenhart [f] have also found the thyroid to vary in its ability to take up iodine.[g]

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[a] By "iodine free thyroid" is meant here, as in an earlier publication (Bulletin 47 of the Hygienic Laboratory), thyroid which does not give even a qualitative test for iodine when 1 gm. of the sample is examined by the Baumann method. It is of course possible, or even probable, that such thyroid contains minute amounts of iodine, and it is possible that these are responsible for the physiological activity of such thyroid. The important point, however, is that such "iodine-free" or iodine-poor thyroid has but a low degree of physiological activity and that this is usually very greatly increased when iodine is administered to an animal.

[b] Neumeister, Lehrb. d. physiolog. Chemie, 2nd ed., 1897, p. 522.

[c] Oswald, Zeitschr. f. physiol. Chemie, 1897, 23, p. 298.

[d] Monéry, Recherches nouvelles sur la fonction iodée de la glande thyroide, Thèse, Lyon, 1903, p. 105.

[e] Jolin, Festschrift O. Hammarsten, 1906, p. 46.

[f] Marine and Lenhart, Archives of Internal Medicine, 1909, 4, p. 253.

[g] The contradictory results of the experiments upon the effect of iodine upon metabolism are probably due to a considerable extent to the thyroid gland reacting differently in different individuals.

These differences may not, however, depend entirely upon the amount of iodine—poor thyreoglobulin although in certain cases of goitre this is apparently the chief factor. Some agency (a ferment, e. g.) may be lacking which is necessary for the conversion of the iodine into a form which the thyroid can utilize.

In view of these facts I formulated the hypothesis that certain diets have constituents useful in building up material in the thyroid, which is able to combine with iodine, or which increase the iodine "receptors" of the thyroid. If this hypothesis is correct then it is to be expected that the administration of iodine to such animals would ordinarily lead to a still greater resistance to acetonitrile. And, conversely, it seemed probable that the diminished resistance to acetonitrile caused by certain diets (eggs and milk, for example) may be due to these diets causing excessive demands upon the thyroid by which certain elements of the latter may be largely exhausted. Thus it may be assumed, as a working hypothesis, that certain diets lead to an extensive elimination of iodine of the thyroid and a resultant diminution of the resistance to acetonitrile (in mice); if this is the case such thyroid should subsequently be able to take up iodine in large amounts with a rapid return to the normal resistance.

The following experiments give considerable support to both of these hypotheses:

Experimental.—That the effect upon the resistance of mice to acetonitrile of the administration of potassium iodide and some other iodine compounds differs markedly in different groups of mice according to the diet which they have received is shown by the following experiments.

Series 81. (Feb., 1908.) (x, 104.)

Groups of 15 young adult mice were placed upon the following diets for about 8 weeks. The only liquid given was water or water containing 0.2 per cent potassium iodide.

[Dose in mgm. per gm. mouse.]

Diet.	Weight (average).	Fatal dose of acetonitrile.	
		Recovered.	Died.
	Grams.		
. Bread (S) and water	19.7	0.65	0.70
. Bread and 0.2 per cent potassium iodide	18.3	.72	.77
. Oatmeal and water	20.15	1.60	1.70
. Oatmeal and 0.2 per cent potassium iodide	18.06	2.20	2.60

In these experiments not only was the resistance of mice fed upon a diet of oatmeal much greater than that of mice fed upon bread but the administration of potassium iodide with the latter diet led to but a slight increase in the resistance, whereas the effect in the case of the oatmeal-fed mice was marked.

Similar results were obtained in the following series.

Series 82. (Apr., 1910.) (xii, 42.)

Groups of young mice (10 in each group) were placed upon the following diets for about 5 weeks.

[Dose in mgm. per gm. mouse.]

Diet.	Change in weight (average).	Fatal dose of acetonitrile.	
		Recovered.	Died.
a. Bread (S)	Increased 5.51 per cent (from 12.7 to 13.4 gms).	0.80	0.90
b. Bread (C)	No change (12.7 gms.)	2.00	2.50
c. Egg (entire)	Increased 44.88 per cent (from 12.7 to 18.4 gms.).	.23	.26
d. Egg (entire)+0.1 per cent potassium iodide.	Increased 44.88 per cent (from 12.7 to 18.4 gms.).	.23	.26
e. Milk, raw	No change (12.65 gms.)	.19	.20
f. Milk, raw, and 0.1 per cent potassium iodide.	Increased 13.49 per cent (from 12.6 to 14.3 gms.).	.14	.16
g. Oatmeal	Increased 17.32 per cent (from 12.7 to 14.9 gms.).	.30	.35
h. Oatmeal and 0.1 per cent potassium iodide.	Increased 23.62 per cent (from 12.7 to 15.7 gms.).	1.00	1.1

Thus potassium iodide administered with egg or milk did not increase in the least the resistance of the mice to acetonitrile; in fact it seemed to diminish it in the case of the milk-fed mice. Oatmeal alone increased the resistance slightly; the slight effect was probably due to the short duration of the feeding. The administration of potassium iodide with the oatmeal increased the resistance very decidedly; the result was in sharp contrast with that obtained by feeding the iodide with egg or milk.[a]

[a] The survivors of groups *a*, *c*, *d*, *e*, *f*, *g*, *h* were placed upon raw milk for about 10 days when their resistance to the nitrile was again determined. The earlier fatal doses are placed in parentheses for comparison.

[Dose in mgm. per gm. mouse.]

Previous diet.	Change in weight (average).	Fatal dose of acetonitrile.	
		Recovered.	Died.
a. Bread (S)	Increased 7.69 per cent (from 13 to 14 gms.)	0.10 (0.80)	0.18 (0.90)
c. Egg	Decreased 11.13 per cent (from 15 to 13.33 gms.)	(.23)	.13 (.26)
d. Egg and potassium iodide	No change (15.75 gms.)	.20 (.23)	.16 (.26)
e. Milk	No change (12 gms.)	(.19)	.07 (.20)
f. Milk and potassium iodide.	No change (12.4 gms.)	(.14)	.10 (.16)
g. Oatmeal	No change (13.66 gms.)	(.30)	.15 (.35)
h. Oatmeal and potassium iodide.	Decreased 7.5 per cent (from 13.33 to 12.33 gms.).	.80 (1.00)	.90 (1.10)

The change to a milk diet caused a diminished resistance; this was least marked in the case of the mice which had received oatmeal and potassium iodide, thus affording another instance of the persistency of the increased resistance caused by this combination.

Age or long-continued feeding seems to have an effect upon the result of the administration of potassium iodide, as is shown by the following experiments:

Series 83. (Mar., 1908.) (x, 108.)

Groups of adult mice were fed as below for about 13 weeks:

[Dose in mgm. per gm. mouse.]

Diet.	Weight (average).	Fatal dose of acetonitrile.	
		Recovered.	Died.
	Grams.		
. Bread and water	19.56	.....	0.35
. Bread and 0.2 per cent potassium iodide	22.87	.....	.40
Oatmeal and water	22.27	2.10	2.30
. Oatmeal and 0.2 per cent potassium iodide	21.95	2.00	2.20

The failure of the potassium iodide to increase the resistance of group *b* is probably to be explained on the absence of material in the thyroid capable of combining with the iodine. It is not so easy to offer an explanation of the failure of the potassium iodide to increase the resistance of group *d;* possibly the long-continued diet of oatmeal was of itself sufficient to increase the resistance to the maximum possible in these mice, and it is of interest to note that the fatal dose in this series was about the same as that in group *d*, series 81, where the potassium iodide had undoubtedly had an effect.

That the potassium iodide administered to group *d* of series 83 had an effect, however, is shown by the fact that when groups *c* and *d* were placed upon a diet of bread and water the members of this group retained their increased resistance longer than did those of group *c*. Thus the fatal dose for these groups after an exclusive diet of bread and water for 20 days was as follows:

[Dose in mgm. per gm. mouse.]

	Weight (average).	Recovered.	Died.
	Grams.		
. (previously on oatmeal)	26.95	0.90	1.00
. (previously on oatmeal and potassium iodide)	20.33	1.50	1.60

The diet of bread was continued for 3 weeks longer and the fatal dose again determined; the results were as follows:

[Dose in mgm. per gm. mouse.]

	Weight (average).	Recovered.	Died.
	Grams.		
. (previously on oatmeal)	24.63	.....	0.45
. (previously on oatmeal and potassium iodide)	24.15	1.10	.....

The continued high resistance of members of group *d* after they had been placed upon a diet of bread is probably to be explained by a storage of iodine during the period when they received potassium iodide.

There was, apparently, no storage of iodine by the mice which had originally received the diet of bread and potassium iodide, for when these were placed upon a diet of oatmeal, although their resistance was increased, this increase was not greater than it was in the case of those which had received no potassium iodide. The experiments were as follows: The mice of groups *a* and *b* (series 83) were placed upon a diet of oatmeal and water and their resistance to acetonitrile tested after 20 days. The results were as follows:

[Dose in mgm. per gm. mouse.]

	Weight (average).	Recovered.	Died.
	Grams.		
a (previously on bread and water)	20.11	0.50	1.00
b. (previously on bread and potassium iodide)	22.24	.50	1.00

After another interval of 20 days (the diet of oatmeal having been continued) a mouse of group *a* recovered from 1.2 mgm. per gm., showing a further increase in resistance.

In the following series also potassium iodide had no effect when administered with oatmeal. The mice were adults.

Series 84. (May, 1910.) (xii, 50.)

[Dose in mgm. per gm. mouse.]

Diet.	Change in weight (average.)	Fatal dose of acetonitrile.	
		Recovered.	Died.
a. Milk, raw	Decreased 8.85 per cent (from 19.2 to 17.5 gms.).	0.10	0.11
b. Milk and 0.1 per cent potassium iodide	Decreased 4.14 per cent (from 19.3 to 18.5 gms.).	.15	.16
c. Oatmeal	No change (19.2 gms.)	.70	.70
d. Oatmeal and 0.1 per cent potassium iodide.	Decreased 6.63 per cent (from 19.3 to 18.13 gms.).	.70	.70

The difference in the resistance between the milk and the milk and potassium iodide fed mice was probably due to the potassium iodide checking the diminution of the resistance caused by the milk rather than to actual increase in the resistance.

Series 85. (Feb., 1908.) (x, 106.)

In this series young mice were kept upon diets of bread and oatmeal for about 8 weeks. One half of each group was then placed upon cakes and the other half upon cakes containing in each 4 gm., 0.05 gm. extract of bladderwrack (containing 0.086 per cent iodine). After 10 days acetonitrile was injected, with the following results:

[Dose in mgm. per gm. mouse.]

Diet.	Change in weight (average).	Fatal dose of acetonitrile.	
		Recovered.	Died.
. Bread (original diet):			
(*a*) Cakes	Decreased 6.7 per cent (from 17.55 to 16.39 gms.)	0.55	0.65
(*b*) Bladderwrack	Decreased 11.6 per cent (from 18.86 to 16.47 gms.)	.60	.65
. Oatmeal (original diet):			
(*a*) Cakes	Decreased 6.8 per cent (from 16.79 to 15.64 gms.)	1.80	2.20
(*b*) Bladderwrack	Decreased 2.4 per cent (from 17.62 to 17.19 gms.)	2.70	3.00

Thus the resistance of the bread-fed mice was not increased at all, or at least but very slightly, by the administration of bladderwrack; that of the oatmeal-fed mice was much increased (probably by at least 40 per cent).

The following series also shows the increased resistance to acetonitrile caused by the administration of an iodine compound to oatmeal-fed mice:

Series 86. (Feb., 1908.) (x, 105.)

The mice had been fed for about 8 weeks on a diet of oatmeal and milk; their resistance to acetonitrile was as follows: Weight (average), 23.72 gms.; recovered, 2.3; died, 2.6.

Half of the mice were placed upon "plain cakes" and half upon cakes containing 0.05 gm. bladderwrack (with 0.086 per cent iodine) each; after 11 days they were again tested with acetonitrile with the following results:

[Dose in mgm. per gm. mouse.]

Diet.	Weight (average).	Fatal does of acetonitrile.	
		Recovered.	Died.
	Grams.		
. Cakes	20.18	1.80	2.00
. Bladderwrack, 0.05+4	21.26	3.00	3.10

All of the above series were performed in February and March, that is, in months when the natural resistance of mice to acetonitrile is high. The following series was performed in June, when the resistance is low:

Series 87. (June, 1908.) (x, 198.)

The mice of this series consisted of adults, many of which had in the late winter or early spring been used for other purposes. On the 4th of April one-half (Group *A*) were placed upon an exclusive diet of bread and water, the other half (Group *B*) upon a diet of oats and water. After about 8 weeks (June 2) each group was divided into four subgroups and one subgroup placed upon each of the following diets: (*a*) cakes, (*b*) cakes + 0.05 gm. extract of bladderwrack, (*c*) cakes + 0.02 gm. iodoform, (*d*) cakes + 0.02 gm. potassium iodide. About a week later the resistance of members of each group was tested to acetonitrile; the results were as follows:

GROUP A (BREAD FED.)

[Dose in mgm. per gm. mouse.]

Diet.	Change in weight (average).	Fatal dose of acetonitrile.	
		Recovered.	Died.
a. Cakes	Decreased 12.5 per cent (from 19.52 to 16.89 gms.)	0.11	0.12
b. Bladderwrack, 0.05+4	Decreased 11 per cent (from 20.67 to 18.40 gms.)	.32	.35
c. Iodoform, 0.02+4	Decreased 15.6 per cent (from 18.66 to 15.74 gms.)	.40	.42
d. Potassium iodide, 0.02+4	Decreased 9.8 per cent (from 19.07 to 17.20 gms.)	.52	.55

GROUP B (OATS FED.)

[Dose in mgm. per gm. mouse.]

a. Cakes	Deceased 0.8 per cent (from 18.42 to 18.27 gms.)	0.40	0.43
b. Bladderwrack, 0.05+4	Decreased 2.7 per cent (from 16.33 to 15.89 gms.)	.65	.68
c. Iodoform, 0.02+4	Decreased 6.4 per cent (from 16.75 to 15.68 gms.)	.77	.80
d. Potassium iodide, 0.02+4	Decreased 4.7 per cent (from 18.44 to 17.58 gms.)	.70	.72

The administration of iodine compounds led to an increased resistance in the case of both the bread-fed and the oats-fed mice, or perhaps (especially in the case of the latter) had prevented a diminution of the resistance. The relative increase in resistance was greater in the case of the bread-fed mice, but the degree of resistance reached was greater in the oats-fed animals; hence the results are in harmony with the hypothesis that a diet of oats leads to the formation of a larger amount of iodine-free thyreo-globulin.

It is difficult to suggest a satisfactory explanation of why the administration of iodine compounds to the bread-fed mice in this series (in June) led to an increased resistance whereas it was practically without effect in the earlier series (February and March).

The difference may have been due to differences in the age of the mice, or in their previous treatment, but it seems more probable that it is connected in some way with the seasonable variations in resistance to which attention has already been called. An observation of F. C. Koch[a] is suggestive in this connection; Koch found sheep thyroids to invariably assay higher in iodine (as much as three times) during the winter months than during June and July.[b] The most plausible explanation of this interesting observation of Koch would, at first thought, seem to be that this difference was the result of different methods of feeding during the winter and early summer (the administration of iodine-containing salt, for example) but this explanation should not be accepted without evidence. Certainly my results showing that mice are least resistant to acetonitrile during the summer months and the results of the experiments of series 87, showing that in June the administration of iodine compounds to bread-fed mice increases their resistance (due, I believe, to the ability of the thyroid to take up iodine at this season), suggest that at this season the iodine of the thyroid is abnormally low or the diet of bread may have led to an exhaustion or reduction of the iodine already present in the gland. Investigations may show that the differences in the iodine content of sheep thyroids observed by Koch may not be due to differences in diet but to diminution of the iodine normally stored in this gland and that this diminution may have resulted from the demands made upon the thyroid by other organs or processes of metabolism during the spring months.[c]

Series 88. (Jan., 1910.) (xii, 2.)

Two groups of young, almost grown mice, 25 in each, were fed, one on a diet of bread and oats and the other upon mush made from corn meal, from November 6, 1909, to December 20, when their resistance to acetonitrile was determined.

[Dose in mgm. per gm. mouse.]

Diet.	Change in weight (average).	Fatal dose of acetonitrile.	
		Recovered.	Died.
1. Bread (C) and oats.....	Increased 26.2 per cent (from 13.80 to 17.42 gms.).....	1.20	1.30
2. Corn meal mush.....	Decreased 3.8 per cent (from 13.80 to 13.28 gms.).....	.80	.90

[a] Koch, Proc. Amer. Pharm. Assoc., 1907, 55, p. 371.

[b] Monéry (Recherches nouvelles sur la fonction iodeé de la glande thyroide, Thèse, Lyon, 1903) and Rossé found the thyroids of sheep in parts of France to contain more iodine in the winter than in the summer; although they speak of this variation being due to the season they apparently consider the different kinds of food received at different periods as having at least an important part.

[c] It would be interesting to determine, for example, if there is a relation between the iodine of the thyroid and the composition of milk; the latter contains more fat and protein in the winter than in the summer months.

The remaining mice in each group were divided into three subgroups and one of the latter placed upon one of the following diets: (*a*) Cakes, (*b*) cakes containing 0.05 gm. extract of bladderwrack (containing about 0.03 per cent iodine), and (*c*) cakes containing 0.01 gm. potassium iodide. After about 10 days their resistance to acetonitrile was again determined.

GROUP A (BREAD AND OATS-FED).

[Dose in mgm. per gm. mouse.]

Diet.	Change in weight (average).	Fatal dose of acetonitrile.	
		Recovered.	Died.
a. Cakes	Decreased 14.3 per cent (from 19.6 to 16.8 gms.)	0.35	0.45
b. Bladderwrack, 0.05+4	Decreased 11.7 per cent (from 17.5 to 15.5 gms.)	3.60	.....
c. Potassium iodide, 0.01+4	Decreased 14 per cent (from 19.3 to 16.6 gms.)	1.60	1.70

The change from a diet of bread and oats to one of cakes led to a diminished resistance. Bladderwrack had caused a markedly increased resistance; potassium iodide had also caused an increased resistance, but this was less than that caused by the bladderwrack,[a] although the potassium iodide contained about five hundred times as much iodine as the latter.

GROUP B (CORN MEAL FED).

[Dose in mgm. per gm. mouse.]

Diet.	Change in weight (average).	Fatal dose of acetonitrile.	
		Recovered.	Died.
a. Cakes	Decreased 7 per cent (from 11.97 to 11.13 gms.)	0.67	0.70
b. Bladderwrack, 0.05+4	Decreased 9.9 per cent (from 14.58 to 13.13 gms.)	.....	.65
c. Potassium iodide, 0.01+4	Decreased 15.1 per cent (from 14.73 to 12.5 gms.)	1.05	1.10

The change from corn meal mush to cakes led to a slight diminution in resistance. The administration of bladderwrack caused no increase in the resistance, whereas potassium iodide had caused an increased resistance.

Comparing the effects of the iodine compounds in Groups *A* and *B*, it is evident that they were more effective in increasing the resistance of the mice which had received a diet containing oats than of those which had received a diet of corn meal mush.

[a] The iodine in bladderwrack is usually much more effective in causing an increased resistance to acetonitrile than that in other compounds with which I have experimented; the iodine compound in bladderwrack seems to have a special affinity for the thyroid. This subject will be discussed in more detail in a publication, by Doctor Seidell and myself, in the Journal of Pharmacology and Experimental Therapeutics, 1910, vol. 2.

Series 89. (Jan., 1910.) (xii, 31.)

Two groups of young, nearly grown, mice were fed, one (Group *A*) upon an exclusive diet of boiled eggs, the other (Group *B*) upon corn meal mush, from November 16 to December 22, 1909, when their resistance to acetonitrile was determined. The results were as follows:

[Dose in mgm. per gm. mouse.]

Diet.	Change in weight (average).	Fatal dose of acetonitrile.	
		Recovered.	Died.
A. Egg	Increased 10.7 per cent (from 16.33 to 18.08 gms.)	0.85	0.95
B. Corn meal mush	Decreased 16.9 per cent (from 16.33 to 13.57 gms.)	.55	.80

The remaining mice of each group were divided into two subgroups, one of which was placed upon a diet of simple cakes and the other upon cakes containing 0.01 gm. potassium iodide. After 10 days their resistance to acetonitrile was again determined, with the following results:

GROUP A (EGG-FED).

[Dose in mgm. per gm. mouse.]

Diet.	Change in weight (average).	Fatal dose of acetonitrile.	
		Recovered.	Died.
a. Cakes	Decreased 9.6 per cent (from 20.17 to 18.24 gms.)	2.0	2.5
b. Potassium iodide, 0.01+4	Decreased 10.4 per cent (from 17.7 to 15.86 gms.)	.8	1.1

It is evident that the potassium iodide had had no effect upon the resistance of the mice. I am unable to explain the unexpected and unusual increase in the resistance of the mice which had received the cakes. It is improbable that it was due to an experimental error, for the same solution of acetonitrile was used in both series and the experiments were performed upon the same days; 4 of the cakes-fed mice recovered and none died from doses of the nitrile ranging from 1 mgm. to 2 mgm. per gm., whereas 5 of the potassium iodide-fed mice died, and none recovered from doses ranging from 1.1 mgm. to 2 mgm. per gm. There is a possibility, however, that cakes containing bladderwrack instead of simple cakes had been fed.

GROUP B (CORN MEAL MUSH).

[Dose in mgm. per gm. mouse.]

Diet.	Change in weight (average).	Fatal dose of acetonitrile.	
		Recovered.	Died.
a. Cakes	Decreased 8.7 per cent (from 15.48 to 14.13 gms.)	0.7	0.75
b. Potassium iodide, 0.01+4	Decreased 10.4 per cent (from 13.43 to 12.03 gms.)	1.2	1.50

Thus potassium iodide had caused a somewhat increased resistance. A few weeks later the following series was performed:

Series 90. (Mar., 1910.) (xii, 36.)

Young mice were fed upon diets of bread and eggs; the bread was the brand designated "C," which always caused a high degree of resistance. After about 5 weeks acetonitrile was injected with the following results:

[Dose in mgm. per mg. mouse.]

Diet.	Change in weight (average).	Fatal dose of acetonitrile.	
		Recovered.	Died.
a. Bread (C)	None	4.30	4.40
b. Eggs	Increased 34.9 per cent (from 12.6 to 17 gms.)	.35	.45

The egg diet had led to a low degree of resistance. It is interesting to compare the results obtained in this series with those obtained in series 89, performed but a few weeks earlier; in the latter the egg diet did not cause a low resistance. The explanation of this difference is probably to be found in the differences in the effects upon the growth in the two cases; in series 89 the mice had increased by but 10.7 per cent in weight; in series 90 by 34.9 per cent.

The survivors of group *a* were divided into two subgroups and placed upon diets of cakes, and cakes containing potassium iodide; those of group *b* were divided into three groups and placed upon cakes, and cakes containing extract of bladder-wrack (with about 0.03 per cent iodine) or potassium iodide. After about 11 days their resistance to acetonitrile was again tested with the following results:

GROUP A (BREAD FED).

[Dose in mgm. per gm. mouse.]

Diet.	Change in weight (average).	Fatal dose of acetonitrile.	
		Recovered.	Died.
a. Cakes	Decreased 13.9 per cent (from 12 to 10.33 gms.)	2.2	3.0
b. Potassium iodide, 0.01+4	Decreased 7.4 per cent (from 11.46 to 10.61 gms.)	4.0	4.5

The mice on a diet of cakes had lost part of their high degree of resistance; those receiving the potassium iodide had retained it.

GROUP B (EGG FED).

[Dose in mgm. per gm. mouse.]

Diet.	Change in weight (average).	Fatal dose of acetonitrile.	
		Recovered.	Died.
a. Cakes	Decreased 12 per cent (from 17.67 to 15.54 gms.)	0.12	0.3
b. Bladder-wrack, 0.05+4	Decreased 12.5 per cent (from 16.59 to 14.5 gms.)	.40	.8
c. Potassium iodide, 0.01+4	Decreased 15.5 per cent (from 16.97 to 14.34 gms.)	1.00	1.1

The resistance of the mice receiving the diet of cakes was still further lowered; that of those receiving the bladder-wrack was not much changed, whereas those receiving the potassium iodide was increased.

SUMMARY OF THE ABOVE EXPERIMENTS.

These experiments lend considerable support to the hypothesis suggested above, viz, that in some cases the effect of diet upon the resistance of mice to acetonitrile is exerted, at least in part but probably only in part, through the thyroid gland. The experiments with oats and oatmeal and eggs are of especial interest. In the earlier parts of this paper many experiments were quoted showing that a diet of oatmeal or of oats usually leads to a marked resistance of mice to acetonitrile; the experiments quoted in this section, which show that the administration of certain iodine compounds with or subsequently to such a diet still further increases this resistance, and the experiments previously reported showing that as far as the resistance toward acetonitrile is concerned iodine exerts its action through the thyroid gland, all point to the conclusion that the resistance caused by an oat diet is in part an effect exerted upon the thyroid. This effect is obtained much more markedly and constantly with young, growing mice.

From these experiments and considerations it seems very probable that it is possible to influence, in a specific manner, by diet, one of the most important hormones in the body; this is a comparatively new principle in dietetics and one which may prove of much importance.[a]

[a] After the completion of most of the above experiments my attention was called to an article by Watson (Lancet, 1907, I, p. 985) in which the author reports that the thyroid of young rats which have been fed on oatmeal are enlarged; he states that the "results appear to indicate that an excessive oatmeal diet has a markedly stimulating effect on the thyroid gland of young animals."

Oats have long been held to have a "stimulating" action upon animals. Pugliese and Brighenti (Jour. de physiol. et de la pathol. gén., 1909, 11, p. 1047) have recently found that the products of the autolysis of oats and of their peptic digestion increases

There are also a number of facts which support the hypothesis that the effect of the egg diet upon the resistance of mice to acetonitrile is due in part to an effect upon the thyroid. Thus the egg diet has an effect just the reverse of that of the administration of thyroid; moreover, the marked increase in the resistance of mice which have had such a diet, which sometimes occurs when potassium iodide is subsequently administered, suggests that the egg diet had led to a condition of exhaustion of the gland.

It is not necessary to assume that this change in the thyroid is the direct effect of the egg diet; it would be more logical to suppose that it is an indirect effect, probably an effect of the rapid growth caused by the egg diet. It is known that a normally functioning thyroid is necessary for the growth of an animal, and it is readily conceivable that a diet which causes an abnormally rapid growth might lead to a temporary exhaustion of the gland. It is interesting to recall in this connection that with the egg diet the lowest resistance was found in those cases in which there had been the most rapid growth; with a less rapid growth there was a higher resistance. It is possible, however, to select a combination of foods which will cause rapid growth and still maintain a rather high degree of resistance to acetonitrile (see below).

These considerations are almost purely theoretical[a]; they are, for the most part, however, open to experimental proof or refutation. But whether the suggested explanations prove true or false the experiments show that it is possible to classify a number of ordinary foods as to whether they affect the organism of the mouse in the same way or in the opposite way as does thyroid. Oats, oatmeal, liver, kidney, dextrose, and certain kinds of wheat bread belong to the former class; milk and eggs to the latter class.

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the strength of the contractions of the heart and of striated muscle and delay the fatigue of the latter.

I have made, with Doctor Seidell, a few preliminary experiments in an endeavor to determine what constituents of oats are responsible for the effect upon the thyroid. From the experiments of series 17 it will be seen that the ash of oats added to bread did not alter the latter's effect upon the resistance of mice to acetonitrile.. In series 26 the aqueous extract of oats added to corn meal seemed to lower slightly the resistance of mice as compared with corn meal and water.

From series 18 it would seem as if the constituents causing the increased resistance were removed by 96 per cent alcohol.

[a] Note during proof reading. The correctness of these conclusions has been proved by feeding the thyroid of mice (kept on certain diets) to other mice and testing the resistance of the latter to acetonitrile. The mice which were most resistant to this poison had thyroids which, when fed to other mice, afforded the greatest degree of protection. These experiments give the direct proof that in some cases the resistance of mice to acetonitrile is due to the activity of the thyroid and also that the acetonitrile test is a measure (at least to a certain extent) of the normal physiological activity of the thyroid in the body. These results will be published in detail shortly.

The question whether these foods affect the human organism as they do that of the mouse must be left for future study; the probabilities are that they do. Careful observations upon man in conditions of hypo- and hyperthyroidism would throw much light upon this subject; such observations, however, do not seem to have been made. Berkeley's remarks [a] upon the great value of eggs and milk in the treatment of exophthalmic goitre and the advisability of eliminating sweets in this disease are very suggestive; it would be interesting to know if certain other foods which experimentally have an effect similar to thyroid (oatmeal, liver, kidney) are contraindicated in this disease. The experiments are of interest in connection with the iodine-free-food treatment which has been advocated for this disease. It is generally recognized that iodine usually aggravates the symptoms in exophthalmic goitre. These experiments suggest that diet is capable of causing much greater changes in the activity of the thyroid than iodine or any other drug and that more careful study should be given it.

The experiments also show how some effects of one food may be retained and other effects more or less eliminated by combining it with other foods. Thus the effect of egg yolk in causing rapid growth is retained when oatmeal or liver is added, but the latter reduces to a considerable extent its property of increasing the susceptibility to acetonitrile. Egg white added to egg yolk had no effect upon either the rate of growth or resistance to acetonitrile.

The above results are suggestive in connection with the oatmeal treatment of diabetes mellitus. It is very probable that hormones other than the thyroid can be influenced in a definite manner by certain diets; the hypothesis that the favorable results obtained in certain cases of diabetes by an oatmeal diet are due to the latter having a special relation to some of the hormones involved in the metabolism of sugar seems much more probable than some of the other hypotheses which attribute them to differences in the carbohydrates.

The experiments on the effect of diet upon the result of the administration of iodine compounds are of interest in another connection: One of the marked tendencies in pharmacology at present (due to a

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[a] Berkeley, Johns Hopkins Hospital Bulletin, 1908, 19, p. 259.

Newman (Lancet, 1909, II, p. 1584) reports a case of exophthalmic goitre in which sour milk seemed to be beneficial; the souring would largely eliminate the sugar which according to Berkeley seems to be contraindicated and which according to my experiments has an effect somewhat similar to small doses of thyroid. The beneficial effects noted by Edmunds (Lancet, 1908, I, p. 227) and by Goebel (Münch. med. Woch., 1902, p. 835), from the administration of comparatively large amounts of the milk of thyroidectomized goats in cases of exophthalmic goitre may have been due in part to the milk *per se* as well as to the presence of an antibody or the absence of iodine.

considerable extent to the influence of Ehrlich) is the endeavor to find drugs which have special affinities for certain organs or parts of organs, drugs which are neurotropic, lipotropic, thyreotropic, etc. As will be shown in a later publication there are certain iodine compounds which seem to be very distinctly thyreotropic. The observations reported above (and others of a similar character to be reported later) suggest that it is possible to modify, by diet, organs so that they may more readily take up certain drugs and it seems that in certain cases more pronounced results may be obtained in this way than by changing the chemical constitution of the drug.

b. EXPERIMENTS WITH GUINEA PIGS.

Only a small number of experiments were performed upon guinea pigs with the special object of determining if a relation exists between the diet and the resistance of these animals to acetonitrile; the results of these experiments were, however, positive. The experiments brought out a number of other points of some interest; some of these will be referred to briefly.

Effect of season.—The fatal dose of acetonitrile for guinea pigs has, during the last 3 or 4 years, been determined several times in nearly every month; the average of these determinations, expressed in mgms. per gm. body weight, is as follows:

January	0.2	June	0.42
February	.25	July	.45
March	.35	September	.40
April	.35	November	.20
May	.35	December	.26

Thus the animals were most resistant in the spring and summer months, i. e., at a time when mice were the least resistant. Since removal of the thyroid tends to increase the resistance of guinea pigs to acetonitrile and the administration of iodine compounds (by which the activity of the thyroid is increased) diminishes the resistance it is probable that an important factor in these seasonable variations are variations in the activity of the thyroid gland; this conclusion is in harmony with the results of experiments on mice and the variations in the iodine content of sheep thyroids already discussed.

We are not in possession of sufficient data to attempt to explain these variations but certain factors may be mentioned. First among these is the diet. All of the guiena pigs were bred in the laboratory and their parentage and diet were known. The diet consisted of dry oats, bran, hay, and "green food;" the latter consisted in the winter and early spring (from November to May) of carrots and cabbage; in the summer it consisted of green rye, alfalfa, green maize, or carrots and cabbage. The animals had access to rock salt throughout the

year. Although the green food of the winter months may have contained a little more iodine (which lowers the resistance of guinea pigs to acetonitrile) than did that of the summer it seems improbable that this or the other slight differences in diet was the cause of the differences in susceptibility. It seems more probable that the latter is associated in some way with seasonable variations of metabolism of unknown origin.

Physiological oxidation processes are, as is well known, increased by cold and the question may arise if the increased susceptibility during the winter months may not be due to accelerated metabolism which would lead to a greater decomposition of the acetonitrile molecule. But, as Rubner has shown, the coat of hair on animals like the clothing of man, largely or totally abolishes the effect of moderate cold upon metabolosm. Moreover the guinea pigs were kept in a uniformly heated room throughout the winter and were not exposed to greater differences in temperature than were the mice used in the preceding experiments, the resistance of which was increased during the winter.

A factor which should receive more careful consideration is the possible relation between susceptibility to acetonitrile and rate of growth. Südmersen and Glenny[a] found the average age of 250 gm. guinea pigs in the 6 months of winter (October to March) to be 44.6 days as compared with 32.8 days in summer. They also found that a larger dose of diphtheria toxin was necessary to kill a guinea pig of the same weight in summer than in winter and that for guinea pigs of the same weight the fatal dose increased with the age.

Effect of feeding thyroid.—The feeding of thyroid lowers the resistance of guinea pigs to acetonitrile, as is shown, for example, by the following experiments:

Series 91. (Sept., 1908.) (xi, 90.)

The thyroid was fed in the form of commercial tablets, three different products being used. The thyroid was fed for 13 days.[b]

A. CONTROLS.

[Dose in mgm. per gm. guinea pig.]

No.	Change in weight.	Fatal dose of acetonitrile.	
		Recovered.	Died.
1	Increased 34.9 per cent (from 235 to 317 gms.)	0.38	.....
2	Increased 44.1 per cent (from 215 to 310 gms.)	.40	.....
3	Increased 40.4 per cent (from 205 to 288 gms.)	.....	0.40
4	Increased 32.6 per cent (from 230 to 305 gms.)	.....	.43
5	Increased 34.6 per cent (from 225 to 303 gms.)	.....	.50

[a] Südmersen and Glenny, Jour. of Hygiene, 1909, 9, p. 399.

[b] The effect of sulphur upon the resistance of guinea-pigs to acetonitrile was tested at the same time; the results will be given here in order to avoid repetition.

B. 0.128 GM. THYROID CONTAINING 0.113 PER CENT IODINE (=0.1446 MGM. IODINE) FED DAILY.

[Dose in mgm. per gm. guinea pig.]

No.	Changes in weight.	Fatal dose of acetonitrile.	
		Recovered.	Died.
1	None (210 gms.)	0.20	.....
2	Increased 13.6 per cent (from 220 to 250 gms.)	.30	.....
3	Increased 7.7 per cent (from 220 to 237 gms.)	.....	0.35
4	Increased 5.6 per cent (from 230 to 243 gms.)	.....	.40

C. [a]0.064 GM. THYROID WITH 0.38 PER CENT IODINE (=0.2432 MGM. IODINE) FED DAILY.

[Dose in mgm. per gm. guinea pig.]

1	Increased 13 per cent (from 230 to 260 gms.)	0.3	.....
2	Increased 2.3 per cent (from 215 to 220 gms.)	.....	0.35
3	None (235 gms.)	.....	.40

D. 0.128 GM. THYROID WITH 0.065 PER CENT IODINE (=0.0832 MGM. IODINE) FED DAILY.

[Dose in mgm. per gm. guinea pig.]

1	Increased 13 per cent (from 230 to 260 gms.)	0.25	.....
2	Increased 11.8 per cent (from 235 to 263 gms.)	.....	0.30
3	Increased 14.4 per cent (from 215 to 246 gms.)	.....	.32
4	Decreased 7.8 per cent (from 205 to 189 gms.)	.....	.40

E. 0.2 GM. SULPHUR IN THE FORM OF PILLS WAS FED DAILY.

[Dose in mgm. per gm. guinea pig.]

1	Increased 3.2 per cent (from 245 to 253 gms.)	0.45	.....
2	Increased 12 per cent (from 240 to 269 gms.)	.....	0.55

[a]Another guinea pig of this series died on the sixth day after the administration of thyroid was begun.

It is evident that the thyroid had in all these cases very distinctly diminished the resistance of the guinea pigs to acetonitrile. The thyroid also caused a retardation of growth. The latter effect was roughly proportional to the percentage of iodine in the thyroid fed; this is another indication that the activity of the thyroid is parallel to the iodine content. I have shown in earlier papers that the increased resistance of mice to acetonitrile caused by the feeding of thyroid is very closely parallel to the iodine content of the latter; this did not hold in these experiments on guinea pigs for the diminished resistance caused by the feeding of thyroid. It is quite probable that the increased resistance caused in mice is a primary effect of the thyroid, whereas the diminished resistance in the guinea pigs is an effect secondary to other effects.

Sulphur caused a distinct increase in the resistance to acetonitrile; the effect was not nearly as great as it was in similar experiments on mice (series 66, for example) and rats.

Oats.—It has been shown above that a diet of oats as compared with many other diets increases the resistance of mice to acetonitrile, and arguments were presented that this effect is probably due in part at least to a stimulating action on the thyroid. Since thyroid and potassium iodide and other iodine compounds administered to guinea pigs diminish their resistance to acetonitrile, it would be expected that oats would have a similar effect if it had a stimulating action upon the thyroid similar to that observed in mice.[a] This supposition was realized in the two series of experiments I have performed.

Series 92. (Mar., 1908.) (x, 121.)

Two groups of guinea pigs of approximately the same age and weight were fed from January 17 to March 7, as follows: Members of Group *A* received an unlimited amount of oats and in addition 5 gms. of carrots and cabbage daily for the first 25 days and thereafter the same amount every second day.[b] Group *B* received only cabbage and carrots (equal parts).

A. (OATS FED.)

[Dose in mgm. per gm. guinea pig.]

No.	Change in weight.	Fatal dose of acetonitrile.	
		Recovered.	Died.
1	Increased 45.8 per cent (from 230 to 340 gms.)	0.35	.....
2	Increased 5.7 per cent (from 225 to 238 gms.)	.....	0.37
3	Increased 3.7 per cent (from 240 to 249 gms.)	.....	.40
4	Increased 54.5 per cent (from 240 to 371 gms.)	.....	[a].45

B. (GREEN FOOD.)

1	Increased 12.9 per cent (from 240 to 271 gms.)	0.40	.....
2	Increased 31 per cent (from 235 to 308 gms.)	.45	.....
3	Increased 6.9 per cent (from 245 to 262 gms.)	.47	.....
4	Increased 23.8 per cent (from 235 to 291 gms.)	.47	.....
5	Increased 17.7 per cent (from 225 to 265 gms.)	.....	0.50
6	Increased 11.3 per cent (from 230 to 256 gms.)	.....	.55

[a] Two others died from 0.45 mgm. per gm. weight.

Series 93. (July, 1907.) (x, 120.)

The guinea pigs were fed for about a month as in series 92, except that the group on oats received a few grams of green food but twice a week.

[a] I do not believe that the reaction of guinea pigs to acetonitrile is by any means as closely related to thyroid activity as that of mice seems to be. Diet, etc., may and probably does affect the thyroids of both animals in the same way, but there is no means of accurately determining the effect in guinea pigs.

[b] As is well known, guinea pigs do not live long upon an exclusive diet of oats, but a very small amount of green food enables them to thrive on it.

A. (OATS.)

[Dose in mgm. per gm. guinea pig.]

No.	Change in weight.	Fatal dose of acetonitrile.	
		Recovered.	Died.
1	Decreased 4 per cent (from 250 to 240 gms.)		0.27
2	Increased 42.6 per cent (from 225 to 320 gms.)		.30
3	Increased 27.4 per cent (from 255 to 325 gms.)		.30
4	Increased 38.2 per cent (from 235 to 325 gms.)		.38

B. (GREEN FOOD.)

1	Increased 66.6 per cent (from 240 to 400 gms.)	0.36	.....
2	Increased 72.9 per cent (from 240 to 415 gms.)	.42	.....
3	Increased 78.7 per cent (from 235 to 420 gms.)	.47	.....
4	Increased 64.6 per cent (from 235 to 383 gms.)	.53	.....

These experiments show that the resistance of guinea pigs to acetonitrile is influenced by the diet. The results are also in harmony with the hypothesis that a diet of oats has a special effect upon the thyroid.

Attention has already been called to the fact that the administration of prostate to guinea pigs diminishes their resistance to acetonitrile; one of the series of experiments on this subject was as follows:

Series 94. (May, 1907.) (vii, 25.)

Group *B* received from 0.38 to 0.51 gms. dried prostate daily for 13 days. The changes in weight and the fatal dose of acetonitrile were as follows:

A. CONTROLS.

[Dose in mgm. per gm. guinea pig.]

No.	Change in weight.	Fatal dose of acetonitrile.	
		Recovered.	Died.
1	Increased 12.2 per cent (from 490 to 550 gms.)	0.28	.....
2	Increased 9.1 per cent (from 240 to 262 gms.)		0.31
3	Increased 18 per cent (from 250 to 295 gms.)		.34

B. PROSTATE.

1	Increased 11.4 per cent (from 245 to 273 gms.)		0.19
2	Increased 13.7 per cent (from 290 to 330 gms.)		.23

Thus prostate has an effect upon the resistance of guinea pigs to acetonitrile similar to that of thyroid.

(c.) EXPERIMENTS ON DOGS.

Only one experiment was made upon dogs to determine if diet has an influence upon the excretion of sulphocyanate after the administration of acetonitrile.

Series 95. (Jan. 6, 1906.) (vii, 9–10 and vi, 150–151.)

Two bitches of approximately the same weight were fed for about 3 weeks on a diet consisting of 50 gms. lean beef and as many Spratt's dog biscuit as they would eat. Acetonitrile, 0.1 mgm. per gm. weight, was then injected into each. The sulphocyanate in the urine was determined, by Lang's method, for five days; in one dog (*A*) 12.6 per cent of the cyanogen of the nitrile appeared in the urine as sulphocyanate; in the other (*B*) 14.7 per cent. Lang recovered in similar experiments upon dogs (diet not stated) 14 and 18.4 per cent of the cyanogen.[a] Dog *A* was then placed upon a diet consisting exclusively of lean beef, and dog *B* upon a diet consisting of boiled rice, cane sugar, and lard in the following proportions: 400:300:50. After 17 days acetonitrile, 0.2 mgm. per gm. animal, was injected into each dog. The meat-fed dog showed in a short time fairly marked symptoms of poisoning; the carbohydrate-fat fed dog showed almost no symptoms until the following day. Sixteen and nine-tenths per cent of the cyanogen of the nitrile administered to dog *A* (meat fed) was recovered from the urine; only 9.5 per cent of that given to dog *B* was recovered.

Thus the meat-fed dog showed somewhat severer symptoms of intoxication and excreted more (1.7 times as much) of the cyanogen of the nitrile as sulphocyanate than did the carbohydrate-fat fed dog. This result may have been due either to the meat-fed dog having decomposed a larger proportion of the nitrile (owing to increased metabolism) or it may have been due to the meat having made possible the formation of a larger amount of sulphocyanate through its larger sulphur content;[b] experiments with hydrocyanic acid would probably have determined this.

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[a] In two series of experiments upon rats 11.8 per cent and 12.8 per cent of the cyanogen contained in the injected acetonitrile was recovered from the urine as sulphocyanate.

[b] The meat-fed dog excreted on this diet a daily average of 3.475 gms. total sulphur (expressed as barium sulphate), of which 2.606 gms. (or 75 per cent) was in the form of sulphates and 0.869 gm. as neutral sulphur. (On the earlier mixed diet 64.1 per cent of the sulphur was in the form of sulphates.) The carbohydrate-fat-fed dog excreted but 0.395 gm. (expressed as barium sulphate) total sulphur, of which 0.1373 gm. (34.8 per cent) was in the form of sulphate and 0.2577 gm. as neutral sulphur. The meat-fed dog thus had a much larger amount of sulphur available for the formation of sulphocyanate if the sulphur of meat is in a form available for this purpose.

2. Experiments with Propionitrile.

Experiments with mice.—Propionitrile (C_2H_5CN) is much more poisonous than is acetonitrile, and the resistance of mice to it is greatly influenced by the diet, as is shown by the following experiments:

Series 96. (June, 1908.) (x, 176.)

The mice belonged to the same groups as those of Series 17; they were fed as below for about 75 days.

[Dose in mgm. per gm. mouse.]

Diet.	Change in weight (average).	Fatal dose of propionitrile.	
		Recovered.	Died.
a. Lean ham	Increased 26 per cent		0.004
b. Milk, raw	Increased 13 per cent	0.005	.007
c. Egg yolk	Increased 39 per cent	.008	.010
d. Milk, boiled 30 minutes	Increased 25.6 per cent	.008	.012
e. Bread and oat ash [a]	Increased 5.7 per cent	.010	.025
f. Potato, boiled	Decreased 7.9 per cent		.015
g. Bread and water	Increased 16.4 per cent	.017	.018
h. Oats and water	Increased 22.9 per cent		.024
i. Cheese	Increased 14.6 per cent	.032	.034
j. Liver (hog), boiled	Increased 10.5 per cent	.050	.054

[a] The mice received daily the ash from about 9 gms. oats intimately mixed with the bread.

In comparing the fatal doses of propionitrile with those of acetonitrile (series 17) it will be seen that the latter are from thirty to sixty times as great as the former. Diet had a pronounced effect upon the fatal dose of propionitrile; this effect was in several cases different from that caused by the same diet upon the toxicity of acetonitrile.

Series 97. (July, 1908.) (xi, 2.)

The mice of this series were of the same groups as those of series 18. The mice were fed as below for 5 weeks.

[Dose in mgm. per gm. mouse.]

Diet.	Change in weight (average).	Fatal dose of propionitrile.	
		Recovered.	Died.
a. Egg yolk and liver, equal parts.	Increased 23.2 per cent	0.010	0.015
b. Egg, entire	Increased 22.5 per cent	.015	.016
c. Egg, yolk	Increased 24.2 per cent	.015	.016
d. Oats, extracted [a]	Decreased 16.0 per cent	.013	.016
e. Egg white and oatmeal, equal parts.	Increased 10.2 per cent	.016	.020
f. Brain (sheep, boiled) and oatmeal, equal parts.	Increased 14.7 per cent	.023	.025
g. Oatmeal	Increased 5.7 per cent	.027	.028
h. Liver (hog), boiled	Increased 1.3 per cent		.030
i. Kidney (sheep), boiled	Increased 20.4 per cent	.042	.044
j. Egg white and liver, equal parts.	Increased 2.0 per cent	.045	.049

[a] Oats were ground and the meal, after sifting, was extracted with 90 per cent alcohol.

The influence of diet upon the resistance of the mice to propionitrile is apparent; the effect was in several instances different from that observed with acetonitrile.

EFFECT OF IODINE COMPOUNDS.

Series 98. (June, 1908.) (x, 198.)

One group of mice (*A*) was kept for 8 weeks upon a diet of bread and water; another group (*B*) upon oats and water. Each group was then divided into subgroups which were fed as below for about a week when their resistance to propionitrile was tested.[a]

GROUP A (BREAD-FED).

[Dose in mgm. per gm. mouse.]

Diet.	Fatal dose of propionitrile.	
	Recovered.	Died.
a. Cakes	0.018	0.020
b. Bladderwrack, 0.05+4	.025	.026
c. Iodoform, 0.02+4	.....	.026
f. Potassium iodide, 0.02+4	.020	.022

Thus bladderwrack caused a distinct increase in resistance; the results with iodoform and potassium iodide were doubtful.

GROUP B (OATS-FED.)

[Dose in mgm. per gm. mouse.]

Diet.	Fatal dose of propionitrile.	
	Recovered.	Died.
a. Cakes	.....	0.024
b. Potassium iodide, 0.02+4	0.030	.....

Potassium iodide caused a distinctly increased resistance to propionitrile, and the effect was greater than in the case of the bread-fed mice.

3. EXPERIMENTS WITH MORPHINE.

(*a*) EXPERIMENTS ON MICE.

Diet has a distinct effect upon the resistance of mice to morphine as is shown by the following experiments:

Series 99. (June, 1908.) (x, 172.)

Mice were fed as below for about 75 days.[b]

[a] Other members of these groups were used in experiments with acetonitrile. (series 87).

[b] These mice were the unused ones and, to a less extent, the survivors of those used in series 17 and 96.

[Dose in mgm. per gm. mouse.]

Diet.	Change in weight (average).	Fatal dose of morphine sulphate.	
		Recovered.	Died.
a. Ham, lean	Increased 26 per cent	0.21	0.22
b. Milk, raw	Increased 13 per cent	.21	.22
c. Milk, boiled	Increased 25.6 per cent	.27	.28
d. Egg yolk	Increased 39 per cent	.33	.35
e. Liver (hog), boiled	Increased 10.5 per cent	.30	.40
f. Cheese	Increased 14.6 per cent	.35	.37
g. Oats	Increased 22.9 per cent	.35	.38
h. Bread	Increased 16.4 per cent	.40	.42
i. Bread and oat ash [a]	Increased 5.7 per cent	.37	.37
j. Potatoes	Decreased 7.9 per cent	.36	.40
k. Egg white, and bread, equal parts.	Increased 6.2 per cent	.50	.52
l. Egg white, and oatmeal, equal parts.	Increased 13 per cent	.55	.....

[a] The mice received daily the ash from about 9 gms. oats intimately mixed with the bread.

A comparison of the results of this series with those of series 17 and 92, when the mice of these groups were tested with acetonitrile and propionitrile, shows that the degree of susceptibility to the three poisons is very different, i. e., the susceptibility to each poison is specific and not dependent upon "general resistance."

The same fact is illustrated also by the following series:

Series [a] 100. (Mar., 1910.) (xii, 38.)

The mice were fed as below for about 6 weeks.

Diet.	Change in weight (average).	Fatal dose of morphine sulphate.	
		Recovered.	Died.
a. Milk, boiled	Increased 4.65 per cent from 12.33 to 12.90 gms	0.28	0.35
b. Corn meal and water	Decreased 7.54 per cent from 12.33 to 11.40 gms	.....	.40
c. Corn meal and boiled milk	Increased 27.33 per cent from 12.33 to 15.70 gms	.35	.45
d. Corn meal and oat extract	Decreased 3.56 per cent from 12.33 to 11.80 gms	.52	.55
e. Bread (C)	Increased 4.46 per cent from 12.33 to 12.88 gms	.65	.75
f. Corn meal and raw milk	Increased 37.14 per cent from 12.33 to 16.91 gms	.70	1.00
g. Bread (S)	None (12.24 gms)	.70	.90
h. Milk, raw	Increased 3.16 per cent from 12.33 to 12.72 gms	.75	.80

The effect of the different foods in altering, in a specific manner, the resistance of the mice to morphine is very evident from these experiments; this is especially marked when the results are compared with those of series 26 in which the poison used was acetonitrile. Thus with acetonitrile the mice receiving the raw milk were the least resistant; with morphine they were the most resistant. Mice receiving one brand of bread (C) were at least four times as resistant to acetonitrile as those receiving another brand (S); no such difference was observed in regard to morphine.

[a] These mice were the unused ones and the survivors of those used in series 26.

The following experiments, although not numerous and perhaps in some cases not sufficiently controlled, may be quoted; the essentially negative results obtained in some cases are of some interest:

Series 101. (Mar., 1908.) (x, 112.)

The mice were fed on the following diets for about 50 days:

[Dose in mgm. per gm. mouse.]

Diet.	Change in weight (average).	Fatal dose of morphine sulphate.	
		Recovered.	Died.
a. Beans, "navy" (boiled)	Decreased 3 per cent	0.20	0.23
b. Peanuts (raw)	Decreased 7 per cent	.25	.30
c. Beef (boiled)	Increased 7 per cent	.28	.30
d. Corn	Decreased 11.4 per cent		.36

Series 102. (Mar., 1907.) (vi, 126.)

The mice were fed as below for 10 days.

[Dose in mgm. per gm. mouse.]

Diet.	Change in weight (average).	Fatal dose of morphine sulphate.	
		Recovered.	Died.
a. Cakes	Decreased 7.7 per cent	0.38	0.43
b. Prostate 0.2+4	Decreased 14.2 per cent		.30

Series 103. (July, 1907.) (vii, 30.)

The mice were fed as below for 10 days.

[Dose in mgm. per gm. mouse.]

Diet.	Change in weight (average).	Fatal dose of morphine sulphate.	
		Recovered.	Died.
a. Cakes	Increased 4.7 per cent	0.43	0.45
b. Parathyroid 0.05+4	Decreased 6.1 per cent	.20	.30
c. Prostate, 0.1+4	Increased 2.6 per cent	.31	.34

Series 104. (Nov., 1905.) (vi, 95.)

The mice were fed as below for 8 days.

[Dose in mgm. per gm. mouse.]

Diet.	Change in weight (average).	Fatal dose of morphine sulphate.	
		Recovered.	Died.
a. Cakes	Decreased 0.9 per cent	0.24	0.26
b. Pituitary, 0.1+4	Decreased 1.3 per cent	.15	.20
c. Parathyroids, 0.2+4	Decreased 1 per cent		.35

Series 105. (Oct., 1908.) (xi, 42.)

The mice were fed as below for 9 days.

[Dose in mgm. per gm. mouse.]

Diet.	Change in weight (average).	Fatal dose of morphine sulphate.	
		Recovered.	Died.
a. Cakes	Increased 0.8 per cent	0.21	0.22
b. Sulphur 0.001+4	Decreased 0.8 per cent	.20	.21

SUMMARY.—These series of experiments, although very incomplete, admit of certain general conclusions. Thus sulphur, which protects mice (and other animals) so markedly against acetonitrile, has no influence upon the toxicity of morphine. Prostate distinctly lowers the resistance of mice to morphine; thyroid [a] has the same action. Both prostate and thyroid increase the resistance of mice to acetonitrile, whereas they both lower that of rats to this poison. They also lower the resistance of rats to morphine. From these results it is evident that the physiological action of these two glands when given per os are in a number of respects similar. Parathyroid and pituitary lowered the resistance of mice to morphine; they had a similar effect upon the resistance of these animals to acetonitrile. Thus toward one poison their action is similar to that of thyroid; toward the other it is the reverse.[b]

The results of the experiments with milk are at first sight very contradictory; in series 99 both raw and boiled milk caused a low degree of resistance to morphine, that with the raw milk being lower than that with the boiled milk. In series 100 boiled milk caused a very low degree of resistance,whereas raw milk caused a very high resistance. On comparing these results with those obtained with acetonitrile with mice of the same groups (series 17 and 26) certain relations seem to appear. Thus in series 17 and 99 boiled milk caused a lower degree of resistance to acetonitrile and a higher resistance to morphine than did raw milk; in series 26 and 100 boiled milk caused a higher resistance to acetonitrile and a lower resistance to morphine than did the raw milk. In other words, milk affected the resistance of mice to acetonitrile and morphine in opposite ways.

Since thyroid also affects the resistance of mice to morphine and acetonitrile in opposite ways, these results suggest that some of the effects of milk upon the resistance of mice to morphine may be due in part to certain effects of the milk upon the thyroid; there is no reason, however, to suppose that such an effect has more than a very subordinate part in determining the resistance to morphine.

[a] Hunt and Seidell, Bull. 47, 1909, Hygienic Laboratory, Studies on Thyroid, I.

[b] These conclusions are expressed with considerable reserve, for the experiments were not numerous.

(b) EXPERIMENTS ON RATS.

That diet has some influence upon the toxicity of morphine for rats is indicated by the following experiments:

Series 106. (Feb., 1908.)

Thirty-four rats of approximately the same age and weight were divided into two groups of 17 each. One group was placed upon an exclusive diet of bread and water and the other group upon a diet of oats and water.

The following changes in weight occurred:

Date.	Average weight.	
	Bread.	Oats.
1907.	*Gms.*	*Gms.*
December 12	61.0	62.0
December 23	63.0	63.0
1908.		
January 3	66.0	62.0
January 17	74.0	62.0
January 23	78.0	73.0
February 10	84.6	81.3
February 17	102.2	89.8

The resistance of the rats of each group to morphine sulphate was now determined; the results were as follows:

Bread and water:

One rat recovered from 0.3 mgm. morphine sulphate per gm. animal.
One rat recovered from 0.31 mgm. morphine sulphate per gm. animal.
One rat died from 0.33 mgm. morphine sulphate per gm. animal.
One rat died from 0.35 mgm. morphine sulphate per gm. animal.
One rat died from 0.40 mgm. morphine sulphate per gm. animal.

Oats and water:

One rat recovered from 0.3 mgm. morphine sulphate per gm. animal.
One rat recovered from 0.37 mgm. morphine sulphate per gm. animal.
One rat recovered from 0.40 mgm. morphine sulphate per gm. animal.
One rat died from 0.41 mgm. morphine sulphate per gm. animal.
One rat died from 0.45 mgm. morphine sulphate per gm. animal.

Thus the resistance of the bread-fed rats was distinctly less than that of the oats-fed ones.

Potassium iodide to the extent of 0.1 per cent was added to the water and the above diets continued for 2 weeks, when the resistance of the rats to morphine was again tested; the results were as follows:

Bread and 0.1 per cent solution of potassium iodide:

One rat recovered from 0.2 mgm. morphine sulphate per gm. animal.
One rat recovered from 0.22 mgm. morphine sulphate per gm. animal.
One rat died from 0.23 mgm. morphine sulphate per gm. animal.
One rat recovered from 0.24 mgm. morphine sulphate per gm. animal.
One rat died from 0.26 mgm. morphine sulphate per gm. animal.
One rat died from 0.28 mgm. morphine sulphate per gm. animal.

Oats and 0.1 per cent solution of potassium iodide:

One rat recovered from 0.2 mgm. morphine sulphate per gm. animal.
One rat recovered from 0.22 mgm. morphine sulphate per gm. animal.
One rat died from 0.26 mgm. morphine sulphate per gm. animal.
One rat died from 0.31 mgm. morphine sulphate per gm. animal.

The resistance of the rats of both groups to morphine sulphate was thus distinctly diminished by the administration of potassium iodide. The effect of the latter is thus similar to that of thyroid[a] and the explanation is probably the same, in part at least, as that of the diminished resistance to acetonitrile of guinea pigs to which iodides have been administered, viz, that it is an effect exerted through the thyroid gland.[b] It is of interest to note that, although the fatal dose of morphine for both groups of rats, after the administration of potassium iodide, was the same, the increase in the susceptibility of the group which had received the diet of oats and water was relatively greater than that of the other group.

Series 107. (Mar., 1910.) (xii, 22.)

Rats were fed as below for about 7 weeks.

[Dose in mgm. per gm. rat.]

Diet.	Change in weight (average).	Fatal dose of morphine.	
		Recovered.	Died.
a. Bread, 2 parts; olive oil, 1 part.	Decreased 4.5 per cent (from 63.00 to 60.14 gms.)	.....	0.27
b. Egg, whole	Increased 95.7 per cent (from 63.00 to 123.3 gms.)	0.27	.30
c. Oats	Increased 23.1 per cent (from 63.00 to 77.57 gms.)	.27	.31
d. Bread (C)	Increased 36.7 per cent (from 60.14 to 82.28 gms.)	.32	.35
e. Corn meal	Increased 16.7 per cent (from 63.00 to 73.57 gms.)	.....	.42

Here again there were distinct differences in susceptibility to morphine; these did not seem to have any relation to changes in rate of growth.

SUMMARY.

1. A restricted diet markedly increases the resistance of certain animals to acetonitrile.

2. Guinea pigs upon a limited diet excrete a smaller percentage of the cyanogen of acetonitrile as sulphocyanate than do those upon an unrestricted diet. This result is interpreted as showing that certain specific processes of metabolism are retarded in partial inanition.

3. Diet has a marked effect upon the resistance of animals to certain poisons; the resistance of some animals may be increased forty-fold by changes in diet.

[a] Hunt and Seidell, Bull. 47, Hygienic Laboratory, p. 77.
[b] Hunt, Journ. Am. Med. Ass., 1907, 49, p. 1323.

4. Certain diets, notably dextrose, oatmeal, liver, and kidney, greatly increase the resistance of mice to acetonitrile; their effect is similar in this respect to the administration of thyroid.

5. The effect of an oatmeal diet in increasing the resistance of certain animals to acetonitrile is probably due in part to a specific effect of the diet upon the thyroid gland; this is an illustration of how an internal secretion may be modified in a definite manner by diet.

6. Diet has, in certain cases, a marked effect upon the reaction of animals to iodine compounds; this effect is probably exerted largely through the thyroid. The condition of the latter is more important than the chemical form in which the iodine is administered.

7. Certain diets (notably eggs, milk, cheese, and various fats) greatly lower the resistance of certain animals to acetonitrile; their effect is the opposite of that of thyroid.

8. Several glands (notably prostate, ovaries, and testes) have an effect upon the resistance of animals to poisons similar to but much less marked than that of thyroid. Other glands (thymus, parathyroid, suprarenals) have either no effect or an effect opposite to that of thyroid.

9. The resistance of animals to propionitrile is markedly influenced by diet.

10. Diet causes distinct but not very marked differences in the resistance to morphine.

11. Season has an important effect upon the resistance of animals to certain poisons; in some cases these effects seem to depend upon seasonable variations in the activity of the thyroid.

12. The experiments show that foods such as enter largely into the daily diet of man have most pronounced effects upon the resistance of animals to several poisons; they produce changes in metabolism which are not readily detectable by methods ordinarily used in metabolism studies. The ease and rapidity with which certain changes in function are caused by diet are in striking contrast with the essentially negative results obtained by the chemical analyses of animals fed upon different diets.[a]

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[a] Compare Steinitz, Jahrb. f. Kinderheilk., 1904, 59, p. 447; Mendel, Biochemische Zeitsch., 1908, 11, p. 281.

LIST OF HYGIENIC LABORATORY BULLETINS OF THE PUBLIC HEALTH AND MARINE-HOSPITAL SERVICE.

The Hygienic Laboratory was established in New York, at the Marine Hospital on Staten Island, August, 1887. It was transferred to Washington, with quarters in the Butler Building, June 11, 1891, and a new laboratory building, located in Washington, was authorized by act of Congress, March 3, 1901.

The following *bulletins* [Bulls. Nos. 1–7, 1900 to 1902, Hyg. Lab., U. S. Mar.-Hosp. Serv., Wash.] have been issued:

*No. 1.—Preliminary note on the viability of the *Bacillus pestis*. By M. J. Rosenau.

No. 2.—Formalin disinfection of baggage without apparatus. By M. J. Rosenau.

*No. 3.—Sulphur dioxid as a germicidal agent. By H. D. Geddings.

*No. 4.—Viability of the *Bacillus pestis*. By M. J. Rosenau.

No. 5.—An investigation of a pathogenic microbe (*B. typhi murium* Danyz) applied to the destruction of rats. By M. J. Rosenau.

*No. 6.—Disinfection against mosquitoes with formaldehyde and sulphur dioxid. By M. J. Rosenau.

No. 7.—Laboratory technique: Ring test for indol, by S. B. Grubbs and Edward Francis; Collodium sacs, by S. B. Grubbs and Edward Francis; Microphotography with simple apparatus, by H. B. Parker.

By act of Congress approved July 1, 1902, the name of the "United States Marine-Hospital Service" was changed to the "Public Health and Marine-Hospital Service of the United States," and three new divisions were added to the Hygienic Laboratory.

Since the change of name of the service the bulletins of the Hygienic Laboratory have been continued in the same numerical order, as follows:

*No. 8.—Laboratory course in pathology and bacteriology. By M. J. Rosenau. (Revised edition, March, 1904.)

*No. 9.—Presence of tetanus in commercial gelatin. By John F. Anderson.

No. 10.—Report upon the prevalence and geographic distribution of hookworm disease (uncinariasis or anchylostomiasis) in the United States. By Ch. Wardell Stiles.

*No. 11.—An experimental investigation of *Trypanosoma lewisi*. By Edward Francis.

*No. 12.—The bacteriological impurities of vaccine virus; an experimental study. By M. J. Rosenau.

*No. 13.—A statistical study of the intestinal parasites of 500 white male patients at the United States Government Hospital for the Insane; by Philip E. Garrison, Brayton H. Ransom, and Earle C. Stevenson. A parasitic roundworm (*Agamomermis culicis* n. g., n. sp.) in American mosquitoes (*Culex sollicitans*); by Ch. Wardell Stiles. The type species of the cestode genus *Hymenolepis;* by Ch. Wardell Stiles.

No. 14.—Spotted fever (tick fever) of the Rocky Mountains; a new disease. By John F. Anderson.

No. 15.—Inefficiency of ferrous sulphate as an antiseptic and germicide. By Allan J. McLaughlin.

*No. 16.—The antiseptic and germicidal properties of glycerin. By M. J. Rosenau.

*No. 17.—Illustrated key to the trematode parasites of man. By Ch. Wardell Stiles.

*No. 18.—An account of the tapeworms of the genus *Hymenolepis* parasitic in man, including reports of several new cases of the dwarf tapeworm (*H. nana*) in the United States. By Brayton H. Ransom.

*No. 19.—A method for inoculating animals with precise amounts. By M. J. Rosenau.

*No. 20.—A zoological investigation into the cause, transmission, and source of Rocky Mountain "spotted fever." By Ch. Wardell Stiles.

No. 21.—The immunity unit for standardizing diphtheria antitoxin (based on Ehrlich's normal serum). Official standard prepared under the act approved July 1, 1902. By M. J. Rosenau.

*No. 22.—Chloride of zinc as a deodorant, antiseptic, and germicide. By T. B. McClintic.

*No. 23.—Changes in the Pharmacopœia of the United States of America. Eighth Decennial Revision. By Reid Hunt and Murray Galt Motter.

No. 24.—The International Code of Zoological Nomenclature as applied to medicine. By Ch. Wardell Stiles.

No. 25.—Illustrated key to the cestode parasites of man. By Ch. Wardell Stiles.

No. 26.—On the stability of the oxidases and their conduct toward various reagents. The conduct of phenolphthalein in the animal organism. A test for saccharin, and a simple method of distinguishing between cumarin and vanillin. The toxicity of ozone and other oxidizing agents to lipase. The influence of chemical constitution on the lipolytic hydrolysis of ethereal salts. By J. H. Kastle.

No. 27.—The limitations of formaldehyde gas as a disinfectant with special reference to car sanitation. By Thomas B. McClintic.

*No. 28.—A statistical study of the prevalence of intestinal worms in man. By Ch. Wardell Stiles and Philip E. Garrison.

*No. 29.—A study of the cause of sudden death following the injection of horse serum. By M. J. Rosenau and John F. Anderson.

No. 30.—I. Maternal transmission of immunity to diphtheria toxine. II. Maternal transmission of immunity to diphtheria toxine and hypersusceptibility to horse serum in the same animal. By John F. Anderson.

No. 31.—Variations in the peroxidase activity of the blood in health and disease. By Joseph H. Kastle and Harold L. Amoss.

No. 32.—A stomach lesion in guinea pigs caused by diphtheria toxine and its bearing upon experimental gastric ulcer. By M. J. Rosenau and John F. Anderson.

No. 33.—Studies in experimental alcoholism. By Reid Hunt.

No. 34.—I. *Agamofilaria georgiana* n. sp., an apparently new roundworm parasite from the ankle of a negress. II. The zoological characters of the roundworm genus *Filaria* Mueller, 1787. III. Three new American cases of infection of man with horsehair worms (species *Paragordius varius*), with summary of all cases reported to date. By Ch. Wardell Stiles.

*No. 35.—Report on the origin and prevalence of typhoid fever in the District of Columbia. By M. J. Rosenau, L. L. Lumsden, and Joseph H. Kastle. (Including articles contributed by Ch. Wardell Stiles, Joseph Goldberger, and A. M. Stimson.)

No. 36.—Further studies upon hypersusceptibility and immunity. By M. J. Rosenau and John F. Anderson.

No. 37.—Index-catalogue of medical and veterinary zoology. Subjects: Trematoda and trematode diseases. By Ch. Wardell Stiles and Albert Hassall.

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No. 39.—The antiseptic and germicidal properties of solutions of formaldehyde and their action upon toxines. By John F. Anderson.

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of *Filaria restiformis* Leidy, 1880=*Agamomermis restiformis*, by Ch. Wardell Stiles. 3. Observations on two new parasitic trematode worms: *Homalogaster philippinensis* n. sp., *Agamodistomum nanus* n. sp., by Ch. Wardell Stiles and Joseph Goldberger. 4. A reexamination of the original specimen of *Tænia saginata abietina* (Weinland, 1858), by Ch. Wardell Stiles and Joseph Goldberger.

*No. 41.—Milk and its relation to the public health. By various authors.

No. 42.—The thermal death points of pathogenic micro-organisms in milk. By M. J. Rosenau.

No. 43.—The standardization of tetanus antitoxin (an American unit established under authority of the act of July 1, 1902). By M. J. Rosenau and John F. Anderson.

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No. 46.—*Hepatozoon perniciosum* (n. g., n. sp.); a hæmogregarine pathogenic for white rats; with a description of the sexual cycle in the intermediate host, a mite (*Lelaps echidninus*). By W. W. Miller.

No. 47.—Studies on Thyroid: I. The relation of iodine to the physiological activity of thyroid preparations. By Reid Hunt and Atherton Seidell.

No. 48.—The physiological standardization of digitalis. By Charles Wallis Edmunds and Worth Hale.

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No. 50.—Further studies upon the phenomenon of anaphylaxis. By M. J. Rosenau and John F. Anderson.

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