# An Experimental Study of the Toxic Properties of Indol.

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# AN EXPERIMENTAL STUDY OF THE TOXIC PROPERTIES OF INDOL.*

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I WISH to bring to your attention this evening certain facts relating to the action of indol upon various animals, including man. These facts possess a considerable degree of practical interest, because indol is a substance produced in some amount in the intestine of most adult human beings as the result of bacterial action upon proteids. The indol produced in the intestine is oxidized within the organism into indoxyl, which, in combination with sulphuric acid, as indoxyl-potassium sulphate, forms the basis of the well-known indoxyl or indican reaction of the urine. It is not uncommon in various derangements of digestion to find the indoxyl or indican reaction of the urine much more pronounced than in health, and the inference from such increase is that an unusual quantity of indol has been formed in the intestine and absorbed from it. The question which will be discussed and in some measure answered in this

* Read before the New York Pathological Society, March 9, 1898.

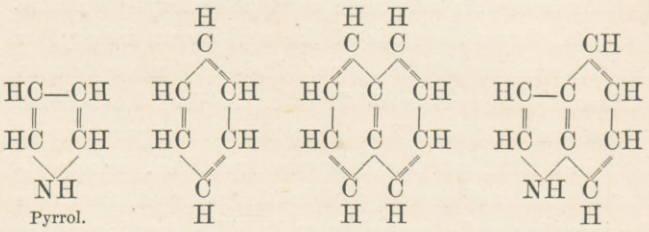
paper is this: What detrimental effects, if any, does the excessive formation and absorption of indol entail upon the human organism? In order to discuss this question in an intelligent manner it is desirable to review systematically the facts that bear upon it. This may be conveniently done by considering:

First: The chemical nature of indol, the conditions under which it is produced, and its transformation into the indoxyl-potassium sulphate of the urine.

Secondly: The action of indol upon animal organisms.

Thirdly: The clinical conditions in which the indoxyl of the urine is increased, and their relations to excessive indol production.

1. *The Chemical Nature of Indol, the Conditions under which it is produced, and its Transformation into the Indoxyl-Potassium Sulphate of the Urine.*—Although this section has important bearings on the problem to be discussed, I shall refer to it only briefly this evening, as it is my intention to make indol production the subject of a special and somewhat technical communication.




Indol is a derivative of the aromatic series and a member of the indigo group of compounds. Its empirical formula is $C_8H_7N$. Its relation to the aromatic

series is best seen by considering its probable constitutional structure, which is represented by a union of pyrrol and benzene in such a manner that pyrrol and benzene have two carbon atoms in common—as, for instance, in naphthalene.

Indol crystallizes in glancing white crystals, has a melting point of 52° C., and volatilizes readily with steam. It has a characteristic fæcal odor, and is partly responsible for the odor of normal human fæces. I have noticed that the odor is less intense when the indol is thoroughly freed from an unknown oily substance * with which it is apt to be associated when derived from putrefying fibrin. Indol is a weak base. It is soluble in water. A solution containing indol, when treated with sulphuric acid and sodium nitrate, undergoes a change in color due to the formation of nitroso-indol. The reaction is an exceedingly delicate one, for it is recognizable in a solution of one part of indol in two hundred thousand of water. The well-known "cholera-red" reaction depends on the formation of nitroso-indol.

Although indol may be produced without the intervention of bacterial activity—as, for example, by heating O-nitro-cinnamic acid with potash and iron filings, and by the action of alkalies on proteids—it is its production as the result of the action of bacteria upon proteids that interests the pathologist.

It is produced by the action of a considerable variety of bacteria, both pathogenic and non-pathogenic. Thus it is one of the products of the activity of most varieties of the *Bacillus coli communis*, of the *Proteus vulgaris*, of the typhoid bacillus, of most vibrios, of the comma bacillus of cholera, of putrefactive bacteria, etc. The

* This substance lowers the melting point one or two degrees.

formation of indol through bacterial activity is distinctly influenced by a variety of conditions. It was found by Hoppe-Seyler,* for instance, that when an abundance of oxygen came into contact with putrefying proteid material, which would ordinarily yield indol, and the carbon dioxide and ammonium carbonate resulting from the putrefactive process were rapidly and entirely removed, indol, skatol, mercaptan, etc., were not formed at all. Salkowski and Blumenthal † found that a slight grade of alkalescence was more favorable to the formation of indol than a somewhat stronger degree of alkalinity. Smith has recently shown that the presence of sugar retards the indol production of the colon bacillus, because micro-organisms act on the sugar rather than on proteids until the former is consumed.

I have found that the addition of the common yeast plant to fibrin putrefying under the influence of the colon bacillus may cause a marked diminution in the usual yield of indol. These examples of influences capable of modifying the production of indol must suffice.‡ A knowledge of them helps us to explain the variations in indol production that occur in the human intestine.

Although there is no close relation between the pathogenic properties of the colon bacillus and its indol

* *Zeitschrift für physiologische Chemie*, Bd. viii, 1884.

† *Zeitschrift für klin. Medicin*, Bd. viii.

‡ It was found by Brieger (*Zeitschrift für physiologische Chemie*, Bd. iii, p. 141) that the entire absence of air greatly slowed but did not wholly prevent the production of indol. There appeared to be no difference between the effect of the presence of a moderate and an abundant supply of air. Salkowski found that indol once formed was not destroyed, even in part, by the progress of putrefaction, but some loss by evaporation took place when air was freely admitted. There is good reason to think, however, that indol undergoes decomposition in watery solutions.

production, both can be increased by the growth of a culture in a medium which contains an unusual amount of proteid material especially adapted for bacterial assimilation.*

It is, of course, not to be understood that indol is the sole aromatic product of proteid putrefaction, although under certain conditions it is the chief one. Skatol, phenol, parakresol, and benzoic acid are other aromatic decomposition products of the proteid molecule.

The indol which was employed in the experimental observations to be described was obtained from the putrefaction of large quantities of pig's fibrin. Thus two thousand grammes of fibrin after exposure to the air for eight days yielded 2.7 grammes of indol. It was found that the addition of cultures of the common colon bacillus from the fæces of a normal individual resulted in a large yield—namely, 4.2 grammes of indol—the quantity of fibrin, the duration of the process, and the temperature being the same as in the case first mentioned.† It is not necessary to refer here to the methods used for the isolation of pure indol, which was prepared for me in considerable amounts by Dr. A. J. Wakeman.

The indol absorbed from the intestine is not excreted as such by the urine, but undergoes an interesting and important change within the organism.

This change consists, first, in the oxidation of indol, and, secondly, in the combination of indoxyl with sulphuric acid to form the indoxyl-sulphate of potassium.

* A. W. Ward. *Journal of Experimental Medicine*, September, 1897, p. 569.

† In a case in which the yeast plant as well as the colon bacillus was added to 1800 grammes of fibrin the yield of indol was much smaller (1.3 gramme), although the putrefaction continued for about two weeks.

It is as the indoxyl-sulphate of potassium that the indoxyl formed within the organism leaves the body in the urine. Other putrefactive products than indol—for instance, skatol, phenol, and kresol—undergo a similar conjugation with sulphuric acid in the organism, and are eventually excreted as potassium salts of sulphuric acid. These bodies are sometimes referred to as ethereal sulphates, sometimes as combined or conjugated sulphates.

The indoxyl-potassium sulphate which is found in the urine is not to be recognized as such without elaborate chemical manipulation. The indoxyl radicle may, however, be easily oxidized into indigo blue or indican, by means of calcium hypochlorite, as proposed by Jaffé, or by means of ferric chloride in hydrochloric acid, as proposed by Obermeyer. This appearance of indigo blue on oxidation is the reaction employed in the routine examination of urine—the so-called indican test, or, as we should say, the indoxyl test. By its help we are enabled to say whether the urine contains more indoxyl than is usual in health, and to detect marked variations from day to day, but it scarcely suffices to make us positive of the occurrence of slight variations.

When we come to inquire into the seat in the organism of this remarkable synthesis of indol and other aromatic compounds with sulphuric acid, it is seen that we have no positive knowledge. The observations of Baumann,* however, render it probable that the liver takes a part in bringing about this conjugation.

* Baumann. Pflueger's *Archiv*, Bd. iii, 1870, S. 448; also, Christian und Baumann. *Zeitschrift für physiologische Chemie*, Bd. ii, 1878, S. 350; also, Baumann. Pflueger's *Archiv*, Bd. xii, 1876, and Bd. xiii, 1876.

That the animal organism is capable of rapidly transforming considerable quantities of indol seems clear from experiments of which the following is an example: Into the femoral vein of a strong dog weighing about thirty pounds was injected an aqueous .228-per-cent. solution of indol at the rate of five cubic centimetres per minute. From time to time small quantities of blood were withdrawn from the femoral vein of the opposite side. Although as large a quantity of indol as half a gramme was introduced into this animal, no indol could be detected in the distillate from the blood drawn. Very minute quantities of indol are readily detected in the distillate of blood to which indol is added outside the body.

Although we are wanting in positive information as to the parts of the body concerned with the indoxyl synthesis we have a little light on the equally interesting question of the significance of this pairing process to the organism. Thus Stolnikow * observed that resorcin and pyrogallol are much more toxic than resorcin-sulphuric acid and pyrogallol-sulphuric acid respectively. In harmony with this observation is the fact that Baumann found phenol to be distinctly more toxic than phenol-sulphuric acid. There are as yet no observations, I believe, relating to the comparative toxicity of indol and indoxyl-potassium sulphate, but it seems safe to infer from analogy that in the case of indol, as with phenol, the conjugation with sulphuric acid is a process by which the poisonous properties of this aromatic product of putrefaction are lessened, or, as one might say, the process exerts a detoxicating influence upon the organism.

There yet remains much to be learned regarding the

* *Zeitschrift für Physiologie*, Bd. viii, S. 280.

influences that favor and that inhibit the formation of indol within the human intestine. In a recently published paper I advanced experimental evidence in favor of the view that the main factor in the production of indol in the intestine is the common colon bacillus, and it is an indisputable fact that conditions which permit the multiplication of this organism are associated with the presence of a strong indoxyl reaction in the urine. It was found that when large numbers of a pure colon-bacillus culture from normal human or dog's fæces were injected in watery solution into a loop of the small intestine in a dog, the urine invariably gave a very strong indoxyl reaction, although it might previously have given a negative reaction. On the other hand, negative results were obtained with injections of pure cultures of the lactic-acid bacillus, which produces little or no indol.

The evidence that the administration of indol is followed by an increase in the indoxyl reaction is beyond criticism, as I have satisfied myself in the case of rabbits, dogs, and human beings. It need not be further referred to.

In concluding this abridged presentation of the leading facts pertaining to the nature of indol and its relation to the indoxyl-potassium sulphate of the urine, it is desirable to reiterate and emphasize the fact that we possess an unbroken chain of evidence connecting the indican of the urine with the putrefaction of proteids and the production of indol. This chain consists of the following links:

1. The fact that certain proteids may be in various ways decomposed so as to yield aromatic derivatives, including indol.

2. The fact that the common colon bacillus, which normally inhabits the human intestine, and some other micro-organisms are ordinarily producers of indol when acting upon proteid media.

3. The fact that indol produced in the intestine is transformed into indoxyl after absorption, and subsequently into indoxyl-potassium sulphate, within the organism, probably in the liver.

4. The fact that the indoxyl of the urine is convertible by oxidation into indigo blue or indican.

2. *The Action of Indol upon Animal Organisms.*— The literature relating to the action of indol upon animals is scanty. The first observation relating to the subject is probably that of Nencki,* who in 1876 observed that a dog to which one gramme of indol had been fed showed no indication of intoxication, but developed active diarrhœa and hæmaturia when it received two grammes in twenty-four hours. Christiani † two years later found that indol, like phenol, was readily absorbed by frogs through the medium of the skin, and gave rise to increased reflex irritability followed by slight transient paralysis when the animals were placed in a solution containing ten milligrammes of indol in a hundred cubic centimetres of water.

These symptoms resembled in every respect the symptoms observed to follow the absorption of phenol. When a frog was placed in twenty cubic centimetres of a one-per-cent. solution of indol several paralytic symptoms appeared after thirty-five or forty minutes. Even in this condition slight external stimuli gave rise to

* *Berichte der deutsch. chem. Gesellsch. zu Berlin*, 1876, S. 299.

† Ueber das Verhalten von Phenol, Indol und Benzol im Thierkörper. *Zeitschrift für physiologische Chemie*, Bd. ii, 1878.

tremor. Death occurred invariably at the expiration of twenty-four hours. It was further found by Christiani that very minute doses of indol gave rise to pronounced and persistent symptoms when injected subcutaneously, the effects of an injection of 1.2 milligramme being still noticeable after forty-eight hours. The abdominal organs in such cases were found to be congested and the liver was colored yellow.

No further observations were made on the toxic properties of indol until 1896, if we may judge by a fairly careful search through the literature relating to the subject. Then Rovighi * published some experiments in relation to the toxic effects of indol, skatol, and phenol. He found that indol and skatol produce essentially the same derangements in rabbits—namely, torpor, somnolence, widespread paresis, feeble heart action, reduction in temperature, and retention of urine and fæces. The fatal doses of indol and skatol for rabbits was found to be 1.5 to two grammes, when given subcutaneously in the course of forty-eight hours. Rovighi found that animals became more sensitive to the poison after the first dose, as though they no longer possessed the power of transforming and excreting it.

Congestion of the liver was found to succeed acute indol poisoning. In chronic poisoning areas of small spheroidal cell infiltration were observed surrounding the bile ducts. The kidneys were the seat of congestion only.

The experimental observations made by me were conducted without knowledge of the work of Rovighi, and cover a somewhat different field. They relate to acute

* Azione dei prodotti tossici delle fermentazioni enteriche nella milza ed il fegato. *Arch. di farmacologia e terapeutica*, iv, fas. 3, 1896.

indol poisoning in rabbits and dogs, to chronic indol poisoning in rabbits, and to the effects of moderate doses, taken by the stomach, on man.

A. ACUTE INDOL POISONING IN RABBITS AND DOGS.

*Experiment No. 1.*—Injection of indol solution in the intestine. Large rabbit weighing about three thousand grammes.

After laparotomy, 195 cubic centimetres of a 0.1-per-cent. solution of indol were injected into the large intestine. During the infusion the pupils became much contracted, but afterward returned to normal. There was some twitching of the muscles during and after the injection. This lasted during several hours. The animal developed no new symptoms and was ultimately chloroformed. Previous to the injection the urine contained no indican. After the injection a strong reaction was present.

*Experiment No. 2.*—Injection of indol solution into femoral vein. Rabbit weighing 1,230 grammes. A 0.1-per-cent. solution of indol was injected into the femoral vein at the rate of five cubic centimetres a minute. After thirty cubic centimetres were injected the animal was much prostrated, the heart action was very feeble, the respiration was weak, and the pupils were very strongly contracted. When the injection was stopped, the pupils widened a little. The animal remained much prostrated and died about two hours later, "gasping" Nothing abnormal was noticeable at autopsy.

*Experiment No. 3.*—Injection of indol solution into femoral vein. Rabbit weighing 2,100 grammes. A 0.1-per-cent. solution of indol was injected into the femoral vein at the rate of five cubic centimetres to the minute. Between five and ten cubic centimetres, momentary contraction of pupils; at ten to fifteen cubic centimetres pupils were normal. After twenty cubic centimetres, pupils were a little smaller than at onset. After forty-eight cubic centimetres, rather violent tonic spasm (not clearly involuntary). After seventy-two cubic centi-

metres, pupils became suddenly contracted. Injection was stopped. Pupils remained small about three minutes, then widened. Twitching began in muscles of face. Respiration was shallow and slow, and heart action was weak. Injection resumed after about four minutes. After ninety-two cubic centimetres there was general fibrillary spasm. The reflex excitability of the muscles was increased. After stopping the injection (at ninety-two centimetres) the animal lay quietly for about two hours, the heart and respiration becoming better. Then there developed irregular general clonic spasm, depressing the heart and respiration. Death occurred apparently from cardiac failure.

*Experiment No. 4.*—Injection of indol solution into femoral vein. A 0.1-per-cent. solution of indol was injected slowly into the femoral vein of a small dog weighing about fifteen pounds. After twenty-five cubic centimetres the pupils were strongly contracted. After fifty cubic centimetres the heart was weak and the respiration slow. Fibrillary contractions occurred, especially marked in the legs. After seventy cubic centimetres there were irregular clonic spasms in the legs. These soon ceased. The animal was unsteady after the injection. At one time he appeared excited and ran round and round the room. Eight hours later the animal was found dead.

*Experiment No. 5.*—Injection of indol solution into femoral vein. A 0.1-per-cent. solution of indol was injected at the rate of five cubic centimetres to the minute into a dog weighing about twenty-five pounds. After about five cubic centimetres the pupils were contracted. After twenty cubic centimetres the pupils were strongly contracted and remained so, the respiration was slowed, and there was slight clonic spasm in the muscles of the leg on the side of the vein infused. This spasm increased and the knee-jerks became much exaggerated. After a time the spasm became continuous and rather violent. After seventy cubic centimetres irregular clonic spasm extended to all four extremities. Respiration be-

came very much slowed and heart action grew feeble. At one hundred and sixty-two cubic centimetres the injection was stopped. The spasm soon ceased wholly and the animal ran about freely. The animal wholly recovered.

*Experiment No. 6.*—Injection of indol solution into femoral vein. A dog was chloroformed and fifty-five cubic centimetres of a 0.1-per-cent. solution of indol introduced into the femoral vein. Only slight contraction of the pupils was observed. The animal was bled to death.

*Experiment No. 7.*—Injection of indol solution into femoral vein. A 0.1-per-cent. solution of indol was injected into the femoral vein of a dog weighing about twenty pounds, at the rate of five cubic centimetres a minute. After fifteen cubic centimetres the pupils were contracted; subsequently they became very strongly contracted. The reflexes were much exaggerated; the heart became slow and weak. After about fifty-five cubic centimetres clonic spasm occurred in the four extremities. The animal was bled to death.

It is clear from the foregoing experimental records that intravenous injections of indol exert marked toxic effects upon the nervous system both in rabbits and in dogs. Both in rabbits and in dogs the characteristic symptoms were cardiac and respiratory depression, general prostration, marked contraction of the pupils, irregular clonic spasm, and increased reflex excitability, including increase in the activity of the knee-jerks. When a quantity of indol sufficient to cause death was injected, the cause of death in several instances seemed to be cardiac rather than respiratory failure. In one instance only (Experiment No. 6) was myosis not a pronounced symptom. In this case the animal had been chloroformed previous to the infusion of the indol solution. It is noticeable that in the first experiment (the only

one in which the indol was injected directly into the intestine) both myosis and twitching were present. Although the effects of intravenous infusion and those of intraintestinal infusion are probably similar, there seems little doubt that the influence upon the nervous system is much more pronounced in the case of intravenous infusions. Observations upon the temperature were not made, nor was it practicable to make studies of the arterial pressure.

The following observations illustrate the effects of repeated small doses of indol, given subcutaneously, upon rabbits.

B. CHRONIC INDOL POISONING IN RABBITS.

*Experiment No. 1.*—Injection of indol subcutaneously. A rabbit, weighing 1,470 grammes, received ten cubic centimetres of a 0.1-per-cent. solution of indol subcutaneously daily for six days. Then, after an interval of five days, the animal received ten cubic centimetres daily during ten days. The only symptoms observed were marked prostration and gradual loss of weight. The animal was well fed and took considerable food. Death occurred sixteen days after the beginning of the experiment. Weight at death, 1,120 grammes.

*Experiment No. 2.*—Injection of indol subcutaneously. A rabbit weighing 1,170 grammes received ten cubic centimetres of a 0.1-per-cent. solution of indol daily during thirteen days. The animal became prostrated and lost weight. Death occurred at the end of thirteen days. At this time the animal weighed 920 grammes.

*Experiment No. 3.*—Injection of indol subcutaneously. A rabbit weighing 1,480 grammes received ten cubic centimetres of a 0.1-per-cent. solution of indol daily during twenty-two days. No symptoms were noted except that the animal became very quiet and lost weight, although he ate fairly well. At the time of

death, twenty-two days after the beginning of the experiment, the weight of the animal was 920 grammes.

These three observations upon rabbits plainly indicate that even small quantities of indol daily, administered subcutaneously, are capable of initiating profound disturbances of nutrition which end in death in the course of a few weeks. The total quantities of indol required to cause death were in the first case 0.16 gramme, in the second 0.13 gramme, and in the third 0.22 gramme. The loss of weight which followed the administration of the indol was the most obvious and striking feature of its action. It amounted in the first case to twenty-three per cent. of the body weight, in the second to twenty-one per cent., and in the third to thirty-seven per cent. It is impossible to say in how far loss of appetite is responsible for this rather rapid diminution in weight. Another prominent symptom was the prostration and diminished activity observed in all three animals. No observations were made upon the condition of the pupils nor was the temperature noted. The immediate cause of death from chronic indol poisoning is not clear, and deserves to be especially investigated.

The histological changes observed in the organs of these animals will be elsewhere described. It is sufficient to mention here that the chief alterations were found in the liver, the capillaries of the lobules being much congested, and the liver cells being the seat of degeneration and pigmentation.

Before considering the influence of the experimental administration of indol on the human subject it may be well to state that a small ringtail monkey, weighing about fourteen hundred grammes, received five cubic

centimetres of a 0.1-per-cent. solution of indol daily for two months without any apparent effect. Later experiments with larger quantities of indol showed the animal to be far less susceptible than rabbits of equal weight.

### C. EXPERIMENTAL INDOL POISONING IN MAN.

Interesting and suggestive as are the results of indol poisoning in dogs, rabbits, etc., they nevertheless fail to afford a satisfactory basis for an understanding of the influence of this substance upon the human organism. Yet it is with its effect upon the human organism that we are chiefly concerned. There are two ways in which the effect of indol upon the human animal may be investigated. One of these is the careful observation of clinical conditions that are characterized by the presence of a markedly excessive excretion of an indoxyl compound. This method has been much employed by clinicians in the study of nutritive derangements. It is open to the very obvious objection that it is hardly possible to study with satisfaction the influence of a single factor in the production of disease where other factors of perhaps equal significance are not only operative, but operative in a more or less variable way. The history of oxaluria and of the symptomatology which has been affixed to it is an instructive illustration of the pitfalls that lie in the course of the observer who relies wholly on the clinical method of studying the pathological factors in nutritive disorders.

The second method that is open to the investigator possesses the great advantage of enabling him to vary one factor at a time in the experiments which he institutes. This method consists in administering to human subjects the substance the influence of which it is desired to determine. If, then, such conditions as food and drink, exercise, mental work, the use of tobacco, etc., be kept reasonably constant, it is safe to assume that unusual symptoms varying concomitantly with the administration of the substance under investigation are dependent on this substance.

This is the course that was pursued in the case of our study of the properties of indol. Three healthy men were induced to take indol in increasing doses, the various hygienic conditions referred to above being kept nearly constant from day to day for a period previous to the administration of the indol as well as during this period. The indol was given in gelatin capsules containing a tenth of a gramme each. In order to minimize digestive derangement from the irritant action of the indol it was administered immediately after meals.

The first observation relates to a man thirty-two years of age, weighing a hundred and fifty pounds, and in exceptionally robust health. Table A gives the main data pertaining to the experiment.

The second observation relates to a vigorous medical student, twenty-five years of age, weighing about a hundred and sixty pounds.

The doses given in this case were very large.

*Observation No. 2.*

| Date. | Quantity of indol taken. | Symptoms. |
|---|---|---|
| January 30th.... | 1 gramme in divided doses. | No symptoms whatever. |
| January 31st..... | 1.2 gramme in divided doses. | Intestinal flatulence during morning. No other symptoms until evening. Then incapacity for mental work; can not memorize. No symptoms during the day. |
| February 1st..... | 2 grammes in divided doses. | Slept only a short time during the night. Restless and very active mentally. Such sleep as was obtained was interrupted by vivid dreams. |
| February 2d..... | 0.6 gramme in divided doses. | Headache on rising. Soon passed away. No other symptoms. |
| February 3d..... | 1 gramme in divided doses. | Sleep much disturbed by dreams. |
| February 4th..... | 1 gramme in divided doses. | Insomnia. |

There can be little doubt that the insomnia in this subject was due to the action of the indol taken, as he is an exceptionally deep sleeper, and his habits of life were unchanged during the period of the experiment. The amounts of indol taken were so large as to deprive the effects observed of much of their interest, it being questionable whether such large quantities are ever formed in the human intestine, except perhaps where the gut is occluded.

Table B shows the changes in the indoxyl reaction and in the ethereal sulphates which were occasioned by the administration of indol.

The third observation was made upon a medical student twenty-six years of age, in good health, but not especially robust, and weighing at the time a hundred and thirty pounds. He was told to keep a record of the pulse, temperature, and respiration, morning and afternoon, and to note any definite symptoms that might arise. The observation upon this person is made up of three different trials, as will be seen by Table C, which takes note of the leading features of the experiment.

The chief effect recorded in the first observation is the occurrence of slight frontal headache and a sensation of "light-headedness" or giddiness. An interesting feature was the occurrence of colic followed by diarrhœa. This being a very exceptional occurrence in the subject of the observation, it can hardly be questioned that it was dependent upon the rather large doses of indol taken during the day. The occurrence of diarrhœa corresponds with the fact that diarrhœa has been observed, as already mentioned, after the administration of indol to dogs. It is noteworthy that although the sub-

ject received 0.5 gramme of indol (a large dose) on the following day, he felt entirely well with the exception of a little unsteadiness in the legs and stiffness in walking upstairs. It occurs to one that the effects of indol may have been minimized through the apparently thorough emptying of the colon which occurred.

The main features of the third observation resemble those of the first. The symptoms were, however, a little more pronounced, although the quantity of indol was smaller. During the first trial frontal headache or a "sensation of fullness in the forehead" was present the greater part of the time. A sensation of dizziness was also noted at one time. Toward the end of the observation the knee-jerks seemed increased as compared with previous days. As soon as the indol was stopped the symptoms wore away, and there was no recurrence of similar disturbances until after the beginning of the second trial, five days after the completion of the first. Then, after the administration of rather large quantities of indol, the original symptoms, especially frontal headache, returned. The headache and prostration were in fact so marked that it was considered best to discontinue the experiment. As in the first trial, the discontinuance of the indol was quickly followed by an entire subsidence of symptoms. The aim of the third trial was to give quantities of indol which, while occasioning definite symptoms, should not cause such pronounced derangements as to make the continuance of the experiment over a longer period of time impossible. The period covered by this trial was eight days. Although marked headache was present only once during the period, a sensation of discomfort in the frontal region was an almost continuous feature of the

experiment. The characteristic feature, however, of the trial was a decided sense of fatigue. The subject of the experiments summed up his experience by saying that the first and second trials gave him headache, while the third trial gave rise to lassitude and inability to work.

In all three cases the influence of the administration of indol upon the indoxyl reaction and upon the combined or ethereal sulphates was pronounced, as may be seen by the tables.

A feature of the third observation which is of some interest is that previous to the use of indol the urine failed to give any indoxyl reaction, but gave it strongly after the indol was begun, only to lose it when the indol was discontinued.

In the second case, in which very large quantities of indol were given, the intensity of the indoxyl reaction was very unusual, and the increase in the ethereal sulphates was greater than I have ever observed in natural pathological conditions.

*The Clinical Conditions in which the Indoxyl of the Urine is increased and their Relation to Excessive Indol Production.*—We come now to the most difficult and important part of our subject, the interpretation of the clinical significance of excessive indol production in the intestine and of its excessive absorption as indicated by the presence of a strong indoxyl reaction in the urine.

One of the obvious difficulties with which one is met on the onset in any attempt to determine the significance of excessive indol absorption lies in our inability to set up a satisfactory standard for deciding what is to be looked upon as a normal indoxyl reaction. We know there are many individuals in good health whose urine yields a certain amount of indigo blue, and we must rec-

ognize that the presence of an indoxyl compound in the urine is a normal characteristic, although in many normal individuals the reaction is commonly entirely wanting. There are, on the other hand, a good many persons who complain of various trivial disturbances, such as headache, depression of spirits, fugitive muscle pains or muscular rheumatism, and various neurasthenic symptoms, whose urines almost regularly yield an indoxyl reaction that is much stronger than is usual in health. It often happens that these symptoms grow less or disappear under influences that coincidently reduce or stop the excretion of indoxyl. Observing this concomitant variation, one is led to speculate as to the relation which the phenomena bear to one another; or, to put it more definitely, to ask whether it is correct to refer any or all of a certain group of symptoms to the excessive absorption of indol. In some respects the conditions of the problem resemble the oxaluria question. In both cases a normal but not necessary constituent of the urine is apparently excreted in excess, especially in persons presenting certain nervous disturbances, and in both cases the symptoms are apt to retrogress when the excessive excretion stops. In both cases we have to recognize the fact that this relationship, which suggests cause and effect, may be one of mere coincidence. In regard to both questions we have to confess that actual proofs of the suspected relation of cause and effect are wanting, and that the symptoms which one is inclined to attribute to a particular agency may be dependent on one or more unknown influences. In the case of indol, the experimental observations just recorded aid us in forming a conception of what symptoms may be attributable to excessive indol absorption. The first and third

observations make it in the highest degree probable that frontal headache, as well as cephalic sensations not strictly to be called headache, may be produced through the agency of indol. It is, of course, conceivable that the occurrence of these symptoms was a coincidence, but, as the correspondence between the head symptoms and the administration of the indol was exceedingly close, the likelihood of mere coincidence, in the case of persons seldom troubled with headache, seems very small—too small to consider seriously. An interesting feature of the headache in the third subject was the improvement which on several occasions followed out-of-door exercise.

We may, therefore, regard headache, especially frontal headache, as one of the conditions referable to indol, but when we come to consider how frequently indol is the chief or sole cause of such headache it is necessary to proceed with the greatest caution. Such experience as I have had in the study of headache leads me to think that most frontal headaches depend upon other causes, and it is only in the cases (which I believe to be few) where the appearance and departure of headache correspond with distinct and wide fluctuations in the indoxyl of the urine that such a causation is to be suspected. Even here it is likely that the suspicion is justifiable only when the reaction is strongly marked. It seems to me likely that sensations of discomfort in the head, hardly amounting to headache, may more often be the result of excessive indol absorption than actual headache, and that the cephalic sensations of constipation may be, in part at least, thus explained. The very pronounced sense of fatigue developed in the third subject suggests that the long-continued excessive absorption

of indol from the intestine may sometimes be responsible for lassitude and a sense of fatigue disproportionate to the amount of mental and muscular energy expended. The very large proportion of strong indoxyl reactions observed among neurasthenic persons lends some clinical support to this view.* It seems to me that the evidence, though not conclusive, strongly favors the view that the long-continued overproduction and absorption of indol is a factor at least in rendering some persons more readily fatigued than normal individuals.

An interesting question which suggests itself is whether indol is capable of increasing the excitability of the lower reflex arc in man. In this connection the positive increase in the tendon reflexes noted in rabbits and dogs is suggestive. The observation that the knee-jerks

* With a view to examining the clinical evidence of a relationship between neurasthenic states and the excessive absorption of indol, I have tabulated all the cases of which I have records, of patients whose chief complaint is the readiness with which physical or mental fatigue or both may develop. In the cases selected, a chronic disposition to easily induced fatigue has been the leading clinical characteristic, and all cases have been excluded in which debility was due to discoverable organic conditions, or in which dyspeptic derangements have been a prominent feature. A list was then made of all cases, of whatever character clinically, in which a strong indican reaction was a feature of the condition. Cases showing only moderately strong reactions were excluded. It was found of 32 cases, in which the clinical characters were those of neurasthenia, that 21 showed a strong indican reaction, and 11 gave either no reaction or only a slight reaction. Fourteen cases, other than neurasthenic in character, gave a strong indican reaction: one case of myxœdema, two of muscular rheumatism, one of acute intestinal obstruction, one of pseudo-hypertrophic paralysis, three of epilepsy, one of urticaria, one of leucæmia, one of tetany, one of arthritis deformans, and one of chronic nephritis. The impossibility of setting up an absolute clinical standard of neurasthenia diminishes the value of these results, but they seem of sufficient interest to mention.

were increased in two of our human subjects is hardly more than suggestive, because the supposed increase may have been wholly a coincidence. More carefully controlled observations in relation to this point are much to be desired. The question whether excessive indol production and absorption in epileptics is capable of influencing the occurrence of seizures is one of much interest. It appears to me that it would be possible to determine positively whether epileptic persons suspected of being influenced in regard to their seizures by intestinal toxæmias are or are not influenced by the administration of indol.

The second observation upon the human subject—namely, that in which a large quantity of indol (two grammes) was taken in less than forty-eight hours without giving rise to any symptoms except flatulence and incapacity for mental work—is most suggestive when considered in connection with the effects produced in the other cases. There can be no doubt that the indol taken by the subject of this experiment was absorbed from the intestine to a considerable extent, for the reaction given by the urine was exceptionally strong. The fact that such slight symptoms were produced indicates a much smaller susceptibility to the action of indol than was observed in the other cases, and emphasizes the fact that this susceptibility is a highly individual thing. Two elements can be distinguished as entering into this susceptibility. One is the character of the nervous system, the other is the ability of the organism to transform indol into less toxic substances—this transformation perhaps occurring chiefly in the liver. It would be most instructive to select subjects for experiment with reference to these two elements. On the one hand, persons

with irritable nervous systems should be compared with persons who react slowly and moderately to external stimuli; on the other hand, normal subjects should be contrasted with patients suffering from extensive damage to the parenchyma of the liver, as in cirrhosis, and in fatty or amyloid liver.

It need hardly be said that the facts collected in this paper constitute no more than the introduction to a satisfactory knowledge of the toxic properties of indol. They have been presented this evening partly for the sake of the facts themselves, and partly to emphasize the importance of studying the products of bacterial activity which are suspected of a toxic agency in the human organism upon the human organism itself when that is practicable.

In summing up, we might answer as follows the question propounded in the beginning of this paper, What detrimental effects, if any, does the excessive formation and absorption of indol entail upon the human organism? The effects of indol upon the human subject, taken in conjunction with a study of the clinical conditions in which the indoxyl reaction is markedly increased, justify us in believing that prolonged and excessive indol absorption is capable of causing headache, especially frontal headache, abnormal cephalic sensations, and indisposition for mental and physical exertion. The latter condition, if prolonged, may perhaps form the basis of a neurasthenic state. Although this is as far as we can safely go with our present knowledge, it is not at all unlikely that further investigation will enable us to detect other effects of excessive indol absorption. That the individual susceptibility varies much seems clear from the results of experiment, and it is like-

ly that this difference in susceptibility relates both to the intensity and to the character of the influence which is exerted. There is no doubt that some robust persons may habitually excrete a large amount of indoxyl-potassium sulphate without showing definite evidence of derangement of health, but these cases are certainly exceptional. While, therefore, we can not regard indol as an indifferent substance in the human organism, we can not regard it as ordinarily exerting highly toxic effects, even when it is absorbed in unusually large amounts. This conclusion accords with what one might on *a priori* grounds expect in the case of a normal decomposition product of proteid food.

*Table A.—Observation No. 1.*

| Date. | Quantity of indol taken. | Symptoms. | Indoxyl reaction. | Preformed sulphates. | Ethereal sulphates. | Ratio. |
|---|---|---|---|---|---|---|
| December 28th... | 0.1 gramme at middle of day. | Toward evening "dull feeling" in front of head; feels slightly giddy. Sensation at times as of slight headache, but can hardly call the feeling a pain. | Faint. | 1.24 gramme. | 0.150 gramme. | 8.13 |
| December 29th... | 0.3 gramme indol during day in doses of 0.1 gramme. | Slight frontal headache most of day; some sensation of "lightness" in head at times. No other symptoms. | Increased. | 1.80 gramme. | 0.318 gramme. | 5.66 |
| December 30th... | 0.5 gramme indol during day. | At 2 A. M. was awakened by very severe colic. Then had large watery movement, followed by relief of colic. During the day felt entirely well. No perceptible effect from indol, except that toward evening there was some unsteadiness in the legs and stiffness in the muscles on walking upstairs. | | | | |
| December 31st.... | No indol ..... | Felt perfectly well during morning. Knee-jerks seem increased as compared with December 27th. Pupils normal; no contraction. | | | | |
| January 1st..... | 0.4 gramme indol in the morning. | Sensation of "lightness" in head; no headache. Otherwise, entirely well. | | | | |

*Table B.*

| Date. | | Indoxyl reaction. | Preformed sulphates. | Combined sulphates. | Ratio. |
|---|---|---|---|---|---|
| January 29th..... | Previous to administration of indol. | Well marked. | 2.44 grammes. | 0.21 gramme. | 11.64 |
| January 30th..... | " " " | Well marked. | 2.39 grammes. | 0.238 gramme. | 10.02 |
| January 31st..... | During administration of indol. | Very strong—black. | 1.345 gramme. | 0.608 gramme. | 1.76 |
| February 1st... ..... | " " " | Very strong—black. | 0.915 gramme. | 0.686 gramme. | 1.33 |
| February 2d..... | " " " | Very strong—black. | 0.603 gramme. | 0.732 gramme. | 0.823 |
| February 3d..... | " " " | Very strong—black. | 1.159 gramme. | 0.484 gramme. | 2.39 |
| February 4th..... | " " " | Very strong—black. | 1.235 gramme. | 0.726 gramme. | 1.70 |
| February 5th..... | " " " | Very strong—black. | 0.769 gramme. | 0.692 gramme. | 1.11 |
| February 6th..... | Indol stopped. | Slight. | 1.973 gramme. | 0.263 gramme. | 7.50 |

*Table C.—Observation No. 3 (First Trial).*

| Date. | Quantity of indol taken. | Symptoms. | Indoxyl reaction. | Preformed sulphates. | Combined sulphates. | Ratio. |
|---|---|---|---|---|---|---|
| December 2d..... | 0.025 gramme after lunch. | No symptoms. | Negative. | 1.832 gramme. | 0.289 gramme. | 6.34 |
| December 3d..... | 0.050 gramme after lunch. | Little effect. A little unsteady in legs. Bad taste in mouth on rising. A little nervous toward evening. "Slight fullness" in forehead during afternoon. No symptoms after dinner. | Strong. | 1.664 gramme. | 0.296 gramme. | 5.62 |
| December 4th.... | 0.2 gramme during day. | Dreams more distinct than usual. No unsteadiness on feet. No perceptible derangement Dull sensation in head, perhaps from dissecting longer than usual. Knee-jerks seem increased. | Strong. | 1.287 gramme. | 0.467 gramme. | 2.76 |
| December 5th.... | 0.2 gramme during day. | Dull sensation in head lasting all day. Slight dizziness during evening. Knee-jerks increased as compared with previous days. | Very strong. | 1.988 gramme. | 0.426 gramme. | 4.69 |
| December 6th.... | Indol stopped. | Head feels well. | Slight. | 2.012 grammes. | 0.188 gramme. | 10.69 |

*Observation No. 3 (Second Trial).*

| | | | | | | |
|---|---|---|---|---|---|---|
| December 10th... | 0.2 gramme indol during day. | Feeling well. A little "fullness" in forehead and slight nausea. | Negative. | 1.695 gramme. | 0.247 gramme. | 6.81 |
| December 11th... | 0.1 gramme at breakfast, 0.2 gramme at lunch, 0.2 gramme at dinner. | Headache continued through the night. Relief after rising, but "heavy feeling" continues. During afternoon felt very tired. Dull frontal headache returned. Headache continued during evening. Slight cramplike pains in legs during walking. | Very strong. | 1.845 gramme. | 0.4404 gramme. | 4.19 |
| December 12th... | Indol stopped. | Headache continues. Bad taste in mouth. By 5 P. M. feeling as well as ever. | Very strong. | 1.524 gramme. | 0.555 gramme. | 2.75 |
| December 13th... | No indol. | No symptoms. | Negative. | 1.686 gramme. | 0.330 gramme. | 5.11 |

*Observation No. 3 (Third Trial).*

| | | | | | | |
|---|---|---|---|---|---|---|
| December 14th... | 0.1 gramme at 7.45 P. M. | Feeling well during day. | Negative. | 1.652 gramme. | 0.352 gramme. | 4.69 |
| December 15th... | 0.3 gramme during day; 0.1 gramme at each meal. | As usual during morning. After dinner, during afternoon, felt tired. Slight pain and stiffness in shoulders, lasting only a short time. During evening, dull feeling in head, hardly headache. | Medium. | 1.337 gramme. | 0.405 gramme. | 3.30 |
| December 16th... | 0.2 gramme during day. | Bad taste in mouth. Sleep much disturbed by dreams. Feels "tired all over." This lasted through afternoon. A little stiffness in shoulders after sitting. Slight pain in front of thighs. | Very strong. | 2.223 grammes. | 0.396 gramme. | 5.62 |
| December 17th... | 0.2 gramme during day. | Bad taste in mouth. Disturbed sleep. A little weakness in legs. Dull feeling in head. After breakfast felt tired all over. Could not study. Dull feeling in head continued; no ache. During afternoon felt tired; weak in knees. Slight pains in head lasting a few seconds. At night, severe frontal headache, coming on gradually since dinner. Can eat, but is not hungry. | Strong. | 1.601 gramme. | 0.339 gramme. | 4.72 |
| December 18th... | 0.2 gramme during day. | Sleep disturbed. Bad taste in mouth. Headache lasted through night. Improvement on rising, but head still dull. Tired all day. Dull sensation in head. | Strong. | 1.596 gramme. | 0.390 gramme. | 4.09 |
| December 19th... | 0.2 gramme during day. | Sleep less disturbed than previously. (Walked a little longer than usual on previous evening.) "Dull, tired feeling" continues. | ..... | 1.913 gramme. | 0.460 gramme. | 4.16 |
| December 20th... | 0.2 gramme during day. | Slept well. Head feels tired and dull. Unpleasant frontal sensation all day. | ..... | 1.676 gramme. | 0.381 gramme. | 4.40 |

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