The evidence so far produced and referred to shows that prenatal death is common and variable in several different groups of mammals, and as it occurs regularly in groups so widely separated, zoologically, as those mentioned, it is most probable that when further investigations are made it will be found to occur in all mammals, but in varying proportions in different groups.

Prenatal death, however, is not limited to mammals but is found also in birds, if death before hatching can be counted as prenatal.

Pearl's results point to a 20 per cent. prenatal mortality in his normal series inasmuch as he obtained 80 chicks from 100 eggs, and the experiments of Cole and Bachhuber indicate that prenatal death in fowls varies in amount with different matings.

It is clear, therefore, that prenatal death is a regular phenomenon in some groups of mammals and probably in all groups. It is equally clear that it is variable in amount in those groups in which it is present, in association with different matings. The variability is marked, and as it points to certain conclusions regarding the cause of prenatal mortality it must be considered in more detail. For this purpose the records of the Clydesdale and thoroughbred horses afford the most extensive data at present available.

The data given in Table II A show that in Clydesdales the variations extend from 0 per cent. to 100 per cent.; 9 stallions mated with 33 mares giving the former, and 7 stallions mated with 31 mares the latter result, whilst practically all the intermediate stages are found in association with one or the other of the 28,241 matings. In thoroughbreds the variations are...
less extreme, the limits being 34·78 per cent. in the case of one stallion mated with 46 mares and 98·07 per cent. in the case of one stallion mated with 52 mares.

The greatest number of matings in any one year which resulted in a prenatal mortality rate of 0·00 per cent. was 7, and the greatest number of matings which gave a prenatal death rate of 100 per cent. was 14; but the first result does not indicate that the stallion concerned was hyperpotent, nor the second result that the stallion concerned was impotent, but merely that the one had the good fortune to meet with seven mares in succession with which he was fertile, and the other the misfortune to meet with eleven mares in succession with which he was infertile; for the records show that when stallions are mated with a considerable number of mares in any one year one or more of them is infertile with as many as fourteen or more mares, and further it is certain that a stallion which was fertile with eleven successive mares in one year was infertile with more than eleven out of a larger number in another year. In this respect the record of the Clydesdale stallion numbered 10/14 is instructive. It shows the following results in four successive years. First year 27 matings, prenatal death rate 44·50 per cent. Second year 29 matings, prenatal death rate 51·80 per cent. Third year 11 matings, prenatal death rate 0·00 per cent. Fourth year 28 matings, prenatal death rate 46·50 per cent. In the third year, therefore, he met with eleven successive mares with which he was fertile, whilst in the other years, in the groups of mares with which he was mated, there were 12, 15, and 13 respectively with which he was infertile; therefore had he had the misfortune to meet with only those particular mares in any given year he would in that year have been associated with a prenatal death rate of 100 per cent.

It appears, therefore, that from breeding experiments alone, unless they were carried out on a very extensive scale, it would not be possible to say that any stallion, or probably any other male mammal, was impotent, for the thoroughbred stallion numbered 15/12 was mated with 52 mares with the production of only 1 foal, and the Clydesdale stallion numbered 3/27 was mated with 103 mares but only 10 foals were produced, that is, the first was infertile with 51 mares and the second with 93 mares, whilst Clydesdale stallion numbered 9/4 was fertile with only 18 out of 114 mares with which he was mated. On
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the whole the records show that whilst the extreme limits of the prenatal death rate are only met with when the number of matings is small, still very high death rates occur when the matings are numerous.

Relatively low as well as relatively high prenatal death rates are also found in association with numerous matings; for example, stallion numbered 6/23 was mated with 100 mares in two years with the comparatively low prenatal death rate of 16 per cent., and stallion numbered 13/20 was mated with 146 mares in the course of four years with a resulting prenatal death rate of 22.70 per cent.

The records contain no evidence which indicates the relative responsibility of the stallions as contrasted with that of the mares in association with the occurrence of high and low prenatal death rates, but the figures given in Table IV. indicate that certain stallions are regularly associated with a relatively high rate, others with a relatively low rate, and some with very variable rates in different years.

### Table IV.

| A. Clydesdale Stallions associated with a relatively high prenatal mortality rate. | B. Clydesdale Stallions associated with a relatively low prenatal mortality rate. | C. Clydesdale Stallions associated with a variable prenatal mortality rate. |
|---|---|---|
| **Stallions** | **No. of Mares.** | **P.N.M.R. per cent.** | **Stallions** | **No. of Mares.** | **P.N.M.R. per cent.** | **Stallions** | **No. of Mares.** | **P.N.M.R. per cent.** |
| 9/4 | 45 | 91.2 | 50-0 | 114 | 84.3 | 100 | 48.9 | 217 | 38.9 | 39.2 | 4/4 | 57 | 28.0 | 54.9 | 38.1 |
| 9/6 | 32 | 68.0 | 50-0 | 48 | 72-8 | 100 | 38.9 | 217 | 33-8 | 38-2 | 10 | 45 | 28.0 | 54.9 | 38.1 |
| 9/11 | 51 | 118 | 84.0 | 13/8 | 36 | 33-4 | 21 | 33-4 | 32-2 | 100 | 48.9 | 39.2 | 4/4 | 57 | 28.0 | 54.9 | 38.1 |
| 9/14 | 57 | 84.0 | 84.0 | 11/11 | 34 | 26-5 | 34 | 26-5 | 31-7 | 57 | 28.0 | 54.9 | 38.1 |
| 9/3 | 88 | 69.4 | 69.4 | 12/19 | 75 | 32-0 | 25 | 32-0 | 31-7 | 100 | 48.9 | 39.2 | 4/4 | 57 | 28.0 | 54.9 | 38.1 |
| 9/7 | 81 | 84.0 | 84.0 | 7/3 | 85 | 26-0 | 41 | 34.2 | 31-7 | 57 | 28.0 | 54.9 | 38.1 |
| 9/9 | 260 | 74.8 | 74.8 | 95 | 74 | 26-0 | 41 | 34.2 | 31-7 | 57 | 28.0 | 54.9 | 38.1 |

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The records of the thoroughbreds give similar results, some stallions being regularly associated with a high, some with a low, and some with a variable prenatal mortality rate in different years, the difference between the highest and lowest rate, in a series of four years, being in the case of one stallion 38.9 per cent.

The data concerning the Clydesdales and thoroughbreds show not only that in those two groups of horses prenatal mortality of shed ova is regularly present and large in amount, but also that the amount is variable in different matings and in association with the same male in different years when probably he was mated with a different group of mares.

The ferret data give no information regarding the variation of the prenatal death rate associated with different males, they merely show that a large amount of prenatal death takes place and that it varies in association with different matings, and Hammond's figures relating to swine and rabbits indicate that similar conditions occur in those two groups of mammals.

The occurrence and variability in amount of prenatal death in several groups of mammals is certain, its causation has yet to be considered; but although the explanation of the occurrence lies in great part in its variability, it is advisable before discussing the cause to inquire into where, when, and how the death takes place.

The Clydesdale and thoroughbred data give no help in this part of the inquiry, for none of the mares were killed, and after the completion of what appeared to be satisfactory service there was apparently no examination of the mares until the later months of gestation; further, there are no records of abortion.

Fortunately the ferrets provide answers to all three questions, and their evidence is confirmed, with regard to certain points, by Hammond's small series of swine and rabbits, by Corner's swine,6 by Huber's rats,12 and by Hill's marsupials, and in addition by some observations made by Meyer on intra-uterine absorption of ova,17 which show that the cause of prenatal death cannot in some cases be attributed to uterine disease.

In ferrets, when the ovarian follicles burst, the ova are usually carried by the rush of liquor folliculi into the middle third of the oviduct, where they meet the spermatozoa and in normal circumstances become fertilised.

The zygotes which are formed remain for five days in the oviduct, gradually passing towards its caudal end. At first they
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lie relatively close together, but generally separated by small intervals; as they pass caudally the intervals between them gradually become greater, and during the sixth day after extrusion they enter the uterine cornu in regular sequence.

During the next seven days those which entered the uterine cornua first pass caudally along the tube, and from the latter part of the thirteenth day to the end of the fourteenth day the chorionic part of the zygote begins to become attached to the decidua, the positions of fixation of the different ova being separated from one another by fairly regular intervals.

It follows, therefore, if the ova or zygotes in the oviduct, during the first five days after insemination, do not correspond in number with but are fewer in number than the corpora lutea in the ovaries, that either some of the ova have escaped into the peritoneal cavity, where they would disintegrate and become absorbed, or that they are retained in the peri-ovarial capsule, or that they have entirely broken down and disappeared, and the normal or abnormal appearance of those which are found in the oviduct is easily ascertained.

There is no reason to think that an extruded ovum would break down and entirely disappear in the course of five days either in the peri-ovarial capsule or in the oviduct, for degenerate ova which have failed to be fertilised, and degenerate young zygotes in the earliest stages of segmentation, are found in the uterine cornua several days later (Fig. 15, Plate III.). It must be assumed, therefore, that such missing ova have escaped into the peritoneal cavity in spite of the small and closely guarded orifice of the peri-ovarial capsule. The assumption is justifiable, not only because other causes of loss do not seem to be present but also because it is certain that ova can escape through the orifice of the peri-ovarial capsule, for as already shown, on the screen, I have been fortunate enough to secure one so escaping.

Occasionally ova fail to escape from the peri-ovarial capsule either into the peritoneal cavity or into the oviduct. I have three such specimens, and in two of the three the retained ovum is in a state of degeneration.

The number of ova which break down rapidly or escape into the peritoneum is considerable, though relatively small, for in ten selected ferrets killed during the first five days after the extrusion of the ova there were 94 corpora lutea in the ovaries and the ova and zygotes in the oviducts numbered only 79, therefore 15 out of the 94 extruded ova had
disappeared entirely, and as no trace of them was discoverable, it is practically certain that they escaped into the peritoneal cavity.

Some of the extruded ova which pass into the oviduct in ferrets do not become fertilised, either because, although apparently normal, they are structurally imperfect, or because they fail to meet the necessary spermatozoon, in spite of the fact that spermatozoa are present, and that other ova from the same ovary are fertilised (Fig. 13a, Plate III.). Such ova may remain surrounded by a degenerating corona radiata even after they have passed from the oviduct into the uterine cornu, as you have seen from specimens already shown, a condition which never occurs in association with normally developing zygote.

A few ova are penetrated by several spermatozoa and develop multiple pronuclei; such ova probably undergo degeneration at later periods, as in other animals under similar conditions, but naturally from the nature of the observations there is no proof that the suggested degeneration does take place in the case of ferrets.

Some ova die during the morula stage of development. In such cases there are no indications of anything abnormal in the oviducts or uterine cornua, and other zygotes of the same group are quite normal. It is not possible to ascribe the death of such zygotes to abnormal conditions of the mother, for the degenerate zygotes had not reached the period at which nutriment is absorbed from the maternal tissues, and nutriment, if any, derived from the surrounding fluid was as fully available to the degenerate as to the normal zygotes.

I have secured only one definitely abnormal specimen between the sixth and the thirteenth days of development, but I have several groups of zygotes between the sixth and the fourteenth day in which one or two are so much smaller than the others that their normality is doubtful although no obvious signs of degeneration were discoverable in them.

After the fourteenth day when the zygotes become attached to the decidua many cases occur in which one or more of the zygotes in a uterine cornu are obviously degenerate. In such cases the gestation chamber containing the degenerate zygotes is decidedly smaller than those adjacent to it which contain normal zygotes, and when sections of the smaller chamber are made it is always found that the zygote it contains is more or less degenerate or abnormal (Figs. 9a and 9b, Plate I.; Figs.
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10a to 12b, Plate II.; Figs. 16a, 16b, 17, 18a, and 18b, Plate III.)

In such cases there are no signs of inflammation. No micro-organisms are discoverable in the sections, and there are no indications that the blood supply of the portion of the cornu which contains the degenerate zygote is in any way different from the blood supply of adjacent gestation chambers which contain normal zygotes.

In ferrets, therefore, extruded ova die in the peritoneal cavity into which they have escaped; in the peri-ovarial sac from which they have failed to escape into the oviduct; in the oviducts; and in the uterine cornua.

They die when they are still ova, either because they are lost in the peritoneal cavity or because they fail to unite with spermatozoa although spermatozoa are present. They die after they have become zygotes, both in the morula stage (Fig. 15, Plate III.) and in the blastula stage (Fig. 10b, Plate II.) before they have become attached to the decidua. They die also after the blastula has become attached to the decidua and after the zygote has differentiated into embryo and appendages; thus the questions of when and where are answered.*

It is more difficult to decide how the zygotes die, but it is always apparently by alterations of their structure, which ends in disintegration.

Whilst the ova are still unfertilised and in the zygote stage, up to the end of the morula period, death is indicated in the ferret by the osmic blackening lipoid material, which is always present in large amount, losing its regular arrangement of spheres of varying but moderate size and running into large irregular masses, and by vacuolation of the nuclear and protoplasmic substance, by nuclear and cellular lysis, and by irregular segmentation.

In the later stages malformations of the germinal area, abnormal adhesion of the zygote to the decidua or absence of the germinal area (Fig. 11b, Plate III.), and nuclear and cellular lysis end in ultimate general disintegration.

The death is not due to inflammation or to micro-organismal attack, but apparently simply to an incapability to live and develop properly under conditions which are quite favourable to immediately adjacent zygotes.

* See Figs. on Plates I., II., and III., which are a few selected from the specimens shown during the lecture.

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Similar conditions have been found in various other groups of mammals.

In Dasyurus, amongst the marsupials Hill,\textsuperscript{11} as already noted, states that he met with a group of 35 ova of which 12 were abnormal, and the cleavage abnormalities which he mentions in other cases would most probably have resulted in death at a later period of gestation.

Stockard\textsuperscript{22} notes that many of the zygotes which must have been present in the gestation chambers which he was able to palpate in his guinea-pigs in the earlier periods of pregnancy failed to produce living young.

Corner\textsuperscript{6} has seen degenerate zygotes in swine in the period before the attachment of the decidua had commenced.

Hammond\textsuperscript{10} found that 15 out of 107 embryos in the uteri of seven sows were atrophic, and his figure of one uterus shows either that the atrophy had commenced at different periods in different embryos, or that it had proceeded more rapidly in the case of some embryos than in others.

Hammond also found that in a series of 38 rabbits, 82 of the 307 zygotes were atrophic, and he is satisfied that the atrophy both in pigs and rabbits was not due to the action of micro-organisms. He notes that in addition to the atrophic zygotes other ova had been shed of which he could find no trace in the uteri, and he suggests that such ova must have wandered into the body cavity; further abnormal morulae and gastrulae have been described in rats by Huber,\textsuperscript{12} and Meyer\textsuperscript{17} found degenerate guinea-pig embryos whose death could but be attributed to uterine causes.

It is obvious from the records quoted not only that prenatal death occurs in many groups of mammals, but also that it occurs in apparently the same way in all the groups in which it has been noted, in different parts of the oviducts and uterine cornua, and at all the different periods of gestation.

In all cases the death is preceded by obvious degeneration or abnormal development, and there is no indication that it is due to bacterial action, whilst the possibility of poisons in the maternal blood or secretions is eliminated by the fact that the majority of the zygotes in multiple pregnancies develop normally, and only a minority, as a rule, die prematurely.

The positions and the time of prenatal death are not difficult to discover, but its cause is more elusive.

The causes which naturally suggest themselves are: the con-
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dition of health of the parents; the environment of the parents; the food of the parents; the age of the parents; excessive use of the male; the environment of the gametes and zygotes; the nutrition of the gametes and zygotes; the constitution of the gametes; the constitution of the zygotes.

In the case of the horses the stallions were certified to be healthy, and there is no reason to suspect the health of the mares.

The ferrets, both male and female, were all healthy animals.

The environment of the stallions and mares was that which they and their ancestors for many generations have been accustomed to, and the same can be said with regard to the ferrets, with the exception of those which were fed and mated in my laboratory.

There is no evidence concerning the condition of most of the animals used by other observers, but presumably they were healthy and were kept in normal environment, whilst Stockard's control guinea-pigs were certainly healthy and they were kept in healthy surroundings.

As the general bodily condition of the horses and ferrets was good, it certainly could have no detrimental effect on their gametes or zygotes; and as the ferrets dealt with in the laboratory gave results similar to those given by the animals provided by the breeders, under whose control the environment was that to which the animals and their ancestors were accustomed, there is no reason to assume that the environment of the parents caused either the prenatal mortality or its variations, unless it is assumed that the environment in which the animals in question now live is not that to which their far-away ancestors were accustomed, and that if the original conditions were returned to the prenatal mortality might perhaps disappear. Such a suggestion, however, is negatived by the fact that atrophic and dead embryos have been found in the uteri of wild animals such as rabbits (Hammond), moles, and hamsters (Strahl and Henneberg, 1902).

The question of food would scarcely have needed mention had it not been that the records of the Clydesdales extend from 1913 to 1918 inclusive, and those of the thoroughbreds from 1913 to 1917 inclusive, that is over one pre-war and several war years, whilst in addition the prenatal mortality rate of the thoroughbreds was less in 1913 than in any other year.
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The yearly results of the thoroughbreds are shown in Table V.

Table V.—Thoroughbreds.

| Year | No. of Stallions | No. of Mares | P.N.M.R. per cent. |
|------|-----------------|--------------|-------------------|
| 1913 | 12              | 659          | 52-04             |
| 1914 | 14              | 769          | 58-77             |
| 1915 | 14              | 864          | 57-75             |
| 1916 | 15              | 748          | 62-16             |
| 1917 | 12              | 600          | 62-83             |

The difference between the results in 1913 and those in the succeeding years made it necessary to institute inquiries into the matter of food, and Mr James Wood informed me that there was no reason to think that the food in any of the war years differed from that of the pre-war period, except with regard to the amount of bran. It is improbable that a difference in the amount of that substance could have any appreciable effect on the prenatal mortality rate, inasmuch as it did not affect the health of the parents, or presumably alter the blood contents of the mother to any appreciable extent. Moreover, the yearly records of the Clydesdales, shown in Table VI., demonstrate that in their case the prenatal mortality rate was less in 1916, 1917, and 1918, than it was in 1913 and the two succeeding years.

Table VI.—Clydesdales.

| Year | No. of Stallions | No. of Mares | P.N.M.R. per cent. |
|------|-----------------|--------------|-------------------|
| 1913 | 56              | 1903         | 48-34             |
| 1914 | 87              | 3029         | 50-54             |
| 1915 | 137             | 6988         | 49-39             |
| 1916 | 154             | 5327         | 46-56             |
| 1917 | 144             | 5332         | 46-02             |
| 1918 | 130             | 5662         | 46-23             |

It appears, therefore, that in horses the variations of the prenatal death rate are not dependent on the food supply of the parents, and the same may be said of the ferrets, for they were fed on the food to which they were accustomed. The other mammals afford no evidence upon the point.

As regards the age of the parents, it is stated that the fertility of mammals varies with their age, and according to Matthews Duncan7 “the initial fecundity of women gradually
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waxes to a climax and then gradually wanes,” and Marshall states that “there can be no doubt that animals, as a general rule, tend to follow a similar law,” whilst Wallace says that sows ought to rear six to eight young in their first litter and ten to twelve in each succeeding litter. Minot found that in guinea-pigs the size of the litters increased with the age of the parents, during the first sixteen months of their lives, and Hammond (1914), quoting from the results obtained by Mr P. G. Bailey, states that in rabbits the litters increase, at all events from the first to the third, but there is no evidence to show whether the results obtained were due to greater production of mature ova during the period of increase or to diminution of the prenatal death rate. Hammond appears to assume that the result is due to increases of ovum production, for he asserts that it appears that fertility can be modified to a certain extent by improving the nutrition of the ovary, and in support of his contention he quotes the results obtained by Marshall, in the case of ewes. Marshall found that “flushing” caused increased fertility, “probably due to the maturation of more follicles.”

The question raised is interesting and discussable, but in the meantime it is of no direct importance for the purpose in hand, which is not to show how ovum production is affected by age or special feeding of the mother, but to discover if possible the cause of prenatal death in the case of ova known to have been extruded. There is, however, an age factor, the age of the male, which presumably might have bearing upon the prenatal death rate, and with regard to this point the records of the Clydesdales fortunately afford evidence, for the ages of all the Clydesdale stallions are known; they vary from three to nineteen years, and the results of their matings at different periods of age are shown in Table VII.

It is obvious from the table that between the ages of four and eighteen years, in the case of Clydesdales, the age of the stallion is not associated with any essential difference in the prenatal mortality rate, and when the disproportion in numbers of the stallions of different ages is taken into account it does not appear that the age of the stallion has any appreciable effect upon the variations of prenatal mortality, except perhaps there is less variation in different matings when older stallions are used than when younger stallions are employed. This result is in accord with the general knowledge that there is no definite ending of the reproductive period in male animals.
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Table VII.

| Ages of Stallions in years | No. of Stallions | No. of Mares with which they were mated | P.N.M.R. per cent. |
|---------------------------|------------------|----------------------------------------|--------------------|
|                           |                  |                                        |                    |
| 3                         | 207              | 6546                                   | 52·1               |
| 4                         | 150              | 5999                                   | 48·0               |
| 5                         | 105              | 4512                                   | 46·6               |
| 6                         | 76               | 3412                                   | 48·3               |
| 7                         | 55               | 2026                                   | 45·0               |
| 8                         | 42               | 1795                                   | 43·7               |
| 9                         | 28               | 1069                                   | 50·5               |
| 10                        | 20               | 1021                                   | 46·2               |
| 11                        | 9                | 531                                    | 46·2               |
| 12                        | 7                | 459                                    | 39·0               |
| 13                        | 6                | 315                                    | 45·4               |
| 14                        | 4                | 84                                     | 41·7               |
| 15                        | 6                | 337                                    | 45·2               |
| 16                        | 4                | 158                                    | 46·9               |
| 17                        | 3                | 41                                     | 48·8               |
| 18                        | 3                | 98                                     | 49·0               |
| 19                        | 1                | 38                                     | 63·2               |

It has been suggested that excessive use of the male is a possible cause of sterility, fertilisable ova perishing because of the exhaustion of the male. The material at my command does not enable me to say whether or not there is any basis for the suggestion, but the records of the Clydesdale stallions show that the number of matings in a season must be very large before any such result follows. In Table VIII, the lowest and highest number of matings of selected individual stallions in different years are given, together with the accompanying percentage of prenatal death rates.

Table VIII.

| Stallions | Lowest Number of Matings | P.N.M.R. per cent. | Highest Number of Matings | P.N.M.R. per cent. |
|-----------|---------------------------|--------------------|----------------------------|--------------------|
| 1/3       | 23                        | 34·8               | 97                         | 22·7               |
| 2/1       | 21                        | 52·4               | 103                        | 41·8               |
| 5/11      | 63                        | 60·4               | 106                        | 51·0               |
| 5/15      | 31                        | 51·7               | 131                        | 47·4               |
| 3/19      | 24                        | 50·0               | 103                        | 33·1               |

The stallions noted in the above table are chosen because they show the greatest differences between the lowest and highest number of matings in different seasons, and the results, so far as they go, seem to indicate that an increase in the
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number of matings up to 131 in one season tends to reduce the amount of prenatal mortality associated with a given stallion.

A somewhat similar though less definite indication is obtained when the matings are grouped in increasing numbers as in Table IX.

| No. of Matings in one Season | No. of Mares | P.N.M.R. per cent. | No. of Matings in one Season | No. of Mares | P.N.M.R. per cent. |
|-----------------------------|--------------|--------------------|-----------------------------|--------------|--------------------|
| 1 to 10                     | 718          | 45.1               | 71 to 80                    | 1794         | 47.0               |
| 11 to 20                    | 1828         | 48.0               | 81 to 90                    | 3038         | 50.0               |
| 21 to 30                    | 2338         | 46.3               | 91 to 100                   | 1708         | 47.0               |
| 31 to 40                    | 3252         | 49.1               | 101 to 110                  | 1260         | 46.0               |
| 41 to 50                    | 3429         | 48.0               | 111 to 120                  | 346          | 37.0               |
| 51 to 60                    | 3617         | 48.0               | 121 to 130                  | 374          | 40.0               |
| 61 to 70                    | 4137         | 52.0               | 131 to 140                  | 402          | 41.0               |

Although Tables VIII. and IX. do not show that exhaustion of the male is not a possible cause of increase of the prenatal death rate, they do show that the use of the male before such exhaustion occurs must be very excessive, and that exhaustion of the male cannot be considered as a potent factor either in the production of prenatal death or in the production of its variations.

With regard to the environment of the gametes as a possible factor in the production of prenatal death, their normal surroundings are the tissues of the genital glands and the walls of the genital passages of the parents, and in healthy animals both groups of organs would presumably be healthy.

It has already been stated that the Clydesdale and thoroughbred stallions were certified healthy, and in the case of the male gametes, therefore, there is no reason to doubt that the gametal environment was normal. As regards the mares there is no evidence, but as none of them are noted as unhealthy it may be assumed that they were healthy and that the surroundings of their ova were normal.

In the case of the ferrets there is no doubt about the normal environment of the gametes, for post-mortem examination both macroscopical and microscopical demonstrated the healthy condition of the ovaries and female genital passages, whilst the males which were used in the laboratory were young and vigorous, and histological examination of their testicles
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proved that those glands were perfectly developed and in full functional activity.

The males used by the breeders were, of course, not killed, but there is no reason to believe that they were not healthy, for the results obtained by their use as before stated were the same as those associated with the males used in the laboratory.

With regard to the nutrition of the gametes and the nutrition of the zygotes, at all events up to the time when the latter become attached to the uterine decidua, we possess very little knowledge, but as we are dealing at present, in the case of the horses, only with parents which were healthy it may be assumed that the nutrition of the gametes and young zygotes was normal; moreover, it is quite certain in the case of the ferrets that the fluid contents of the oviducts and uterine cornua were normal, and that the contents of the efferent ducts of the males used in the laboratory were also quite normal.

It is also certain, in the case of the ferrets, that the fluid contents of the oviducts and uterine cornua were not the cause of the death of the extruded ova and the young gametes which were found in a state of degeneration, for dead and normally developing ova and young zygotes were found in the same passages and therefore in the same fluid surroundings.

There is no reason to believe, therefore, that under ordinary circumstances the prenatal death rate is influenced by the fluid contents of the oviducts and uterine cornua, nor is there any reason to suppose that the death of the zygotes which have become attached to the uterine decidua is caused by any interference with their nutrition due to the condition of the decidua, for in ferrets a dead zygote or degenerate zygote is frequently situated between two normal zygotes, and there is no evidence that the blood supply of the walls of the gestation chamber of the dead zygote differs in any way from that of the blood supply of the walls of the adjacent gestation chambers.

As prenatal death occurs regularly in healthy animals placed in normal surroundings, and it is not, apparently, influenced by the food of the parents, the age of the parents within certain limits, or by the very frequent use of the male, and as it is practically certain that in healthy animals the nutrition and environment of the gametes and zygotes is normal, the inevitable conclusion is that the cause of the death which overtakes more than 50 per cent. of the extruded ova of thoroughbreds, 48 per
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cent. of the extruded ova of Clydesdales, and probably not less than 35 per cent. of the extruded ova of ferrets, is due to the constitution of the gametes and zygotes.

In Clydesdales and thoroughbreds there is no reason to suppose that the extruded ova and spermatozoa were not normal. In ferrets I have never seen in a mature and normal ovarian follicle an ovum which did not appear to be normal in constitution, and the spermatozoa which were found in the oviducts were in all cases normal in appearance.

In ferrets some, but relatively few, ova escape into the peritoneal cavity and there disappear; they therefore add a little to the prenatal death rate, but not more than 5 per cent. at the most, though in other mammals, not provided with periovarial capsules, the loss by escape into the peritoneal cavity may be relatively greater than in ferrets. It is clear also in the case of ferrets that some of the extruded ova fail to unite with spermatozoa although spermatozoa are present, that other ova which show multiple pronuclei are probably penetrated by several spermatozoa and so form polyspermic zygotes which presumably die, but the ova which fail to unite with spermatozoa and those which form polyspermic zygotes are relatively very few.

The majority of the extruded ova become zygotes, and of those the majority which die in the prenatal period die after they have become attached to the decidua, that is from the fourteenth to the forty-second day of gestation. The death rate of ferrets' ova during the first thirteen days after insemination appears to be about 20 per cent., whilst the rate during the remaining period of twenty-nine days is about 30 per cent., and the greater part of the prenatal death rate is due to the death of zygotes.

The ferrets show that some ova, though they are apparently normal, are nevertheless incapable of uniting with some spermatozoa, and that other ova, although they are capable of uniting with spermatozoa which are present, form, by the union, zygotes which are incapable of living to the end of the prenatal period under circumstances which appear to be quite normal and in which other ova and spermatozoa form zygotes from which viable young are evolved.

The records of the Clydesdale and the thoroughbreds, on the other hand, show that the spermatozoa of certain stallions are incapable of uniting with the ova of some mares to produce
viable young, whilst they produce normal zygotes which give rise to normal viable young with the ova of other mares.

The conclusion to which the evidence available points is that the alteration of the constitution of the ova and spermatozoa which is so favourable for the production of the individual variations that are such a constant feature of animal life, and which presumably takes place during the maturation of the gametes, is also the cause of the formation of many gametes whose capability for union with gametes of the opposite sex is limited, and of others whose union with gametes of the opposite sex results only in the formation of abnormal zygotes, that is zygotes incapable of evolving a new individual devoid of visible abnormality and capable of living through the normal period of life of an individual of its species, under the ordinary circumstances and in the absence of accident, micro-organisinal attack, and artificial acid. It is therefore a structural peculiarity of the gametes which is the cause of sexual incompatibility.

Most probably some of the gametes of each sex are modified in the way suggested during the maturing divisions, and those of some individuals more than others. The experiments of Cole and Davies, by double mating with rabbits, point to differences of the spermatozoa as a more potent cause than differences of ova. They mated an albino male and a pigmented male, sometimes the one first, sometimes the other, with the same females, and as a result of the twenty-three double matings young were born of which only 24 were albinos; obviously, therefore, more spermatozoa of the pigmented male than of the albino were capable of forming fertile unions with the ova of the females used.

The data provided by horses and ferrets, supplemented by those which can be gleaned from notes made with regard to other mammals, point therefore to the conclusion that a large amount of the prenatal death which occurs in mammals is normal, that it is not dependent upon disease of the parents, detrimental environment, insufficient nutrition, or disease of the gametes, but is, in a sense, a side issue of the process which gives rise to the variations which appear so universally in all mammals and probably in all living beings.

It has already been noted that the prenatal death rate of the extruded ova of Clydesdales is 48 per cent., that of thoroughbred ova 58·68 per cent. In the case of ferrets the rate appears to be about 35 per cent., and it is apparently about
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the same in swine, but in the case of the latter animals the data are not sufficient to justify a definite conclusion. In rabbits, so far as data are obtainable, the rate appears to be somewhat over 37 per cent. There is then no doubt that the rate of prenatal death is high in several groups of mammals.

As the prenatal death rate is undoubtedly high in several groups of widely different mammals, there is every reason to believe that it will eventually be found to be not less high in other groups, including man.

If prenatal death is constant and normal, the obvious corollary is that in some animals abortion also is normal.

The abortion of ova which have failed to be fertilised, and of young zygotes which have died before becoming attached to the decidua, will, in many cases, be unnoticed, for it will occur without causing any definite inconvenience to the female, whilst thereafter the mucous membrane of the uterus will return quickly to the condition favourable for a new conception; but if the death of the zygote occurs after the attachment to the decidua has commenced, and still more if after the attachment is completed, the conditions are more complicated and are likely to result in more definite inconvenience.

The continuance of gestation after the attachment of the zygote to the decidua depends not only upon the normal development of the zygote but also upon the normal development of the decidua, the latter being controlled by the growth and development of the corpora lutea.

If any zygote dies after the fixation period, the gestation, so far as it is concerned, is brought to a termination, and it is necessary for the maintenance of the normal birth rate that it—the dead zygote—shall be removed as soon as possible.

The removal is provided for differently in different groups of mammals. In those which produce multiple young at birth the dead zygotes, in all but the latest stages, are absorbed, for any other process would result in the death of some or all of the other zygotes, and the birth rate of the group would be considerably reduced in view of the fact that, in animals which have multiple young, the death of one or more of the zygotes is of frequent occurrence, as is shown by the results noted in ferrets, swine, and rabbits.

As soon as the zygote dies, its influence on the decidua ceases; that membrane no longer furnishes nutriment to the zygote, and it is no longer preyed upon by the zygote; on the contrary, it...
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absorbs the degenerated and disintegrated zygote, and then returns to the condition of the ordinary mucosa of the intervals between the gestation chambers.

Absorption, however, takes a very considerable time, and it would obviously be detrimental to the birth rate of animals which have a long gestation period, and which only produce one young at each birth period, as in the case of the human subject. In such cases, therefore, death of the zygote is followed, as a rule, very quickly by abortion, and thereafter, in a comparatively short time, the uterine mucosa regains a condition favourable for a new gestation.

As soon as the zygote is dead, changes occur in the decidua such as those which Mall found in human uteri. (Compare Figs. 9a and 9b, Plate I., and Figs. 12a and 12b, Plate II.) Such changes are commonly attributed to degeneration or disease of the decidua, and are looked upon as the cause of the death of the zygote. There is no doubt that disease of the decidua may cause death of the zygote, but in all those cases of abortion which occur in association with healthy animals the cause is the death of the abnormal zygote, and the changes in the decidua are not properly described when they are termed degenerative; they might more correctly be termed regressive, for they are adapted to bring about, as soon as possible, a normal prooestral condition of the uterine mucosa.

In view of the very general belief expressed by obstetricians that abortion is abnormal and is very frequently due to disease, and the popular belief that the human birth rate ought to be very much higher than it is, behind which lies the further belief that every ovum under favourable conditions should produce a living child, the conclusions derived from the investigation of healthy animals under normal conditions may be looked upon as possessing some practical importance—at all events they must be taken into consideration when any estimate is being made of the possible birth rate of any given group of animals.

The four chief conclusions to which the evidence produced points are:

1. That some sterility is normal and unavoidable.
2. That a considerable amount of prenatal death is normal or usual, and, under ordinary circumstances, cannot be avoided.
3. That a considerable number of abortions are not only normal but necessary, for they are adapted to prevent diminution of the birth rate.
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(4) That the condition of the uterine mucosa associated with normal abortions is not degenerative or diseased, but normal, and that any treatment of it is not only unnecessary but will probably also be detrimental.

If we assume that every 100 married human females should produce each year 100 children, then I find from data very kindly given to me by Dr Newsholme and the Registrar-General for Scotland that the prenatal death rate in association with married women between the ages of 15 and 45 years in England for the period 1876-1880 was 70.3 per cent. It had increased by 1910 up to 78.71 per cent. In Scotland in 1908 it was 74.96 per cent., and in 1917 it was 81.89 per cent.

Unfortunately we have no knowledge and no means of ascertaining what the normal human prenatal death rate is, but if we assume it to be somewhere about 40 per cent., which is probably below the actual amount, then in England, in 1910, 38.71 per cent. of the whole was not normal, and in Scotland, in 1917, 41.89 per cent. was not normal; therefore of the total prenatal mortality rate of extruded human ova placed in favourable circumstances for fertilisation, about half, presuming the normal rate to be 40 per cent., is due to causes which are in a sense unavoidable, and no treatment of the mothers either general or local will do any good, whilst it may do much harm.

The present communication is not concerned with the remaining and avoidable part of the prenatal mortality, but it must be pointed out that the assumption that the prenatal mortality rate of human beings is 40 per cent. is only based on indications given by horses, ferrets, swine, and rabbits. It may be lower or higher, but is more probably higher than lower, for human beings are living in much more artificial conditions than are the other animals mentioned, and they are more exposed, under present-day conditions, to agencies which have a detrimental effect on the gametes and zygotes.

It is well known that high velocity rays have a detrimental effect on gametes.

Alcohol given to guinea-pigs and fowls by inhalation is injurious to the gametes, even to the third and fourth generation of the descendants of those treated; it is therefore quite possible that, taken in other ways, it is also injurious (Stockard, Cole and Davies).

Lead administered to the male reduces the birth rate of both rabbits and fowls (Cole and Bachhuber).
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So far experiments of importance have only been made with alcohol, lead, and high velocity rays, and it is quite possible that many substances used as foods, drinks, and condiments may prove harmful to gametes and zygotes when taken in excess. It is not improbable, therefore, that the normal human prenatal death rate associated with the conditions under which we are now living, is higher than 40 per cent. That, however, at present, is a mere speculation.

**Summary.**

(1) A considerable amount of prenatal death is normal in mammals.

(2) It is due partly to the inability of the gametes of certain individuals to unite with one another and partly to the production of abnormal zygotes by the union of certain gametes.

(3) The inability to unite, and the production of abnormal zygotes when union occurs, are not dependent on disease or abnormal environment of the parents.

(4) When prenatal death occurs, as it does in many cases, after the zygote has become attached to the decidua the death must be followed by the absorption or the abortion of the zygote.

(5) Abortions which follow normal prenatal death are themselves normal, and the changes found in the uterine mucosa in such cases are regressive and useful, and not inflammatory or degenerative.

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EXPLANATION OF PLATES I.-III.

PLATE I.

Fig. 1. Uterine cornu of a ferret in the 13th day of gestation, showing normal and abnormal gestation chambers. The chamber most to the front on the left side of the fig. contained a degenerate zygote. § natural size.

Figs. 2a and 2b. Opposite views of a uterine cornu of a ferret in the 14th day of gestation. In 2a two small gestation chambers which contained degenerate zygotes are seen. In 2b a normal chamber is shown; it lies midway between the two abnormal chambers. § natural size.

Fig. 3. Part of a uterine cornu of a ferret in the 15th day of gestation, showing a normal and an abnormal gestation chamber. § natural size.

Fig. 4. Portions of a uterine cornu of a ferret in the 16th day of gestation, showing four normal and one abnormal gestation chamber. § natural size. See also Figs. 9a and 9b.

Fig. 5. Uterine cornu of a ferret in the 22nd day of gestation, showing four normal and one abnormal gestation chambers. § natural size. See also Figs. 12a and 12b.

Fig. 6. Part of a uterine cornu of a ferret in the 23rd day of gestation, showing one normal and two abnormal gestation chambers. § natural size.

Fig. 7. Part of a uterine cornu of a ferret in the 28th day of gestation, showing two gestation chambers which contained normal embryos, and one chamber which contained an abnormal embryo. § natural size.

Fig. 8. Part of a uterine cornu of a ferret in the 31st day of gestation, showing two gestation chambers which contained normal embryos and one chamber which contained an abnormal embryo. § natural size.

Fig. 9a. Section through the ventral part of one of the normal gestation chambers seen in Fig. 4. In the lower or ventral part of the fig. a transverse section of

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the embryo is seen. Below and on each side of the embryo is part of the placenta, showing the normal arrangement. × 4. Haematoxylin eosin.

FIG. 9b. Section through the abnormal gestation chamber seen in Fig. 4. A part of the remnant of the zygote is seen in the form of two triangular black dots with connecting lines. Below the remains of the zygote is the regressive placental area. × 4. Haematoxylin eosin.

PLATE II.

FIG. 10a. Section through a gestation chamber of a ferret in the 15th day of gestation. The chamber contains a degenerate zygote. × 4. Osmic preparation, unstained.

FIG. 10b. Part of the gestation chamber shown in Fig. 10a. × 20. The degenerate zygote is a small vesicle with no definite embryonic area. Compare with Fig. 10d.

FIG. 10c. Section through part of a normal gestation chamber from the same uterine cornu as the preparation shown in Fig. 10a. × 4. Osmic preparation, unstained.

FIG. 10d. The ventral part of the gestation chamber seen in Fig. 10c. Showing a transverse section of the normal embryonic area and the normal structure of the placenta.

FIG. 11a. Section through an abnormal gestation chamber from a uterine cornu of a ferret in the 15th day of gestation, showing the ventral part of the zygote fused with the ventral part of the wall of the placental area of the gestation chamber. × 4. Osmic preparation, unstained. Compare the size of the ventral part of the placental area with that of the corresponding region of the normal gestation chamber shown in Fig. 11c.

FIG. 11b. The median part of the ventral wall of the gestation chamber shown in Fig. 11a. × 20. The embryonic area is absent, and the placental part of the chorion is fused with the ventral wall of the gestation chamber instead of with the sides only, which is the normal condition at the 15th day.

FIG. 11c. Part of a normal gestation chamber, from the same uterine cornu as the specimen seen in Fig. 11a. × 4. Osmic preparation, unstained.

FIG. 11d. The ventral part of the gestation chamber shown in Fig. 11c. × 20. The embryonic area of the zygote is distinct, and at each side of the placental part of the chorion is fused with the placental area of the uterine mucosa. In the specimen shown the embryonic mesoderm has separated from the placental part of the chorionic ectoderm on the left side of the preparation, and at each side of the embryonic area the amniotic ectoderm has broken off from the chorionic ectoderm, the rupture being due to shrinkage during the preparation of the specimen.

FIG. 12a. Normal placenta, from part of one of the normal gestation chambers shown in Fig. 5. 22nd day of gestation. × 20. Haematoxylin eosin.

FIG. 12b. Part of the regressive placenta from the abnormal gestation chamber shown in Fig. 5. × 20. Haematoxylin eosin.

PLATE III.

FIG. 13a. Section of an abnormal unfertilised ovum, from the uterine cornu of a ferret killed sixty-eight hours after insemination. The ovum is surrounded by the remains of the corona radiata.

All the nuclear structures which would have been present in a normal ovum have disappeared. × 200. Iron haematoxylin. Compare with Fig. 13b.

FIG. 13b. Section of a normal zygote, from the same uterine cornu as the ovum shown in Fig. 13a. × 200. Iron haematoxylin. The zygote is in the eight cell stage, but parts of only three cells are seen in the section.

FIG. 14. A normal blastocyst, from a uterine cornu of a ferret killed six days after insemination. × 200. Iron haematoxylin.
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Fig. 15. A degenerate zygote, from a uterine cornu of a ferret killed fifteen days after insemination. × 200. Iron haematoxylin. The black masses around the oolemma are the remains of the persistent and degenerated corona radiata.

Fig. 16a. A portion of the ventral part of a normal gestation chamber of a ferret in the 17th day of gestation. × 4. Haematoxylin eosin.

Fig. 16b. A portion of the ventral part of an abnormal gestation chamber, from the same uterine cornu as the specimen shown in Fig. 16a, showing an abnormal embryonic area with a blastoporic aperture in the middle of the embryonic region. × 4. Haematoxylin eosin. Compare with Fig. 16a.

Fig. 17. A portion of the ventral part of an abnormal gestation chamber from another ferret in the 17th day of gestation, showing a blastoporic aperture in the middle of the embryonic region. × 4. Haematoxylin eosin.

Fig. 18a. Part of the ventral portion of a normal gestation chamber of a ferret in the 17th day of gestation, showing a section of the caudal part of the embryo and the allantoic diverticulum from the hind-gut. × 20. Haematoxylin eosin.

Fig. 18b. Section through an abnormal gestation chamber, from the same uterine cornu as the specimen shown in Fig. 18a, showing the abnormal narrowness of the gestation chamber, and the rudimentary condition of the caudal part of the embryo and the allantoic diverticulum from the hind-gut. × 20. Haematoxylin eosin.