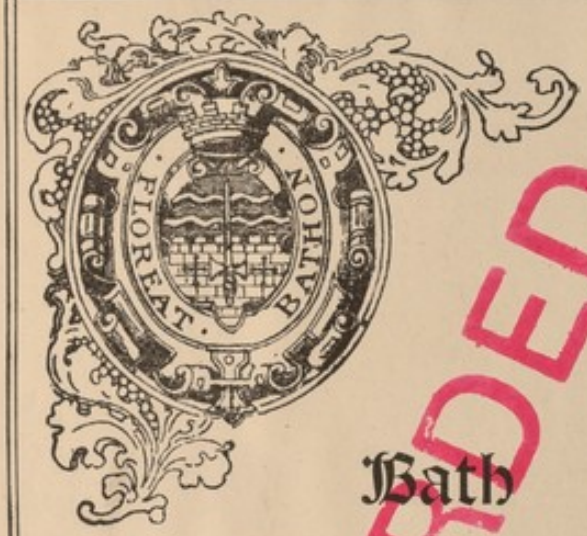
The Harveian Oration on some developments of Harvey's doctrine "Omne vivum ex ovo" : delivered before the Royal College of Physicians of London on October 19, 1925 / by Sir Frederick Mott.

THE HARVEIAN ORATION

SOME DEVELOPMENTS OF HARVEY'S DOCTRINE "OMNE VIVUM EX OVO" ON OCTOBER 19, 1925

SIR FREDERICK MOTT



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Some Developments of Harvey's Doctrine "Omne Vivum ex Ovo"

DELIVERED BEFORE THE ROYAL COLLEGE OF PHYSICIANS OF LONDON ON OCTOBER 19, 1925

BY

SIR FREDERICK MOTT, K.B.E., M.D., LL.D., F.R.C.P., F.R.S.,

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MR. PRESIDENT AND FELLOWS OF THE COLLEGE, permit me to thank you for the great honour you have done me by confiding to me the task of delivering this year the Harveian Oration.

The great discovery of the Circulation of the Blood marked a new epoch in medicine, for experimental physiology had lain dormant for fourteen centuries—since the time of Galen; but it is not my purpose to discuss this subject, which has been so fully and ably discoursed upon by many of my predecessors. The subject of Harvey's other great work, "De Generatione Animalium," stands with equal honour by the side of his doctrine of the Circulation of the Blood. Thus Verwoorn, the late distinguished physiologist of the University of Jena, speaks of it and, moreover, affirms that: "the

doctrine *Omne Vivum ex Ovo* which has obtained vast significance in the Science of Life, and in the various forms in which it has been expressed in recent times, controls all modern physiological views of organic reproduction."

Harvey's investigations concerning the generation of animals were very fully described by a previous distinguished orator only three years ago, and I can fully agree with all the expressions of admiration of this work given by Dr. Herbert Spencer, who remarks: "The bulk of Harvey's 'Generatione' consists in his careful observations and descriptions of the development of the ovum and fœtus in all stages in birds, animals and man."

Harvey, in his Preface to his work "De Generatione Animalium," remarks "how base a thing it is to receive instruction from others' comments without examination of the objects themselves. The rather as the book of Nature lies so open and is so easy of confirmation." Here we find the spirit of the conscientious investigator, which together with great logical acuteness characterized Harvey's personality and work.

Had the compound microscope been invented in Harvey's time he might have discovered the spermatozoa, and this might have led him to know and understand what, he says, neither the schools of the physicians, nor the discerning brain of Aristotle could explain: viz., the manner of "*how the cock and its seed does mint and coin the chicken out of the egg.*"

Time will not permit me to give an account of the series of researches which led up to our present knowledge of the morphological basis of reproduction, but I will, however, give a brief résumé in so far as it is necessary for the consideration of Heredity in relation to Mental Disease.

Omne vivum ex ovo.—The life of the individual begins from the moment of penetration of the spermatozoön into the egg when the conjugation of the male and female gametes occurs. The spermatozoön provides one half of the nuclear matter (chromosomes), the ovum provides the other half. The spermatozoön carries into the ovum the centrosome, and in the process of repetitive cell division which follows it acts in such a way that every cell of the body contains an equal amount of nuclear material derived from each parent in respect to the hereditary material of the species. The discovery of the special sex chromosome in spermatozoids of insects shows that two sets of spermatozoids may be produced: those with an odd sex chromosome which gives males, those with a pair of sex chromosomes which gives females; or as occurs in some insects, one chromosome is small, that of the future male, and one large, that of the future female. Racial characters may not be equal in the amounts of nuclear matter in the form of chromomeres or genes derived from each parental stock, and still less those due to familial ancestry, to which the greater number of mutations in man may be ascribed.

Although there is disjunction of the paternal and maternal chromosomes, yet if these chromosomes are constituted by a series of genes or hereditary factors arranged in linear order, it follows that the crossing over of blocks of these genes may lead to fusion or transference and replacement of blocks of genes representing respectively maternal or paternal unit characters. Moreover, this crossing over of groups of genes in alignment offers a germinal mechanistic explanation of facts observed by Galton in *Natural Inheritance*, where he says :—

> We appear severally to be built up of a vast host of minute particles of whose nature we know nothing, or any one of which may be derived from any one progenitor but are usually transmitted in aggregates, considerable groups being derived from the same progenitor. . . . In the process of transmission by inheritance, elements derived from the same ancestor are apt to appear in large groups, just as if they had clung together in the pre-embryonic stage, as perhaps they did.

The main facts of heredity were clearly set forth by Lucretius in " De Rerum Natura " :—

> Sometime, too, the children may spring up like their grandfathers and often resemble the forms of their grandfathers' fathers, because the parents often keep concealed in their bodies many first-beginnings mixed in many ways, which first proceeding from the original stock one father hands down to the next father ; and then from these Venus produces forms after a manifold chance and repeats not only the features, but the voices and hair of their forefathers. And the female sex equally springs from the father's seed and males go forth equally formed from the mother's body ; since these distinctions *no more proceed from the fixed seed of one or other parent than our faces and bodies and limbs : the birth is always formed out of the two seeds :* and whichever parent that which is produced more

resembles, of that parent it has more than an equal share; as you may equally observe, whether it is a male child or a female birth.

The late Dr. Ormerod, in his oration, 1908, pointed out that Harvey recognized "that moles and warts and cicatrices of the progenitor are sometimes repeated in the descendant after many generations."

Lucretius recognized then that there must be two seeds, one from the father and the other from the mother, kept concealed in their bodies. How exactly the conjugation took place he had no notion. But modern development of Harvey's doctrine "*omne vivum ex ovo*" has shown that, concealed within the fertilized ovum are not only the paternal and maternal germinal determinants of the physical characters of species, sex, race and familial ancestry. Experience and investigation show that the psychic raw material, out of which the furniture of the mind will be fashioned, is also contained in the fertilized egg. We can understand why the voice, as Lucretius remarks, may resemble that "of the forefather," because if there is a resemblance in the anatomical structure of the face and neck, there will be a resemblance in the anterior and posterior resonators and nasal cavities which together determine the quality of the overtones and the timbre of the voice.

[1]A study of eighteen pairs of brains of parents and offspring, of members of the same co-fraternity, have

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[1] *Vide* Bibliography, 1, 2.

shown a resemblance of the convolutional pattern of the brain. And why not also a resemblance in the reproductive-endocrine glands system, in which the emotions largely have their roots?

One of the most valuable contributions to our knowledge of character and temper depending upon an "inborn disposition impressed by Nature," was Galton's inquiry into "The History of Similar and Dissimilar Twins," which shows that temper and the raw material of character are inherited; for he found that identical twins brought up under a different environment remained temperamentally the same and of the same disposition; whereas dissimilar twins brought up in the same environment remained temperamentally different. We can only explain this on a chromosome mechanistic basis by the supposition that in identical twins two male gametes conjugate with two female gametes in one ovum. But this inquiry of Galton's shows, too, how much conduct and character depend upon inheritance. Moreover, an inquiry which I instituted, and which was carried out for me by Miss Agnes Kelley, in the Parish of Bethnal Green, showed that like tends to beget like.

This inquiry was made with the object of comparing the heredity and social conditions of a certain number of insane, mentally defective, and normal persons. Sixty cases were taken in each group. The first group was of adult patients in the London County Council asylums; the second of high-grade mental defectives; the third of normal children from the elementary schools. The last two groups were at schools in different districts of Bethnal Green. Every care was taken

to make as full and complete a family and social history as possible, and pedigree charts were constructed. The report was published in Part II, Annual Report of the Board of Control, 1915, and the following is a very brief summary of the results of this inquiry.

Insanity was very much more prevalent in the pedigrees of insane persons than in those of mental defectives—namely, in the proportion of 50 per cent. as against 25 per cent. of the defective cases. Conversely, mental deficiency was more apparent than insanity in the family histories of the defective children ; while the charts of the normal school children only showed insanity and mental deficiency in a very small percentage of cases.

Good trades and high wages were rare in the mentally defective group. Though there were a few exceptions, the general type of employment was poor, and 75 per cent. of the fathers were casuals and unskilled workers.

There was a corresponding dead level of poverty in the home conditions of these cases and the incapable mother was very conspicuous in this group. In few of the asylum cases, and among still fewer of the mental defectives, could the home conditions be described as good, while one-third of the homes in each of these two groups were classed as " homes in which the food was quite inadequate, the clothing very poor, and bare necessities were lacking." The normal group showed a decided improvement in industrial conditions and in the care of home and children, and there were very few cases of intense poverty or neglect. There was, further, a very striking contrast in the dependence on parish and charitable assistance among the families of the normal group on the one hand, and of the insane and mentally defective groups on the other. The normals not only applied less often to the parish, but they were also less well known to charitable agencies.

But mental deficiency exists in all grades of society, and in a number of cases heredity does not explain how it is that a child is born an idiot or imbecile and how the brain is arrested in its development.

The foundations of moral and intellectual characters are inborn, but the influence of education, example, and environment generally is much more potent for good or evil than in the case of physical characters. Unfortunately the high-grade imbecile and moral imbecile are fertile, and as they have only a narrow margin of highest control they readily yield to the impulses of the passions and animal instincts, or are unable to resist temptation when opportunity offers. Speaking of this raw material of character, which in a great many instances results from a failure of the latent potentialities of the fertilized ovum, Sir Thomas Browne (whose birthday it is to-day) clearly recognized the inborn disposition when he said: "Bless not thyself that thou wert born in Athens, but among thy multiplied acknowledgments, lift up one hand to heaven that thou wert born of honest parents, that modesty, veracity, and humility lay *in the same egg* and came into the world with thee."

One of the objects to which Harvey himself desired the Lecturer on the Foundation to direct his discourse was "to exhort our Fellows and Members to search out the secrets of nature." I shall therefore offer no apology if I devote most of the rest of the oration to my own endeavours to obey this injunction by a brief description of some of the researches[1] I have made in connection with

[1] For full accounts of these researches *vide* Bibliography 6-17 inclusive.

the function of reproduction and genetics, especially in their relation to certain mental diseases.

From time immemorial the influence of the sexual function on physical structure, character, and conduct has been known, but it is only within recent times that experimental investigations and clinico-anatomical observations have shown that this influence is dependent upon an internal secretion of an interstitial gland of the testis and ovary respectively, which can function independently of the genetic structure. The testis secretes a hormone which determines, prior to birth, the physical and mental sexual characters, and at puberty the secondary sexual characters. The reproductive organs are functionally correlated with the endocrine system of glands, especially the cortex adrenalis, the pituitary, and the thyroid. As the sex instinct gradually matures, a progressive mental and bodily evolution takes place in the male and female, in accordance, not only with the innate dispositions due to sex, race, and familial ancestry, but with the evolution of character, due to good or bad habit formations. Habits acquired in early life, although not germinal and transmissible, nevertheless form such stable organized reflex patterns in the nervous system as to be capable of profoundly influencing such inborn dispositions as the moral sense, the self-regarding sentiments, the emotions and passions, and their proper control. At the adolescent period a new great vital urge,

stronger even than self-preservation, energizes all the organs and tissues of the body, especially the nervous system, for the supreme biological end of reproduction and preservation of the species.

I will now give a short account of my own investigations regarding the interstitial cells in man and their functions. Examination of the testis of a full-term twin fœtus showed tubules containing embryonic spermatogenic cells; between them, lying in loose connective tissue, were seen abundant polygonal cells with a round nucleus lying in an eosin-stained cytoplasm. Many of the cells had the appearance of young cells. There was plenty of evidence of nuclear mitosis, and I came to the conclusion that numbers of the cells had attained maturity and were on the way to a regressive atrophy, leaving only the nuclei. These cells contain a lipochrome substance and lipoid granules. I found that at about the fourth month the seminiferous tubules are twice the size of those at birth; instead of being separated by loose connective tissue containing abundant Leydig cells, they are closely approximated, the Leydig cells have almost disappeared, and there are no lipoid granules visible. At the eleventh year I observed very little change in the size of the tubules, and the interstitial cells are only discernible by examination with an oil-immersion lens. Little or no interstitial lipoid is seen. There are commencing manifestations of nuclear activity and karyokinetic figures, but no

spermatids or spermatozoa. The Leydig cells do not reappear until puberty, when the generative function commences, and the sexual hormone from the interstitial cells begins again to pass into the circulation and determine the bodily and mental secondary sexual character.

Seeing that the male sexual hormones are active for probably more than six months in pre-natal and post-natal periods, it follows that this influence must have been operating on all the somatic cells, including the nervous system, during all that time. If there be an elective storage of the sexual hormone in the nervous system, as Steinach's experiments indicate, then a masculine behaviouristic tendency may thus early be engraven upon the nervous system. Moreover, by the sensitizing influence of the testicular hormone, the primary male characters are in this early stage made dominant in all the bisexual somatic cells. The belief in the occurrence of male sex-dominance at an earlier age than the existence of a secretion of the female sex hormone has received fresh support in the very interesting solution of the riddle of the "free martin" by Lillie.[1] He reports a case in which the female characters of a female twin calf were more or less completely suppressed and certain male structures developed as a result of anastomosis of the placental blood-vessels with those of the associated male twin calf.

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[1] Bibliography, 18.

This can only be explained by the influence of a soluble and diffusible hormone derived from the male and carried to the female by the circulating blood.

There can be no development of sex characters without all the other organs of internal secretion participating; all of the ductless glands, and especially the thyroid, the pituitary, and the adrenal, are influenced by the internal secretion of the sexual glands, and the latter are undoubtedly influenced by the former; indeed, there is a harmonious functional interrelation between the reproductive organs and the whole endocrine system.[1]

I have recently investigated a case of dystrophia adiposo genitalis affecting an epileptic imbecile, aged 29 at death. There was no hair on the face; there was polyuria and marked sugar tolerance; there was infantilism of the external genitals; the atrophous undescended testes were no larger than peas and showed microscopically both interstitial cells and spermatogenic cells replaced by fibrous tissue and fibroblasts. Associated with this testicular atrophy was a markedly atrophous pituitary and atrophous thyroid gland; moreover, the cortex adrenalis was much diminished in thickness.

The increase in growth of the long bones of youths castrated in early life is due to retardation

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[1] *Vide* Bibliography, 10, 12, 15, 16.

of endochondral ossification, and supports the view that the internal secretion of the testis controls calcium metabolism. Similarly, in the female there is a relation between the ovarian internal secretion and calcium metabolism, for removal of the ovaries benefits and sometimes cures osteomalacia. Again, the release of calcium from the pelvic bones during pregnancy and parturition may be regarded as a physiological process brought about by an internal secretion of the ovary, the phosphate of lime thus released being utilized by the mammary gland.

It is generally assumed that the source of the sexual hormone of the female is connected with the development of the Graafian follicle, and that the cells of the zona granulosa and the internal thecal cells of the follicle secrete a specific soluble substance which passes into the blood and determines the female characters. It may, therefore, be supposed that a continuous conversion of primordial follicles into immature Graafian follicles, from earliest infancy onwards, provides a feminizing hormone to counteract the pre-established male dominance in the bisexual cells of the body. This formation of atretic follicles, and subsequently corpora atretica, continues until menstruation occurs and maturation with dehiscence of the follicles takes place. I have found that ovaries at birth and in early infancy contain numerous immature Graafian follicles. Should this follicle formation not occur to a normal physiological extent, it is conceivable that, having

regard to the selective action of the hormone on the central nervous system, as revealed by Steinach's experiments, there would be a tendency to masculinization especially revealed in mental qualities. The whole of the somatic cells of male and female are, until the dawn of adolescence, engaged in growth and self-preservation, in preparation for reproduction and preservation of the species.

Disorders and diseases of the mind have long been associated with two conditions—namely, heredity, and the critical periods of human life (adolescence, when the sex instinct matures, and the climaterium, when the sex instinct wanes). These are physiological conditions. Pregnancy, parturition, and lactation in the female are likewise physiological conditions.

Two distinguished Harveian Orators, the late Dr. Ormerod and Sir Bryan Donkin, have dealt with the subject of heredity in relation respectively to nervous diseases and criminology, based upon wide experience, but neither of these has treated of the relation of heredity to insanity based upon the study of pedigrees, statistical data, and pathological findings.

Evidence of Heredity in Certain Types of Mental Disease.

There are three types of mental disease in which the naked-eye appearances of the brain do not afford any indication of an exogenous cause of the disorder

and loss of mind presented by the symptoms during life. I include them in one group, and they are termed respectively dementia præcox, manic depressive insanity, and involutional melancholia—the two latter may terminate in dementia.

Through the study of a large number of carefully constructed pedigrees by myself and co-workers, extending in many instances to four or five generations, and of statistics based on a card system extending to 4,000 related individuals, who have been or were at the time in one of the ten London County asylums, I have come to the conclusion that there is a signal tendency to *antedating* in respect to these types of insanity ; that is to say, if a parent suffered with manic depressive insanity, or a parent or grandparent with involutional melancholia or senile dementia, one or more of the descendants may suffer during adolescence with dementia præcox. In the construction of pedigrees I was particularly struck by the fact that two, three, or even four or five members of the same co-fraternity at about the same age suffered with mental disease—usually dementia præcox, sometimes associated with manic depressive insanity; not infrequently dementia præcox with imbecility. This is a more striking proof of hereditary transmission than when mental disease is transmitted in successive generations.

When there is evidence of insanity or epilepsy in both stocks, or a general neuropathic tendency indicative of mental instability, the liability to

dementia præcox is greatly increased in the descendants; therefore in advising (as one often has to do) in regard to marriage, evidence pointing to these special forms of mental disease in both stocks on one side, still more when on both sides, even if shown in collaterals, induces one to say definitely from a eugenic point of view that it would be inadvisable—inasmuch as the risk of an insane inheritance for the children is so much the greater.

Moreover, in some of the pedigrees it looked as if there were segregation of unit characters, for I was able to find healthy children who married and had a healthy grown-up progeny in the same co-fraternity with cases of dementia præcox, manic depressive insanity and imbecility. But, as the late Dr. Ormerod and Sir Bryan Donkin pointed out in their interesting Harveian Orations, there are too many complicating factors to permit of Mendelian principles, which are so striking in animals where breeding can be controlled, being applied in relation to mental diseases. I have to omit here the statistical data, but I should like to refer to one result of them, because it supports my premiss. Prior to the war the number of cases of dementia præcox admitted to asylums was about equal in the two sexes, likewise the average age incidence (about 23 years). During the war there were half as many male admissions of dementia præcox as females whose parents were or had been

in the London County asylums. The age of these males averaged 17.5 instead of 23.5; the reason being that those over that age had been conscripted, and I may state as confirmatory of this inference that 14 per cent. of the insane in the Army were cases diagnosed as dementia præcox.

The Nature of Dementia Præcox.

By a comparison of the mental and bodily conditions of an acquired mental disease—general paralysis of the insane—with the mental and bodily conditions found in dementia præcox, I shall endeavour to show that in dementia præcox there is a vital defect of the reproductive organs, and of the brain in particular, and probably of the whole body, especially of the endocrine glands.

I have investigated spermatogenesis in 108 cases dying in hospitals and asylums at different ages and in different bodily states, including normal death from shock of injury. I have found it active from puberty to old age (81), with individual variations in degree. In cases where severe chronic disease occurred in early life there has been found absence or deficiency of spermatogenesis. In adults dead of shock following accident, tuberculosis, dysentery, broncho-pneumonia, enteric fever, or gangrene of lung, active spermatogenesis was found. It was absent in several cases of prolonged extensive suppuration, and in several cases of cancer. But

these were diseases in which an active prolonged cell nuclear proliferation had taken place.

In general paralysis local patches of atrophy of the testes with dense fibrosis occurred in many of the cases examined, but with very few exceptions, in a large number of cases, active spermatogenesis in all stages was found in spite of intercurrent disease. The atrophied patches were due either to gonorrhœal epididymitis or localized syphilitic inflammatory affection of the testes. The dense white fibrous patches microscopically examined exhibited tubules consisting of thickened basement membrane without Sertoli cells or spermatogenic cells of any kind. The atrophic process was not due to a regressive atrophy, as in dementia præcox, but to a previous chronic inflammatory process. This, moreover, was shown to be the case by the fact that normal tubules with active spermatogenesis and Leydig cells could be found in the midst of the atrophied tubules. In spite of this secondary atrophy which affects the testes of many paralytics, the average weight of the pair after removal of the epididymis and tunica vaginalis is 8 grm. heavier than the testes of dementia præcox; whereas in the majority of cases of dementia præcox examined an emulsion of the testes revealed no spermatozoa, the converse was found in paralytic dementia.

In twenty-seven cases of dementia præcox of which the testes were examined, either a commencing, a partial, or a complete primary regressive

atrophy was evident by the morphological and microchemical changes in the spermatogenic epithelial cells and the interstitial cells, with a corresponding thickening of basement membranes and overgrowth of interstitial connective tissue. With a few exceptions these testes of dementia præcox cases showed less evidence of active spermatogenesis than the testes of an old senile case aged 81 at death. In 27 per cent. of the cases the interstitial cells showed the pigmentary degeneration found in old age.

It is possible that the large percentage of marked regressive atrophy of the testes was due to the fact that the greater number of the organs were obtained during the War when only youthful cases were admitted to the asylums. Many of these may have been cases of dementia precossissima.

I have no time to deal with the very important question of the influence upon the germ-plasm of circulating toxins in the blood. But the study of the testes of 108 cases dying of all forms of disease, and yet, except in dementia præcox and imbecility, showing with very few exceptions active spermatogenesis, appears to me to find a solution in the fact that a barrier of lipoid granules, similar in chemical composition to the lipoid granules in the cortex adrenalis, was found. These granules consist of a lecithin-cholesterin ester. The cholesterin acts as an antitoxin. Now I found in cases of microbial toxæmia that the lipoid-cholesterin ester disappears

from the cortex adrenalis, and some people speak of this gland as antitoxic in function on this account. It seems to prove that Nature will provide as long as it can for the protection of the germ-plasm. There is evidence to show that these lipoid granules are connected with oxidation processes, and would therefore protect the germ-cells against poisons like alcohol circulating in the blood. Whereas in general paralysis clumps of eosin-stained cells could be seen in sections of the testes with a low-power magnification, in the great majority of cases of dementia præcox eosin-stained clumps were not visible ; the appearances suggest a failure of these interstitial cells to maturate. Fibroblasts and dense fibrous tissue tend to replace the Leydig cells. It is less easy to show the regressive atrophy in the ovaries for various technical reasons, but the study of 100 patients dying in hospitals and asylums led me to the conclusion that there is, similarly to the male reproductive organ, a tendency to regressive atrophy of the reproductive organs in the female in dementia præcox, as evidenced by the deficiency of the chromatin in the nucleus of the primordial follicles, their disappearance and replacement by fibroblasts. The organ shows a sclerotic condition even in many young women suffering with this disease.

To the first volume of *Libro en Honor* of Ramón y Cajal's seventieth birthday I contributed a paper upon " The Genetic Origin of Dementia Præcox,"

giving the clinical history and pathological findings in the brain and reproductive organs of a case of acute dementia præcox. The following is a summary :—

There was a family history of insanity on both sides. A brother died in Charing Cross Hospital from a self-inflicted bullet wound of the brain. The testes were sent to me in 1916, as I had asked for the testes of cases dying of injury ; pronounced regressive atrophy was found. I put them aside, after finding they were very abnormal, and forgot all about them. Five years later I was asked to see a case at Claybury Asylum of acute adolescent insanity, and I was struck by the patient's name and by the history of the brother having died from a self-inflicted bullet wound. I then recollected the name and recognized that it was the brother who had died in Charing Cross Hospital. There was a history of a sister who had been admitted four times to an asylum with manic depressive insanity with sexual delusions : a brother and sister were normal ; all the five were highly intelligent. The blood and cerebro-spinal fluid examined during life were both sterile ; and there was only slight leucocytosis. The patient died eleven days after admission. The duration of the mental symptoms was about two months ; they were characterized by depression, suicidal tendency and delusions of persecution. He died of heart failure with cerebral congestion and œdema. The testes, freed from tunica, albuginea and epididymis, weighed only 8 grm. each, which is less than half the normal weight. They presented a uniformly grey instead of a white appearance, quite like the organ in advanced cases of dementia præcox. The microscopic appearances of regressive atrophy were in all respects a counterpart of those I had found in the testes of the brother. Sections of the testis revealed tubules in all stages of primary regressive atrophy. Some of the tubules showed only a thickened basement membrane lined by Sertoli cells without any spermatogonia or spermatocytes ; in others there were all stages of regressive degenerative atrophy of the spermatogenic epithelium, shown by a diminution or even absence of nuclear chromatin in spermatogonia, spermatocytes and

spermatids. Where spermatids or spermatozoa were seen there was evidence of a microchemical or morphological change similar to the condition I have found and described in several early cases of dementia præcox. The interstitial tissue displayed an overgrowth of fibroblasts, the cells of Leydig were diminished in size and numbers, the nuclei of the cells were deficient in chromatin, smaller than normal, irregular in shape instead of round, the cytoplasm was deficient in eosin-staining substance, and the appearance of the cells generally was that of a regressive atrophy. Pronounced nuclear and cytological changes were found in the cortical neurones generally, but the small stellate cells of Cajal were particularly affected.

The microchemical and morphological changes of the nuclear material of the cortical neurones and of the testis in this case indicate an hereditary biochemical deficiency of nuclear material in two structures essential for the preservation of the individual and the species. It has been asserted that the nuclear changes in the reproductive organs and the cortex of the brain in this disease are due to tuberculosis. In neither of these two young men was there any evidence of tuberculosis, but a strong family history of mental disease on both paternal and maternal sides.

Parallelism of Dementia with Cortical Destruction in General Paralysis.

In general paralysis the degree of dementia can be correlated with the degree of decay and degeneration of the cortex caused by the spirochætal infection and the escape of toxins into the cerebrospinal fluid. There is a proportional extent of

chronic inflammatory change, thickening and adhesion of membranes, and atrophy of the convolutions, obvious to the naked eye and sufficient to account for the loss of mind. The parallelism is shown in the fact that if there is well-marked speech defect, the left hemisphere will weigh usually 20 to 40 grm. less than the right.

Chance is everything, hereditary disposition nothing, in this disease. There is chance of the individual being infected, but less than 5 per cent. of those infected, owing to colonization of the spirochæte in the brain, suffer from general paralysis. Likewise chance is everything in the juvenile form due to congenital syphilis.

No Macroscopic Changes in Dementia Præcox to Account for Loss of Mind.

In dementia præcox the macroscopic appearance of the brain exhibits nothing abnormal, and even microscopic examination shows little. How can the mental symptoms, then, be correlated with the microscopic changes found in the cortex? Before considering this matter more fully let me state what are the fundamental symptoms of dementia præcox: they are a weakening of judgment, of attention, of mental activity, of creative ability; the dulling of emotional interest; loss of energy; and, lastly, the loosening of the inner unity of psychic life. The biological view I take is that there is an inherent defect in the fertilized ovum, which shows itself in

later life in two structures connected with the primal instincts of self-preservation and preservation of the species, and in those very structures where active nuclear formative processes take place—namely, the cortex cerebri and the reproductive organs.

The brain does not waste in dementia præcox because the axon remains alive and the white matter surrounding the axon does not degenerate. Now the grey matter of the cortex, where all the essential chemico-physical processes take place, according to Donaldson, does not amount to more than one-fiftieth part of the white matter of the cerebrum. Yet if there is functional or structural synaptic dissociation there will result a corresponding failure of psycho-physiological processes and disintegration of the psychic unity according to the nature and degree of dissociation. Accordingly, to the naked eye, the brain may appear normal, and even microscopic investigation may not disclose in many cases (where the mental symptoms are mainly due to suspension of function) histological changes sufficient to account for the symptoms, as in manic depressive insanity where the patient returns to normal mentality.

It may be asked how we can explain the dissociation (schizophrenia) from a physiogenic point of view. I should say by genetic inadequacy—namely, an inherent defect of the *vita propria* of the neurones, especially of those developed from the

telencephalon. This portion of the neural tube is the latest to develop phylogenetically and ontogenetically. The countless millions and millions of neurones which constitute the cortex of the cerebral hemispheres have developed from a relatively very small portion of the original neural blastema. At birth further neuronic formation ceases, and further formative activity consists only in growth and extension of nerve-cell processes. This continues until at 3 years the brain has attained a size nearly three-fourths of that of the adult. After this, growth proceeds slowly until adolescence. There may be a varying amount of pre-natal complete arrest of neuronic development, affecting especially those neurones of the highest level which are of latest evolutionary development—namely, the supra-granular layer of pyramids—and various grades of amentia may be the result. There may be various degrees of partial arrest of growth and extension of the dendrons, by which there is only incomplete synaptic junction of many neurones of the highest evolutional level. Such a condition may lead to a failure in the highest level of control without much morphological evidence of a mental defect. Lastly, there may be an inherent lack of durability of the neurones by which they are incapable of performing their functions of storage and transformation of energy during the life of the individual. In normal physiological conditions the neurones should be capable of functioning as long as the whole organism

lives. Through an inherent defect they are apt to fail to function at the critical periods of life—namely, adolescence, the climacterium and senescence; physiological conditions of stress—gestation, parturition and lactation—may occur in the female. Again, such causes of psychological stress as emotional shock, anxiety states with repression and especially frustration of the sex instinct, causing endocrine disturbance and insomnia, are exciting causes of the onset of disordered functions of the highest level of neurones. If a deficiency of thyroid secretion can arrest structure and thereby function, producing cretinous idiocy, it is not surprising that a deficiency of thyroxin in the blood should cause slowing of nervous function when the growth of the neurones is completed. But the thyroid gland's function is correlated with the whole reproductive endocrine system.

A noticeable histological feature in the brains I have examined of cases of dementia præcox is a morbid change in the nucleus. This change was first described by Nissl as occurring in the cortical cells. It was later described by Alzheimer and by most investigators since. It shows a swelling, with often irregular infolding of the nuclear membrane, and deficiency or absence of the basophil staining of the intranuclear network by Nissl stain. Moreover the nucleolus may show a tendency to an acidophil reaction. In the light of recent researches on the chromosomes in relation to heredity this defect of

nuclear chromatin, which occurs also in the reproductive organs, suggests a primary genetic defect.

Now the nucleus of the neurone plays undoubtedly an important part in the function of transformation and discharge of energy from the cell. Although the Nissl granules are artefacts and do not exist in the living cell, yet their presence in the body of the cell and dendrons, and the microchemical reactions they give—showing that they contain phosphorus and iron—indicate that in the living neurone there is a continuous interaction between the surface of the granules and the nucleus by the mediation of the cytoplasm. There is evidence that the granules which are contained in the body of the living neurone and its dendrons, but not in the axon, may form an oxygen surface, and that the iron of the nucleus may act as a catalase; now, if there is a nuclear failure, as histological observations show, this may account for the neurones being unable to transform and discharge energy along the axon. The neurone is still able to live and its axon is not wasting, therefore the brain does not waste. How, then, can we associate this evidence pointing to a defect in the specific functions of the evolutionally latest and highest developed level of the brain with the philosophical teaching of Hughlings Jackson? The latter, in his discourse on "The Factors of Insanity," points out that positive symptoms such as illusions, hallucinations and delusions, which are so frequently met with in this disease, are evi-

dence of functional activity brought into relief by the negative condition of the highest evolutional level.

It may be asked, what, then, is the original cause of this abnormal variation in the inborn *vita propria* of the fertilized ovum? It has been suggested that syphilitic antecedents may be the cause of dementia præcox, but I have been unable to find proof of this after examination of the cerebro-spinal fluid of a large number of cases of dementia præcox. It is a fact that these diseases do occur although less frequently in primitive peoples, only the symptoms, such as hallucinations and delusions, are coloured by their social usages, customs and beliefs. The history of the Jews points to the fact that eighteen centuries of persecution have eliminated all those who have not a quick apprehension of danger and the means to avoid it. They have had to live by their wits rather than by physical strength. They have imagination, creative ability in arts, science and finance on the whole superior to the Christians among whom they live; consequently, they have by natural selection and survival of the fittest acquired a high degree of plasticity and liability to instability of the highest evolutional level of the brain, leading to a greater prevalence of neuroses and psychoses than among the Christians.

The Part of Heredity in the Ætiology of Mental Disease.

Antedating, by bringing on the mental disease at an early age, leads to segregation, which, together with regressive atrophy of the reproductive organs, tends to stop procreation. Moreover, the lowered vital resistance leads to tuberculosis; 80 per cent. of cases of dementia præcox die of active pulmonary tuberculosis, a marked contrast to general paralysis. We observe there is thus a tendency to end or mend a degenerate stock.

Lastly, from a practical consideration of the subject of insanity, it is very necessary to recognize that the germ-cells of every person who is certified as insane and sent to a mental hospital are not necessarily possible potential transmitters of a mental disease. General paralysis of the insane and many other microbial infections leading to disordered mental functions are acquired diseases and are not hereditary. Neither is it right to assume that simple senile decay affecting the brain is transmissible, yet a large percentage of inmates of asylums are sent there on account of senility. These legal administrative conceptions of mental disease must therefore vitiate all statistics in respect to heredity as a cause of mental diseases, because based upon data in which admission to a mental hospital is in many instances the sole evidence. This does not apply to the same extent to carefully recorded pedigrees; but even these are not free

from error, for often all the information that can be obtained is that one or more members of the stock had been in an asylum.

How is the public to know the difference between an inborn tendency to insanity *ab initio* in the ovum, true heredity, and a condition which may arise after conjugation of the male and female germs while the developing embryo is still in the body of the mother? As Sir Bryan Donkin pointed out, congenital disease was confounded with hereditary disease even by medical witnesses who gave evidence before the Royal Commission on Feeble-mindedness. The term "hereditary syphilis" is a misnomer. Much may happen while the embryo is still *in utero*. The normal biological processes of nutrition of the developing embryo may fail; abnormal mechanical conditions may arise in the uterus, interfering with the proper development of the embryo; or mechanical conditions in the process of development of the embryo may arise, interfering with the development of structure. Of all the structures in the body of the embryo likely to be affected by a departure from normal dynamic biological conditions of growth, the great brain or cerebrum is the most likely. The neo-encephalon — new brain — of mammals appears first as two hollow buds from the telencephalon, which by rapid cellular proliferation grow upwards and backwards to cover up completely the basal ganglia and mid-brain to form

the cerebral hemispheres. In that process many mechanical failures and accidents may occur, interfering with the vascular supply or nutrition of the rapidly proliferating cells, whereby the process may be arrested altogether, as in anencephaly, or partially arrested, as in the brain of the idiot or low-grade imbecile. There is evidence of a possible vascular cause through a lack of correspondence in the normal rate of growth of the dura mater and soft membranes and the growth of the brain. Owing to this the veins enter the longitudinal sinus in a direction opposite to the current of the blood-stream in the frontal lobes—an anatomical condition which favours venous stasis. This I have put forward as an explanation of the fact that the frontal lobes are the seat of early and most pronounced meningo-encephalitis and atrophy in paralytic dementia, because the spirochætes, being anaerobic, would develop more easily where there is venous stasis. Again, prolonged labour and difficulties in delivery requiring the use of instruments may be responsible for injury of the brain.

Idiots and imbeciles occur in all grades of society (frequently they are the first-born), and it is not at all uncommon to find nothing in the paternal or maternal family history—even when a pedigree can be obtained of three or four generations—to account for this pronounced failure of development of the anatomical basis of mind. The late Dr. Ashby considered that 25 per cent. of the cases of idiocy

and imbecility were due to causes other than heredity.

I feel that the subject is one which still requires an enormous amount of patient investigation before any definite conclusions can be arrived at, and I am more than ever convinced of the wisdom of what Harvey's great contemporary Bacon wrote in his *Advancement of Learning, Divine and Human*: "First, therefore, in this, as in all things which are practical, we ought to cast up our account, what is in our power, and what not; for the one may be dealt with by way of *alteration*, but the other by way of *application* only. The husbandman cannot command, either the nature of the earth or the seasons of the weather; no more can the physician the constitution of the patient, nor the variety of accidents. So in the culture and cure of the mind of man, two things are without our command—points of nature, and points of fortune."

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