THE MONGOL: A NEW EXPLANATION.

(Fourth Communication.)

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IT is now recognized that mongolism results from defects inherent in the germ-plasm. This has been proved by numerous observers, including Bauer, Orel, Halbertsma, Brousseau and others, who have investigated the occurrence of mongolism in uniovular and biovular twins.

Halbertsma argued that if twins are homologous " germinal affections will be equally present in both ", and he and others have found that " cases of twin mongols of different sex do not exist ". He is of opinion that mongolism is germinal in its origin, and not acquired during intra-uterine life. Strauch concluded that " an endogenic factor exists in one of the gametes in the ætiology of mongolism ". Brousseau states, " This theory of defects inherent in the germ-plasm can alone explain the existence of mongolism in one twin while the other is altogether normal both mentally and physically ".

These somewhat recently recognized findings have by some been considered to be in conflict with the explanation of mongolism, published in a series of three short papers in this Journal a few years ago under the above heading. I have frequently been told so, and I have been asked by one of the above-mentioned authorities if I would in another paper account for the occurrence of mongolism in one only of twins. Further, it has been stated* " that it is hardly conceivable that, on Clark's hypothesis, one embryo only should have been subjected to an excess of thyroid secretion . . . ". " The theory breaks down in fact beneath its own weight." The explanation I gave to account for mongolism was, briefly, " a fœtal hyperthyroidism ceasing at birth ". I used the term " hyperthyroidism " as synonymous with Graves' disease, or exophthalmic goitre, and to avoid conveying the idea of a simple overflow of thyroid secretion from mother to fœtus, I mentioned the possibility of over-susceptibility of the fœtus to thyroid hormone, but I did not discuss the cause, for the reason that " the cause of exophthalmic goitre is not known ".

My contention is that mongolism is the aftermath of fœtal Graves' disease, and the problem of the mongol is the problem of Graves' disease. If this is

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so, the ætiology and origin of Graves' disease and mongolism will be the same; if different my contention is wrong. Have, then, these two diseases the same origin and ætiology? A definite and complete answer to this question may not be available, but there is evidence to show that both diseases twin as other germinal diseases, proving the germinal origin of both diseases; there is also support for the view that the factor in the germ responsible for both diseases is a hereditary factor. Reference to literature on these questions shows that authoritative opinion favours the view that heredity is the fundamental cause of Graves' disease, and that the onset of the manifestations of the disease is finally brought about by such factors as infection, sexual disturbances, shock, worry or mental strain. If Graves' disease is hereditary it must be germinal in origin, and should present itself in twins in the same way as mongolism and other diseases of germinal origin.

Of mongolism it can be said definitely that it twins in germinal fashion, and is therefore of germinal origin; the ætiology and origin of mongolism and Graves' disease, then, are similar, indeed they may be identical if the germinal defect responsible for mongolism is a hereditary factor. A number of observers do hold that mongolism is a hereditary disease, but this cannot be said to be the generally accepted view. The sterility of the mongol at first sight appears to negative heredity, but recent proof of the germinal origin of this disease and the possibility of its being the intra-uterine form of exophthalmic goitre require re-examination of the question, What part does heredity play in the ætiology of mongolism? There is evidence that, in addition to heredity, external factors are concerned in the cause of mongolism, so that environmental factors play a part in the ætiology of both diseases. When mongolism occurs in twins it always presents itself in both twins, if the twins are uniovular, but in one only if biovular. This is strong proof that the germinal defect is the essential and major factor in the ætiology of mongolism.

The hereditary factor may be a unit character, it may be connected with the endocrine system, the periphery, the central or autonomic nervous system. Such a factor seems more likely to bring about a definite and familial disease, such as exophthalmic goitre, than the imaginary "neuropathic" or "morbid" hereditary factor so often suggested.

There is much to justify one in saying that what is true of mongolism as regards origin and ætiology is also true of exophthalmic goitre. Following the line of investigation which proved the origin of mongolism, I find in the literature the following reports of exophthalmic goitre occurring in twins. Glatzel reports:

(1) Morbus Basedowii in one of dissimilar twins, æt. 18, the brother being healthy and normal.

(2) Uniovular twins, æt. 11, enlarged soft thyroid in both.

(3) Biovular twins; in one sister, at age of 32, morbus Basedowii has developed; the other is free from all such symptoms.

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Neff records exophthalmic goitre in homologous twin girls. The disease was noted in one at 8 and in the other at 10 years of age.

It will be observed that in every case exophthalmic goitre has occurred in twins as germinal diseases do.

The statistics are small but significant, and coincidence is not likely to explain them.

In the opinion of many authorities it is an hereditary factor in the germ plasm which plays the important part in the production of exophthalmic goitre. A large number of families have been reported in which the disease has occurred in more than one member of the same generation, and in several members of successive generations. In two families reported by Cantilena and Sottas, the disease affected parent, child and grandchild. Rosenberg reported a family in which the father and two daughters suffered from the disease, the younger daughter married a man whose mother and two sisters had Graves' disease, and of their family of 11, 10 were stillborn or died in infancy and only 1 survived. Osterraicher recorded a family in which Graves' disease appeared in three generations, and affected 11 out of 16 members of the family. Many other somewhat similar family histories have been recorded. Cockayne has shown that the phenomenon of anticipation common in other hereditary diseases is also shown in the transmission of exophthalmic goitre, and he quotes from other observers examples of families presenting the disease in this way, *e.g.*, in a mother the disease began at the age of 33, was fully developed in her daughters at 27 and 25, and earlier still in her two sons. In Climenko's family it appeared at 39 in the parent, at 27 in the child, and at 10 and 6 in two grandchildren. Cockayne has also shown that exophthalmic goitre is frequently transmitted through apparently healthy individuals—the disease may be present in several children whilst the parents appear to be healthy. Cockayne is of opinion that a constitutional weakness of the thyroid gland or a thyroid diathesis is inherited. Morrison considers there is a strong familial predisposition to exophthalmic goitre. Fraser believes in a constitutional factor which may be inherited and inborn. Warthin is of opinion that all cases of exophthalmic goitre possess a definite pathological constitution. Many more hold similar views.

Much that has been written in favour of an hereditary factor playing the fundamental part in the production of exophthalmic goitre can be said of mongolism. Mongolism has been shown definitely to have its origin in the germ-plasm. It shows the same tendency to occur as a familial disease. Sisters, brothers and cousins are to be found affected, and, taking into consideration that mongols have no offspring and therefore never appear as parent in pedigrees, it is remarkable how similar the family tendency is in these two diseases. Much better proof of heredity may be forthcoming if the connection between exophthalmic goitre and mongolism is recognized. Orel reviewed the literature up to 1926, and reported 19 cases of familial mongolism. Since

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then, Brousseau has contributed another list, and other instances of 2 and more mongols occurring in a family have been reported. The following reports are of interest. Babonneix and Vilette recorded 4 mongols in one family; the mother had 2 miscarriages during the first years of marriage, and out of 10 children born viable, 6 died in infancy. The 4 surviving children were mongols.

Borovsky, in 1928, observed 3 female mongols, the offspring of two sisters. In one of these families the father had married previously and had 5 normal children by his first wife; all four parents were healthy and showed no endocrine or nervous disorder. In 1917 Ch. Herrmann reported two mongols in one family. The mother married twice. The child by her first husband was normal. By her second husband she had three children, the first a mongol, the second a normal child and the third a mongol. Both parents were healthy, and the mother perfectly well during all her pregnancies. Herrmann adds, "it is hardly conceivable that a constitutional disease in the mother, which gave no symptoms, could produce alternately a normal child and a mongolian imbecile". (In exophthalmic goitre families, parallel cases to this occur not infrequently.)

Herrmann has stated that the evidence that mongolian imbecility is a unit character and recessive, although not conclusive, is certainly suggestive. Bauer believes that the cause of mongolism is much more likely to be genotypical than paratypical. Penrose says, "there is strong evidence that mongolism is due to heredity . . . . There seems to be a good *prima facie* case for regarding susceptibility to the condition as hereditarily determined . . . it is concluded that if due allowance be made for environment the proportion of susceptible individuals must be very much higher than is usually supposed in infected families". Since mongols do not bear children, the tainted genes must die with the mongol, and, unless there is another source, the disease would become extinct. But it does not, and the question arises, Where do these tainted genes come from? Supporting the view that mongolism is intra-uterine exophthalmic goitre, it is suggested that the genes producing mongolism may be the genes holding the hereditary factor of exophthalmic goitre. It will be asked why more cases of exophthalmic goitre are not reported in families producing mongols. This may be because complete pedigrees are rarely given, and because the hereditary factor is often transmitted by apparently healthy parents. On the other hand, it is possible that many of the offspring of those who transmit exophthalmic goitre—premature infants and those dying in early infancy—suffer from mongolism. The disease must often be missed in such cases, for it is known that attention is often first called to a mongol infant's condition at about the age of twelve months. Valuable information might be obtained by following up the histories of the sisters, brothers and cousins of mongols and their offspring. Mongols die young, and little is known of the adults of their own and future generations.

Further support for an hereditary factor in the ætiology of mongolism has

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been recognized in the uniform picture mongolism presents, and the resemblance between one mongol and another. Certainly this uniformity and resemblance is more likely to be brought about by something particular than by something general.

The resemblance between mongols is often remarkable: "they appear to be members of the same family, and parents sometimes fail to recognize their own children in a group of this type". A hereditary explanation of itself fails to explain this resemblance unless the ancestor whose likeness is transmitted is revealed. On the other hand, the exophthalmic goitre theory explains this resemblance thus: the face of every mongol is disguised during fœtal life, because a mask bearing the distinctive features of exophthalmic goitre is impressed upon it.

Since it has become known that the pathogenesis of mongolism is in the germ-plasm, many causes which formerly seemed possible can be excluded. It has been suggested that such causes as ovarian degeneration or immaturity, exhaustion of procreative powers, defective developmental impulse, environmental effects on the germ, also shock, fright and mental worry, and those conditions in the pregnant mother obtaining at the end of a large family and the approaching climacteric, may be the cause of mongolism. But these factors must be regarded as minor ones, for such conditions cannot of themselves explain how the uniformity, the resemblance, the brachycephalic head, the changes in and around the orbits and the many other distinctive features of the mongol are brought about. Some further explanation is required. The non-essential character of some of these conditions is also evident since the disease is known to occur without them. Again, if Jansen and Van der Scheer are right, mongolism commences about the sixth or seventh week of intra-uterine life, so that some of these conditions above mentioned, *e.g.*, ovarian degeneration, exhaustion of procreative powers, and other environmental factors acting on the germ may be excluded, leaving those conditions which affect the pregnant mother as the possible determining factors, *i.e.*, fright, shock or worry, conditions in the pregnant mother over 40 following a long series of pregnancies and approaching the climacteric, and other conditions which may bring about endocrine imbalance.

It has been stated that it is impossible to conceive exophthalmic goitre occurring in one only of twins *in utero*, as mongolism is known to occur and as exophthalmic goitre occurs after birth in biovular twinning. Reports have been mentioned showing that in adult life, and also in childhood, exophthalmic goitre occurs in both twins in uniovular and in one only of twins in biovular twinning. Why should not further anticipation occur and the same rule be followed *in utero*? The difficulty apparently arises through under-estimating the possibility and importance of a hereditary factor being present in one fœtus and absent in the other, or it may be that the importance of the thyroid secretion in the ætiology of exophthalmic goitre is overestimated.

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A consideration of the following views on the ætiology of exophthalmic goitre will show that in biovular twins one fœtus may have exophthalmic goitre and the other be not so affected.

Warthin's theory of the cause of Graves' disease appears to be gaining favour in this country and in America, and perhaps more pronouncedly so in Germany and Italy. Briefly stated, it postulates that sufferers from Graves' disease present a definite pathological constitutional entity which is predetermined at birth, and only those possessing it will develop Graves' disease. The potentiality may, however, remain latent or quiescent during the whole or large part of the subject's life. Warthin prefers the term "Graves' constitution" in the absence of any convincing proof that thyroid hypersecretion is the ætiological factor. Further support comes from other authorities; some doubt whether Graves' disease is a disease of the thyroid at all, arguing that thyroid pathology and goitre symptomatology cannot be accurately correlated, and most of the symptoms of Graves' disease may be present without goitre. Again, Zondek holds that the hormonal factor in endocrine diseases is overestimated: "endocrine diseases may proceed from varied points of the hormonal system, including the nervous system and the periphery. Basedow's disease does not proceed from the thyroid". Bram expresses similar views, and states that when thyroid swelling exists it is not the cause of the disease, but incident to a series of events constituting the syndrome. Now, if these views are correct, it is difficult to understand how exophthalmic goitre can occur in biovular twins *in utero* in any other way than mongolism presents itself, *i.e.*, one fœtus may suffer from exophthalmic goitre or its aftermath, and the other be not so affected. I leave out of consideration the very rare possibility of two mongols occurring in a biovular twin birth, which does not appear to have been recorded so far. Environmental factors undoubtedly play a part at least in determining the onset of both exophthalmic goitre and mongolism. If Warthin is right and the potentiality to exophthalmic goitre is inborn, yet may remain latent for life, then a secondary factor must be necessary to determine the onset of the disease. The difference in the age at onset of the disease in uniovular twins may be similarly explained; in one pair of uniovular twins exophthalmic goitre commenced in one twin at the age of eight and in the other at the age of ten. Clinical observation, too, strongly favours a secondary ætiological factor in determining onset. The environmental factors which precipitate the onset of exophthalmic goitre *in utero* may be different from those which bring about the disease after birth, and yet it is significant that the factors commonly believed to bring about the manifestations of exophthalmic goitre in the adult are shock, fright and mental worry, and these same conditions in the pregnant mother are said to be a cause of mongolism. Comby observed worry, fright or shock during the early months of pregnancy in 43 out of 70 mothers of mongols.

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Secondary factors in the ætiology of mongolism have already been mentioned, and that they play a part in determining the onset of the disease is supported by the fact that the mongol has a special position in the family. If mongolism were a purely hereditary disease the mongol would occupy no special position, for genetic law can have nothing to do with position in the family. But the contrary is the case. Shuttleworth in 1886 pointed out that nearly one half of mongols were the last born of a long family ; which of the factors, the advanced age of the mother or her exhaustion by previous pregnancies or her approach to the climacteric is the most potent, he left in doubt. Spicer observed that mongols came often at the end of a large family, but did not consider this an important ætiological factor, since several of his cases were the first children of young mothers. Hill found that 50% of mongols were late members of a large family and born after the mother had reached 40. He believes, however, that the most potent cause of mongolism is the presence of some depressing influence during the gestation period of the mother. Turner and Penrose, after a careful statistical study of this question, point to a marked deficit of first-born mongols as compared with expectation. In a more recent contribution Penrose shows clearly that " the incidence of mongolism increases with the maternal age, the only exception being that there is a greater incidence amongst pregnancies before the age of 25 than between the ages of 25 and 34. There seems, in fact, to be a definite inverse relation between the frequency of the condition and the child-bearing activity of the mother ". It is just possible that this finding may be connected with " Graves' constitution ", for Warthin points out that in those possessing the " Graves' constitution " the period of reproductive ability is much shortened although fertility is undiminished.

Making use of the figures just quoted from Penrose and assuming my proposition to be correct, it follows that there will be a higher incidence of those born susceptible to exophthalmic goitre in pregnancies between the ages of 25 and 34 than outside this period, and in consequence the exophthalmic goitre patient might be expected to occupy this approximately mid-position in the family. Evidence of this has not been found in the literature, and it may be that those in whom Warthin states the disease remains latent throughout life rectify the incidence, so that the exophthalmic goitre patient may occupy no position in the family and thus conform to genetic law.

It is reasonable to conclude that in mongolism, as in Graves' disease, a susceptibility to the condition is inherited. Determining factors are, as in Graves' disease, shock, fright, mental worry, sexual disturbances, or those conditions present in a pregnant mother, over 40 years of age, after a long series of pregnancies and approaching the climacteric (these conditions probably give rise to maternal endocrine disturbance). In any case the latter appears to be a potent determining factor, and gives the mongol a position in the family such as Penrose describes.

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As regards the ætiology of mongolism, authoritative opinion is at the moment divided; some favour heredity, others prenatal environmental conditions. If my thesis is accepted, both are right.

For many years mongolism and exophthalmic goitre have been considered quite distinct and different diseases, and as such they have been subjected to very careful observation and critical examination, and the accumulating facts point now, more than ever, to the possibility that these diseases are the same disease—that mongolism is the result of fœtal exophthalmic goitre.

Consideration of the facts presented seems to justify the following deductions: Exophthalmic goitre may occur *in utero* just as it does in after life, for the necessary hereditary factor and environmental conditions are at times both present *in utero*. When exophthalmic goitre occurs *in utero* in twins, it will present itself in uniovular and biovular twins in the same way as mongolism: in both exophthalmic goitre and mongolism a susceptibility is inherited; the determining factors in both diseases seem to be the same environmental conditions. In mongolism the environmental condition ceases at birth.

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