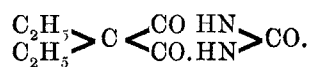


VERONAL POISONING.<sup>1</sup>

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THE chemical formula of veronal is—



It is chemically described as malourea, or diethyl malonyl urea, or diethyl barbituric acid. "Veronal" is a registered trade name, and another name of the same character also used for this compound is "hypnogen." Veronal is a white crystalline powder, odourless; melting point, 191° C. It has a bitter and somewhat nauseous taste, it has an acid reaction to litmus, and it is only slightly soluble in cold water. At 20° C. 1 part is soluble in 146 to 147 of water, at 90° C. 1 part is soluble in 23 of water, and at 100° C. 1 part is soluble in 15 of water. Veronal is easily soluble in alkaline solutions. It is soluble in alcohol, ether, acetone, or acetic ether, but it is not readily soluble in chloroform. Veronal was discovered in 1902 (Professor E. Fischer and Professor J. Mering). It was prepared<sup>2</sup> by treating diethyl malonic acid ester with urea and sodium ethylate. Another good method of preparing veronal is by treating diethyl malonyl chloride with urea.

Veronal has for the past seven years been very widely used in this country as a hypnotic. Indeed, its use has become well known to the public, so that there is reason to believe that commonly the drug has been taken for insomnia without the advice or prescription of a medical man. It is undoubtedly a powerful hypnotic. Messrs. Merck and Bayer, the introducers of the drug, claim that they have always understood that it was "an exceedingly potent hypnotic," and that they have always laid stress on the danger of exceeding the therapeutic doses. A letter to this effect from the Bayer Company, Limited, appeared recently.<sup>3</sup> There is no doubt that soon after its introduction veronal became popular as a hypnotic, and it is quite certain that its exceedingly potent action was not fully appreciated by the medical profession and still less so by the public. It is spoken of as "a sleep-producing drug of a relatively harmless character"<sup>4</sup>; and Professor Bradbury<sup>5</sup> has described it as "one of the quickest, safest, and most reliable hypnotics." These statements, of course, referred to therapeutic doses, but it is to be feared that it has been sometimes assumed that because the drug is harmless in therapeutic doses it may be given in doses considerably in excess of this. It is most important that the medical profession and the public should realise that the therapeutic dose cannot be exceeded with safety except in very special cases.

The therapeutic dose of veronal for an adult is given in the British Pharmaceutical Codex for 1907 as 5 to 15 grains; while in the latest edition of that work (1911) the dose is given as 5 to 10 grains, an indication that perhaps the potent action of the drug had not been fully recognised in 1907. The Bayer Company in a recent pamphlet on veronal give the dose for an adult as 5–10–15 grains, but they state "it should be clearly understood that in ordinary cases of insomnia the 5 grain dose is quite sufficient for an adult, and that the dose should only be repeated after a reasonable interval." In a single therapeutic dose it usually acts fairly quickly, producing sleep within an hour or so, and the sleep lasts for several hours.

Toxic symptoms may occur after the administration of veronal, and these may be the result of: (1) a special idiosyncrasy causing a susceptibility to a small or moderate dose; (2) an excessive dose having been taken; (3) repeated small doses as in the veronal habit. The toxic symptoms which occur after a single large dose are drowsiness, headache, and sometimes ataxy accompanied by a reeling gait. The patient falls into a deep sleep from which he can only be roused with difficulty. In severe cases the sleep deepens

into coma, and the patient becomes cyanosed with rapid and often stertorous breathing. In this stage it is very common for a marked rise of temperature, even to 103° F. or more, to occur, and a physical examination of the lungs will probably show areas of dullness on percussion, increased vocal resonance, bronchial breathing, and moist sounds. In other words, all the clinical signs of pneumonia will be present. These signs will be accompanied or followed by those of a general œdema of the lungs, such as moist bubbling râles all over. It is quite easy for a severe case of veronal poisoning to be mistaken for pneumonia, and I have known the mistake made on several occasions. When the condition of deep coma and pulmonary symptoms develops after the taking of a large dose of the drug it is uncommon for recovery to occur. Sometimes a condition of coma and high temperature will last for as long as four days before death supervenes, but after a very large dose death may occur in less than 24 hours.

It is said that digestive disturbances, nausea, and vomiting occur from the drug. These undoubtedly occur in chronic veronal poisoning (veronal habit). In my experience they are uncommon in cases where a single large dose is taken. Skin rashes have been described as a result of veronal. These are erythematous in type and of a rubeoliform or scarlatiniform character. It is stated that occasionally urticarial rashes occur and also extreme pruritus and œdema of the face. In my experience skin rashes are not common after veronal. It is said that urinary disturbances, such as suppression, albuminuria, hæmatoporphyrinuria, and hæmaturia, may occur from the drug. I have not observed these symptoms except slight albuminuria. In several severe cases of veronal poisoning I have noticed a remarkably free excretion of urine, but often the urine has to be withdrawn by the catheter when the patient is in a comatose condition.

In chronic veronal poisoning (veronal habit) the patient often develops an abnormal mental condition, visual hallucinations are common, and also delusions may occur; the whole mental balance may be upset and a sort of double self exist subjectively. In these cases tremors and marked ataxy are common, and the condition may resemble cerebellar disease. The speech is often affected, and thick and indistinct, and disturbances of sight may occur. The gait in these cases is commonly quite reeling, similar to that of a drunken person. The veronal habit causes a complete disorganisation of the moral sense, just as is the case with the morphia and cocaine habits.

In cases of renal disease veronal is much more toxic than with normal patients. Also it is important that constipation should be avoided if the drug is being given frequently, since otherwise toxic symptoms may develop. In these conditions a cumulative action may occur if it is given in therapeutic doses continuously.

*Fatal dose.*—Cases of death have been recorded after taking veronal, even with such small doses as 10 grains. In these cases probably other factors were present, and death was not entirely due to the drug. In a healthy adult it may be taken that a dose of about 50 grains would be dangerous, and might be regarded as an average minimum fatal dose. It is well known that much larger doses have been taken without death resulting, but in these cases serious symptoms such as deep coma have occurred, and there has been grave danger. On the other hand, fatal cases are recorded from doses of 1 gramme (15 grains).

It must be remembered that in the recorded cases of fatal veronal poisoning the patients have often been the subject of some other disease, or of some other form of poisoning, such as alcohol, morphia, &c., and the veronal taken may have not been entirely responsible for the fatal issue. Also it must be borne in mind that in fatal cases of veronal poisoning it is usually almost impossible to say what was the exact dose taken, since the early onset of coma usually prevents any information being obtained from the patient. A reference to the cases of which details are given will illustrate this.

*Tolerance to veronal.*—Undoubtedly tolerance may be established in some cases, but a great tolerance comparable to that in morphia and cocaine takers does not occur. Even in cases where patients are accustomed to taking the drug it must be accepted that a dose of about 50 grains is likely to produce deep coma which may be followed by death.

*Treatment of acute veronal poisoning.*—If the patient is

<sup>1</sup> A paper read at the Seventeenth International Congress of Medicine, August, 1913.

<sup>2</sup> E. Fischer: *Liebig's Annalen der Chemie*, 335, 334, 1904.

<sup>3</sup> *Brit. Med. Jour.*, July 5th, 1913.

<sup>4</sup> Dixon Mann: *Forensic Medicine and Toxicology*, 1908.

<sup>5</sup> Allbutt's *System of Medicine*, vol. viii., 1910, article on Insomnia.

seen soon after taking the drug—i.e., within four hours—it will always be most advisable to pass into the stomach a soft stomach tube to which is attached a piece of plain rubber tubing about 3 feet long, in the end of which is a glass funnel. There is no risk in the careful passage of a soft stomach tube. The mouth should be kept open by means of a suitable gag while the tube is being passed, and the passage of the tube down the oesophagus is readily brought about by first guiding the end with the left forefinger placed in the mouth. About 20 inches of stomach tube should be passed beyond the teeth, the tube being gently pushed down with the right hand. During the process of passing the stomach tube the mouth should be in the mid-line of the body, the head not being rotated. When the tube is in the stomach no air will issue from its funnel end. Some warm water should now be placed in the funnel, and the funnel raised, so that the tube becomes filled with water. Before the funnel is empty it is quickly depressed, and this will start a syphon action, so that the contents of the stomach can be syphoned out. These should be carefully reserved for future analysis. When the stomach has been emptied as completely as possible it is very advisable to wash it out thoroughly by introducing about 2 pints of warm water and then syphoning this off. This washing out should be repeated three or four times and the stomach emptied as completely as possible. Before withdrawing the tube about 1 pint of hot strong coffee with some milk in it, and an ounce of castor oil or other suitable aperient, should be introduced and left in the stomach. The stomach tube is now withdrawn.

The above details have been given because it is sometimes imagined that there is risk in washing out the stomach in cases of veronal poisoning. There is no risk if the operation is carefully performed within a few hours of taking the poison. The risk of not doing this is infinitely greater. After six hours or so from taking the poison most of it will probably have passed from the stomach into the intestine, so that washing out of the stomach is not likely to be of much avail in removing the poison. Unless the patient is *in extremis* the stomach tube may often then be passed with advantage and a rapid washing out performed, strong coffee being introduced as described above.

Cardiac stimulants should be given, such as strychnine hydrochloride gr. 1/30, with digitalin gr. 1/100 every four hours. Warm normal saline should be given subcutaneously, and also rectal injections of normal saline containing 4 per cent. of glucose should be given in amount of 15 oz. every four hours. If there is much cyanosis oxygen should be given, and when the pulse is feeble the oxygen may with advantage be passed through a wash-bottle containing absolute alcohol, since the combination of oxygen and alcohol vapour is a valuable cardiac stimulant. During the comatose state attention must be paid to the bladder, the urine being drawn off by a catheter if necessary. Any urine passed must be carefully preserved for analysis. If urine is not being excreted freely injections of the hypodermic solution of caffeine may be given every four hours. Other stimulants that may be given if necessary are camphor and pituitary extract hypodermically.

It must be remembered that in acute veronal poisoning the state of coma which comes on soon after taking the drug may last several days. It will therefore be necessary to feed the patient. Warm milk, and milk and coffee may be given every four hours, either by the stomach tube or by a nasal tube carefully passed.

*Post-mortem appearances.*—Marked cyanosis is often present at the time of death, and this may persist after death, there being bluish discolouration of the lips and face, and also of the finger-nails. Post-mortem staining is usually well marked. The heart usually shows marked dilatation, this condition affecting the cavities of both sides. Usually the dilatation is more marked in the right auricle and ventricle than in the corresponding cavities on the left side. The great veins are full and the blood is often fluid. The air passages are congested and contain mucous exudation. The lungs show almost always marked hypostatic congestion and oedema in their dependent parts, and portions so affected commonly sink in water. Frequently patches of pneumonic consolidation are present in the lungs, and lymph may be present on the pleural surface of these areas. The pneumonic areas may be quite extensive, and they are to be distinguished from the general hypostatic

congestion and oedema above mentioned. No characteristic changes occur in the stomach and intestines. The brain and abdominal viscera usually show marked congestion.

In conclusion, it may be said that the post-mortem signs of veronal poisoning are not specially characteristic. They are those of death from gradual heart failure, complicated by oedema and hypostatic congestion of the lungs. Such signs may be commonly found in death from natural causes.

*Toxicological analysis.*—There are no very characteristic chemical tests for the drug. Veronal gives well-marked crystals which are not readily soluble in water, but readily soluble in weak caustic soda solution. The melting point of veronal, 191° C., is very useful for identification, but it is necessary that it be isolated in a pure condition, otherwise its melting point will not agree with the theoretical. Recrystallisation once or twice may be necessary before a constant melting point is obtained, and sometimes purification by treatment with blood charcoal is necessary. The amount isolated from a given case may be sufficient to admit of purification and determination of the melting point, but often the quantity of poison found is too small to permit of this. If a substance is isolated which is crystalline and identical in melting point with veronal, valuable confirmation is obtained by mixing the substance found with veronal and taking the melting point of the mixture. This will be unaltered if the substance found is veronal.

Veronal solution gives no precipitate with the reagents commonly used as alkaloidal precipitants. Veronal solution if boiled with solution of caustic potash (20 per cent.) is not decomposed, and the addition of Nessler's reagent gives no brown colouration. Veronal in the solid form if fused with caustic potash gives a nasty rancid smell. If the tube is cooled and water is added and then Nessler's reagent a well-marked brown colouration is produced. Veronal solution, if treated with two drops of dilute nitric acid and then with Millon's reagent, gives a white gelatinous precipitate, soluble in excess of the reagent.

Veronal is extracted from viscera by taking a given weight of the organ (about 120 grm.). This is cut up finely and treated with 95 per cent. alcohol, just acidified with acetic acid. The extraction with alcohol is continued for 24 hours at 35° C. The alcoholic liquid is poured off, and the residue is treated with fresh alcohol as before. Four extractions are made. The alcoholic extracts are mixed, filtered, and evaporated to a syrupy consistence. Absolute alcohol (about 200 c.c.) is now added, and the mixture allowed to stand for a short time. It is then filtered, and the filtrate is evaporated to a syrupy consistence. The liquid is now taken up with water and the turbid mixture is filtered. The filtrate should be concentrated by evaporation below 35° C. to about 15 c.c. If the liquid is not highly coloured it may be extracted with ether (two volumes) successively for four times. The ethereal solutions are filtered, mixed, and gently evaporated in a weighed glass dish. The residue will contain the veronal present. It may be white and crystalline, but usually there is some brown tint, and further purification may be necessary.

Where the aqueous extract of the viscera is much coloured it is better to treat it with slight excess of lead acetate; the mixture is filtered and the excess of lead acetate removed by precipitation with sulphuretted hydrogen; the liquid is again filtered and concentrated by evaporation in a current of air to about 15 c.c. The liquid thus obtained is extracted with ether as above described. Any veronal present will be obtained in a fairly pure state. The residue, purified if necessary, is carefully tested for veronal by the above-mentioned tests.

Veronal is a poison which is distributed fairly evenly throughout the body; thus the abdominal viscera do not appear to have that selective action for the drug which they show with arsenic and some of the alkaloidal poisons. It is a drug which is rapidly excreted by the kidneys, and in a fatal case of veronal poisoning, where the patient has lived for 24 hours or more after taking the poison, it is probable that a considerable quantity will have been excreted in the urine. It follows, therefore, that the amount found in the whole body after death will not represent all the poison taken. In fatal cases of veronal poisoning, where death occurs after 24 hours, something like 40 to 50 per cent. of the poison will probably have been excreted in the urine before death. It is always most important that the urine excreted should be saved for analysis.

*Extraction of veronal from urine.*—About 200 c.c. of urine are taken. If a larger quantity is available this may with advantage be concentrated to 200 c.c. by evaporation at a low temperature. The urine is treated with a slight excess of acetate of lead solution, and the mixture after standing is filtered. The excess of acetate of lead is precipitated by sulphuretted hydrogen and the liquid is filtered. The filtrate is evaporated at a low temperature to about 60 c.c., a little blood charcoal is added, and the mixture filtered after standing a few hours. The filtrate is concentrated by evaporation at a low temperature to about 30 c.c. This is extracted with double the volume of ether three times, the ethereal extracts are mixed, filtered through a dry paper, and are evaporated to dryness at a low temperature. The crystalline residue is submitted to the tests for the drug, and the crystals are carefully compared with those obtained by evaporation of an ethereal solution of veronal.

*Statistics of veronal poisoning.*—A table is appended showing the returns of the Registrar-General for deaths from veronal poisoning occurring in England and Wales up to 1910. The later returns are not yet published. By the kindness of three coroners of large districts—viz., Mr. C. Luxmore Drew, Mr. W. Schröder, and Mr. G. Vere Benson—I am enabled to give up to date the cases of veronal poisoning in their respective districts. Statistics are very valuable as giving an indication of the frequency of cases of veronal poisoning, but it must be remembered that (1) cases of death which are really due to veronal poisoning may be overlooked and mistaken for pneumonia or other condition producing coma; (2) often veronal may be an accelerating factor in causing death, but some other toxic influence or disease plays an even more important part in bringing about a fatal issue, so that in some cases where “veronal poisoning” is the alleged cause of death it cannot be fairly regarded as being entirely responsible.

Veronal Poisoning: Statistics for England and Wales.

Year.	Accident.		Suicide.		Man-slaughter.	Murder.	Total.
	Males.	Females.	Males.	Females.			
1904	—	—	—	—	—	—	—
1905	—	—	—	—	—	—	—
1906	—	1	—	—	—	—	1
1907	1	—	—	—	—	—	1
1908	2	—	2	—	—	—	4
1909	6	5	—	2	—	—	13
1910	7	5	2	1	—	—	15

Cases of Fatal Veronal Poisoning in Three Coroners' Districts.

Year.	District of Mr. Luxmore Drew.	District of Mr. Schröder.	District of Mr. Vere Benson.
1909 ... ..	1	2	0
1910 ... ..	1	0	2
1911 ... ..	1	3	1
1912 ... ..	3	0	1
1913 ... .. (Up to July.)	1	1	1

The following recent cases, which have been investigated by Dr. B. H. Spilsbury, of St. Mary's Hospital, and myself, are of interest and show the importance of considering the details of each case.

- CASE 1.—Female, aged 27. The patient was probably addicted to alcohol. She was found unconscious in her bedroom, and death occurred after 42 hours. Empty bottles which had contained veronal tablets were found in the room. The post-mortem examination showed bright red post-mortem staining and cyanosis of the finger nails. The heart showed dilatation of all the cavities and brown atrophy of its muscle. The lungs showed marked oedema and hypostatic congestion; portions sank in water. *Verdict* of coroner's jury: “Death from veronal poisoning.” There was no knowledge of the quantity of the drug taken.
- CASE 2.—Female, aged 60. The patient was addicted to the taking of veronal, trional, and morphine. She was comatose for a few hours (at most eight) and died. In the bed was found a hypodermic syringe which contained morphine. An empty veronal bottle was found in the bedroom. A recent hypodermic puncture was present on the left thigh. The heart showed dilatation. The lungs showed hypostatic congestion and oedema. A large malignant growth was present in the stomach, and a scirrhus growth was present in the right breast. *Verdict*: “Death from veronal and morphine poisoning.” In this case it is doubtful if veronal really played any important part in causing death.
- CASE 3.—Male, aged 54. The patient had suffered from tabes dorsalis for two years. He was found dead in his dressing-room two hours after being seen by his wife in a conscious condition. A

- tumbler was found in the room containing a small quantity of veronal. The evidence in this case showed that the deceased could not have taken more than 20 grains of the drug, and probably much less was taken (about 5 grains only). The post-mortem signs showed dilatation of the heart and brown atrophy of its muscle. The lungs showed oedema and hypostatic congestion. *Verdict*: “Syncope from heart disease accelerated by veronal taken to produce sleep while patient was suffering from tabes dorsalis.” In this case it is doubtful if the drug was a factor in causing death.
- CASE 4.—Male, aged 37. The patient was found in his bedroom unconscious, and he remained comatose for about 78 hours before death. He was cyanosed and had all the clinical symptoms and physical signs of acute pneumonia. The temperature was from 100° to 105° F. the last two days. An empty bottle which had contained veronal tablets was found in the bedroom. The deceased was known to be addicted to the drug. Post-mortem examination showed marked post-mortem staining, dilatation of the heart, and hypostatic congestion and oedema of the lungs. *Verdict*: “Death accelerated by veronal poisoning.” In this case probably a large dose was taken, but no exact evidence could be obtained.
- CASE 5.—Female, aged 38. The patient suffered from an adherent pericardium with calcification. There was marked ascites and oedema. She became unconscious, and died after about 13 hours. Dilatation of the heart and hypostatic congestion and oedema of the lungs were present. The evidence in this case showed that probably 125 grains of medinal were taken. *Verdict*: “Death from heart disease, accelerated by medinal, taken with suicidal intent.”
- CASE 6.—Male, aged 39 years. The patient was found in a comatose condition, and died after being in a state of coma for about 80 hours. Post-mortem examination showed dilatation of the heart, and the lungs showed hypostatic congestion and oedema with patches of acute broncho-pneumonia. Veronal was found in the urine. Two empty tablet bottles were found in his bedroom. The deceased was known to be a veronal taker. *Verdict*: “Death from heart failure and pneumonia, accelerated by veronal poisoning.” In this case there was no evidence as to the quantity taken. The deceased was suspected of being addicted to alcoholic excess.
- CASE 7.—Female, aged 42. The deceased had threatened to poison herself by veronal. She was seen alive at 2 P.M., when she said she was going out for a walk. She was found dead in bed 20 hours afterwards. Post-mortem examination showed marked post-mortem staining and cyanosis of nails and lips. There was marked dilatation of the heart. The lungs showed hypostatic congestion and oedema; also there were patches of acute broncho-pneumonia in both lungs. *Verdict*: “Death from veronal poisoning (suicidal).” There was no evidence of the exact dose taken, but it was probably over 100 grains. (125 grains of veronal were known to have been purchased three weeks before death.)
- CASE 8.—Male, aged 56. The patient had a fall of over 20 feet, fracturing the sternum and four ribs. He died about 48 hours afterwards. After the injury he was given therapeutic doses of paraldehyde and veronal, which were prescribed by his medical man. The heart showed dilatation and fatty degeneration of its muscle. The lungs showed hypostatic congestion and oedema. *Verdict*: “Death from shock following injuries accelerated by paraldehyde and veronal taken as hypnotics.” In this case it is extremely doubtful if death was in any way accelerated by veronal.
- CASE 9.—Male, aged 62. The patient took 53 grains of veronal. He became comatose, and on examination was found cyanosed, with temperature of 103° F., respiration 66, and rapid, feeble pulse. There was marked dullness over the whole of the upper lobe of the left lung, with crepitations and marked tubular breathing. He was treated for veronal poisoning and made a complete recovery. The coma lasted about 24 hours. The recovery in this case was remarkable, as it does not usually follow such very grave symptoms as were observed.
- CASE 10.—Male, aged 28. A post-mortem examination showed some dilatation of the heart. The lungs showed hypostatic congestion and oedema and a small patch of pneumonia in the lowest lobe of the right lung. Chemical analysis showed veronal to be present in all the organs examined. The amount calculated as being present in the whole body was 75 grains. The evidence in this case showed that the deceased had taken a large dose of veronal, after which he rapidly became comatose and died after about 32 hours. Probably in this case a dose was taken of something like double that found in the body. *Verdict*: “Death from veronal poisoning, but there was no evidence to show how it was administered.”
- Medinal* is the mono-sodium salt of veronal. It is very soluble in water and is therefore more rapid in action. Its toxicology is otherwise exactly similar to that of veronal.
- Veronal, by its bitter taste and insolubility in aqueous solutions, could not easily be administered to a normal person in a poisonous dose without the taste being recognised; also the gritty insoluble particles might be detected. Medinal, though very soluble, has a bitter, nauseous taste which would almost certainly be recognised by a normal person taking it. The alkaline nature of medinal causes the drug to alter the colour of wines such as hock, &c., and this change in colour might arouse suspicion were any attempt made to administer the drug in this way unknown to the taker.
- Propional* is dipropyl barbituric acid. It is more poisonous than veronal, but otherwise its toxicology is similar.
- Luminal* is diphenyl barbituric acid. It is more poisonous than veronal, but otherwise its toxicology is similar.
- Preventive measures.*—Veronal and its derivatives and allied substances are undoubtedly very useful therapeutic agents when carefully prescribed. It is most important, however, that powerful hypnotic drugs of this character should only be taken with the knowledge and consent of a medical practitioner and on his written prescription. It

would also be advisable if the dispensing of such prescription were not repeated without the written sanction of the medical man. The frequency of cases of veronal poisoning in this country has caused His Majesty's Privy Council to approve of the following addition to the Poisons and Pharmacy Act of 1908: that "diethyl barbituric acid, and other alkyl, aryl, or metallic derivatives of barbituric acid, whether described as veronal, proponal, medinal, or by any other trade name, mark, or designation, and all poisonous urethanes and ureides," ought to be deemed poisons within the meaning of the Pharmacy Act, 1868, as amended by the Poisons and Pharmacy Act, 1908, and ought to be deemed poisons in Part II. of the Schedule of Poisons to that Act. The effect of this resolution is that veronal and the other substances named and included in it can only be sold by a qualified pharmacist, and that all of these substances must be labelled "Poison," and must bear the name and address of the vendor.

The dangers from veronal poisoning are to some extent safeguarded by this valuable addition to our legislature, but the best safeguard of all will be a loyal coöperation of pharmacists with the medical profession in protecting the public from the abuse of drugs which have a potent though useful therapeutic action.

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## A CLINICAL STUDY OF THE CHIEF FUNCTION OF THE PERITONEUM.<sup>1</sup>

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THE chief function of the peritoneum is that of a "per-enteric trap for the reception and annihilation of micro-organisms which *constantly* and *normally* (i.e., without producing symptoms) permeate the intestinal wall." It is part of the duty of certain organs intimately connected with the peritoneal cavity, of which the liver, stomach, and the intestines are the chief, to excrete the toxic products formed therein, including, in times of stress, the bacteria themselves, with the minimum risk of contamination to the remainder and more important parts of the body.

In animal life the coelom is next in antiquity to the archenteron or primitive alimentary canal. When the organism consisted only of an outer layer, ectoderm, protective, sensitive, and reproductive, and an inner, endoderm, digestive and absorptive, the even distribution of nutritive material was a simple matter. When, however, a third layer, mesoderm, was developed, primarily for support and locomotion, secondarily for reproduction, any further progress in usefulness of this layer would be considerably hampered if its proper supply of nutriment continued to depend upon a correspondingly complex evagination of the alimentary canal amongst its cells. This difficulty would be solved by cleavage of the mesoderm into an inner thin layer, the splanchnopleure, and an outer layer, the somatopleure, with a cavity between (the coelom) containing fluid kept in motion by the movements of the organism. Not only did this cavity serve as a nutriment distributor, but it also became a receptacle for the products of metabolism; the cavity was therefore placed in direct communication with the exterior. In addition the reproductive cells were shed into its interior and thus found an easy exit. In the trochosphere larva of the polychæta we find a large perienteric cavity, which is not the coelom (it is, in fact, the original blastocele), and for reasons which I cannot enter into here it is clear that none of the above functions are required of it, for it is practically a coelenterate, the mesoderm being relegated to the very hinder end near the anus. Why, then, this persistence of the blastocele? I suggest that here we get the first glimpse of the utility of a per-enteric cavity as a trap for organisms. I may reasonably assume that along with the food a large number of cocci, bacteria, and protozoa would pass into the alimentary canal of this animalcule, some of them actively hostile. With a large number of these the cells of the endoderm would be

able to deal, but it can be imagined that from the number or virulence of the invading organisms the resistance of this first line of defence would be not infrequently overcome. It is important that the contents of the canal should be rid of this contamination before they reached the hinder end, for here, surrounding the endoderm, are the mesodermic bands which contain the elements essential, not only for the development of the adult polychæte, but, in the form of reproductive cells, for that of countless numbers of annelids. Any bacteria, therefore, which succeed in defeating or eluding the endodermic cells only break into, they may even be enticed into, a lethal chamber containing lethal fluid, which frees itself of toxins through the primitive "pronephridia."

To proceed a step further on the road of evolution, let us consider the coelom of the earthworm, with which you are no doubt familiar. It is strikingly large, though the distribution of nutritive material and conveyance of the products of metabolism are performed by an elaborate blood circulatory system, whilst the formation of reproductive cells has been relegated to one or two segments only. We have to explain why—(1) the coelomic cavity is relatively so large, a characteristic of this and allied types; (2) it communicates directly with the exterior by dorsal pores after the eighth segment; (3) dorsal pores are not found in the first eight segments; and (4) in spite of the existence of a circulatory system the nephridia still open by bell-shaped ciliated mouths directly into the coelomic cavity.

To take the last first, it might be urged that the organism did not as yet depend upon the circulation entirely for the conveyance of metabolic products to the cells of the nephridial tubules, and that, even if it did, the funnels had not had time to degenerate; to which my reply is that tubules in direct communication with the exterior open by funnel-shaped mouths into the coeloms of the various orders right up to and including vertebrates, even the aminota, and this in spite of a continually improved and elaborated circulatory system. The obvious reason is that the coelomic fluid contains material which is better conveyed directly to the purifying cells of the nephridial tubules than through the systemic circulation. In the case of the earthworm it might still be true that a large part of the products of metabolism is thrown directly into the coelom and then extracted by the nephridia, but even a cursory examination of the higher orders would show that in their case this could scarcely be. The poison which contaminates the coelomic fluid is not the result of metabolism, but of bacteria which have permeated the intestinal wall; the cilia of the funnels guide this fluid down the tubule; the water, or part of it, now purified, is reabsorbed by the cells of the tubules into the general circulation, so that the coelomic fluid is cleaned of its poisons without risk to the body tissues. The earthworm has a partiality for what the gardener calls "fat stuff"—i.e., material teeming with bacteria of all kinds and grades of virulence—passing immense quantities of it through its alimentary tract in the course of its lifetime. I would have you believe that the single layer of ciliated epithelium and a few layers of chloragogen cells are not the only defence against the entrance of these hordes of bacteria into the body tissues. If they were, no earthworm would survive a day, and the result to the community would be appalling. Darwin has pointed out that these animals are an important agent in the formation of mould; I venture to add, in its purification also. On the contrary, they pass in their myriads, some killed, some maimed in the struggle with the first line of defence, into the coelomic cavity, where they are effectually dealt with by the amoeboid cells and the bactericidal fluid of the coelom. The particulate relics of both sides are swept out through the dorsal pore, not down the nephridial tube, the mouth of which is guarded by cilia which prevent the blocking up by such particles of the delicate slender tubule. The coelomic fluid is purified in the way I mentioned above. This, I think, explains the large size of the coelomic cavity in these scavengers, and the presence of the dorsal pore behind the pharyngeal segments, which, owing to the fact that there is no absorption by the thick-walled pharynx, and therefore no stagnation of foodstuff, would not require one. And herein lies the keynote of my theory. Around that portion of the alimentary tract where foodstuff containing bacteria is *stagnated* for the purpose of *absorption*, nature has developed a fluid-containing cavity designed for

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