Studies previously reported from this laboratory (1) present evidence that the oral administration of amidopyrine is followed by anemia in dogs fed a deficient diet which is causative of black tongue. Neither amidopyrine alone, in the amounts employed, nor the diet alone, resulted in anemia under the experimental conditions observed. The anemia could be cured, moreover, by supplementing the diet with a factor in which it is deficient, even though the administration of amidopyrine was continued. This phenomenon of an increased susceptibility of the blood to amidopyrine under conditions of dietary deficiency, suggested the existence of a general principle which might also apply to the aromatic compounds produced by endogenous metabolism. Of those compounds, indol has been selected for study since some information is available concerning its metabolism.

Indol has been much studied chemically but relatively little as concerns the pathological effects which result from its administration. Houssay (2) has reported studies of the conjugation of indol and has reviewed the literature on the subject. Houssay concludes that indol is converted into indican by the liver, since that conversion occurs normally after removal of the intestine and after nephrectomy, but not after heptectomy. Excretion by the kidney is proved by the presence of indican in the urine and by its accumulation in the blood after the removal of both kidneys. Büngeler (3) injected indol into mice and observed that anemia resulted, but since he was concerned only with the development of leukemia, the studies of the erythrocytes are not sufficiently detailed to be analyzed. Furthermore any procedure involving the injection of indol is not applicable, since unconjugated indol is not present in the circulating blood under any but the most abnormal circumstances (Houssay, 2). Certain facts exist, however, which suggest that the aromatic compounds derived from endogenous sources may play some rôle in causing disease. Tönnis and Horster (4) in a series of papers have described the production of indicanuria and anemia in dogs with surgically formed, inactive, open jejunal segments. Relief of anemia as well as the associated symptoms seems to have followed the administration of liver extract in these animals.
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Methods

The animals employed were mongrel dogs of about 7 kilos in average weight. They were kept under standard conditions in individual cages with bedding of wood shavings.

The so-called normal diet was one which is fed as a routine and empirically is known to be capable of maintaining dogs in good health over a period of several years. It is a mixture of cooked beef, bread, and dog biscuit. The black tongue diet is that described by Goldberger (5). It is known to cause acute black tongue when fed, without supplement, for a period of from 5 to 12 weeks. In an extensive study the feeding of this diet has never been known to cause symptoms in normal dogs after a shorter interval. The corn meal, peas, and casein were mixed and cooked for 2 hours in a steam cooker. The remaining ingredients were then added and thoroughly mixed. The animals were fed daily and were allowed to eat as much as they chose.

Blood was taken from the jugular vein in a standard amount of potassium oxalate for routine examinations. Determinations of the numbers of erythrocytes and leukocytes were made in standard pipettes and counting chambers. The hemoglobin was estimated by the Sahli method, employing a glass standard. The Sahli tubes were carefully calibrated and checked at frequent intervals by the O2-combining capacity method of Van Slyke.

The indol used was a commercial crystalline product of reasonable purity. It was fed in ordinary absorbable capsules which were placed in the back of the animal’s pharynx and forced with the finger to a point where they were swallowed. The animals were carefully observed to see that no capsules were regurgitated. The liver extract used was the powdered material (Eli Lilly and Company) of which 4 gm. are derived from 100 gm. of liver. It was made up to a 50 per cent solution in water and fed by stomach tube. Reduced iron (ferrum reductum U.S.P.) was used in a few experiments. It was administered in absorbable capsules containing 1 gm. each. The vegex was the commercial salt autolysate of brewers’ yeast made up to a 50 per cent solution in water.

Experimental

In all, 11 different types of experiments were made as follows: Indol was administered: (1) while a normal diet was fed; (2) as a brief experiment to dogs in a state of deficiency following the feeding of the black tongue diet; (3) during periods of deficiency and during subsequent periods when the diets were supplemented with yeast; (4) throughout successive periods of normal and deficient diets; (5) during periods of deficiency and during subsequent periods when the diet was supplemented with liver extract; (6) while an exclusive diet of milk was fed; (7) while a basal diet was fed which is not causative of
black tongue; (8) while the animals voluntarily abstained from food.

(9) The effect on liver function of the administration of indol was
tested. (10) The effect of splenectomy on the anemia-producing
effect of indol was observed. (11) The levels of indol and indican in
the blood were observed.

In this communication certain of the experiments are reported to-
gether for the sake of brevity.

Acute Hypersusceptibility to Indol

Experiments 1 and 2 (Text-Figs. 1 to 9).—The black tongue diet was
fed until the first signs of erythema of the labial mucous membrane ap-
peared. This period varied from 6 to 10 weeks in different experi-
mental animals. Indol was then fed in amounts of roughly 100 mg.
per kilo of body weight. A prompt and very marked fall in the num-
bers of erythrocytes occurred, a decrease from 5,000,000 to something
over 1,000,000 cells per mm.$^3$ of blood in less than 1 week being com-
mon. The anemia was associated with a normal or moderately
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elevated leukocyte count and distinctly increased numbers of platelets. The animals became pale and lethargic but continued to take food in most instances. Examination of films of the blood revealed a striking

Goldberger diet + 1 gm. indol q.d.

![Graphs showing changes in hemoglobin (Hb%), MCV (μ), G.L., and RBC (millions)]

Text-Fig. 3. Dog 3

Text-Fig. 4. Dog 4

Goldberger diet + 1 gm. indol q.d.

![Graphs showing changes in RBC (million)]

Text-Fig. 5. Dog 5

Text-Fig. 6. Dog 6

Text-Fig. 7. Dog 7
variation in the size and shape of the erythrocytes. If the administra-
tion of indol was continued the anemia occasionally terminated
fatally but not infrequently an incomplete remission took place,
marked by an increase of the circulating reticulocytes to levels between
10 and 20 per cent and an increase in the number of erythrocytes to
between 2,000,000 and 3,000,000 per mm. 8

Control animals taking a normal diet and fed the same amount of
indol as those just described showed in most instances no decrease in
erthrocyte levels greater than the variations which are normal for
the dog. Occasionally a well defined drop in erythrocytes to levels

\[
\text{Goldberger diet + 1 gm. indol q.d.}
\]

in the 3,000,000 per mm. 8 range occurred, but this was distinctly
unusual and was promptly recovered from, although the drug was
continued. In no instance did any animal eating the normal diet
show a degree of anemia which approached that regularly obtained
in the animals fed the deficient diet.

\textit{Chronic Hypersusceptibility to Indol and the Treatment of the
Anemia with Yeast}

\textit{Experiment 3 (Text-Figs. 10 and 11).—Previous studies had shown
that the symptoms following regularly the feeding of the black tongue}
diet without supplement could be prevented by the administration of yeast rich in the vitamin B₂ (G) complex, Goldberger (5). Accordingly the effect of supplementing the diet with a suitable yeast source of that vitamin was tried in animals with anemia resulting from the administration of indol during a state of deficiency. The results are shown in Text-figs. 10 and 11. Following the supplement with yeast a prompt and decided rise in the levels of the blood took place which could be maintained as long as the supplement was given, although the administration of indol was continued throughout the
experiment. When the supplement was discontinued, however, progressive anemia appeared.

*Chronic Hypersusceptibility to Indol and the Treatment of the Anemia with Liver Extract*

*Experiments 4 and 5 (Text-Figs. 12 to 18).*—Goldberger (6) has shown that liver extract (Lilly N.N.R.) is preventive of the symptoms of black tongue which resulted from the feeding of the diet used in our experiments. Since the same liver extract is also preventive and curative of pernicious anemia in human beings the effect of its administration was studied in the chronic anemia in the dog resulting from indol and the deficient diet.

In three animals, Nos. 12, 13, and 14, text-figs. 12, 13, and 14, the black tongue diet was fed until a definite state of deficiency was considered to have been established. Indol was then administered as in Experiment 1 and the anemia promptly developed. Liver extract (Lilly N.N.R.) was then fed by stomach tube in 10 gm. amounts daily. In every instance an increase in the number of circulating erythrocytes took place, associated with an increase in the levels of hemoglobin. The supplement of liver extract was discontinued as soon as approximately normal levels of the blood were obtained, but the feeding of indol as well as the deficient diet was continued.

As would be expected from the results of the short experiments, after an interval of from 3 to 5 weeks from the time when the supplement of liver extract was omitted, a slow, progressive decrease in the levels of erythrocytes and hemoglobin appeared and continued until only between 2,000,000 and 2,500,000 erythrocytes per mm.³ were present. This was considered to be a suitably severe form of anemia for test. The levels of reticulocytes varied somewhat during the periods of the anemia. In certain instances they were irregularly elevated for a time and in others no elevation above 2 per cent appeared. In every experiment the reticulocytes were allowed to become stabilized at low levels before therapeutic test. When a severe anemia, with reticulocytes stabilized at a low level, had been obtained, liver extract 10 gm. (Lilly N.N.R.) was administered daily by stomach tube. In every animal a prompt and decided rise of reticulocytes occurred. Levels of from 10 per cent to 75 per cent were obtained within 10 days after
treatment was begun. The number of reticulocytes promptly fell and this was followed by a rise in the levels of erythrocytes and hemo-

globin. Simple supplement of the diet with liver extract was not sufficient to restore absolutely normal values for the blood in every experiment, and where this was the case a normal diet was substituted.
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for the deficient one. This move effected complete cure of anemia in every instance despite the continued feeding of indol.

In the greater number of the observations, Nos. 15 to 18, a control period was observed, during which the normal diet and a standard amount of indol were fed. In some instances, as in animals 15 and 17 there was no fall of blood levels but occasionally, as in observations 16 and 18 a mild decrease of erythrocytes and hemoglobin occurred which promptly disappeared as soon as sufficient time had elapsed to allow the normal hematopoietic mechanism to accommodate for the increased demand put upon it by the administration of indol. After the normal diet had been fed sufficiently long to establish the fact that the indol was tolerated without anemia, the black tongue diet was substituted and the administration of indol was continued. As in the experiments just described a gradual fall of the numbers of erythrocytes and of hemoglobin resulted until a severe degree of anemia was established. As before, a considerable variation in the numbers of reticulocytes was observed in the first part of the period of anemia but in due time they became stabilized at low levels. The institution of therapy with liver extract, other factors remaining unchanged, was followed by the expected reticulocyte peak and by an increase of blood values to levels which approached the normal. A striking feature of the response to the administration of liver extract was an increase in the number of leukocytes, although they had not been notably few during the severe phase of anemia. This increase usually preceded the increase in erythrocyte numbers by several days and coincided with the appearance of elevated levels of reticulocytes.

The histological changes in the bone marrow will be described in a separate communication. It suffices to state here that biopsies of femoral marrow, removed during a control period before the experiment was begun, showed a normal distribution and the expected orderly maturation of cells with all stages of development represented. Specimens of femoral marrow removed by biopsy and at autopsy at the height of the anemia showed a very marked increase in the cellularity of the marrow with a lack of mature forms, both of the red and white cell series. Biopsies of marrow after weeks of the administration of indol with a normal diet showed no significant variation from normal.


Protocols of Experiments 4 and 5.—

Animal 12.—
Dec. 22. Goldberger diet begun. Weight 17.5 kilos.
Feb. 13. General condition excellent. R.B.C. 4,330,000. Hb 48 per cent. W.B.C. 10,000. Retic. 0.8 per cent. From this point a slow fall of the levels of the blood took place, possibly because no further extension of hematopoiesis was possible under the experimental conditions.
Mar. 8. General condition improved. R.B.C. 2,229,000. Hb 26 per cent. W.B.C. 74,800. Retic. 8.0 per cent. The marked elevation of white count and beginning of a rise of reticulocytes indicates the onset of remission.
Mar. 15. General condition excellent. R.B.C. 2,910,000. Hb 48 per cent. W.B.C. 19,500. Retic. 1.4 per cent. The rise of reticulocytes has subsided and an increase of levels of the blood is in progress.

Animal 13.—
Feb. 15. Pale and weak but eating well. R.B.C. 1,990,000. Hb 36 per cent. W.B.C. 11,600. Retic. 1.2 per cent. Treatment with liver extract, 10 gm. daily by mouth, was begun.
Feb. 19. General condition slightly improved. R.B.C. 2,050,000. Hb 29 per cent. W.B.C. 42,600. Retic. 18.8 per cent. The elevated leukocyte and reticulocyte counts indicate the impending remission.
Mar. 1. General condition excellent. R.B.C. 3,370,000. Hb 66 per cent. W.B.C. 13,000. Retic. 1.4 per cent. The numbers of leukocytes and reticulocytes have become normal and the increased levels of the blood are clearly in evidence.
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Hb 74 per cent. W.B.C. 12,100. In a second experiment with similar course this animal was destroyed at the height of the anemia and the bone marrow subjected to histological study.

Animal 14.—

Nov. 30. Feeding of Goldberger diet begun. Weight 10.5 kilos.


Jan. 11. Animal in poor condition; not eating the diet. R.B.C. 1,150,000. Hb 21 per cent. W.B.C. 76,200. Retic. 24.6 per cent. This was the first day of the change in the number of leukocytes and reticulocytes as an indication of the beginning of the induced remission.

Jan. 23. Animal in excellent condition. Eating well. Liver extract discontinued. R.B.C. 4,540,000. Hb 63 per cent. W.B.C. 10,000. Retic. 0.8 per cent. From this point on there was a prolonged slow drop in the levels of the blood.


Mar. 1. Animal very weak and pale. R.B.C. 750,000. Hb 10 per cent. W.B.C. 139,900. Retic. 0.8 per cent. The anemia was so severe that it was supposed that the animal's life was in danger in spite of the intravenously administered liver extract. Actually in light of subsequent observations the rising leukocyte count and the drop of general blood levels should have been taken as an indication of the onset of remission. Therapy was changed to orally administered liver extract however.

Mar. 3. The reticulocyte count has risen today to 22.8 per cent and the animal is markedly improved. Since the peak of reticulocytes has occurred only 48 hours after the institution of oral therapy, it is quite clear that it is in reality due to the parenterally administered substance.

Mar. 5. General condition excellent. Animal eating well. R.B.C. 1,880,000. Hb 35 per cent. W.B.C. 6,800. Retic. 13.6 per cent.

Mar. 12. Animal apparently well. R.B.C. 3,360,000. Hb 48 per cent. W.B.C. 10,900. Retic. 0.4 per cent. The peak of reticulocytes is well past and a clear remission of the anemia is in progress.

Apr. 30. General condition excellent. R.B.C. 3,860,000. Hb 53 per cent. W.B.C. 11,400. As was so frequently the case in these studies, liver extract,
though completely effective in causing remission, rarely enabled the animal to attain a completely normal level of the blood. Accordingly a normal diet was substituted for the Goldberger diet, the administration of indol being continued.

May 21. Normal levels of blood have been obtained. Experiment discontinued. R.B.C. 5,150,000. Hb 88 per cent. W.B.C. 11,000.

**Hypersusceptibility to Indol Resulting from Diets of Milk**

*Experiment 6 (Text-Figs. 19 to 21).—* All the studies of deficiency disease which have involved the use of the Goldberger diet causing

black tongue have been open to certain objections. Among them is the fact that the clinical syndrome of black tongue does not occur when the simple diet of Cowgill, which lacks the heat stable fraction of the vitamin B complex, is fed (Zimmerman, 7). Moreover, the Goldberger diet is exceedingly high in its content of corn and throughout the literature of pellagra there runs a strong suggestion that corn has some peculiarly specific action in causing stomatitis and central nervous system lesions. Rhoads and Miller (8) have shown that the Goldberger diet is not free of the heat stable component of the vitamin
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B complex which is required for growth in rats, since rats fed that diet grow at a normal rate. Certain other species, notably guinea pigs and swine, however, will not survive when fed the diet unless it is supplemented with liver extract (9, 10). Evidence has been advanced recently by Birch, György, and Harris (11) as well as by Street (12) that black tongue can be produced by feeding simple basal casein, fat, and glucose diets supplemented with crystalline vitamin B₁ and pure flavin (B₂). In view of the slight doubt concerning the cause of the peculiar syndrome which follows the feeding of the Goldberger

![Graph showing Hb(%) and RBC (millions) over 4 day intervals]

Milk diet + iron + 1 gm. indol p.o.q.d.

Text-Fig. 20. Dog 20

diet, however, it was necessary to control the experiments which have been described by combining the administration of indol with some diet which contained no corn. In a series of unrelated experiments dogs were fed a diet composed exclusively of milk (200 cc. per kilo of body weight daily). To our surprise the animals developed characteristic stomatitis of black tongue and died after a period of about 2 months. Here then was a diet which was known to be rich in flavin, and which was presumed to be rich in the remainder of the vitamin B₂ complex, but which caused black tongue. The objections which could be raised to the experiments on corn diets could be avoided by
feeding milk. Furthermore, although chronic black tongue, produced by treating insufficiently the acute phase of the disease, will result in anemia irregularly, the feeding of milk alone to adult dogs has never done so in our experience. Accordingly a series of animals were fed an exclusive diet of milk and were given the usual dose of 100 mg. per kilo of indol daily, reduced iron 1 gm. daily was administered as a supplement (Text-figs. 19 to 21). Exactly the same anemia occurred as was the case when the Goldberger diet was fed. Severe anemia developed which could be cured by feeding a normal diet or by supplementing the diet of milk by liver extract even though the administration of indol was continued.

 TEXT-FIG. 21. Dog 21

Failure to Induce a Susceptibility of the Blood to Indol by Feeding a Basal Diet

Experiment 7 (Text-Figs. 22 and 23).—To control further the dietary factors involved in the experiments, animals were fed the basal diet described by Cowgill (7), and indol was administered at the same time. Both factors of the vitamin B complex were omitted from the diet in the hope that it would be possible to establish the susceptibility of the blood to indol as being due to a lack of some part of that complex. The results were somewhat irregular but in general the indol was tolerated without severe anemia, quite contrary to the absolutely uniform anemia obtained by feeding indol with a Goldberger diet (Text-figs. 22 and 23).

This result was unexpected to some extent and no well substantiated
explanation can be advanced at this time. It is possible, however, that the very high content of casein of this diet may furnish a sufficient amount of the anti-black tongue factor to prevent the susceptibility to indol. It is striking that although the diet is supposedly a basal ration it never gives rise to the symptoms of black tongue. Further studies of this question are in progress, since possibly the rations of Birch, György, and Harris (11), or of Street (12), containing less casein and causing black tongue would cause the hypersusceptibility to develop.

Susceptibility of the Blood to Indol Following Voluntary Abstention from Food

Experiment 8 (Text-Fig. 24).—The effect of dietary on the tolerance of the blood to indol is well shown in this experiment. Fig. 24 shows
the course of the anemia in one such animal. Although the black tongue diet was offered each day the food was completely refused. A severe anemia developed promptly, in sharp contrast to the result following the administration of the same amount of indol when a normal diet is taken.

Liver Function Not Affected by Indol

Experiment 9.—Experiments have been published by Miller and Rhoads (13) which show that liver function, as measured by the power of that organ to excrete bilirubin intravenously injected, decreases in the deficiency which results from feeding the black tongue diet. This finding of deranged liver function is in accord, furthermore, with the beneficial effect of therapy with liver extract. It is required to show, however, in a control experiment that indol per se does no damage to liver function. Accordingly the experiment was made of administering 1 gm. of indol daily to 2 dogs taking a normal diet and following the power of the livers to excrete bilirubin. No change was seen in this function over a period of 1 month and no anemia developed. It was concluded that indol did not injure the hepatic function under the experimental conditions observed.
The Effect of Splenectomy

Experiment 10.—In view of the therapeutic effect of splenectomy on certain hemolytic anemias in human beings it was of importance to ascertain whether or not the operation would prevent the development of indol anemia. Accordingly splenectomy was performed in 2 dogs and complete recovery was allowed to occur. The deficient diet was

then fed and after 4 weeks indol was administered. Anemia of the same degree as that seen in the non-splenectomized animals appeared at the usual time.

The Levels of Indol and Indican in the Blood

Experiment 11 (Text-Figs. 25 and 26).—The pronounced difference observed between the susceptibilities to indol of normal and deficient
animals suggested that the deficient state resulted either in some change of the rate of absorption of indol from the intestinal tract or of its conversion to indican. These possibilities were subjected to experimental test. By the method of Sharlit (14) the levels of indican in the blood following the oral administration of 1 gm. of indol were ascen-
venous administration of indol. No difference could be seen between the normally fed animals and those on deficient diets.

**DISCUSSION**

Certain factors in the experiments which have been described warrant discussion. As seen in the text-figures, the feeding of indol to dogs on a normal diet does result occasionally in a mild anemia which promptly disappears. Histological studies of the bone marrow during this phase of preliminary slight anemia show normal maturation of erythropoietic cells and some increase in number. It is quite apparent that indol feeding is a strain, though a mild one, on hematopoiesis in normally fed dogs and that it is readily compensated for by an increase of functional marrow. When the deficient diet is fed, however, a wholly different picture results from the administration of the same quantity of indol.

The rapid and profound drop in red cells strongly suggests an actual destructive process. In view of the known life of the red cell, anemia would develop much more gradually were only maturation interfered with. Proof of the hemolytic nature of the process will be presented in a subsequent communication.

From the histological appearance of the marrow it seems clear that a great increase in the number of immature marrow cells is a feature at the height of the anemia. Only two possibilities exist to explain this change: (a) that the deficient diet lacks a factor which is required for the maturation of erythropoietic cells, and (b) that all cells beyond the stage of erythroblast and myeloblast are destroyed in a hemolytic process which is stopped by something contained in liver extract. The early rises of reticulocytes indicate that the marrow can manufacture young cells, or, if the pure hemolytic theory be accepted, that not all reticulocytes are hemolyzed. According to Dock (16) an increase of reticulocytes is as much a feature of cessation of hemolysis as it is of the supplying of a specific maturation factor. From the evidence at hand the final answer cannot be obtained; subsequent communications will deal with this question in greater detail. It is entirely possible, indeed probable, that both processes play some role.

Sufficient information is not available from these experiments to discuss the question of oral *versus* parenteral therapy. Suggestive
evidence is at hand from Experiment 3 which favors the view that liver extract parenterally administered is effective. From the studies of Richter, Ivy, and Meyer (17) it is clear that the dog's stomach has little anti-anemia potency for the human being, and this is also true for the liver of the dog. Castle (18) and his coworkers have shown that the anti-anemia principle in liver extract is dependent upon the interaction of a dietary constituent of normal gastric juice.

Since the dog has neither the gastric nor the liver factor we infer that in hematopoiesis it uses the dietary factor as such without the interaction with the gastric factor which is required in the human being. Helmer, Fouts, and Zerfas (19) have shown that liver extract is rich in the dietary factor and it is our belief that in the dosage employed this factor is the effective one in the dog experiments. Until more purified fractions for the treatment of pernicious anemia in the human being are available it seems unwise to continue experiments with liver extract parenterally injected. The results may always be open to the objection that sufficient dietary factor is present to produce an effect.

An analogy inevitably suggests itself between the experimental disease just described and pernicious anemia in the human being. The points of similarity are striking: mucous membrane lesions, gastrointestinal disturbances, characteristic changes in the morphology of the erythrocytes, absence of hemorrhagic phenomena, low reticulo-cytes, and a characteristic response to the administration of liver extract. Certain well defined differences are also apparent. Macrocytosis is not a feature since as many or more microcytes are present in the smear than are macrocytes. No serious degree of indolemia or indicanuria can be demonstrated in pernicious anemia and although suppression of maturation in the bone marrow is a feature in the human being, the cell type which predominates in the marrow in these experiments on dogs cannot be proved to be the cell which is predominant in pernicious anemia. No claim is made that the experimental disease has any connection with any disease state of human beings.

The objection will be advanced to these experiments that in the studies reported by Rhoads and Miller (20) the occurrence of anemia in chronic black tongue produced by feeding a Goldberger diet alone has been described. In that publication it is specifically stated that
only after a prolonged chronic disease has been produced by treating insufficiently the acute phase does any anemia occur. Even then it occurs irregularly and is of mild degree. At no time has severe anemia been observed in this laboratory in experiments on a large number of animals during acute black tongue. Furthermore in the experiments presented here the controls with milk diets and the voluntary refusal of food rule out any specific effect of the black tongue diet, other than the deficiency.

It appears that under particular dietary circumstances the feeding of indol to dogs produces an effect which is not apparent when a normal diet is fed. Furthermore the effect may be caused to disappear by supplementing the diet with the factor in which it is deficient. Since neither the mode of action of the Goldberger diet, nor the active constituent of liver extract are known exactly it would be idle to speculate at this time concerning the exact mechanism by which the anemia is produced.

CONCLUSIONS

1. Indol, orally administered, causes anemia when certain deficient diets are fed.
2. The same amount of indol causes no considerable hematologic disturbance when normal diets are fed.
3. The anemia can be cured by supplementing the diet with liver extract, or by substituting a normal diet for the deficient diet.
4. Neither the diet alone nor the administration of indol alone produces marked anemia under the experimental conditions observed.

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