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Part I.—Original Articles.

The Problem of Heredity, with Special Reference to the Pre-Embryonic Life.(1)

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PART I.

Introductory.

SCIENCE, whose high aim it is to investigate Nature, to understand her secret workings, and thus to win for man the mastery of Nature, must set out with the conviction that Nature is intelligible, comprehensible, and conquerable. In the domain of biological science the problem of heredity occupies a position of great importance, one full of interest to every student of life. For the serious thinker who has not only looked backwards and studied the past of the human race but is inspired by ideals and desires for its future good, the subject of heredity provides an inspiring theme for contemplation and study. The development of our knowledge and the history of human endeavours to reach a complete understanding of the phenomena and conditions of heredity form one of the most interesting chapters in human evolution. Theories of heredity, like theories regarding other phenomena of life, have been

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expressed in three sets of terms: theological, metaphysical, and scientific. It required no skilled observation of early man to see that in the act of fecundation the male furnished the seminal substance, whereas the female seemed to furnish nothing except the receptacle or "mould," in the form of the womb, within which the fœtus was formed. Thus, what was more natural than to suppose that heredity was solely paternal, that the male element was the germ or seed, and the female organs the soil, in which, by some mysterious process, growth and development of the germ took place. This view of heredity has been expounded in the *Manava Dharma-Sastra*, one of the ancient sacred books of the Hindus (Delage, *L'hérédité*, 1903, p. 380). The same view, more or less modified according to the prevailing state of knowledge, was current among the ancient Greeks (Eristratos, Diogenes, and others). Galen and the school of philosophers of Alexandria also upheld the doctrine of the paternal factor of heredity, and thus constituted themselves the school of the Spermatists. Spermatist views prevailed for many centuries, and when towards the close of the seventeenth century Leeuwenhoeck discovered the presence of spermatozoa by the aid of the microscope, the spermatists had a season of rejoicing. Hartsoeker (1694) supposed that within the spermatozoon there was a little being, a human being, in miniature, with all its parts and organs complete, and figured a spermatozoon (highly magnified, of course) in which the little "homunculus" is to be seen seated within the "head" of the former with its arms and legs folded together in small compass, somewhat like a fœtus *in utero*. The theory of the spermatists was not destined to remain in undisputed possession of the field. The rival school of Harvey in the sixteenth century taught that the semen or sperm did not fertilise the ovum nor even enter the womb, but that it fertilised the entire constitution of the mother by a sort of contagion which rendered her capable of acting as the stimulus of development for the ova in the uterus, and Descartes, in the early part of the seventeenth century, entertained the same views. The ovists now claimed that all the organs of the future being already existed, preformed in miniature, in the ovum, as opposed to the spermatists, who claimed the same preformed structure for the spermatozoon. To the ovists, therefore, the act of fecundation was only an impulse or stimulus to development communicated by the male

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element to the ovum ; the male contributed nothing material in forming the parts and organs of the fœtus which existed, preformed in the ovum, so that the child was the product of the mother alone. Among the upholders of the ovist theory in the eighteenth century were Malpighi, Haller, Bonnet, and Spallanzani. Difficulties, however, arose over both these theories of exclusive inheritance, for the ovists could not explain how the offspring sometimes resembled the father rather than the mother, and the spermatists could not account for cases of close resemblance between the mother and offspring, while neither could, again, account for cases of the mixed or blended resemblance of the offspring to both parents. The theory of preformation gradually lost its interest and its vitality, and received its death-blow at the hands of Wolff (1759), who, not only by theoretical arguments but by indisputable facts as to the nature and process of development of the hen's egg, demonstrated the baselessness of the fancies of the pre-formationists, whether of the spermatic or ovarian school. Finally, there gradually grew up in the nineteenth century the modern view that the male and female (germ and sperm) cells of the respective parents contributed in equal, or nearly equal, proportions to the constitution of the embryo, and that the environment and nourishment of the fertilised ovum during its growth and evolution in the womb was a third factor of importance, especially in the case of those animals which went through a long period of intra-uterine growth and evolution, as in the case of man and the higher mammals.

The problem of heredity was roused to life from its slumbers by the embryological work of von Baer in the early half of the nineteenth century, by the philosophical inquiries of Herbert Spencer and the biological observations of Darwin in the sixth decade of the nineteenth century, and by the pathological investigations of Morel during the same period.

Significance of Heredity.

The term " heredity " connotes and comprises a number of so-called " laws " or generalisations drawn and formulated from a vast body of facts in human experience. Thus it has been observed from time immemorial that plants produce seeds and seedlings " after their kind "—that is, closely resembling the

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parents in their general features of form and function and in many special features also ; that animals produce young after their kind ; and that man begets offspring which are the image and likeness of himself. These are facts of universal experience, and constitute a universal belief of mankind. Authors have sometimes dwelt on the subject and endeavoured to trace in their own inborn traits and peculiarities the characters of their parents. Thus says Goethe :

"Vom Vater hab' ich die Statur,
Des Lebens ernstes Führen ;
Vom Mütterchen die Frohnatur,
Die Lust zu fabuliren."

This constitutes the positive aspect of heredity. But a negative side also exists. For while on the one hand the positive uniformity of Nature's teachings in regard to heredity is striking and convincing enough, on the other hand it has been noted that Nature does not produce lawless freaks, that "grapes are not gathered from thorns, nor figs from thistles." The belief embodied as a "law" of Nature that in the case of every living species of plant and animal the offspring grows up and reproduces closely the co-ordinated characters of the phylum, order, class, genus, and species to which it belongs is the outcome of facts of observation, and of experience, which by their countless number, constancy, and uniformity, have acquired in our minds almost the aspect of necessity. Indeed many thinkers have professed to see in heredity a fatalism from which there is no escape. Man, they tell us, is not master of his fate ; he is the victim, the slave of heredity. "Science finds no ego or will," says Ross, an American writer, "that can maintain itself against the past. Heredity rules our lives like the supreme primæval necessity that stood above the Olympian gods. It is the last of the fates, and the most terrible. It is the only one of the gods whose name we know. We are possessed not by demons but by those who have gone before—our progenitors. These are the real ghosts which throng our lives, haunt our footsteps, remorseless as the furies. We are followed by the shades of our ancestors, who visit us not with midnight squeak and gibber, but in the broad noonday, speaking with our speech and doing with our deed. On the stage of life we actors recite speeches and follow stage direc-

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tions, but the speeches and the directions were written for us long before we were born." Heredity thus casts its shadow over us and holds us in its remorseless grip; it has not only its purely scientific aspect but its practical bearings on human life.

The classification of the data of human knowledge and experience in regard to heredity may be made under the following headings: (*a*) the breeding and rearing of animals, and especially of those animals which are situated high in the scale of evolution among the vertebrata; (*b*) the cultivation and propagation of plants (horticulture and agriculture); (*c*) the reproduction by man of his own species over a period of many thousands of years. The uniform and consistent experience of mankind in these matters, accumulated during thousands of years, constitute the basis on which has been erected the doctrine of heredity. During the nineteenth century efforts have been made to reduce the vast and extensive data into systematic groups of facts, to examine these facts critically, to eliminate errors and fallacies, and thus to establish an unshakable foundation for the laws of heredity in man and animals, in both health and disease. We have already alluded to the work of Herbert Spencer, Darwin, and Morel in this connection. While philosophers and biologists like Spencer and Darwin concerned themselves mainly with animals and plants and with the normal aspects, so to speak, of the problem of heredity, Morel and the school of neurologists, physicians, and pathologists, whom he has inspired, have cultivated and studied the medico-biological problems of heredity. The vast growth of medical and pathological knowledge in the closing years of the nineteenth century has left us rich with the special investigations into pathological heredity embodied in the works of Charcot and his pupils of the Salpêtrière School, Magnan, Dejerine, Legraine, Möbius, Lombroso, Ferri, Benedikt, Bruce Thompson, Wiglesworth, and a whole host of other workers.

Recapitulating the data and methods for the study of heredity, we may arrange them under the following heads of study: (1) animal breeding and rearing, including the study of hybrids; (2) human propagation and the transmission of physical, mental, and moral traits; also genealogical studies; (3) botanical investigation of plants and their variations; (4) human and

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comparative embryology in regard to the light it throws on the processes of development and descent; (5) the pathological aspects of heredity as shown in the transmission of disease and degeneracy in the human race.

The Track of Heredity and the Departures therefrom or Variation.

Continuity of cell-life, or of the living protoplasm, in some way not as yet fully understood, from parent to offspring, is regarded as the fundamental process of heredity. It is a phenomenon of complex character and difficult to express in exact anatomico-physiological terms in so far as it concerns man and the higher organisms. For the process is a compound or complex of several factors—a *continuity* which is only partial and particular, and which in many cases is interrupted by discontinuity, a *transmission* which is itself seldom entire but is usually modified in the process of transmission, and a *development* (ontogenesis) which is affected by malign and benign agencies, whose influence is often certain, though the exact sequelæ may be unpredicable. It is thus evident that but little can be predicated with certainty as to the final characters of the product—the net evolutionary result—of such complex and variable factors. Thus instances may and do occur, not infrequently, in which anatomical characters or peculiarities which we in our ignorance call "trifling" may be hereditarily transmitted in certain families from generation to generation. Peculiarities of gait and of gesture are often thus inherited. Handwriting has been known to exhibit similar peculiarities in father and son, while in some instances a special feature of the face, or formation of the hair, or "birth-mark" may reappear so markedly in successive generations as to become a notorious family characteristic. In this connection reference may be made to what are now matters of general historical knowledge, such as the Bourbon nose of the French royal family, the characteristic Napoleonic features, and the Hapsburg lip of the royal family of Austria, which have been noted in several generations of each of these imperial and royal families. Or going further afield and taking consideration of Ethnic types, we may call attention to the Semitic nose of the Chosen People, the slanting orbit and eyebrow of the Celestial, the prognathism

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and thick everted lips of the Negro, the tablier and steatopygia of the Bushmen and Hottentots. Such special characters of families and races, as well as those recorded above in reference to the imperial families of Europe, are frequently "prepotent" in hereditary transmission. Breeders of stock are well acquainted, from experience, with the prepotent characters of the males (sires) or females (dams) they breed from, and according to the market values of such characters a scale of charges is set up by the owner of the sire or dam whose service is desired. In regard to prepotency of features I am myself acquainted with a family whose type of jaw and under-lip formation unmistakably recall the Hapsburg type, but who have not the least relationship to the Hapsburgs of Austria. The feature is preserved with remarkable persistency, being present in the grandfather, in most of his sons and daughters, and in each of the seven families of children of the third generation descended from three sons and four daughters of the second generation. [An excellent *résumé* of some of the classical instances of prepotency is given by Vernon in his *Variation in Animals and Plants* (1903), pp. 147–152.]

But while heredity does operate with such prepotency in regard to particular traits and features, it would not be obviously for the good of the race or family if heredity always operated with such unyielding rigidity and fatalism as is shown in prepotency. For in a world wholly and exclusively dominated by its iron laws organisms would be incapable of progress and of adaptation outside the rigid grooves laid down, and existence would be rendered impossible in an environment where plasticity, adaptability, and progress were necessary for the continuance of the very life of the individual. Organisms which cannot vary, and vary in favourable directions, so as to adapt themselves to altered conditions of habitat and environment must *ex necessitate* perish. And thus, indeed, as the history of the geological record shows us, have species, genera, and families of plants and animals perished in the world's past, leaving no descendants at the present day. If heredity is, for convenience of expression, conceived as a power or force, we cannot accept it as the one power which wholly and exclusively dominates the succession of generations of plants and animals in this world. The fatalism and rigidity of heredity must be continually relaxed and tempered with the freedom and

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plasticity of variation. Only under the compromise and conjoint operation of these two would there be produced offspring and individuals of a practically perfect or progressive type, capable of survival under the many and varying conditions of the physical, material, and social environment, because possessed of the two-fold capacity of general constancy to the generic and specific type of its class (the outward expression of heredity), and possessed also of the capacity of varying and adapting itself to changing condition and higher evolution (the outward expression of variation). Variation is thus as much a necessity of life, as indispensable and inevitable a factor in the progressive evolution of newer and higher forms of life from the older and simpler, as heredity is for the conservation of generic and specific types. Thus only has been rendered possible that majestic evolution of living forms of plants and animals which has characterised our cosmos. The almost universal tendency to foster conservation of action and habit proper to the type, to keep variation, in other words, within conservative limits, is seen in the feeding and tending of the young, and to some extent educating them, among all higher animals (birds and mammals). Among social species this is a factor of particular importance. For this care, tending, and instructing is not merely a system by which waste is prevented, but it prevents the young generation from deviating widely from the line of development it has begun to follow. That heredity and variation indissolubly co-operate as factors in evolution must now be regarded as established beyond a doubt. But the relative values assigned to the co-factors heredity and variation differ in the estimates of different authors, and the difficulties of the problem are increased when we have to do with special complicating factors which make their appearance when dealing with the study of man—factors of "artificial" nature, which constitute "civilisation," on the one hand, and the pathological factors of disease and degeneracy on the other. For these factors potently affect and influence his life from the cradle to the grave in the highly complex, varying, and unstable environment in which he has placed himself, a being apart from the rest of the animal creation. Let us now consider a few facts in regard to variation before proceeding further.

When we study the adult progeny of a single pair of human

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parents we notice that they differ from one another as regards any one character within a certain limited range. Occasionally gross obesity or on the contrary a lean and spare habit may affect different members of the offspring. But excluding extreme variations, due probably to pathological conditions, it is probable that living even under approximately equal conditions of life, diet, and work, the weights of the individual members would vary from each other, and from the mean at all periods of life. On the other hand, stature is a quantity that exhibits less variation than weight. Excluding again the effects of diseases of metabolism which may give rise to extremes of stature, *e.g.*, dwarfish arrest of growth in rickets and cretinism, or exaggeration of growth in gigantism and acromegaly, it may be stated that under conditions of average health (a vague criterion certainly, but the best practical one) the offspring at different ages will exhibit variations of stature. From some inquiries and studies which I have conducted in this direction recently, I am inclined to the view that weight is a slightly more variable quantity than stature in families, largely owing to conditions which operate throughout life in the one case (weight), whereas they cease to operate early in the other (stature). For stature is a matter of growth (quantitative), which is not nearly so much influenced by conditions of diet, habit, work, as is weight. Moreover fixity of stature is attained early (practically at the twenty-second year), and then no circumstances of food, work, habit, or even disease will alter stature, since the hard bony framework has attained fixity and cessation of growth in the long axis of the body. Nothing can make it an inch shorter or longer. What conclusion do we then reach as to the result of our comparison? We conclude that whereas a plastic tissue or structure like the connective tissue of the body, which harbours the deposition of fat and acts as a food or fat store, is highly susceptible to variation, and can be made to vary in response to circumstances, on the other hand, in the osseous framework which determines stature we have a rigid and refractory mechanism which has early lost its plastic power, and which of necessity has preserved (because it *should* preserve) its dimensions unchanged in an animal body, which is a mechanical-muscular apparatus on the correct and steady working of which life essentially depends. Hence the mechanial basis of the framework varies but little. When we

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take other characters, such as the anatomical structure of the hair, the complex shape of the ear, and the colour of the eyes, we find that these are more constant throughout life and less variable than weight or stature. According to the researches of Sir Francis Galton, the lines and markings on the fingers and palms of the hand also exhibit a remarkable constancy and invariability in each individual from childhood to old age, and no two persons' hands are identical in their marking and patterns.

It is important in the scheme of nature that all the tissues and organs of the body should not develop at an equal pace, that some tissue-elements and organs should remain plastic, changeable, educable so to speak, and modifiable by the environment throughout nearly the whole of a lifetime, while other organs and structures should attain early to rigidity and lose their plastic properties of growth and adaptation, the whole aggregate of relatively plastic and relatively rigid characters having being co-ordinated in the course of evolution for the continued existence and well-being of the organism in question. Here, for instance, we may refer to the advantages of the endoskeleton over the exoskeleton as a bio-mechanical apparatus. The exoskeleton, like armour, sadly limits the wearer of the same. It limits the growth of the crustacean or insect enclosed in its rigid armature, and during the whole period of growth of the body periodical castings off (ecdysis) of the shell are necessitated. At such times and while the new armour is being formed, the naked body is exposed to injury and dangers of many sorts, while the drain on the nutrition of the system for the re-growth of each new shell or set of armour is serious. These drawbacks do not exist in the case of the vertebrata, whose endoskeleton furnishes a superior bio-mechanical apparatus, and whose unarmoured and supple skin surface gives them larger areas of sensibility with higher potentialities of kinæsthetic development. Hence we find animals of this type the winners in life's race—fishes of the sea, birds of the air, and especially mammals of the land.

Thus we see the *raison d'être* of the early development of the endoskeletal apparatus in the direction of fixity and stability of structure and of stature, the necessary physical basis for the perfect working of the neuro-muscular apparatus. On the other hand, a highly plastic and educable cerebral system, super-

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posed on a lower bulbo-spinal motor mechanism or δουλος which has already at birth attained considerable advancement in structure and function, is obviously also a desideratum for the highest animals and man. Such a desideratum is realised in the nervous structures in question, in increasing degrees of perfection, as we ascend the scale of the mammalia from the lower forms up to man. Man is thus a creature of hereditary endowments which unfold themselves at very different periods of his life. The nervous, and especially the cerebral, organisation of man, which constitutes the crown and acme of evolution in the cosmos, is undergoing growth and development in complexity of structure and function from the intra-uterine stage to the close of the period of adolescence—a period of thirty years. This great organ is the bearer of hereditary endowments of the most varied and manifold character. The vast material for study and the richness of this field largely unexplored as yet by workers on the subject of variation should tempt many to this study. The whole sphere of the insanities, neuroses, and psychic degeneracies affecting the human race offers such a field for the study of heredity and variation as would well repay exploration. A study of the pathological aspects of variation will also introduce us to the subject of degeneration, an element or factor of variation which, though neglected by zoologists, is of the utmost practical and scientific importance to the physician and the alienist. The whole of the subject of variation in its pathological aspect promises to grow before long into a problem which will demand the serious attention of society. As I have stated elsewhere ("The Newer Aspects of the Pathology of Insanity," *Brain*, 1894, pp. 549–550): "the insanities, like other variations in the organism, are subject to natural selection, and may be perpetuated in the race through favouring causes, and in this way hereditary qualities and potentialities for good and evil leave their seams and tracts in the organisation of the human brain, rendering it potent under suitable stresses of the environment to issue in insanity, vice, and crime."

Regression.

Among recent workers on the problem of heredity Sir Francis Galton has laid special stress on a principle or law of develop-

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ment which he calls "Regression towards the mean standard." "The laws of regression tell heavily," says he, "against the full hereditary accentuation of morbid tendencies . . . . The law is evenhanded: if it discourages the extravagant hopes of a gifted father that his children will inherit his powers, it no less discountenances extravagant fears that they will inherit all his weakness and disease." As illustrations of regression may be mentioned the following: A number of sweet-pea seeds are collected from plants which have been grown from *seeds of known size.* The peas thus collected are found to be on an average more mediocre (*i.e.*, closer or more approximately equal to one another in size) than the parent seeds. Data regarding the stature of families were collected by Galton, by means of which he was not only able to substantiate the fact of regression, but to calculate with some approach to accuracy the actual amount of regression occurring in members (ancestors, descendants, and collaterals) of families. More recently Karl Pearson, who has investigated the same side of the question and attempted to express the deductions in the form of a mathematical formula (*Philosophical Transactions*, 1896, A. p. 253) has concluded that the "co-efficient of regression was the ratio of mean deviation of offspring of selected parents from the mean of all the parents." The law of regression was applied by Galton not only to the regression between parents and sons, and grandparents and grandsons (lineal regression), but also to that between brothers and brothers (collateral regression), and from a careful study of the data and measurements, collected mostly by himself, he was able to assign certain values to those two forms of regression. Pearson also investigated the subject mathematically, and found that, starting from Galton's law of ancestral heredity, it was possible to calculate the co-efficients of regression (or correlation) between an individual and any of his kinsmen, either direct or collateral. He calculated the co-efficient of regression between "mid-parent" (*i.e.*, the mean of the two parents) and son to be 0·6, or somewhat less than that found by Galton. Between grandparent and grandson it was 0·15, between great-grandparent and great-grandson it was 0·075. Between brothers it was 0·4, or considerably less than the co-efficient found by Galton. Although differences exist as to the actual value assigned to these factors, the differences are explicable, the agreement in

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general is closer, and it may be accepted that Galton's general conclusions approximately represent the truth. It may, perhaps, be asked how it is that if regression acts continuously on the series of generations succeeding any given generation, the members of the later generations do not tend to greater and greater rigidity of type with incapacity for variation. The reason for this is shown in the fact, borne out by Galton's tables of statistics given in his *Natural Inheritance*, p. 208, representing the numbers of adult children of various heights born of 205 " mid-parents " of various heights. A study of this table shows not only that regression exists, but that the offspring produced by these mid-parents are, as a whole, no less variable than the " mid-parents " themselves. The offspring are, in fact, slightly more variable in stature, since a mid-parental stature, being made of two parental statures, is obviously on an average less variable than either stature individually. Thus whereas the mid-parents vary roughly in height between about 74 and 64 inches, the children vary between 75 and 62 inches. The table therefore shows that though the children are, on an average, more mediocre than their parents, yet the general variability of the race (as regards stature) is not diminished. The contents of the table also contain special items as regards the progeny of tall, medium, and short parents. Tall parents have many tall children, a moderate number of medium children, and a very small number of short children ; medium parents have many medium children, and moderate numbers of tall and short children ; short parents have many short children, a moderate number of medium children, and a very small number of tall children.

The law of regression may be considered to be in large measure supported and substantiated for sweet-peas, for man, and for Basset hounds, largely owing to the observations of Galton and his followers who have investigated the subject statistically. The law is of great value in the breeding of pedigree stock and the like on a large scale ; but it is a law of averages as regards inheritance and is in reality a logical sequel of the law of ancestral heredity, proving that all ancestors, however remote, are able to leave the impress of their individuality on their descendants in diminishing proportion to their remoteness in the line of descent. Galton's law of ancestral heredity (*Proc. Roy. Soc.*, vol. lxi, p. 401, 1897) is that the

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two parents contribute between themselves one half (or 0·5) of the total heritage of the offspring, while the four grandparents contribute one quarter (or $0{\cdot}5)^2$, the eight great-grandparents one eighth (or $0{\cdot}5)^3$, and so on. Thus the sum of the ancestral contributions is expressed by the series ($\frac{1}{2} + \frac{1}{4} + \frac{1}{8} + \frac{1}{16}$ . . . . .), which, being equal to 1, expresses the whole heritage.

Mutation.

Mutation is in one sense the very antithesis of regression. It plays an important part as one of the co-factors in the phenomena of life alongside of heredity, variation, and regression. Studies and observations of the variations occurring in plants and animals, especially under domestication or cultivation or other conditions different from those which prevail in the wild state, show that mutations may occur not infrequently in both the animal and plant kingdom. Mutations occur while the plant or animal is young or rudimentary, and probably before or during the embryonic state. Continuous variation occurs (for such is the definition of "continuous") only in accordance with the mathematical law of probability as laid down by Quetelet, and involves only the size, weight, or number of the organs or parts which are concerned in it, but does not include variations in quality. The character of a plant as a whole, says De Vries, is composed of definite units. These definite units, or "elementary characters," of the species are associated with material bodies, each "elementary character" having its special form of material body. Transition states between these elementary characters are rare, as those between chemical molecules. (*Journ. Roy. Hortic. Soc.*, April, 1901.) This is the view adopted by De Vries as to the difference between continuous variation and mutation. "Mutations," says MacDougal (*American Naturalist*, November, 1903), "ensue in the rudimentary state of the individual. . . . Mutative alterations are not the direct result of external factors and are perfectly transmissible." The subject of mutation first attracted attention in Europe probably when in 1690 Sprenger, the apothecary of Heidelberg, who had under cultivation in his garden plants of the species *Chelidonium majus*, noted the sudden and unexpected appearance

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of a type with laciniate leaves among the plants in his garden. "This form, which is also distinguished by other characteristics, was found to be constant and self-maintaining in competition with the parental type, *and has remained distinct to the present day without artificial selection*, and no specimens have ever been seen which could not be traced back to the original lot of individual plants in Heidelberg." Darwin referred to the subject of discontinuous variation or mutation and came to the, conclusion that new forms (permanent) which arose by "sport" or mutation were not self-maintaining, and therefore died out. Dollo, according to De Vries, was the first to announce definitely the conclusion "that species might originate by mutation" (1893). Bateson (*Materials for the Study of Variation*, 1894) summarises his own views in the following words: "It [the evidence of variation] suggests in brief that the discontinuity of species results from the discontinuity of variation." Korschinsky has published a most valuable historical account of the better authenticated instances of types which have originated by mutation (*Flora*, 1901, vol. lxxxix, pp. 240–363). His paper is a complete critical digest of the facts, and forms a logical prelude to the great work of De Vries. De Vries was the first to make a well-regulated series of scientific observations on the origin of new types or mutations in the cultivation of certain species of plants of the genus *Oenothera* (Natural Order Onagraceæ). The parent species, *Oenothera lamarckiana*, from which De Vries obtained mutant forms, has been, says MacDougal, "constant in its characters in cultivation in Europe and America, and also when growing wild. This type is not identical with any known family of the American flora, and is most nearly allied to *Onagra biennis grandiflora*, from which, it is suggested, it might have arisen by mutation. The mutant derivatives of the parent form, *Oenothera lamarckiana*, are found to be constant in their characters, with no connecting link or intergrading (transitional) forms, as illustrated by the cultures of the plant *Oenothera nanella* and *Oenothera rubrinervis* in the New York Botanical Gardens during 1902–1903. . . . The mutants are clearly separable from the parents and from each other by physiological and taxonomic standards. Further, the specific character of the mutants was borne out by their behaviour when hybridised with one another."

So far as the origin of mutations is concerned, it seems

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clearly established that the pre-mutative alterations affecting seed-plants ensue in the *vegetative* and *sexual* cells previously to the formation of the embryo in which they first appear. The facts of discontinuous variation, now numerous, well-observed, and authentic, have been used by De Vries to build up a theory or generalisation that new species can and do sometimes originate by mutation. "New types of specific rank, taxonomically separable and physiologically distinct and constant have (without intergrading and connecting forms) arisen in *Oenothera* and others by discontinuous variation." That mutation is a method of evolution in the genesis of species is proven, but it will probably take us some decades of further observation before we can fully estimate the position-value of mutation as a factor among the various co-factors of the evolution process. As regards the origin or genesis of species, we may say some have originated by mutation, some have arisen as the result of hybridisation, others give evidence of having arisen by the prolonged natural selection of small continuous variations of a favourable character, while others, again, have arisen under pathogenic conditions, and given rise to descendants of degenerate character which usually tended to perish in a few generations. Nothing in the nature of living organisms demands that all species should have originated or become extinct in the same manner, or that one single factor—one single method of procedure—should have been followed. The study of "mutations" of pathogenic origin show us that monstrosities and malformations of embryonic development comprise the largest number of these. They are extreme variations from the normal path and are well known to physicians. These pathological variations, however, will be considered separately in a later chapter. Restricting ourselves here to mutations in their normal biological aspect only—to those mutative forms of plants and animals which may form the starting-points of new species—the following items of information are added to the foregoing.

Mutations occur in animals, wild and domestic. Among examples of this are the *ancon* or otter-like breed of sheep which arose as a "sport" or mutation in Massachusetts, and of which an account (too well known to require quoting here) is given in Darwin's *Variation of Plants and Animals* (vol. i, p. 457, second edition). Darwin has with indefatigable

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perseverance traced out and collected other instances also, *viz.*, the mauchamp breed of sheep, the niata cattle, turn-spit and pug dogs, jumper and frilled fowls, short-faced tumbler pigeons, hook-billed ducks, etc., all "sports" or mutations which "suddenly appeared in nearly the same state as we now see them." "So it has been," adds Darwin, "with many cultivated plants." The race of Manx cats seems to afford the example of a mutation (the tailless condition associated with certain other minor correlative characters) which is prepotent in transmission to the offspring. Brookes refers (*Heredity*, 1883, p. 298) to the spike-horn buck of the Andironacks which arose as a mutation in a wild species. A. G. Mayer records a newly arisen species of Leptomedusæ, discovered at Tortugas, Florida, in which the individuals are marked by *pentameric* radial symmetry instead of the normal or orthodox tertramerous symmetry of these Medusæ, the mutation extending to radial canals, tentacles, gonads, lips, etc. The angle of divergence between the radially arranged system of bodily structures in this mutative species is 72° as against 90° in the other Eucopidæ (*Scientific Bullet.*, Brooklyn Institute, 1901). The same author has studied the colour patterns of Lepidoptera (butterflies and moths) as influenced by racial tendency and natural selection. Out of 1173 species (including 453 of Papilio, 30 Ornithoptera, 643 Hesperidæ, and 47 Castina), he finds that the characteristic differences between the species of a genus, or between the genera of a family, and the peculiar conditions prevalent in each, on the whole support the view that new species have often arisen by mutative variation, independent of the environment. De Varigny has recorded (*Experimental Evolution*, 1892, p. 101) a wonderful example of variation by cultivation of a plant, *Tradescantia virginica*, from the original trimerous type to tetra-, penta-, hexa-, hepta-, and di-merous forms. The famous case of mutation in the peacock may be referred to here (Darwin's *Plants and Animals under Domestication*, vol. i, p. 290). Among the peacocks belonging to Sir J. Trevelyan's flock, which was composed entirely of the common species, there arose suddenly—*i. e.*, by mutation—a new form, the black-shouldered peacock (*Pavo nigripennis*). The new form increased "to the extinction of the previously existing breed," and was regarded by several leading authorities as a distinct "species." And yet this mutative form of the peacock, the

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black-shouldered form, as referred to, has been known to have had a similar mutative origin five times in England, says Darwin. There is no real reason, therefore, why such changes should not occur also at times among plants or animals living in the wild state. It may be that ocular demonstration of the mutative origin of wild species is almost impossible to obtain. Negative evidence proves nothing in such a matter. We have witnessed mutations repeatedly occurring in plants and animals—among cultivated plants of field and garden and among the domestic animals and the flocks and herds of man; for these are "familiar friends," and any mutations or "sports" arising among them are at once detected, while their further developmental history can be followed. But if a mutative species were to spring into being in the wild state, as the *Ancon* sheep or the *Pavo nigripennis* did under domestication, how could the fact of its occurrence in wild nature be ascertained and established beyond a doubt? If the first members of a species newly arisen by mutation were found, the fact of their discovery would tell us nothing as to their mutative origin; the naturalist or explorer who made the discovery would record it as a rare or hitherto undiscovered species, and there the matter would end.

Among the lowest forms of vegetable life mutative variations seem to occur with facility under artificial conditions of culture as well as in a state of nature. Thus Lepschkin, in the course of his investigations on certain forms of yeast (Schizosaccharomyces), obtained a new form, probably mutative, which, had it been met with in nature, he says, would have been placed rather in the eudomyces than in the saccharomyces (*Centr. für Bakteriol.*, 1903, p. 145). Raciborski has shown that *Basidiobolus ranarum*, a mould fungus which is easily cultivated, may by growth in a one *per cent.* solution of ammonium sulphate or a ten *per cent.* solution of ammonium chloride develop into and pass through a "palmella" stage, isolating itself as spherical cells with thick walls, etc.—a phenomenon which is unknown in the case of any other plant of the mould fungi. Similarly, Chodat and Huber have found that in an alga such as *Pediastrum* the normal formation of daughter colonies does not occur in rich—*i. e.* concentrated—culture media, and that the cells are liable to become metamorphosed into large hypnocysts (*Bullet. Soc. Botanique*

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Suisse, 1895). Richter states also that he has seen abnormalities produced and perpetuated in other fresh-water algæ which have been exposed in cultivation, for one or two generations only, to the influence of salt water (*Flora*, 1894, p. 4). As a general summary of facts it may be stated that unicellular plant organisms tend to undergo mutation and to transmit their mutation with greater facility than plants of higher and more stable organisation.

Mutations also occur with special frequency and facility in some of the higher plants, while others are scarcely known to vary at all. There is a wide difference in this respect even among cultivated plants; some species vary enormously and others but little. This variability is to all appearance "not correlated with age of cultivation, degree of cultivation, or geographical distribution," says Professor Bailey, of Cornell University. As the result of extensive horticultural studies and experiments (*Proceedings of the Amer. Assoc. for the Advancement of Science*, 1894; *Botan. Gazette*, 1894, p. 381; and *The Survival of the Unlike*, 1896), he adds that "the chief antecedent factor in directing this variability is probably the age of the type or species. New types in geologic time are polymorphous: old types are monomorphous and finally tend to extinction." The most flexible or plastic types of cultivated plants are such as have probably not yet reached the zenith of their evolution—herbaceous plants, like cucurbits and begonias; while many species of the orders Ranunculaceæ, Onagraceæ, and Polygonacæ, growing in the open, wild or cultivated, show variability in a high degree. On the other hand, the various kinds of cereals (Gramineæ), which are old types, have practically reached a condition of stability, and under cultivation show but a minimal tendency to variation.

Mutations or "sports" may occur in the branches of plants, starting probably as "bud-mutations." The term "bud-variation" has often been used for such, but considering that the changes manifested are true mutations or "sports," the term "bud-mutation" seems preferable on the ground of accuracy. These bud-mutations occur in full-grown plants in their flower-buds or leaf-buds. A number of classical examples of bud-mutation are now known, *e.g.* the development of nectarines (by mutation) from the flower-buds on the branches of a peach-tree, the production of moss-roses from the buds on the branches of a

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common rose, the appearance of russet apples on the branches of a Greening apple-tree. The same branch of a peach-tree may bear both peaches and nectarines, and of an orange-tree both oranges and lemons. Sports or mutations may occur also in the foliage leaves, the place of normal shoots and leaves being taken by such mutative forms as variegated or cut-leaved shoots and weeping leaves on otherwise normal trees. These bud-mutations of plants are no more intelligible than the mutations arising from seed-production and the cultivation of seeds. Mutative variations may arise in flower buds and leaf buds, in stems, aerial and subterranean, from bulbs and tubers, or even, says Bailey, from the adventitious buds of roots. The characters of the mutations are as various and marked as those originating from seeds. "If you ask me why it is that the nectarine was produced as a 'sport' upon the branch of a peach-tree, I will ask you why it is that nectarines have also been produced from peach-stones. The answer to the one answers the other." A further proof that bud-mutations and seminal variations are essentially similar in kind and quality lies in the practical fact that selection can be practised for the improvement and definiteness of forms originating by either means. Thus Darwin records the observations of Mr. Salter, who has brought the principle of selection to bear on variegated plants propagated by buds, and has thus greatly improved and fixed several varieties. (The plan or *modus operandi* of the horticulturist is described on p. 91 of Professor Bailey's work, but need not be quoted here.) By following with perseverance this plan during three or four successive seasons a distinct and fixed variety can generally be secured. This practice, says Bailey, is now well known to gardeners, but we see that Nature, with her vast and unlimited resources, may "select" in the same manner here and there. Cultivated plants not only tend to develop sports in the form of variegated, cut-leaved, or weeping shoots, but colour variation and "doubleness" (including ligular variations) may sometimes predominate. Many of our best known roses, carnations, crysanthemums, violets, and other garden plants have originated as bud-sports. The fact is so well known that critical gardeners are always on the alert for such variations. Every gardener will recall the "sporting" tendencies of the *Perle de Jardins* rose, and the fact that several commercial varieties have sprung from it by bud-sporting. As early as 1865 Carrière, an eminent

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floriculturist who had paid great attention to this particular subject, gave a descriptive list of 150 named bud-sports of commercial importance, and remarked at length upon their frequency among cultivated plants. Since the record of 150 (commercial) varieties of plants as known commercially in France, and which had originated as bud-mutations according to the list prepared by Carrière (1865), there has been an increase of the horticultural variations of like origin, and it has been estimated by Bailey that there were "no fewer than 300 named horticultural varieties grown at the present moment (1895) in this country (the United States of America) which had a like origin." It is also known that there are a number of species of plants, in which seeds are practically unknown, and which yet run into many varieties, as the pine-apple, banana, and bread-fruit, and the various onions and horse-radishes, as also the several varieties of weeping willows which never bear seed in the United States and are only propagated asexually.

Mutations of the nature of peloria may in many plants be perpetuated by seed, as also "doublings" and malformations. Thus in the case of *Celosia cristata* (Nat. Ord. Amarantaceæ), the well-known coxcomb, a form of malformation (fasciation) which occurs as a sport can be transmitted. Goebel writes (*Science Progress*, October, 1896): "In plants with which I experimented I found that the transmissibility of the fasciation by heredity is absolute; even when I cultivated the plants in sterile sands they always exhibited this phenomenon, even in the second generation." De Vries states that the facts recorded in his work (*Die Mutationstheorie*, 1901) show "that species originate by sudden sports, and that each of these occurrences is a true physiological process; that all such suddenly produced forms are separated from one another by as sharp and numerous characters as are most of the so-called minor species." In concluding this chapter, and with it the first part of this memoir, I wish to state that I conclude that variation is at least of three, if not of four, kinds—*viz.*, the continuous variation which occurs according to the law of probability in organisms, and manifests itself in generalised or localised fashion; the mutations which may occur in a state of nature (wild) or of civilisation (domestication); and pathogenic variation, which is evidently a different phenomenon (often indicated by physical and psychical "stigmata" of degeneracy),

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which is the peculiar inheritance of civilised man. To these may perhaps be added meristic variations which border on the pathogenic. These four are probably distinct processes.

Part II.

The Pre-embryo.

In the human species and in all the various classes of mammals and vertebrates, reproduction takes place by the sexual union or conjugation of two gametes, the sperm-cell and the germ-cell. These cells when they have matured within the parental body are capable of undergoing no further development individually: each cell has reached a condition of equilibrium which tends to terminate in dissolution if the two are not able to unite. When, however, by the act of sexual union these gametes are enabled to conjugate, this equilibrium is destroyed, a new condition of affairs is set up, a new evolution is initiated, *viz.*, the genesis of a new being—the embryo. The embryo is developed from the fertilised ovum by growth, cell-multiplication, and differentiation of structure, these processes being carried on in an environment which differs for the different classes of animals, but is constant for each species. The environment may in some cases be the sea, or the water of a river, lake, or pond, into which the ripe ova are extruded by the female. The ova may be fertilised by the spermatozoa of the male during the process of extrusion of the ova (*e. g.*, the common frog), or they may be "spawned" over by the male immediately after the female has laid them (*e. g.*, many fishes). In all such cases the impregnated ovum has for its environment the fresh or salt water of the ocean, river, lake, or pond which constitutes its habitat. The individual ova are clothed with a membrane (zona pellucida) and often embedded in a gelatinous envelope in the form of strings or loose masses, so that the rigour of the environment is modified by the jelly-like envelope. This envelope is derived from the parent during the passage of the ovum from the ovary through the oviducts to the exterior, being a provision of Nature to secure for the growing ovum in the initial stages of development and cell-division a special, though temporary, physico-chemical environment, the composition for which is uniform and constant for each species.

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The earliest steps in embryogenesis are thus taken under conditions as favourable and proper to each species as possible; indeed, in this as in other respects, we find that as we ascend the scale of animal life, adaptive mechanisms of a more perfect condition are provided for the same purpose. Thus we have the albumen, membranes, and shell of the egg in the case of reptiles and birds on the one hand, and the provision of a uterus for mammals on the other.

The study of embryogenesis and descent have led biologists to formulate a law or "recapitulation theory," to the effect that the developmental phases passed through by the embryo represent, broadly speaking, a recapitulation of its ancestral history, that ontogenesis is an epitome of phylogenesis. "Each animal in the course of its development from the ovum climbs up, as it were, its own genealogical tree." Such is the recapitulation theory hinted at by the brilliant Agassiz in the early part of the nineteenth century, suggested more directly by von Baer, first clearly enunciated by Fitz Müller and Haeckel, and since then extended by the embryological researches of Kowalevsky, Haeckel, Metchnikoff, Balfour, Hertwig, and others. The tendency of modern research in comparative embryology has been to give additional support to von Baer's doctrine, enunciated by him in 1828: "Embryonic states can only be correctly compared with embryonic states, but not with adult states. The more different two forms are the further back in their development must we go to find similar stages."

Unfortunately, we do not possess in the case of the human embryo, says Hertwig, a single observation upon the process of fertilisation of ovum by spermatozoon, upon the mitosis and cleavage of the ovum into two, four, and eight blastomeres, and the formation of a solid cell-mass (morula), or upon the formation and differentiation of the blastodermic layers, or upon the establishment of the primordia or organ-anlagen of the embryonic body—in a word, upon the whole of the pre-embryonic life which belongs to the period of the first two weeks after fertilisation. We know that maturation of the ovum has taken place since the extruded pair of polar bodies has been seen beneath the vitelline membrane (Nagel). We have to assume, however, the occurrence of the other phenomena, *viz.*, (*a*) that fertilisation takes place in the Fallopian tube or oviduct, or less frequently within the body of the uterus by the union of ovum

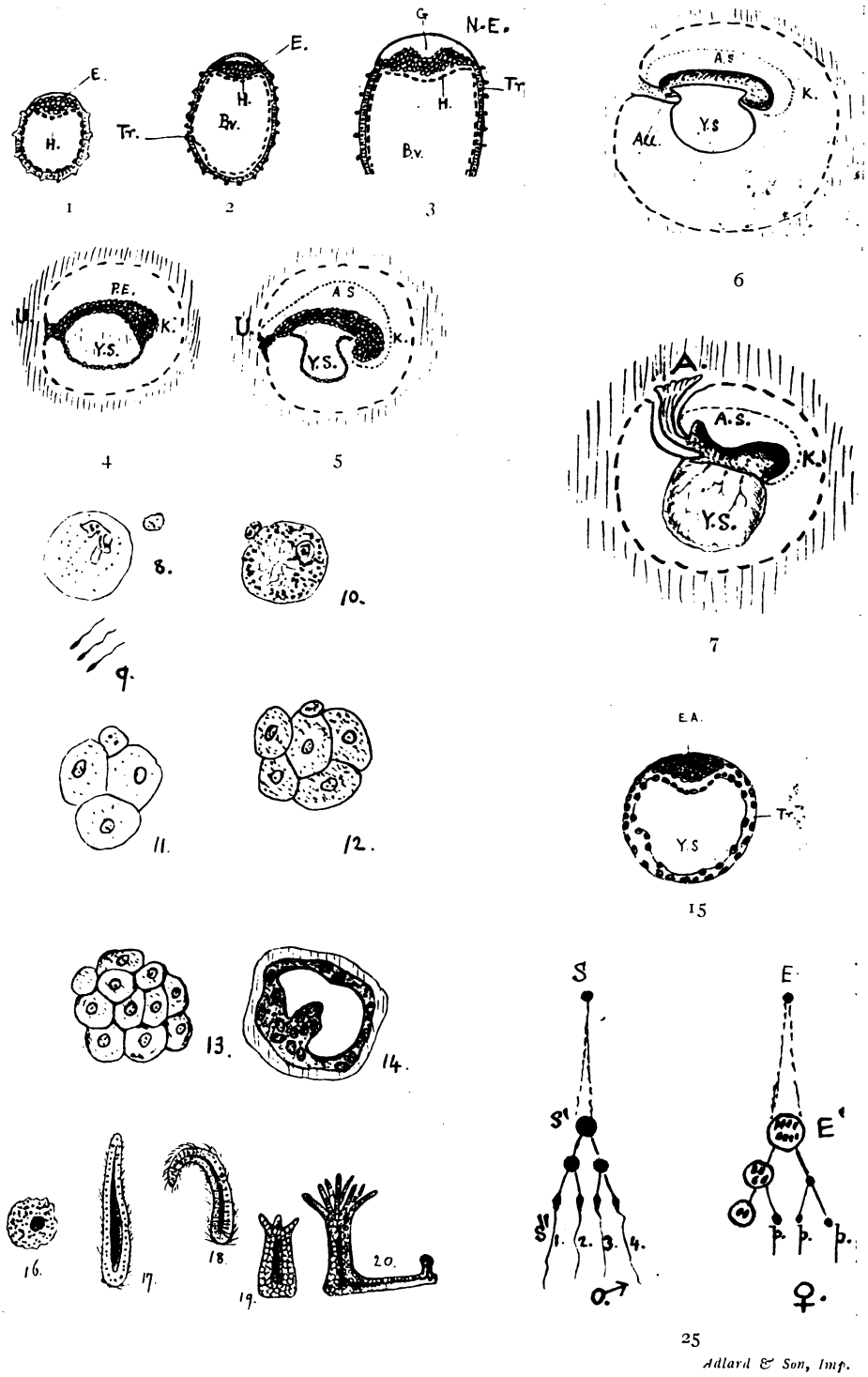
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and spermatozoon; (*b*) that the fertilised ovum undergoes segmentation into a mass of cells (morula and blastula) which becomes attached to and embedded in the uterine mucosa during the first week, the area of contact being slightly eroded and excavated for the reception of the ovum, while the uterine epithelium grows up around and closes over it in the form of a capsule. Within this covering the cell-mass forms a sac, on the inside of which the cells which are to form the future embryo aggregate and increase into a thickened knot of cells (pre-embryonic disc), while the rest of the sac-wall functions as a trophoblast (Figs. 1, 2, and 3). During the first week the blastodermic disc proliferates, expands, and undergoes differentiation into an anterior (cephalic) and posterior (caudal) pole, while the hypoblast has formed an inner lining for the blastodermic sac, and numerous mesoblast cells are beginning to appear. The primitive chorion is formed, followed by the amnion (Figs. 4 and 5). The ventral yolk-sac now becomes more apparent as a sac by constriction at its front and sides below the embryonic mass. The organ-anlagen of the embryo are not yet differentiated, since the cells are few in number, and though rapidly multiplying, have not all taken up their proper positions. The youngest known human ova that have been studied are of the estimated ages of twelve to fifteen days (His), the blastodermic sac being about one fifth inch in diameter, and the pre-embryo within it about one tenth of an inch. They have all been obtained from miscarriages or suicides (His, Coste, Allen Thomson, Schroeder van der Kolk, Reichert, and Kollman).

We may study as an example His's 2·15 mm. embryo (Fig. 6). Here the line of attachment of the amnion extends almost the entire length of the embryo-shield, beginning in the neck region and ending in the rear. The yolk-sac is not yet constricted into sac proper and duct, for the opening to the enteron is large (wide) and elongated antero-posteriorly.

The following is the description of Coste's embryo 2½ weeks old (Fig. 7). The cephalic end of the embryo is fairly well differentiated from the yolk-sac. The yolk-sac itself is continuous ventrally with the rudiment of the archenteron throughout nearly the entire length of the latter. The anterior and posterior portions of the enteron end blindly. The neural groove has developed along the dorsum of the embryo, but remains patent fore and aft, having closed only in the

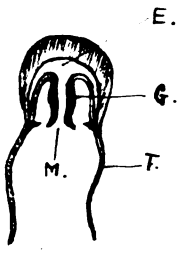
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FIGS. 1, 2, and 3.—Development of pre-embryo of Hedgehog (semi-diagrammatic, after Hubrecht). The lettering applies to all the three figures.
E. Epiblast. N.E. Neuro-epiblast. G. Neural groove. Tr. Tropoblast. H. Hypoblast. Bv. Blastodermic vesicle.
Note.—Fig. 1 represents the blastodermic sac, and consists of the epiblastic and hypoblastic layers forming the trophoblast, which is beset with small villi. The cells form a thickened disc dorsally at E, which is the future "embryonic area." Fig. 2, is a more advanced stage with commencing formation of the dorsal amniotic space. Fig. 3, is a still more advanced stage, and the neural plate and groove are beginning to be formed.

FIG. 4.—Pre-embryo of the first week (side view), semi-diagrammatic (human).
P.E. Pre-embryo. K. Cephalic end. Y.S. Yolk sac. U. Uterine wall. (The dotted line represents the primitive chorion.)

FIG. 5.—Pre-embryo of the middle of the second week, semi-diagrammatic.
A. S. Amniotic sac. The rest of the lettering signifies the same as in Fig. 4.

FIG. 6.—Pre-embryo of 13 days old.
All. Allantois. The rest of the lettering as in Figs. 4 and 5.

FIG. 7.—Embryo of 15 to 18 days old.
A. Allantois. The lettering as in figures preceding.

FIGS. 8—15.—Showing the cleavage and cell-divisions in the pre-embryo of Tarsius spectrum (Hubrecht). These figures are slightly diagrammatised sketches.
Fig. 8. Ovum after extrusion of first polar body.
Fig. 9. Spermatozoa.
Fig. 10. Ovum after extrusion of second polar body (impregnated).
Fig. 11. Tetrad of blastomeres.
Fig. 12. Stage of eight blastomeres (five only visible).
Fig. 13. Morula of about 32 cells (sixth cell generation).
Fig. 14. Blastula.
Fig. 15. Blastula, showing Embryonic Area, Yolk Sac, and Trophoblast.

FIGS. 16 to 20.—Fig. 16. Fertilsed egg of a Hydromedusa (*Clava squamata*).
Figs. 17 and 18. Planula-larva (free-swimming, ciliated) of the same.
Fig. 19. Young asexual sessile hydroid, or hydrula.
Fig. 20. Adult asexual stoloniferous hydroid.

FIG. 21.—Longitudinal section of a Hydromedusa (medusoid, sexual, free-swimming form).
M. Mouth at the end of the manubrium. G. Gonads (sperm- or germ-cells) in the wall of the manubrium. E. Enteric cavity.

FIGS. 22, 23, and 24.—Fig. 22. Oocyte of new-born infant.
Fig. 23. Oocyte of young girl.
Fig. 24. Oocyte of adult woman.

FIG. 25. Diagrams of maturation of spermatocytes and of egg-cells.
S. Young spermatocyte of new-born male child. E. Young oocyte of new-born female child. S′. Mature spermatocyte. S″ (1, 2, 3, 4). Four spermatozoa, descendants of mature spermatocyte. E′. Mature oocyte, which gives rise to an egg-cell and three polar bodies (*p.*, *p.*, *p.*).

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centre. The lateral mesoblastic somites begin to appear. The allantois is beginning to grow out from the ventral portion of the caudal region, carrying with it a few developing blood-vessels. There is, however, no union of the allantois with the uterus, no placental formation as yet, and nourishment for the growing embryo is derived partly from the yolk-sac and partly by osmosis from the maternal lymph by the trophoblast. The stomodæum is partially formed, but its floor is not yet opened through, and a thin partition intervenes between stomodæum and archenteron. (The stomodæum opens into the archenteron in the middle or latter part of the third week.)

The following is a description of a slightly older embryo of 3½ weeks: The allantois, now grown as large in size as the entire embryo body, has come into contact with the uterine wall, bringing with it a broad expanse of blood-vessels and capillaries, which, interdigitating closely with the soft and highly vascular tissue of the uterine mucous membrane, forms a solid organ, the placenta, which serves henceforth as the organ of nutrition and respiration. The yolk-sac, or what remains of it, has shrunk into a tiny vesicle with a slender tubular neck, while the enteron is closing longitudinally (ventrally) into a true tube open anteriorly into the stomodæum and developing a similar opening nearly complete posteriorly (the proctodæum). Amniotic fluid is now abundant, and the embryo floats freely in it. The neural groove is closed along the whole length of the bulbo-spinal tube. Four pharyngeal arches have developed at the side of the neck, each with a groove or depression behind it. The five processes (fronto-nasal, right and left lateral nasal, and right and left upper mandibular) growing from the basi-cranial region are partially united to form the upper face. (Failure of union gives rise to harelip and cleft palate.) The thyroid begins to develop as a solid bud in the floor of the pharynx. The embryo has at the end of the fourth week acquired a very characteristic form, corresponding closely in shape, in size, and in internal structure with a chick embryo of the fourth day or a rabbit embryo of the eleventh day. It has attained decidedly mammalian characters. For our knowledge of the stages of development and of their probable characters during the pre-embryonic stage, *i. e.* during the first two weeks after fertilisation of the ovum, we have to rely upon embryological studies carried out on mammals, such

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as the observations of Hensen (1883), Kupfer (1882), Selenka (1883), van Beneden and Julin (1884), Heape (1883 and 1886), and Hubrecht (1896, 1902) on the rabbit, guinea-pig and other rodents, the opossum, mole, bat and hedgehog, and especially upon the recent work of Hubrecht on the development of *Tarsius*. An account of Hubrecht's observations on the embryological development of Tarsius, an animal intermediate between the lemurs and the apes, is briefly given below, with illustrations, in view of the great importance of the facts and results obtained by that distinguished author, and the light they throw on embryological processes. The placentation of *Tarsius spectrum*, says Hubrecht (*Fürchung und Keimblatt bildung bei Tarsius spectrum*, 1902), is of the deciduate type, while the arrangement of the fœtal membranes with the diminutive yolk-sac, rudimentary allantois, and large extra-embryonic cœlom, is identical with that found in man and monkeys, but nowhere else. After the extrusion of the first polar body from the ripe egg the nucleus is pale and baggy-looking (Fig. 8). After extrusion of the second polar body, impregnation, and fusion of the two pronuclei, division takes place into two and subsequently into four blastomeres arranged in the form of a tetrahedron (Fig. 11). The cells in the tetrad stage are of practically equal size, and attached to the angle between two of them can be seen the second polar body. At the next stage of cell-division (eight cells) the blastomeres are adpressed into an oval, flattened mass of cells, five being visible on one aspect (Fig. 12), with the polar body superposed on one of them. Cell-multiplication thus proceeds, the cells getting individually somewhat smaller with each division until the seventh cell generation, a morula of 30 (to 32) cells, is reached (Fig. 13). The next stage is the blastula, in which the cells arrange themselves as a hollow sac of cells, at first a single layer deep, except at one portion of the blastula sac (Fig. 14), where a dense aggregation of cells takes place three or four cells deep. This latter is the embryonic disc or knot of cells, from which (by further cell-multiplication, growth, and differentiation) the embryonic organs are to be built. At present it is only an embryonic knot of cells, while the attenuated single layer of cells constitutes the rest of the sac, the whole being contained within the zona pellucida or vitelline membrane. In the ninth and tenth cell generations the em-

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bryonic knot of cells has grown and expanded, and is now a lens-shaped disc of cells about five cells deep in its central part, the edges being prolonged as before to form the sac—blasto-sac (Fig. 15)—which, however, has had an inner layer of hypoblast cells developed, so that the sac wall is now two-layered. The outer layer is called the trophoblast and shows minute villous elevations, and the whole sac wall probably acts as a food absorbent. The primitive chorion and the amnion are formed at the close of this stage, which may be termed the gastrula stage. The caudal and cephalic ends of the embryo are now differentiated: the amniotic sac has developed dorsalwards and laterally, investing the yolk-sac at its junction with the embryo body, and the neural groove has been formed. This takes us to the end of pre-embryonic life and fills up the actual gap in our knowledge of human embryology.

The Law of Oogenesis and Spermatogenesis.

The details of pre-embryogenesis described in the foregoing chapter commence with the act of fertilisation, or conjugation of sperm- and germ-cell. These cells have already pursued each a long line of development in the body (ovary or testis) of a parent before it could make itself fit to enter into conjugation. These processes in the life-history of the sperm- and germ-cell consist of the following stages.

The descent of the primordial egg-cell.—When the impregnated ovum cleaves and divides into two equal and apparently equipotential blastomeres it might be assumed that (in cases where each such blastomere represents all the structures and potentialities of its fellow) each would be the parent of one half of the embryonic body if development went on normally through the tetrad, morula, and gastrula stages. But if the blastomeres were separated without injury and each permitted to undergo independent development, each might develop into a complete embryo (homologous twin) since each was the equipotential of the other, and the early separation of the two restored each separated blastomere to the condition of what the parent egg-cell was before cleavage. If the capacity for such restoration were perfect, a perfect but miniature morula, gastrula and embryo would be expected to be formed. Evidence which will be fully given in a later chapter on experi-

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mental embryology bears this out. The same applies to the cells of the next cleavage—in the third generation of four blastomeres. After this, however, differentiation begins appreciably, though in the case of the egg of the medusæ (Clytia, Laodice) and of the echinoderms (Echinus and Sphærechinus) even a one eighth blastomere of the fourth cell-generation will develop symmetrically into a morula and blastula in both, and occasionally to a gastrula in Echinus and Sphærechinus (Boveri, Driesch, Loeb, Morgan). Hence the eight cells of the fourth generation here are still equipotential: there is as yet no differentiation into incipient tissue cells.

As the process of gastrulation goes on cell-differentiation gradually shows itself. The cells that are to be the parent cells of nerve-cells (neuroblasts), of muscle-cells (myoblasts), of outer epithelial cells (tectoblasts), of gastro-intestinal epithelial cells (gastroblasts), and of vascular tissues, begin to differentiate. Among others the primordial germ-cells also are thus differentiated. Thus appear the primordial pair (theoretically right and left single cells) of germ-cells in the body of the gastrula or cœlomula. It is possible, then, by counting the total number of cells in the gastrula or cœlomula to determine very approximately the ordinal number of the cell-generation in which the first pair of germ-cells (or the first germ-cell) is formed and makes its appearance.

The nature of the germ-track.—The primordial germ-cells appear early in a few species of animals, such as the Diptera (flies), the Daphnidæ (water-fleas), and certain parasitic "worms" of low organisation. The earliest evidence of the appearance of the primordial germ-cell is shown in the Diptera (Weissmann), where in the third generation of four blastomeres one of the four is seen to have a larger amount of nuclear chromatin than its three sister-cells. In the Daphnidæ (Phyllopod Crustacea, of microscopic size) the primordial germ-cell is recognisable in the seventh cell-generation (demi-gastrula stage of sixty-four cells). In Rhabiditis nigrovenosa, a parasitic worm, the primordial germ-cell appears in the ninth or tenth cell-generation (middle or end of the gastrula stage). Finally, in the marine worm Sagitta the primordial germ-cell appears in the eleventh generation, when the gastrula stage has been passed and the cœlom is developed (cœlomula stage). It must be remembered that in small animals of minute size, lowly organisation, and

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ephemeral life of a few weeks only, the appearance of the primary germ-cell as early as the *seventh* cell-generation (as in the Daphnidæ) is really comparable, in terms of the life-span, to an appearance of the germ-cell (say) in the tenth cell-generation of an amphioxus, or a later generation in a mammal. The differentiation of primordial germ-cells is delayed, in the higher forms, as is the differentiation of primordial muscle-cells, nerve-cells, and other tissue-cells. For the first few cell-generations, cell-multiplication must be gone through rapidly, to furnish, especially in the mammalia, the building material for the extra-embryonic structures as shown by Hubrecht for the hedgehog, and other mammals. The cell-knot (group of cells) which is to furnish the building elements of the embryo-anlagen appears compact and remains so for some time, not having as yet proliferated and expanded to form the embryonic shield. Hence, says Weissmann, in vertebrates the appearance of the primary germ-cell occurs much later than in Sagitta, which shows it in the eleventh generation. In Hydrozoa, according to the peculiar and sedentary or sessile life pursued, and the proneness to budding and colony formation, the formation of the germ-cells may be delayed still further, a long period marked by an asexual stage occurring before the sexual persons (medusoids) arise. The life-stages are fertilised egg, free-swimming planula, sessile hydrula, stoloniferous hydroid-stock, medusa, and gonads (Figs. 16–21). The "germ-track" therefore in this instance cannot be said really to exist; the ovum develops into a planula, then follows an asexual hydroid, which itself may undergo budding until two or more generations are passed through, before the sexual medusoids begin to be developed. *The only "track" that exists is a track composed wholly and exclusively of many generations of somatic-cells, and from the last of these the germ-cells arise.* "The ancestors of these germ-cells," says Weissmann, "are somatic cells." In short, a "series of the various species of animals might be drawn up in which the formation of primordial germ-cells begins at very different degrees of remoteness from the egg-cell" (Weissmann). I believe that Weissmann is but using the sober language of fact when he says: "In most of the higher metazoa this [the first appearance of the primary germ-cells] only occurs after the formation of thousands or even millions of cells" (The *Germ-*

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plasma, 1895, pp. 192-3). The rest of the genealogy of the germ-cells is briefly told. The primordial germ-cells divide and increase in numbers. The majority of these are aggregated in the cœlomic genital area, where the ovaries and testes are accordingly formed. A small minority, however, of these cells (about 10 *per cent.* or less) may in the early cell-divisions which occur within the gastrula or cœlomula migrate or be disseminated throughout other parts of the embryonic body, remaining probably as single cells to die and be absorbed later, or to furnish the starting-points of neoplasms. The primordial germ-cells have a glassy appearance of the cytoplasm (as revealed in the skate and other fishes), the nucleus is slightly bilobed in appearance, and the perinuclear region is full of particles of a food material which stains darkly with certain dyes. As these cells proceed to multiply and increase in number their further fate may be traced in the gonads or sexual organs. Here the cells which are destined to become the future ova and spermatozoa increase numerically until an aggregate of several thousands or scores of thousands (rarely millions) are formed. It is only a simple mathematical calculation to ascertain the number of cell-generations that this represents from the primordial germ-cells to the terminal generations of ova and spermatozoa in their teeming millions, *i. e.*, assuming that every germ-cell descended from the primordial germ-cell divides into two, and that the process is repeated exactly in the same way generation after generation, that no cell dies in any generation, and that no cell is arrested in development or ceases to divide to the very last. Although the primordial germ-cells are distinguishable from young somatic cells in early embryonic life, the question as to what determines the subsequent differentiation of these cells into the parent cells of male and female gametes is not quite known. The primordial germ-cells are sexually indifferent, being neither pro-male nor pro-female. Their transformation to ova or spermatozoa "is not due," says Wilson (*The Cell*, 1902), "to an inherent predisposition, but is a reaction to external stimulus, . . . the stimulus given by the character of the food." At the period of birth in the female infant, or at a date very soon after, the eggs in the ovaries as actually counted are found to have reached the numerical limit of their growth. During the sixteen years of childhood they

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undergo internal changes of which as yet little is known beyond the barest outlines (Figs. 22–24). At the onset of puberty, however, characteristic (qualitative and quantitative) changes occur, constituting "maturation." These consist in the phenomena of nuclear division and extrusion of polar bodies, or, in the case of the sperm-cells, the division of the parent cell twice into four granddaughter-cells or young spermatozoa. In both kinds of cells the maturation stage comprises two cell-generations, as is graphically shown below (Fig. 25). Details of these processes need not be here given, as the text-books give all the necessary information.

Part III.

The Law of Pathogenesis.

It is clear that the exclusive view, propounded and held by Weissmann and his followers, of the charmed life of isolation led by germ-plasma in its progress during the ages through the bodies of animals is really a metaphysical concept which does not accord with facts of Nature as revealed to us in the study of both human and animal life. The germ-plasma, as the alleged material substratum of a certain class of phenomena, is subject to the laws which govern the physical movements of atoms and molecules—the law of chemical reactions and the law of the persistence of force. As a living substance it is subject similarly to the physico-chemical and mechanical influences of that which is not itself, but in which it lives, multiplies, grows, moves, and has its being, *viz.*, the living body or soma which constitutes its environment. And, therefore, changes in the soma or environment of the germ-plasma modify the latter, and conversely changes in the germ-plasma influence the soma. The object of our inquiry is to trace out, and to understand if possible, how agencies for good or evil acting on the soma may affect the germ-plasma, and what are the results, good or evil, which would follow and manifest themselves in the issue or offspring. A whole series of biological and pathological observations are now available, thanks to the special investigations of medico-biological investigators in this department. In the vast realm of facts and data of this branch of study we must in this chapter limit ourselves to a few that concern

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only the human race and the higher animals. They are—the action of alcoholism, plumbism, syphilis, and tuberculosis on the individual and on his progeny. Does alcohol taken by the parent have any effect *viâ* the parent on the germ-plasma or the germ-cells? Does modification, for good or evil, of the germ-plasma or germ-cells result, and is this manifested in the offspring born of such parents? And the same question will be asked with regard to plumbism, syphilis, and tuberculosis.

Hereditary sequelæ of alcoholism.—Hereditary transmission from the parent to the embryo may take place in one of three ways: first, the germ-cell or ovum may be altered or damaged as the result of grave constitutional disease acquired by the mother at or before the time of conception, a similar occurrence as the result of constitutional disease or toxæmia being possible for the sperm-cells of the father. Secondly, the impregnated ovum during the pre-embryonic stage (which we have defined in previous chapters) may be subjected within the uterus to the action of toxic, cytolitic, and other morbific agencies circulating in the maternal blood-plasma which nourishes it through this stage. Thirdly, the embryo may be affected *via* its placental attachment to the mother (on or after the fourth or fifth week of intra-uterine life—the period of placental embryonic life). It is clear that these three several modes of "hereditary" transmission are not identical, and that they should be discriminated and not confounded together. Under hereditary transmission in the strict sense we include only those modes of transmission which are specified above under the headings "first" and "secondly," and these will now be considered a little more in detail. Take the case of a female infant who is born with ovaries containing the mother-cells of future ova, as the male infant is possessed of testes containing the parent-cells of future spermatozoa. The ova proper and the spermatozoa have themselves not as yet "arrived"; the miniature parent-cells which give rise to them within the ovaries and testes have to undergo a process of growth, development, and maturation through the long period of at least sixteen years before puberty is attained. During this long cycle of changes whereby the elaborate and highly complex organisation of germ-cell and sperm-cell is completed and attained, although we know relatively little as regards the intimate details, we know that the

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whole series of changes culminating in the maturation process is fraught with consequences of the utmost importance for the future being that is to be born from the union of ovum and spermatozoon. A veritable field of investigation lies open here for the experimental investigator. The ovaries and testes are furnished with a rich vascular blood-supply for the purposes of nutrition, growth, and elaboration of structure and internal evolution of the ova and spermatozoa during the long period of sixteen years. During this period the germ- and sperm-cells are subjected to the action of nutritive, toxic, thermal, gaseous, and other changes of the blood-plasma which continually bathes and nourishes them, and carries away the by-products of their metabolism. The plasmic environment of the germ-cells cannot, of course, vary excessively without death resulting, but, within the limits which enable life to continue, the action of disease, degeneration, and pathogenic agencies has full play; the growing and maturing sexual cells in the ovaries and testes are affected by noxious as well as by beneficial agencies—by changes in food-supply, warmth, oxygen, and all the normal necessaries of life, as well as by inanition, pyrexia, impure gases in the blood, toxic and cytolytic substances in the blood in fevers, by toxins of defective bowel and renal elimination (auto-toxæmia), by alcohol, lead-poisoning, food-poisoning, and the thousand and one factors which assail and affect the human constitution. Damage may be thus sustained by germ- and sperm-cells while still immature, or in the maturation stage, or during and after conjugation and in the pre-embryonic stage. Thus are produced, *de novo*, by the action of potent extraneous agencies acting on the parent organism and *via* the parent organism on the germ and sperm-cells, or on the impregnated ovum and the pre-embryos, pathological characters, or morbid changes. Do the offspring born of such germ and sperm-cells, or developing from pre-embryos subjected to such pathogenic influences, (*a*) live to full-term or abort, or miscarry; and (*b*) if they live to full-term and are born, do they exhibit in body and mind, in childhood or later, the signs and stigmata of their affliction and lesion sustained, impressed, and inherited *ab ovo, ab spermate, et ab præ-embryone*? And are these offspring, if the burden and blemish—the diathesis—of their heritage is potent enough, capable of transmitting it to the third generation? These are questions of the profoundest importance,

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matters sometimes of life and death. I state here, after a due consideration and study of the vast body of pathological evidence and facts for fifteen years, and after much thought, discussion, and deliberation, that the teaching of pathology is positive, clear, and irrefutable. Let us take concrete instances.

In the case of married couples who have permitted themselves immoderate alcoholic indulgence in the *first few days or the first week* of the honeymoon (Combemale, *Les Descendances des Alcooliques*, Paris, 1888), but who have otherwise led lives of temperance before and after the event, feeble and imbecile first-born children have often been the gift of Nature for their indiscretion. Sabatier (*Thèse de Paris*, 1875) has also, after a long and careful inquiry and study of peasant families in France, arrived at the same conclusion. As a typical case of the many investigated by him may be taken the following. A robust and intelligent peasant, a native of Auvergne, following the custom prevailing in many villages of his district, passed the *first three weeks* of his married life in drinking and jollification, "being in a state of moderate alcoholic intoxication all the time." Nine and a half months later there was born unto his wife a girl of imbecile mind, with myopia and nystagmus, bad-tempered, and of odd (bizarre) and changeable nature, who was unable to learn to read or write. Sabatier also mentions numerous examples of married couples who habitually practised Malthusian principles to limit their families. "But occasionally they gave themselves up to alcoholic festivities for days, forgetting," he quaintly adds, "for the time being their Malthusian principles and procreating children, most of whom turned out to be deformed, idiotic, or epileptic." Demeaux had shown earlier, from a series of observations made by himself (*C. R. Acad. de Sci.*, November 1st, 1861), that "alcoholic intoxication at the time of conception was a cause of epilepsy in the child." Dehaut (*ibid.*, October, 1861) and Vougier (*ibid.*, December, 1861) have furnished cases and observations of the same character. Voisin (article "Epilepsie" in Jacoud's *Dictionnaire de Med.*, 1886) states that in inquiring into the history of the cases of epilepsy under his charge at the Salpêtrière he found "twelve cases in which he was able to assure himself that the cause of the epilepsy was that conception had occurred when the parents were drunk (*en état d'ivresse*)." Grenier (*Thèse de Paris*, 1887) studied the cases of 188 idiot and imbecile children, and was

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able to trace seven of these to drunkenness of the parents in the first few days of married life. The whole body of facts brought together above refers to temporary intoxication and drinking, and not to chronic drunkards. They illustrate *the action of alcoholism on the germ- and sperm-cells and on the pre-embryo.* Combemale (*loc. cit.*, 1888) cites a very instructive case, among his series, of a man, æt. 22, who was the second child of a family of six. He was begotten by his father while in a state of "alcoholic intoxication and exaltation." The child born of this act was neurotic, and had during all his life marked nervous manifestations and disorders of nutrition (*manifestations nerveuses et des troubles nutrifs accusses*). He was delicate in health, suffered from neuralgia and intolerable cephalalgia at 10 years. At the age of 13 years the cephalic symptoms (*cephalées*) prevented all study and intellectual work; at 16 he developed epilepsy and vertigo, and soon after he became hypochondriacal and underwent cerebral degeneration and mental and moral deterioration (*dementia præcox*) which necessitated his being placed in an asylum. The father, a well-to-do man, had several mistresses maintained in various houses, and was the father of several other children. Though given to occasional alcoholic indulgence he abstained from cohabiting when in a state of intoxication, *and his other children born of his sober moments were not afflicted bodily or mentally like the patient referred to here.* The patient's mother herself was a woman of greedy habits and bad temper, but free from neuroses and with a healthy family history. The influence of temporary intoxication of the parents on the offspring begotten by them has drawn the casual attention of observers of older times (Pinel, Esquirol, Seguin, Lucas, and Morel), but it was reserved for the followers of Morel and the other writers of the French school quoted above, and of later observers (Déjerine, Legrain, Möbius) in the last quarter of the nineteenth century to collect and establish a body of facts showing once and for all the soundness of this theory of pathological heredity. [The reader desiring fuller information should consult the *Thèses* of Sabatier and Combemale (1875 and 1888), the works of Voisin and Grenier (1886, 1887), and the special chapters in their memoirs on the subject of alcoholism and heredity by Déjerine (1886), Legraine (1895), and Möbius (1900)].

In the Presidential Address at the annual meeting of the

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Medico-Psychological Association, Dr. Wiglesworth (*Journal of Mental Science*, October, 1902) deals clearly and comprehensively with alcoholism as a cause of insanity and hereditary degeneracy in the human race. Alcoholism in the progenitors, says Dr. Wiglesworth, basing his study on 3450 cases of insanity examined at the Rainhill Asylum during a long series of years, is a fruitful cause of idiocy, mental defect, insanity, and other nervous diseases in the offspring. Alcoholism is, of course, frequently associated with mental disease in the family histories of insane patients, but for the purposes of inquiring into the special action of alcohol, he found that of the total number of 3450 cases a definite history of alcoholic excess unassociated with insanity in one or both parents was traceable in 578 instances. Separating the sexes, it was found that 327 of these cases were males and 251 females. "Doubtless some few of these cases of alcoholic excess may have been veritable examples of dipsomania . . . a neurosis allied to insanity; but as most of such cases usually show mental disorders at some period or other of their course, the majority of them will have been included," he adds, "in the tables of hereditary insanity," with which we need not concern ourselves here. The figures given in this paragraph exclude such cases. The actual frequency of alcoholic intemperance in the ancestry of the insane is probably larger than what the above figures indicate, for the friends of patients often conceal or deny the existence of drunkenness. The figures therefore apply, says Dr. Wiglesworth "only to cases of gross and palpable excess." In regard to the *modus operandi* of the alcohol, it is regarded as a "direct poisoning of the germ plasma itself by the alcohol circulating in the blood, and a consequent direct injury to the cells of which this structure is composed, and which by reason of this injury are prevented from developing into a stable organism." Regarding thus the vast population of a public asylum, composed of insane patients who have been observed and studied for a number of years, it is found that 17 *per cent.* of all cases of insanity, taken together, are due to alcoholic parentage, as distinct from and exclusive of other causes, such as epilepsy, organic brain disease, tuberculosis, or insane parentage. If the alcoholic poisoning of the germ-cells and ovum have reached a certain degree of intensity, imbecility or even profound idiocy may be expected to result, "while if of less

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degree the injury may manifest itself in the various forms of adolescent insanity when adult life is developing or has been attained to." If both parents are alcoholic, the damage sustained by the germ- and sperm-cell might be sufficient to render them incapable of fertile union, or to result in the production of an embryo which becomes aborted in early pregnancy, or dies *in utero* and becomes a miscarriage.

An inquiry on a large scale into the hereditary sequelæ of alcoholism was carried out by Dr. T. Crothers, of Hartford, Connecticut, U.S.A., and a committee of physicians appointed in 1888, of which he was chairman. The collection of material by skilled physicians and specialists (clinical histories and cases) went on for thirteen years, and was carried out with great care. An account of this research has been recently published (*Quarterly Journal of Inebriety*, Jan., 1901), based on the investigation of 1744 cases of inebriety, not including, however, cases of actual alcoholic insanity. The chief conclusion reached was that the injury produced by the alcoholism of parents not only affected the nervous systems of the immediate progeny, but that the ill-effects (diathesis and degeneracies) were also transmitted through them to the later progeny of the third generation with almost positive certainty in some form, *e.g.*, as a neurosis, a cerebral defect, or a drink craving. Thus, of 1744 inebriates it was found that 1080 were traceable to parental intemperance, and in only 390 was it an acquired habit. Forty-nine of the patients were classed as instances of epileptoid-alcoholic type. The patients of this class were not epileptics in the true sense, but they were hereditary alcoholics of a particular pathological type, whose individual symptoms (of alcoholism and excitement) were of sudden and stormy development, "not strictly or regularly periodic, but developing out of the clear sky in an impetuous storm, and then disappearing and leaving little trace behind." Finally, various groups of patients were met with (in the progeny of alcoholic parentage) in whom fatalistic tendencies to drink were observed, or who manifested precocious sexual instincts which would be gratified by any means whatever or were given to morphia and drug habits. Sound, well-balanced men and women of good intelligence and *morale* were very seldom met with among the offspring of the alcoholic families which formed the subject of the inquiry.

The special influence of maternal inebriety on the offspring.—

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It has been observed by many writers that those classes of individuals who exhibit marked incapacity or inability to adapt themselves to normal social conditions—*e. g.*, many feeble-minded and imbecile subjects, and a considerable proportion of habitual criminals, tramps and vagrants and prostitutes—are largely the offspring of alcoholic parentage. Thus of a series of 1000 idiots investigated by Bourneville (*Comptes Rendus de Bicêtre*, 1896) at the Bicêtre, Paris, an alcoholic parentage was ascertained to be the etiological factor in 62 *per cent.* When both idiots and imbeciles were included the proportion was 41 *per cent.* Marro, of Turin, found an alcoholic parentage in 46 *per cent.* of habitual criminals, while 45 *per cent.* of the inmates of Swiss prisons for juvenile offenders showed a similar history of ancestral alcoholism. Madame Tarnowsky, a Russian lady physician, found that 82 *per cent.* of Russian prostitutes were the offspring of alcoholic parents. Observations of this kind might easily be multiplied. In an article in the *Journal of Mental Science*, of 1899, Dr. Sullivan, of H.M. Prison, Parkhurst, states that he pursued an opposite method of inquiry to the above to determine the influence of maternal inebriety on the offspring. He took for the subject of his inquiry, not alcoholism in the ancestry of the degenerate, but degeneracy in the descendants of the alcoholic. For this purpose he studied a number of women who were habitual drinkers, and who had borne children, selected from the female population of Liverpool Prison. To render the conditions of investigation accurate and free from fallacy, all women exhibiting a phthisical or syphilitic taint or history were excluded, as well as cases which had a neurotic taint indicated by a specially early and violent cerebral reaction to alcohol (dipsomaniacal and epileptoid cases). Eliminating all these, 120 cases remained for study.

In the criminal as in the insane alcoholic it is well known that the stresses of alcohol fall with peculiar vehemence on the brain, while the bulbo-spinal cord and the non-nervous organs of the body suffer less intensely. In the female cases comprised in Dr. Sullivan's inquiry the effect of alcohol on the central nervous system was well marked and conspicuous. Thirty-one of the 120 cases had suffered from one or more attacks of alcoholic delirium, while 24 others without actual delirium suffered from visual hallu-

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cinations at times. Suicidal impulses, paræsthesiæ of the skin, and cramps in the extremities were noted in a considerable number also. (Inquiries in their families revealed the fact that similar symptoms were present in alcoholic relatives—not in prison—of the patients.) The study of the progeny of these 120 unhappy women showed that 600 children were born to them. Of the 600 children, 265, or 44·2 *per cent.*, lived over two years, while 335 (55·8 *per cent.*) *died while under two years, or were still-born*, a striking commentary on the feeble and degenerated condition of the progeny of alcoholic mothers. With a view to establish comparisons with a healthy non-alcoholic standard, inquiries were made and trustworthy details collected concerning 21 of the families to which these women belonged, and with regard to female relatives (sisters and daughters) of sober habits who had contracted marriage with sober males, and had borne children. Thus, of 28 sober mothers (sisters or daughters of the alcoholic mothers referred to above) there were born 138 children. Of these 138 children 33 (or 23·9 *per cent.*) died under two years of age. Thus the death-rate among the children of the alcoholic women was nearly 2½ times as great as that among the infants of sober mothers *of the same stock*. Another fact established by the observations was the progressively increasing death-rate in the progeny of alcoholic families where three or more children were born to a family. This will be clearly seen from the following table, which gives the respective proportions of dead or still-born children among first-born, second-born, third-born, etc.:

Table showing the Progressive Increase of Mortality in the later Progeny of Alcoholic Parents.

Order of birth.	Cases.	Dead or still-born.
First born	80	33·7 *per cent.*
Second born	80	50·0 ,,
Third born	80	52·6 ,,
Fourth and fifth born	111	66·7 ,,
Sixth to tenth born	93	72·0 ,,

These figures and percentages illustrate very clearly the progressively augmenting results of the maleficent influence of maternal alcoholism in the offspring.

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The study of individual families in which this degeneracy of progeny resulting from alcohol could be traced for more than two generations affords results of striking interest, corroborative of the above. The following is an average instance of such a family history traced over two generations. The first generation begins with a woman aged 34 years, who has had several convictions and imprisonments for drunkenness and disorderly conduct. She took to drink after her first baby was born, beer and spirits; she developed gastric cramps and catarrh, and had one attack of delirium tremens. Occasionally she was hysterical; attempted suicide twice. Husband also drank, but never had delirium tremens. His and her parents were sober. Six children were born to her. The first was quite healthy. The second and third were living and fairly healthy. The fourth child, aged six years, is of low intelligence, habits wet. The fifth child is still more degenerate, an epileptic idiot, aged four years. The sixth child was still-born, and the seventh a recent abortion.

Influence of paternal inebriety.—While the observations of Sullivan apply more especially to the progeny of inebriate women, the following observations of Robinovitch are drawn from women who have developed temporary but recoverable mental disorder from alcoholism, and who were seen in the first instance at the clinic of St. Anne's Asylum, Paris, during the years 1898 and 1899 (*N. Y. Medico-Legal Journal*, December, 1900). These cases might almost be termed borderland cases between sanity and insanity. They therefore offer an interesting contrast and complement to the female cases before mentioned. These cases, fifty in number, were only accepted as suitable for study, says Dr. Robinovitch, after excluding cases of real insanity, with mental irresponsibility, owing to insane impulses or delusions; cases of chronic mental derangement; cases of chronic alcoholic insanity; and cases of congenital mental and moral defect (congenital idiocy and imbecility). All the fifty cases were found to be traceable to and due to alcoholic parentage; and in other members (progeny) of these families other indications of alcoholic degeneracy were revealed on inquiry. It was also found that in the vast majority of these families *alcoholism of the father was the predominant factor, and that it existed as the sole factor in over* 90 *per cent.*, alcoholism of the mother only existing in about 3 *per cent.*, and of both parents in about 6 or 7 *per cent.* One typical family

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history is appended from Dr. Robinovitch's records. A man of drunken habits and bad temper, a drinker of absinthe, married a woman of normal disposition who enjoyed good bodily health. There were eight children of the marriage, one of whom is the patient (referred to below). The following is the history of the progeny. The first child, a female, was feeble-minded, and grew up to become the mother of an illegitimate child; another, a male, was timid and odd in conduct; two others (males) were dull in mind and incapable of earning a living. The patient (referred to above) was born at full-term, walked at the age of three years, and talked at the age of five. At sixteen he began to exhibit vicious propensities, frequented disreputable places, and was convicted of attempts at rape on young children. He enlisted at the age of eighteen years, and was shortly afterwards discharged for larceny. He became an absinthe-drinker, low, depraved, and criminal in his tendencies. He was eventually placed in an asylum. "His life," adds Dr. Robinovitch, "was one continual manifestation of vice and criminality."

A study was also made by the same author of the progeny of the alcoholic families which furnished the preceding fifty cases. Alcoholism on the father's side, as already stated, was found to exist in over 90 *per cent.* Of a total of 127 children born to these fifty families 50 "were suitable subjects for asylums and the prison," 40 died in infancy or prematurely, and 37 were still living. Of the 37 living 27 were in good physical condition; the rest were sufferers from meningitis (4 cases), convulsions (3 cases) and other diseases, and one of them was beginning to manifest criminal tendencies.

A remarkable case of the hereditary degeneracies following alcoholism of both parents.—The discussion of alcohol and the hereditary degeneration of the progeny may be concluded with the recital of the following remarkable modern instance—remarkable in that the investigation has been thorough, the result instructive and unmistakable, and the record lengthy in its scope, embracing four generations, as published by Dr. A. MacNicholl, of New York, in the *Quarterly Journal of Inebriety* for July, 1902. The genealogical table and the history of this family illustrate the results of degeneracy and disease arising mainly from alcoholism in a family traced and studied as follows:

First generation.—The head of the family was a well-to-do

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man of good social position, of English parentage, living in the United States. He married a lady of Huguenot descent of good social position. Both of them lived well, indulged in social gaieties, and took wine habitually and daily. To them were born two daughters, whose further history is here unfolded.

Second generation.—The elder daughter developed in early life a fondness for wine and spirits, gave herself up to the wildest alcoholic and sexual excesses, became the mistress of several men and contracted loathsome venereal diseases. She died a raving alcoholic maniac at the age of 40.

The younger daughter also developed in early life a fondness for wine and spirits. She married a wealthy banker and indulged in a gay life of excesses which led to a mental breakdown at the age of 38 years. She bore eight children.

Third generation.—Two of these, boys, grew up to be drunkards, showing at the age of 50 and 60 years respectively the signs of chronic alcoholic brain degeneration. Six of the issue following were girls, five of whom died of phthisis between the ages of 20 and 35. The remaining girl survived and married a healthy man of "moderate" alcoholic habits. She and he, however, drifted later into alcoholic excess and led fast lives. Their children constituted the next generation.

Fourth generation.—Seventeen children were born of this ill-fated union, ten of the children dying from phthisis before the age of 5 years. [Attention may be directed *en passant* to the remarkable facility to contract phthisis which occurs in the progeny of alcoholic parents.] Of the seven surviving children the following are, in brief, the life histories:

A, the eldest, a girl, exhibited great moral perversion, became a professional singer and prize-fighter, was drunken and dissolute, and became the mother of several illegitimate children. *B*, a boy, grew up to be a moderate drinker, and contracted phthisis, from which he was suffering at the age of 45. *C*, a boy, became an insurance agent, drank moderately, and exhibited suicidal tendencies on more than one occasion. *D*, a boy, habitual drinker and morphia-taker, had delirium tremens several times and ended his life at 35 by an overdose of morphia taken while drunk. *E*, a girl, married early, took to drink and developed suicidal melancholia. *F*, a boy, a typical psychopath. At the age of 12 he was an industrious and studious boy, but

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peculiar in his ways. At 21 he married, was lazy, indolent, and neurasthenic. At 23 a confirmed drunkard, neglectful of his home. At 24 he abandoned his wife and 2 children, and at 28 he committed suicide by drinking carbolic acid. *G*, the last (the seventeenth) of this unfortunate family, received a High School education, and at the age or 21 was the subject of moral perversion and suicidal impulses. The whole family tree, tainted by alcoholism, traced during the four generations of its existence, exhibited almost every form and grade of mental degeneracy and deterioration with a high rate of mortality of offspring, in the most remarkable manner. A fearful commentary on hereditary transmission!

Pathogenic action of alcohol on the sperm- and germ-cells.—Féré, of Paris, has, in a series of experiments conducted on the influence of the vapour of alcohol and absinthe on incubating eggs during the pre-embryonic stage (*Comptes Rendus, Société de Biolog.*, Paris, vol. lii., pp. 231, 471, 601, 681, 790) afforded convincing evidence of the influence of alcohol on the developing pre-embryo. These experiments on normal eggs, carefully selected and placed in incubators and subjected for a few days during the first week of the process of development to the influence of the vapours of small quantities of alcohol, or of absinthe, gave interesting and instructive results, tabulated below.

No. of eggs.	Toxic agent.	Results of development of the eggs.		
		Normal.	Undeveloped embryos.	Monstrous or defective (imbecile) development.
a. 84	Alcohol	63·1 *per cent.*	15·5 *per cent.*	21·4 *per cent.*
a. 24	Alcohol	62·5 „	16·6 „	20·8 „
b. 84	Alcoholic solution of absinthe	25·0 „	31·0 „	44·0 „

Thus, while alcohol in small doses produced 63 *per cent.* of normal births, 16 *per cent.* of undeveloped (partially developed and dead-born) embryos, and 21 *per cent.* of monstrosities (malformations) and defective development ("chickens of idiotic and imbecile grade," says Féré, which could not "run

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about or pick up food or feed and help themselves"), the addition to the alcohol of traces of absinthe reduced the normal developments to 25 *per cent.*, increased the undeveloped and dead-born embryos to 31 *per cent.*, and of monstrous and defectively developed chickens to 44 *per cent.* The conclusion to be drawn is obvious as regards the comparative evil effects of these two toxic agents. Using in another series of experiments forty-eight eggs, in two batches, each batch exposed to slightly larger quantities of the vapour of alcoholic solution of anise and of absinthe, the following results were obtained: (*a*) For alcohol and anise the result was 42 *per cent.* of normal chickens, 25 *per cent.* of undeveloped and dead-born, and 23 *per cent.* of monstrosities and defective development, while for (*b*) alcoholic solution of absinthe there were 17 *per cent.* of normal chickens, 21 *per cent.* of undeveloped and dead-born, and 62 *per cent.* of monstrous and defective development. *Z*iegler, in his experiments with the fertilised ova of Echinus and Strongylocentrotus (*Biolog. Centralbl.*, 1903, p. 448) to test the action of alcohol on the impregnated ovum, found that ½–1 *per cent.* of alcohol injured and retarded development to a moderate extent, but that there were marked individual differences in susceptibility. One and a half to two *per cent.* of alcohol in the sea water seriously deranged development and was thus highly toxic, as Rauber had previously found, for various animals. The cleavage, says *Z*iegler, was slow and often abnormal. The blastocœl tended to be too small; only a few blastulæ were formed, the remaining ova died before. Gastrulation was sluggish, the mesenchymic cells had not the normal arrangement, a skeleton was not developed or, if formed at all, was abnormal. The few plutei larvæ which developed were monstrosities lacking well-developed arms and did not live long, death being the almost constant issue. With 3 *per cent.* alcohol the injury and arrest of development were greater, and death often occurred before even the gastrula stage was reached. The action of alcoholism on the ovarian and testicular elements of dogs and of man have been experimentally and microscopically studied. Magnan and others have found in the testicles of the dog the occurrence of a granulo-fatty degeneration, with feeble vitality and mobility of the spermatozoa; and other observers have recognised and described similar changes in man.

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The whole body of facts, of observations, and of experiments on the influence of alcoholism on the sperm- and germ-cells, and on the pre-embryo, summarised above clearly indicate and demonstrate the pathogenic potency for material evil possessed by alcohol and exerted on the offspring of alcoholic parentage.

Plumbism.—We need not dwell at any length on the special toxic effects of lead-poisoning of the mother on the germ-cells or the pre-embryo. Lead-poisoning of the mother produces distinct injury of the embryo *via* the maternal blood-plasma which carries the lead in solution. Moreover, a grave anæmia is also produced by lead-poisoning, and deficient nutrition or even death of the embryo results. There are always serious changes, says von Jaksch (Nothnagel's *Special Therapy* 1897, vol. i p. 207), in the introgenous metabolism of the body resulting in an excessive production of uric acid, owing to an excessive destruction, by the lead, of nuclein-containing substances. Rennert pointed out in 1882 that women, otherwise healthy, employed in the pottery factories (where lead is used in glazing and the women are exposed to the dangers of infection from lead fumes) in Germany had frequent abortions or gave birth to children who were deaf-mute, macrocephalic, or otherwise mentally defective (Talbot *On Degeneracy*, 1902, p. 119). Early abortion occurring in lead-poisoning is due to the intensity of the toxæmia and anæmia, the conjoint action of which is to produce death of the embryo. In milder cases of lead-poisoning the child may survive, but at its birth may exhibit the characteristic symptoms. Thus Oppenheim, of Berlin, has described a case where the child was born in a state of feeble bodily nutrition with foot and wrist-drop and local muscular atrophies, a condition traceable to lead-poisoning of the mother. In this case, however, the characters of the lesion indicated that the morbid process (toxic action of lead) was sustained in fœtal and not in embryonic life.

Syphilis.—Syphilis may produce death and abortion of the pre-embryo in the first month of intra-uterine life or immediately afterwards. The cerebral lesions of syphilis sustained by the pre-embryo or the embryo may produce symptoms which vary from profound idiocy to imbecility. Syphilis attacking the pre-embryo and embryo produces developmental malformations and monstrosities of embryonic development according

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to the exact period of infection. Among these are anencephaly, spina bifida, meningocele and encephalocele, hare-lip and cleft palate, ectropion vesicæ, and deformed auricles, malformations which are here given in chronological order of their origin in the embryo. The first and second of these may be caused during the third week of intra-uterine life, the last two in the fourth and fifth weeks, and the others at intermediate times. All these malformations are thus of pre-embryonic or early embryonic origin, due to the action of the syphilitic virus within the first month of intra-uterine life.

Such an array of definite facts as those collected and presented above in regard to alcohol, plumbism, and syphilis can be extended to include the pathogenic action of other agencies, such as tuberculosis, which space prevents us from dealing with here.

Finally, as regards bacterial and other toxins and their effect *via* the maternal blood-plasma on the embryos of pregnant rabbits and cats, brief reference may be made to the recent experiments of Charrin and Delamare on cats, rabbits, and guinea-pigs (*C.R.*, 1901, p. 955, and *Thèse de Paris*, 1904), which show from a large and careful series of experiments that toxic and cytolytic agents generated within the maternal body by bacterial agencies or by surgical (experimental) lesions of large visceral organs (*e.g.*, ablation of one half of the liver, or of the pancreas, but not ablation of one kidney) of the mother acted on the pre-embryo or embryo in such wise as to induce in it special visceral lesions and profound disturbances of nutrition, the actual tangible and visible results being seen in the necropsies performed on the fœtus at or near full term. The results included abortions, still-birth at about full term, nanism or idiocy, osseous malformations like *chondrodystrophia fœtalis*, and other malformations. In fact, these experiments and their results fall into line with those of Féré on incubating eggs of which we have given a fairly full summary already, and they unite in confirming the clinical and pathological conclusions previously drawn regarding heredity and the pre-embryonic life.

General Conclusions.

1. Preformation theories of the spermatist type have been

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proved to be baseless, one-sided, and valueless. Yet they were necessary stages in the development of knowledge.

2. The modern view is that the male and female (germ and sperm) cells of the parents contribute in equal or approximately equal proportion to the constitution of the pre-embryo, and that the special intra-uterine environment and nourishment of the fertilised ovum during its growth and evolution in the parental body constitute a third factor of importance, and that this is especially the case in those animals whose gestation period is prolonged (mammals). While the above are the normal factors which co-operate in the production of the progeny, a fourth (accidental or pathogenic) factor may enter as a complication—a fact with important practical bearings, especially for the human race.

3. In the course of animal evolution Nature exhibits in the successively later and higher stages a gradually increasing perfection of the mechanism for keeping constant the immediate environment of the fertilised and developing ovum until considerable progress—well on to post-embryonic or fœtal life—has been attained. Thus, starting from the lower vertebrate forms in which the eggs are extruded into the water (sea or fresh-water animals), we find protective envelopes developed to hold the eggs together in strings or masses (fishes and amphibia), the gelatinous envelope of each egg serving as a special environment during embryogenesis. As we ascend higher the eggs are provided with shells and membranes enclosing a large food supply, a more constant environment and a longer period being thus rendered available during embryogenesis. In warm-blooded animals a thermostatic mechanism is provided, and in the mammals a long period of intra-uterine placental life is also passed through, the medium which surrounds the embryo during the long period of uterine development being kept remarkably constant by these means. Everywhere we see in Nature the increasing purpose of life and of heredity in affording the fertilised egg a more and more constant and perfect environment during the critical period of its development. The only factor of any importance which is apt to disturb this is the pathogenic factor, which is one especially applicable to man.

4. In building up our knowledge of heredity, five classes of facts have been found to be useful, if not indispensable, *viz.*, the facts and knowledge of animal breeding, human breeding,

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plant breeding, the laws of human and comparative embryology, and the laws of pathogenesis.

5. Heredity and variations—antagonistic forces of the organic world—have to co-operate and combine in order to render the evolution of the higher forms of life possible. Variations are as much an indispensable factor in the progressive evolution of newer and more complex forms of life from the older and simpler as heredity is for the conservation of the generic and specific types. But the relative values assigned to these factors are different in the estimate of different authors, and the difficulties are increased in the case of man because artificial complicating factors of civilisation, degeneracy, and pathogenesis are present in his case which the biologist has hitherto taken no account of.

6. Zoologists and palæontologists believe that variation must have been greater in early phylogenetic stages than at the present time. Some of the facts of palæontology when closely scrutinised "do lend support to the view that when the first existing forms of life were being established variation was considerably greater than to-day" (Sedgwick, B.A. Address in *Zoology*, 1899). "In the process of evolution in the higher forms of life there has been a gradual diminution in the range of variation of the different characters of the body—a gradual diminution of the responses of these characters to changes of the environment. Characters which, in the early stages of evolution, were probably plastic have become rigid. . . . The study of species teaches us that in all cases (except, perhaps, in some examples of degeneration) the plastic condition of the characters was antecedent to the rigid; that in the earliest stages of evolution the condition of extreme plasticity and ready response to changing external conditions were necessary for the survival of the species; and that, in the later stages, when special adaptations to special circumstances were developed, a certain rigidity or indifference to changing external conditions was equally necessary for its survival" (Hickson, B.A. Address in *Zoology*, 1903).

7. Galton's law of regression holds good for man and animals, but only for averages. What may result in individual cases cannot be predicted by its application.

8. Mutation, which is in one sense the very antithesis of regression, must be regarded as a special event, where, by

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the infrequent combination and cumulative effect of physiological or pathological forces a "saltatory" variation is produced which has the character of stability and hereditability. Many examples of it have occurred in plants and animals, and it is to be regarded as established that new species have originated from existing species by mutation. An increasing knowledge of Nature favours the adoption of this attitude of mind. The increasing importance of mutation demands the attention of all future investigators in heredity and evolution.

9. Variation, in the widest sense, is of three or four kinds or modes, as manifested in the organic world—*viz.*, the continuous variation which occurs in organisms normally and according to the law of probability; mutation which occurs in a state of nature (wild) or of civilisation (domestication); pathogenic variation, which is of the nature of a pathological accident and is often a peculiar inheritance of civilised man; and perhaps meristic variations, which border on the pathogenic. These distinct processes obviously require different modes of study for their elucidation.

10. The "recapitulation theory" is essentially true when properly interpreted. The developmental phases passed through by the embryo represent, broadly speaking, a recapitulation of its ancestral history; ontogenesis is an epitome of phylogenesis. "Each animal in the course of its development from the ovum climbs up, as it were, its own genealogical tree." In interpreting the features of embryogenesis, von Baer's law should be borne in mind: "Embryonic states can only be correctly compared with embryonic states, but not with adult states. The more different two forms are, the farther back in their development must we go to find similar stages."

11. The human ovum and spermatozoon (gametes) undergo, after union or conjugation into a *zygote*, a series of changes regulated by the character of the conjugating elements and the nature of the medium in which they live, move, nourish themselves, multiply and develop (embryogenesis). In higher animals, and especially in the Simiæ, the development of the early stages has been described by Hubrecht in his researches on Tarsius. The germ-track, which precedes the appearance of the primordial germ-cells, may lie, and often does lie, in somatic cells. "A series of the various species of animals may be drawn

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up," says Weissmann, "in which the formation of the primordial germ-cells begins at very different degrees of remoteness from the egg-cell. . . . In most of the higher Metazoa this (the first appearance of the primary germ-cells) only occurs after the formation of thousands, or even millions, of cells."

12. The doctrine of the charmed life of "isolation" of the germ-plasma is not in accord with facts, especially those facts derived from pathological study. The study of alcoholism, syphilis, plumbism, and other toxæmias, demonstrates this conclusively, as also the clinical data and genealogical tables of heredity and alcoholism collated or referred to in the foregoing chapters. Experimental evidence also supports the view, taken in this memoir, of the law of pathogenesis.

13. The special and separate influences of maternal and paternal inebriety are also proved by varied and extensive evidence quoted before, and evidence (on a smaller scale) has been quoted to substantiate the same theory as regards plumbism and syphilis. Thus it is found that 62 *per cent.* of cases of idiocy are due to alcoholic parentage (Bourneville); that, taking idiocy and imbecility together, 41 *per cent.* are of alcoholic descent (Bourneville); that 20 *per cent.* of asylum cases of insanity are the hereditary product of alcoholic parentage exclusively (Wiglesworth); that 46 *per cent.* of habitual criminals (Marro) and 45 *per cent.* of juvenile offenders are the hereditary issue of alcoholism; that 82 *per cent.* of the prostitutes in Russia are the outcome by direct descent of inebriate parents (Tarnowsky); that the lethal effect on the offspring of alcoholic mothers is high as revealed by a mortality rate of 56 *per cent.* for all new-born and young children below the age of two years, a mortality which is two and a half to three times as great as that of the sober married sisters of such inebriate women (Sullivan); and that nearly 90 *per cent.* of borderland cases between insanity and criminality in women in Paris (inmates of St. Anne Asylum) are attributable to the alcoholism of the parent, especially of the father (Robinovitch); moreover, that the pathogenic action hereditarily acting for evil and degeneracy in the progeny can also arise from other poisons than alcohol, such as absinthe, plumbism, and syphilis.

Addendum.—The concluding part of the present memoir, dealing with the physico-chemical and organic basis of heredity

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and of variation, will be published in a future number of the *Journal of Mental Science.*

(1) Being part of a paper read, with lantern demonstration, at the meeting of the Medico-Psychological Association at Oxford, February 12th, 1904.

Mental Depression and Melancholia considered in regard to Auto-intoxication, with special Reference to the presence of Indoxyl in the Urine and its Clinical Significance; Essay for which was awarded the Bronze Medal of the Medico-Psychological Association, 1904. By ARTHUR A. D. TOWNSEND, M.D., Senior Assistant Medical Officer, Barnwood House, Gloucester.

THE more modern and advanced opinion of the present day, not of necessity the most correct, regards toxic action as the most important factor in the pathogenesis of insanity. According to this view insanity is not regarded as primary disease of the brain, but secondary, and due to toxins derived from elsewhere acting upon the cortical nerve-cells, disordering their metabolism, and thus affecting their functional activity, damaging, or destroying them. The older psychologists are evidently disinclined to accept the toxic theories of the younger school, and cling with pertinacity to their opinion that mental disease is as a rule primary, and that the physical manifestations of ill-health result from a disordered central nervous system, and undoubtedly many of the facts they produce in support of their argument are difficult to refute; on the other hand, it is necessary for those who advance the theory of toxæmia as the essential factor in the production of insanity to marshal facts supporting their contention. By the term "auto-intoxication" we indicate toxins evoked within the body as a result of disordered metabolism, first, such as takes place in chronic Bright's disease, myxœdema, diabetes, etc.; and secondly, in the contents of the gastro-intestinal tract. Within the limits of this paper I propose only to deal with the second division, *viz.* auto-intoxication from the gastro-intestinal canal, for the cases coming under this group are by far the more numerous and important. For a long time I have strongly held the opinion, as a result of my own observations, that a very large

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