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Review of mongolism : with special emphasis upon theories of its etiology

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A REVIEW OF MONGOLISM WITH SPECIAL EMPHASIS UPON THEORIES OF ITS ETIOLOGY

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TABLE OF CONTENTS

INTRODUCTION

A. History of Mongolism as a Syndrome

In 1886 J. L. H. Down, M. D.[9] London, England said,

> "I have been able to find among a large number of idiots and imbeciles which came under my observations,....that a considerable portion can be fairly referred to one of the great divisions of the human family other than the class from which they have sprung.
>
> The great Mongolian family has numerous representatives, and it is to this division, I wish, in this paper, to call special attention. A very large number of congenital idiots are typical Mongols. So marked is this, that when placed side by side, it is difficult to believe that the specimens compared are not children of the same parents. The number of idiots who arrange themselves around the Mongolian type is so great, and they present such a close resemblance to one another in mental power, that I shall describe an idiot member of this racial division, selected from the large number that have fallen under my observation.
>
> The hair is not black, as in the real Mongol, but of a brownish colour, straight and scanty. The face is flat and broad, and destitute of promience. The cheeks are roundish, and extended laterally. The eyes are obliquely placed, and the internal canthi more than normally distant from one another. The palpebral fissure is very narrow. The forehead is wrinkled transversely from the constant assistance which the levatores palpebrarum derive from the occipito-frontalis muscle in the opening of the eyes. The lips are large and thick with transverse fissures. The tongue is long, thick, and is much roughened. The nose is small. The skin has a slight dirty yellowish tinge, and is deficient in elasticity, giving the appearance of being too large for the body."

He felt that "....there can be no doubt that these ethnic features are the result of degeneration." As to the time of development of the condition he said, "They are always congenital idiots, and never result from accidents after uterine life."

He felt that the condition was directly attributable to tuberculosis in the parents. Dr. Down described the mongoloid individual as having

> "....considerable power of imitation, even bordering on being mimics. They are humerous, and a lively sense of rediculous often colours their mimicry. Their faculty of imitation may be cultivated to a very great extent, and a practical direction given to the results obtained."

He went on to describe speech difficulty and poor circulation.

This is one of the earliest reports of the condition of mongolism. Today we, of course, do not agree with all that Dr. Down said but one is surprised to find that medical thinking has followed his line of thought as to causes of mongolism.

It is the purpose of this paper to present briefly the subject of mongolism touching briefly on the stigmata, theories of etiology, both old and recent, and to present recent advances made in the field of biochemical study of the disease. Needless to say this review could by no means be exhaustive but is an attempt to glean out some of the important highlights related to mongolism as reported in the vast literature.

B. The Incidence of Mongolism

1. Incidence in the group of Northern European Extraction

In the United States the incidence of mongolism is greater than that of poliomelitis.(37) Approximately 9,000 mongoloids are born annually in the United States or about one mongoloid

for every 600 live births.[3,21] In New England the incidence is 0.34 percent and this in spite of the excellent prenatal care. In Sweden a figure of 0.25 percent is reported and in England 0.6 per cent.[19]

2. Variation of Incidence in Ethnic Groups

In other ethnic groups the incidence seems to be much lower. Among the American Negroes the condition is 10 times less frequent than among people of European descent. Unofficial figures gathered in Italy indicate an incidence of one mongoloid in 7,000 live births in spite of prenatal care which is considerably less thorough than that given in the New England area.

3. Incidence of Mongolism in the Sexes

Some authors have asserted that males are more frequently affected than females, but thorough study has apparently shown males and females to be about equally affected.[31]

4. Incidence with Advancing Maternal Age.

One of the earliest recognized constant factors was the increased incidence of mongolism with advancing maternal age, especially after 40 years of age. This subject shall be enlarged upon later in this discussion. It has been observed that the mean maternal age varies slightly if there is a familial incidence of mongolism. When a familial incidence is present the mean maternal age is 33 years; when no other

cases have occurred in the family the maternal age is 36.2.[19]

5. Familial Incidence

No conclusive evidence points to a familial incidence of mongolism which is greater than could be expected on the basis of chance alone.[30] This is further touched upon in the discussion of etiological factors.

6. Incidence of Mongolism in Institutions

About 10 per cent of all institutionalized mental defectives are mongoloids. They compose the largest group of mental defectives which can be unequivocally catigorized.[42]

II. THE DIAGNOSIS OF MONGOLISM

A. Physical Stigmata Associated with Mongolism

The whole body of the mongoloid is involved in the pathologic developmental process and some of the stigmata shall be discussed.

1. Skull

The skull of the mongoloid often has a shortened fronto-occipital diameter. The skull may or may not be subnormal at the biparietal diameter with an unusually flattened occiput and is in the low normal range with respect to its diameter.

2. Eyes

The eyes of the mongoloid have small, upward slanting palpebral fissures, with medial epicanthal folds of skin. Other abnormalities frequently found in the mongoloid eye

include unusually thick skin of the eyelid and conjunctival susceptibility to inflammation and chronic changes. The ciliary body of the lower lid is often enlarged and the eyelashes few and short. Cataracts are common often developing enutero or in childhood. In addition the movements of the eye are abnormal with frequent occurrences of strabismus as well as nystagmus.

3. Ears

What is considered by some[2,42] to be one of the most diagnostic points of mongolism is the presence of malformed ears with their overhanging upper helix, flattened tragus and in later life the "lop-eared appearance. The ear is frequently located low on the head with the resultant changed angle of penetrance of the external auditory canal.

4. Nose

The nose in the mongoloid has a flattened bridge due to an underdevelopment of the nasion bone. The cartilogenous portion may grow with advancing age resulting in a typical pug-nosed appearance.

5. Mouth

The lips appear cracked and dry and because the tongue becomes fissured and the papillae hypertrophied it is said to be "scroted".

The deep voice found in some mongoloids is apparently related to a hypothyroid condition.

6. Neck

Extra folds of lax skin are often present in the lateral and posterior cervical regions. The short appearing neck is due to the straight vertebrae and the flat occiput.

7. Spine

The spine is often straight with a dorso-lumbar kyphosis.

8. Abdomen

The abdomen is pear-shaped with poor muscle tone and "pot-belly". Frequently an umbilical hernia and diastasis recti are present.

9. Male genitalia

The male sex organs are underdeveloped. In 50 per cent of cases the testes are undescended at time of birth. The penis is usually short and infantile but may be long and thin. In the adult pubic hair is soft and silken with female distribution. A beard, if present is sparse and mostly on the edge of the mandible.

10. Female genitalia

Female sex organs show some variation also. In infants the labia majoria are frequently over sized and labia minoria undersized. In older mongoloids the minoria are often protruding and the clitoris hypertrophic. The breast may after

puberty appear to be quite well developed, but their size is due to subcutaneous fat only. The nipples are often small and underdeveloped.

11. Extremities

The extremities present some of the most dependable signs of mongolism. One of these is the widely spaced first and second digits of short, stubby hands and feet. There are a transpalmar and longitudinal plantar creases present in many cases. The little finger isoften incurved due to mal-development of the second phalanx.

There may be associated with this shortening only one furrow on the palmar surface of the little finger. The finger prints have certain constant characteristic patterns, the refinements of which shall not be described here.(33)

12. Muscle Tone

Muscle hypotonia, a cardinal sign of mongolism in infancy, prevails into adult life.

13. Cardiovascular System

The incidence of some form of congenital heart disease has been estimated as high as 75 per cent at birth. Of those who live beyond the age of 10 years, 25 per cent are found to have a demonstrable cardiac lesion, the most common of which is a septal defect, usually atrial. Benda(2) considers even more important the general "infantilism of the vascular

system". The aorta is thin and the main trunks are undersized. Other cardiovascular anomalies include aortic and pulmonary stenosis, patent ductus arteriosis and dextrocardia. In addition to this the vascular supply to all body parts is poor, including the brain, thyroid, etc.

14. Others

In addition to the characteristic mal-formations already listed almost every conceivable anomaly has been reported in mongoloids but these are not helpful in the diagnosis of the individual case. There has been reported an increase in the number of anomalies or stigmata with a second mongoloid in one family.(16) Recently several groups have reported on increase in the incidence of leukemias in mongoloid. Such reports have come from United States(22,28) and from Britain.(5,13,18)

B. Histologic Abnormalities

The tissues of the mongoloid have been described by many investigators and include almost every organ system of the body. For the purposes of the discussion we shall point out only some of the more common abnormal findings.

1. Nervous system

A. Brain

The frontal lobes of the brain are often decreased in size and grossly look smoother due to a decrease in the number of gyrae. The third cortical layer often shows a

small ganglion cell content. Glial elements appear to be increased out of proportion to the nervous elements. Even microscopic changes such as intracellular fat bodies and poor staining qualities of the Purkinje cells are described.[2,5,27] Cerebellar underdevelopment is marked.[3]

b. The spinal cord

Benda[2] divides the changes seen in the spinal cord into two groups; (1) mere retardation, ranging from hypoplasia to true (2) arrest of development with pathological differentiations. Features seen include a wide open central canal in all or part of its course, irregular ependymal proliferation, hypoplastic grey matter, lack of separation of the Clark columns, glial proliferation and asymmetrical or even absent posterior columns.

2. The Pituitary

Because of the slow growth encountered in mongolism the pituitary has been the subject of extensive study. Several types of microscopic pathology have been described. Various staning qualities which are not constant have been demonstrated. Some glands lack chromophilic cells completely, whereas in others chromophilic cells predominate to the exclusion of other cells. Degenerated chromophilic cells have been described.

3. The Thyroid

Thyroid pathology described includes, resting colloid goiter, colloid goiter with signs of possible toxic activity, fetal glands without colloid formation, fetal cell nests with some colloid formation in the periphery and Hashimotos thyroiditis.

4. The Adrenals

The adrenal glands were found to be essentially normal and though small at birth without marked evidence of "fetalism". The adrenals grow and develop adequately. A tendency to nodule formation or the development of small adenomata has been described.(2)

5. The Liver

Fatty degeneration of a marked degree has been observed in a high percentage of mongoloids even before one year of age. By two years this has increased even more markedly. These findings are suggestive of a metobolic deficiency already active at birth.

6. The Gonads

At birth the gonads are quite normal in appearance. The male testes fail to develope though interstitial cells may be present. Spermatocytes are conspicuously absent. Ovaries which in most cases are somewhat atrophic are mature enough to promote the menstrual cycle and instances of

mongoloids giving birth to children have been reported.

7. Leukocytes

Dr. Ursula Mittwock[5] describes some unusual features of polymorphonuclear leukocytes in mongoloids. She describes fewer lobes in the nuclei of mongoloids than in normal. The female children had fewer "drumsticks" in the nuclei than controls. It is not probable that infections are the cause of the fewer lobes since the leukocyte count is not necessarily increased.

C. The Physical Development of the Mongoloid

1. Causes of Retarded and Limited Growth

Mongolism is a developmental and growth disorder which is evident at birth and becomes more so with advancing age. Because of a lack of basic experimental data the exact cause of this retarded and limited development has not in the past been clearly elucidated. Recent biochemical studies indicate that there is a metabolic deficiency, apparently at the cellular level. Techniques which are adequately refined and specific have not yet been developed to give us the information needed to understand the intricacies of the abnormal biophysical activity in the mongoloid.

Recent studies indicate that perhaps there are chromosomal aberrations in the mongoloid. With out present knowledge of the role of chromosomes in physical development it is not

difficult to see that many questions may soon be answered.

We do know that abnormalities in function of pituitary, thyroid, pancreas, liver, etc. can give abnormal growth. Growth in the mongoloid generally follows certain patterns and reaches certain levels characteristic of the group as a whole.

2. Skeletal Growth

Bone growth is decelerated. At the time of birth the skull bones are poorly fused, the fontanelles are large, the eye sockets are small, the nose bones underdeveloped, the mandible and maxilla are undersized, the basilar bones of the skull are underdeveloped, the pelvis is small and the long bones are slender and delicate. The teeth are slow in developing but the incidence of caries is low in mongoloids.

Retardation of growth is most conspicuous in the first three years of life. In the next ten years the growth may be normal, but because of the slow start the children always appear smaller than normal. Growth the stops early especially around thirteen years of age. The result is that few mongoloids exceed 150 centimeters in body length.(2,8)

3. Weight Gain in the Mongoloid

During the first year most mongoloid infants are under-

weight. For the next 3-4 years their weight gain is normal. At 5 years of age a more marked increase in weight becomes noticeable and from then on the mongoloids are overweight.

4. Body Disproportions in Mongolism

While the body appears well proportioned in childhood, in the adult extremities appear short and the head small in proportion to the trunk.

5. Sexual Development

Generally speaking the gonads remain underdeveloped, especially in the male. Sexual activity is essentially absent. Approximately 70 per cent of mongoloid females menstruate between the ages of 18 and 30 years. There are several instances in which mongoloid females have given birth to children. In one well documented case a normal child was born to a mongoloid mother.(17)

6. Diminished Physiologic activity

The mongoloids have a decreased metabolic rate with BMR values in the range of -5 to -30 plus. This feature is further demonstrated by hypothermia. The blood pressure is low, the circulation is abnormal and the mongoloid is susceptiable to infections.(2)

7. Motor Development of the Mongoloid Infant

Development of motor functions is always slow in the mongoloid child. Characteristically he is lethargic and

muscularly flaccid. No doubt part of this flaccidity is related to retarded development of the central nervous system. This may be more graphically illustrated by correlating the development of such functions as sitting, walking, talking (words), and toilet training with the mongoloids I. Q. in terms of absolute time, thus; a child with an I. Q. of 0-24 will sit at age 15 months, he will walk at 30 months, etc. Similarly a child with an I. Q. of 50-69 will sit at 12 months, walk at 26 months. etc.(34)

TABLE I

Distribution of I. Q. Level of Development Onsets in Four Activities*

	Intelligence Quotient				
Activity	0-24	25-49	50-69	70-79	N
Sitting	15 mos.	12 mos.	11 mos.	11 mos.	40
Walking	30 mos.	25 mos.	26 mos.	18 mos.	38
Words	30 mos.	35 mos.	34 mos.	24 mos.	40
ToiletTraining	38 mos.	48 mos.	36 mos.	36 mos.	30

* Taken from Quaytman's discussion of "The Psycholocial Capacities of the Mongoloid Children in a Community Clinic." (See bibliography).

D. The Mental Status of the Mongoloid

All observers agree that all mongoloids are always mentally retarded.[3] Malzburg[41] reports that of 880 mongoloids seen in New York 24.5 per cent were idiots (I. Q. = 0-24), 71.6 per cent were imbeciles (I. Q. = 25-49) and 3.8 per cent were morons (I. Q. = 50-69). Some have reported percentage of 2.5 per cent as borderline moron levels (I. Q. = 70-79).[34]

Quaytman[34] points out that the social ages and social quotients (S. Q.) of mongoloids seen in his clinic are "significantly higher than their associated mental ages and intelligence quotients."

TABLE II

Comparison of Distribution Between I. Q.'s and S. Q.'s*

I. Q. Range	0-24	25-49	50-69	70-79
Number	2	28	9	1
Per Cent	5%	70%	22.5%	2.5%
S. Q. Range	0-24	25-49	50-69	70-79
Number	0	13	24	3
Per Cent	0%	32.5%	60%	7.5%

S. Q. - (Social Quotient)

* Taken from Quaytman's discussion of "The Psychological Capacities of the Mongoloid Children in a Community Clinic." (See bibliography).

Another way to state this is that whereas the average mongoloid seen in Quaytman's clinic, 70 per cent are mentally in the range 25-49 (imbecile), socially the average mongoloid (60 per cent) is in the range of the moron (50-69). Whereas he is socially 4 years old, mentally he is one year under that age.(34) With this Benda(2) agrees and says "the mental age does not adequately reflect the personality patterns of mongoloid children....their emotional interaction with other persons makes these children participate in the activities of their surroundings".

The mongoloid is a good imitator and this helps him develop in social abilities. It is pointed out that to achieve academically one must be able to "conceptualize". In this ability the mongoloid is wanting. Mongoloids then seem to develop fairly intact personalities.

If treated well, given love and affection they become very lovable and affectionate little people. And have been thus described after being observed in an institution,

> "As playmates, they are always hugging and kissing one another with vague but genuine smiles and affection. They come up and put their arms round the stranger as confidently as a puppy jumping up on a visitor and though not understanding a word said to them good naturally answer yes to any questions hoping that will please. They also enjoy music and singing." (2)

Stubbornness has been described as being a characteristic pattern of behavior in the mongoloid and seems to "depend on their inability to shift quickly from one subject to another and

to react to new impressions....This is contrasted with a lack of attention and the distractability of many subnormal patients."[2]

Benda[2] goes on to state that he believes the pattern is a reflection of the type of nervous system development "in which the central 'long-circuiting" system of the cortex, serving the evaluation of sensory stimuli and responses and serving, therefore, intelligent interaction with the environment, remains immature and underdeveloped."

There is evidence that the second of mongoloid sibs is usually more mentally retarded.[16] The reason is not apparent, of course, in the absolute sense. It may be conjectured that there is less maternal "protection" (as described in discussion of the Single Recessive Gene Theory of Etiology).

Another point of interest is the early mental decline of the mongoloid. They become senile early. Early distruction of brain tissue has been described[27] and may well be due to the inadequate vascular bed in the brain.

E. The Differential Diagnosis of Mongolism

The differential diagnosis of mongolism is rather simple in the full blown case. At first glance one might confuse mongolism and cretinism. In the small infant the diagnosis is often uncertain even to the experienced practitioner. Since therapy of an infant cretin should be instituted immediately it is important to make an early accurate diagnosis.

Several authors[2,42] feel that the only pathognamonic sign of mongolism in the neonatal period is the peculiar mal-development of the head, especially of the basilar bones. In addition, one author[42] feels that the following signs are those most frequently found in neonatal mongolism: (1) malformed ears; (2) the extra folds of lax skin in lateral and posterior cervical regions; (3) the widely spaced first and second digits of the short, stubby hands and feet, including abnormal palmar and plantar creases and markings; (4) the incurved fifth finger; (5) the muscular hypotonia and hypermobility of the joints.

Recently, there has been described the occurrence of bony abnormalities in the pelvis of the very young infant which are evident by x-ray and of great assistance in the diagnosis of mongolism. Two cardinal diagnostic features are evident in the very young mongoloid infant. (1) There is flattening of the under edges of the ileum resulting in a decreased angle between a line drawn parallel to that under edge and a horizontal line. (2) The wings and bodies of the ilia are widened. These roentogenologic findings are clearly diagnostic in 4 of 5 mongoloids, are suggestive in 4 of 20 and uncertain or normal in less than 1 out of 20.[7]

Whereas the false diagnosis of mongolism in a cretin could be disasterous, the same is not true with respect to the mongoloid infant's well being. The parents, of course, would be in for a great disappointment were they to find that their child, whose

condition they had supposed was remediable to treatment was actually set in a mold of underdevelopment from which was no chance of escape.

III. THEORIES OF THE ETIOLOGY OF MONGOLISM

Numerous theories of etiology of mongolism have been postulated since the syndrome was first described.

A. The Environmental Theory of Mongolism

Many of the theories of the etiology of mongolism have revolved around the concept of the effect of the external environment on the embryo or fetus. Attempts have been made to explain the extensive defects on the basis of one or a combination of causal entities. Some such causes are said to be intrauterine infections, fetal anoxia, gestational hemorrhage, threatened abortion, disorders of the uterus, an "accumulation of diseases in the mother round the year of birth of the mongol" (Oster, J. 1953), and ovarian insufficiency of same type (Geyer, H. 1939). Myers (1938) showed an increased incidence of dysthyroidism in mothers of mongols.(33) Norris(30) states that there is a definite increased incidence of "shocks" in the early months of pregnancy "particularly" in the mothers of mongoloid infants. By "shock" the author refers to prolonged physical and emotional stresses placed on the mother early in pregnancy.

Oster in Denmark, after studying 1006 cases in Denmark, feels that mongolism is probably not a hereditary disease.

Benda(3) is one of several staunch adherrants to the environmental theory. In enlarging upon the environmental theory he says,

> "The mongoloid has gone through a period of inhibited development which has affected the organism as a whole and has interferred with those (above mentioned) developments, the metabolism of which was most active at the time of dearth. Therefore, all those organs are affected which had been most susceptible to any deficiency by their increased need of oxygen and other nutritional factors. The mongoloid at birth is a veteran of a fetal battle in which he has been exposed to a serious deficiency in essentially nutritional factors."

He goes on to emphasize that normal development "is not only the creation of certain structures but the completion of these structures at a specific time and if the time factor is neglected we are not able to understand through mere structural analysis what is happening." It is felt that the critical time is between the 4th and 9th weeks of pregnancy, when the embryo is rapidly differentiating and cells are becoming specialized. Since no evidence can be gathered in most cases from mother's as to the occurrance of disease processes of this particular time of pregnancy, it is felt that these environmental factors must be subclinical.(5)

After birth the mongoloid remains retarded and it is felt that he "suffers from an essential disorder of central growth regulation" and just what is the cause of this growth retardation is not known in spite of intensive research. Benda feels that this growth center involves deficiency in the brain-pituitary axis. A vicious cycle develops between the immature nervous system and endocrine system "keeping the mongoloid child constantly out of

tune with normal development" with the result that the child, left to its own resources, falls behind in its physical and mental growth. This idea is akin to the concept proposed by Roessle and Van der Scheer[2] who consider mongolism to be due to a primary inferiority of the brain with a secondary growth disorder. They feel that the physical growth defect results from pathology of the brain apparently aside from a direct relationship to endocrine function.

B. Mongolism and Maternal Age

One factor which was recognized early was the increased incidence of mongolism with increasing maternal age.

The incidence of mongolism varies in a very apparent way with maternal age.[4,33] The mean maternal age at the birth of a mongol child averages about 37 years; whereas the mean maternal age for all births is 29 years. Until the maternal age group of 30 to 34 years is reached the incidence remains at 1 per 1000 births, and after this it rises to 2-3 per cent.[33] Benda feels that with the very old mother the incidence may reach 10 per cent. Almost 40 per cent of mongols are born to mothers 40 years of age or older.

When familial cases are studied and maternal age shows interesting variations. If one takes the cases of mongoloids without other known cases in the family one finds the mean maternal age to be 36.6 years (S.D. = 7.1). In those instances where a

TABLE III

MATERNAL AGE DISTRIBUTION OF MONGOLISM (ENGLAND AND WALES)

Maternal Age in Years	Absolute Incidence*		Relative Incidence	
	(a) Observed	(b) Expected	(a)/ (b) Comparison with Control	(c) Previously Calculated from Families
15-19	5	21.47	0.23	0.59
20-24	29	121.48	0.24	0.27
25-29	45	178.92	0.25	0.17
30-34	92	129.66	0.71	0.52
35-39	154	69.87	2.20	2.40
40-44	179	21.58	8.29	8.07
45-	41	2.02	20.80	15.07
All Ages	545	545.00	1.00	1.00

* N. B. The incidence at birth in the general population is 0.15 per cent.

This table is part of a discussion contained in Chapter 10 of the book, Biology of Mental Defect by L. S. Penrose. (See Bibliography # 33.)

sib is affected the mean maternal age is 34.3 (S. D. = 7.4). If a maternal relative is affected the mean maternal age is 33.0 years (S. D. = 7.3).

TABLE IV

DISTRIBUTION OF MONGOLOID IMBECILES WITH RESPECT TO MATERNAL AGES AT THEIR BIRTHS

Maternal Age Group	Male Cases	Female Cases	Observed Total Number	Expected Total Number	Ratio Observed to Expected	Absolute Incidence per 1000 Birth
15-19	1	2	3	7.75	0.39	0.6
20-24	5	4	9	29.62	0.30	0.5
25-29	12	7	19	34.06	0.56	0.8
30-34	7	7	14	25.79	0.54	0.8
35-39	19	12	31	16.74	1.85	2.8
40-44	15	17	32	6.30	5.08	7.6
45-49	6	7	13	0.71	18.31	27.5
All Ages	65	56	121	120.97	1.00	1.5

This table is part of a discussion, "Mongolian Idiocy (Mongolism) and Maternal Age by L. S. Penrose. (See Bibliography # 31.)

Perhaps antigenic incompatability develops with increased maternal age with resultant transient immune reactions against the embryo in its early developmental stages.

This phenomenon of increased incidence of mongolism with increased maternal age has been used to argue for the validity of both the environmental theory as well as the genetic theory. It is not the purpose of this paper to attempt to reconcile the arguments of these or other theories to which this outstanding feature of maternal age could be applied.

No increased incidence of mongolism has been found with increased paternal age aside from increased maternal age.

C. The Genetic Theory

1. The Incidence of Familial Mongolism

Studies of families in which numerous cases of mongolism occur have produced some interesting observations, none of which, however, give us clear conclusions as to the exact mode of genetic action in the production of mongolism.

Penrose[31] points out that it is difficult to be sure that the familial incidence of mongolism is greater than could be expected on the basis of chance coincidence. He has, however, found in his survey of cases of sibships in the mentally defective that mongolism is 10 times more common among the sibs of mongols than is the occurrence of mongols as sibs of other types of mental defectives. Some of this increased incidence of mongoloid sibships may have to be discounted on the basis of a biased selection of material. Penrose[31] feels that the incidence is still

too high to be explained away by biased selection along, stating that the actual probable increase in incidence of mongolism in families with mongoloids is actually at 2-3 times that found in the general population.

2. Twinning and Mongolism

Twin data seems to indicate that mongolism has a genetic background. Monozygotic twins are, in every reported case, concordant, whereas twins who have been determined to be dizygotic are not infrequently discordant.

Such findings are difficult to explain on the basis of environmental factors since both of a pair would have the same intrauterine influences.

There is further evidence which is not completely reliable but suggestive of the genetic origin of mongolism. This has to do, among other things, with the frequent occurrence of characteristic mongoloid "microsymptoms"(19) found in close relative of typical cases. Among such symptoms are a fissured tongue, the transverse palmar crease and abnormal sigmentation of leukocytes in otherwise normal persons.

3. The Single Recessive Gene Theory of Etiology of Mongolism

Penrose(31) states that he prefers the hypothesis of a single recessive gene as being responsible for mongolism though he sees no evidence "excluding the view that suscept-

ibility is determined by a single common intermediate gene or by several common genes with alternative and additive effects."

If mongolism is the result of a single recessive gene one would expect a homozygous condition to exist in 1 out of 25 of the general population, calculated on the basis of the frequency occurrence of the condition at a late maternal age. If this is the case, the single gene occurs at a frequency of 1 in 5 (20 per cent) (the square root of 25). With advanced maternal age the incidence actually does approach 1 in 25. A homozygous condition then produces a fetus with a mongoloid diathesis, (i. e. he is predisposed to develop as a mongoloid). To make use of the recessive gene theory it is necessary to conjecture that a certain number of the homozygous individuals in the population are "protected" by certain maternal qualities. The homozygous embryo or fetus would be a mongoloid were it not for this protective maternal factor. As the mother grows older she may lose this protective ability and the children born are mongoloids. In England and United States the prevalance of mongolism is less than 0.2 per cent. On the basis of this incidence then we assume that 26 of 27 homozygous persons are actually "protected". We see then ($\frac{26}{27} = \frac{4}{100}$ ∴ = 96.2; 100 - 96.6 = 3.8%) that 3.8 per cent of homozygous

individuals are unprotected. This means that 0.148 per cent of the general population are unprotected and develop as mongoloids. Just what these protective influences are is not clear, but are possibly related to a maternal diathesis resulting from maternal homozygosity. With increasing age, especially after age 35 years, the mother with a mongoloid diathesis begins to lose the protective influence over the developing homozygous fetus. At the age of 45 years and over these protective influences appear to be negligable. At that maternal age the number of mongoloid births approaches the predicted number of homozygotes in the general population.(19) This is not in agreement with Benda's idea that the incidence of mongolism reaches a high of 10-12.5 per cent or more. If the incidence reached 10-12.5 per cent and homozygosity, were the prerequisite for development of a mongoloid then the genotype would have to occur more than 1 in 25 of the general population.

In addition there is proposed the theory that the homozygous single recessive gene is actually semi-lethal, accounting for a slightly lower than expected incidence of mongolism and with a high percentage of misscarriages among mothers of mongoloids.(19)

As has been pointed out there is a variation in the incidence of mongolism in various ethnic groups. This may

be explained on a genetic basis when one recalls that genetically determined conditions tend to show up in one population more than in another. For example the rh negative factor is present in 15 per cent of Caucasians and only about 5 per cent of the Japanese.

4. Inconsistencies of the Recessive Gene Theory

As has been mentioned the average age of the mother is younger with a familial history of mongolism. It is suggested that this skewness of the maternal age curve may be explained thus. If that group of homozygous mothers who are usually protected (just under 4 per cent of the total population) are mated to a heterozygous husband the mongoloid tends to be born at a younger maternal age.[19] This does not fit too well into the scheme of maternal protection, but religates the lack of protection to the genetic make up of the baby.

Jervis[19] goes on to point out another inconsistency of single recessive genetic theory. The incidence of the condition remains unchanged in spite of the fact that mongoloids fail to reproduce and with their death those genes are lost.

5. Other Genetic Concepts

Other theories of the genetics of mongolism have been proposed. Hanhart, it is pointed out by Penrose,[32] has

proposed that the causative single gene is dominant. If so, its frequency in the general population would be 1 in 50, (or one-half the homozygous single recessive), resulting in a mongoloid fetal diathesis also of 1 in 50.

Some observers who felt that mongolism had an increased incidence among males, proposed that it was in some way a sex linked gene. More exhaustive studies have revealed only a slightly increased male predominance.(31)

D. Etiologic Implications of Recent Studies in Chromosome Number of Man

Recently new light has been shed upon the etiology of mongolism. There is evidence that the mongoloid's chromosome complement consists of the complement usually present in the normal person and additionally of a small chromosome. It is justifiable to believe that, the genes must act through biochemical action. If the nature of this action can be determined, a method may become evident for preventing or neutralizing the morbid influence genetically supplied.

Painter (1921) calculated the chromosome number of man to be 48. Koller (1937) confirmed this number and from the behavior of spermatocytes calculated the number of chromosomes as $2n = 48$ ($n = 24$, the haploid number as seen in mature germ cells).

Tijio and Levan (1956) and Ford and Hammerton (1956), using improved methods, demonstrated the number of chromosomes in normal

man actually to be 46.[11,13] There are 22 pairs of autosomes and one sex chromosome pair (xx in females, xy in males). The chromosome compliment in mongolism was first investigated by Mittwoch (1952)[29] who reported it to be approximately 48 in the spermatocytes of a mongoloid male. Jacobs (1959)[18] using the latest and most reliable techniques, demonstrated a diploid number of 47 chromosomes in blood and buccal cells of six mongoloid individuals, three male and three females. Similar findings were reported by Ford and associates (1959)[13], in an individual demonstrating both Klinefelter's syndrome and mongolism. The additional chromosome demonstrated in Jacobs' studies is among the smallest chromosomes, and somewhat difficult to differentiate from the Y chromosome. The rest of the chromosomes did not appear different from those in normal diploid set. "It is improbable though not impossible that the additional chromosome in mongolism is a Y chromosome."[18] If the additional chromosome were a Y chromosome and the individual were a female the chromosome make up would be that demonstrated in Klinefelter's syndrome (XXY).[13] It is felt that the extra chromosome found in cells of mongoloids is an autosome.

As has been pointed out there are increased numbers of mongoloids born with increasing maternal age. It has also been pointed out by Penrose (1957) that the mongoloid child resembles its mother antigenically more closely than the father. These

facts seem to point to the source of the primary disorder as resting with oogenesis. Perhaps mongoloids are "trisomic". "Trisomicism" results when both members of a homologous chromosomal pair fail to segregate. In the process of meiosis this would result in failure of a haploid set in each gamets.(37) If then the ovum with the extra autosome units with a normal sperm, the zygote formed will have a resulting diploid number of 2n+1 instead of the normal 2n. It is not difficult to comprehend the biochemical and structural abberations which might occur in an individual with such a chromosomal compliment.

Perhaps a door to an entirely new phase of medical knowledge and progress has been opened.

Already the increased incidence of leukemia in mongolism reported by various sources seems to be connected in some way with the chromosomal composition. Perhaps other carcinomas are also related to some abnormal chromosomal composition or disease process.

IV. BIOCHEMICAL STUDIES IN MONGOLISM

As already stated whatever the genotype, the genes act through biochemical processes. If the morbid processes in mongolism can be elucidated, perhaps a way to counteract them can be found. Accordingly this review includes consideration of biochemical studies in mongolism that already have been made.

A. Vitamin Absorption Studies

Recent well controlled studies indicate that the older mongoloid child tends to have a lowered gastrointestinal absorption of vitamin A in oil as compared to a normal child of the same age ($P = 10^{-2}$).[38] This was born out by comparison of both vitamin A tolerance and of fasting "A" levels in the normal and mongoloid child. The older age group was chosen because earlier studies have shown that vitamin A absorption is decreased in normal infants as well as in mongoloid infants. It has been found that mongoloids frequently exhibit such dermatalogic conditions as xerosis, palmar and plantar keratosis, seborrhiec dermatitis and acne vulgaris, and it is felt that these conditions may be related to aberrations in vitamin A absorption.

Some studies comparing urinary excretion of water soluble vitamins and/or vitamin metabolites in mongoloids and non-mongoloids before and after vitamin load tests showed the following results: (1) Relatively little differences in the urinary excretion of thiamine, ribaflavin, niacin, n-methylnicotinamide and vitamin C before load tests. (2) Relatively insignificant difference in urinary excretion of thiamine and ribaflavin after load tests. (3) A significantly decreased excretion of n-methylnicotinamide and creatinine by mongoloids after the administration of 100 mg of nicotin-

amide. This last test presents the possibility of a defect in the methylating ability of the mongoloid.(14) The same authors present experimental data indicating a difference between mongoloid and non-mongoloids in the excretion of vitamin B and pyridoxic acid and a marked and rapid effect of a vitamin B_6 load in decreasing urinary oxolate. After pyridoxine administration, mongoloids excreted more pyridoxic acid and less vitamin B_6 than the non-mongoloids. These investigators noted no difference in folic acid excretion in the two observed groups.(15)

B. Eosinophile Count after ACTH and Adrenalin Administration

A study has been made to evaluate, in the mongoloid, that adrenal and pituitary function which controls the eosinophile count. After ACTH and adrenalin administration it was found that 30 per cent showed abnormal reaction to ACTH and 60 per cent reacted abnormally to adrenalin.(3)

C. Gonadal Hormone Excretion Studies

Urinary 17-ketosteroid studies reveal some mongoloid female levels to be unusually high while male patients have values in the female range. This indicates that the 17-ketosteroids in both mongoloid male and female are adrenal in origin and not varied greatly by gonadal hormones.(3)

D. Thyroid Function Studies

In addition to the histologic abnormalities already

mentioned in which follicles may be absent, there are functional aberrations as well. Twelve per cent of mongoloids have a low protein bound iodine. In one study of mongoloids the 24 hour I-131 uptake ranged from 12-32 per cent with an average of 23.9 per cent (S. D. = 5.4). In three patients it was below 20 per cent as compared to an average of 29 per cent (S. D. = 5.1) in 64 euthyroid individuals. The butanol extractable fraction of plasma radio-iodine and turnover rate of the radio-iodine (biologic half-life) did not reveal a statistically significant difference between the mongoloid and euthyroid. Other observers[9] again have not found significant changes in the protein bound iodine in mongolism in general except in individual instances.

E. Serum Protein Studies

Hyper gamma globulenemia in mongoloids has been described independently by several investigators. The elevation in serum gamma globulin tends to become more pronounced with the age of the patient. The exact cause of this elevation is not known but appears to be principally the result of antigenic stimulation, liver disease, infection or hypersensitivity reaction or neoplasms containing a concentration of gamma-globulin.[6,38] It has been assumed that the increase in gamma-globulin is due to increased <u>production</u> regardless of whether <u>catabolism</u> is interferred with or not. There has been

noted a concomitant decrease in serum albumin.[38]

F. Urinary Beta-aminoisobutyric Acid

Another biochemical finding which should be mentioned here is the increased urinary beta-aminoisobutyric acid (BAIB) in mongolism. BAIB, a urinary amino acid, has been demonstrated to be a reductive product of thymine. It has been inferred from a study of numerous English and Italian families that the ability to excrete increased amounts of BAIB is inherited as a simple recessive.[41] BAIB is also increased in urine of patients with myelogenous leukemia. There is no evidence that increased BAIB excretion in leukemics, and the increased incidence of leukemia in mongoloids is significant. No mention is made of an increase in mongolism or leukemia in the families demonstrating increased urinary BAIB.

G. Serum Lipids and Lipoprotein

Elevated serum lipid[1] and lipoprotein[25] levels have been reported.[6,38]

H. Glucose Metabolism

A series of well controlled glucose metabolism tests including, intravenous glucose tolerance tests, insulin tolerance tests, and epinephrine tolerance tests were carried out.[35] The glucose tolerance test[20] performed on mongoloids of all ages revealed two rather important abnormalities in the re-

sulting curves. First 52 per cent of the glucose tolerance curves were abnormal. (A normal glucose tolerance curve is defined as a curve in which the blood level does not exceed 250 mg. per cent after intravenous glucose, shows a marked drop by 30 minutes and returns to fasting levels by one hour.) The author reports the following three types of abnormality in the glucose tolerance curve: (1) very high peak in blood sugar (intravenous glucose tolerance curve) but dropping to fasting levels in sixty minutes. (2) a high peak with a delayed drop to fasting levels. (3) normal peak but delayed drop to fasting levels.

Second, the incidence of abnormal glucose curves increases with advancing age. Further observations included low fasting blood sugars and 13 per cent of the cases at hyperglycemic levels.

Insulin tolerance tests resulted in a greater than normal fall in blood sugars to an average of 57 per cent of the fasting blood sugar levels, indicating an increased sensitivity to insulin. Inspite of blood sugar levels as low as 20 - 30 mg. per cent the mongoloid patients exhibited no evidence of hypoglycemia. No normal response to the insulin tolerance tests were recorded in the eight patients studied, (i. e. no return to fasting levels in 60 minutes.)(35)

The epinephrine tolerance test revealed a diminished

response indicating decreased gluconeagenesis.[20]

Such studies of glucose metabolism abnormality would again lead us to think of dysfunction on the cellular level, this abnormality being conditioned by a genetic influence.

9. Serum Calcium

Calcium levels have been reported by several authors to be significantly lower in the mongoloid.[6,38] In one study 10 of 18 mongoloids had serum calcium of less than 9.0 mg. per cent.

Already some of these biochemical tests have been used in the diagnosis of deficiencies, if not in mongolism as a whole then in individual mongoloids. Successful treatment may be instituted in some instances. Future work will no doubt further the diagnosis of specific defects and the successful treatment of these.

V. CARE OF THE MONGOLOID

A. Life Expectancy of the Mongoloid

It is estimated that the mortality rate for mongoloids is about 9 times normal.[33] Two decades ago the average life span was 10-15 years. Factors contributing to an early demise aside from congenital heart disease were respiratory, digestive and streptococcal infections. Unquestionably the life expectancy has been lengthened but cannot be

expressed in terms of years. The introduction of antibiotics and other measures have contributed to the increased life expectancy.

The morbidity rate is still very high. Diseases of the respiratory tract predominate. Anatomical variations contributing to respiratory disease include poorly developing sinuses and a shallow posterior pharynx is easily occluded by lymphatic hypertrophy.

B. Care of the Mongoloid in Home and/or Institution

When a mongoloid is born into a home the family is faced with the unusual problem of educating and training a child who, they know can never achieve a normal mental, physical emotional and social status. The training of a mongoloid requires understanding, wisdom and perseverance. It is important that a qualified person should spend some time with the parents explaining the implications of mongolism and outlining a plan of training and education. Such parents should be made aware of outside help made available through organizations, hospitals and institutions, state and private.

Care during the first years of life does not differ much from that of the normal child. The Late C. A. Aldrich, however, frequently advised that the mongoloid child be separated from the family as soon as possible, preferably without the mother seeing the infant. Most authorities do not agree with this

philosophy. Yannet (1953)[43] says, "It is my impression that, with few exceptions, the mongoloid child profits significantly from an environment which includes the advantages of a mother-child relationship during the first few years of life". Some of the unhappiest parents are those who were persuaded to institutionalize their mongoloid child in infancy. Most home situations allow for the child to remain in the home for the first few years of life.

Keeping in mind that the child's mentality will never exceed that of a four to seven year old, it becomes apparent that a formal academic education is less important than a training program to help the child become well adjusted in his personal relationships. Just like normal children, mongoloids are susceptible to emotional problems and they meet many frustrations associated with constant failure. Even if they are to be institutionalized later they will benefit greatly by the constant personal attention available in the home.

When the mongoloid reaches school age a special training program may well be started. In some localities special training centers are available for those defectives who are educable. State institutions are developing better programs for the mentally defective's training and care.

It has been repeatedly stated that a mongoloid child

in the family may prove to be the source of serious emotional difficulties which may effect the whole family unit, especially other children. Other children in the family can adjust if properly educated in their relationships to the defective sib.

C. Specific Therapeutic Measures in Handling the Mongoloid

1. Thyroid

Aside from the treatment and prevention of infections with antibacterial agents, thyroid has been the only demonstrably effective agent used in mongolism. Thyroid seems to act as a synergistic and catalytic agent. Sheldon and Skeen are quoted[3] to have shown that thyroid function is necessary to "release growth potentialities". Thyroid is also necessary to build bone and cartilage. Improvement has been noted with respect to activity, adiposity and constipation, but without beneficial effect on the individual's mentality unless hypothyroidism is actually present.

2. Pituitary Extract

Since the main problem in mongolism seems to be related to growth and development, Benda[2,3] has considered the possibility of benefit from pituitary extract from immature animals. Ojective proof of its benefit must yet be demonstrated.

3. Glutamic Acid

About ten years ago glutamic acid was introduced as a very beneficial adjuvant in improving the mental development of mongoloids.[2] It was felt that glutamic acid was the only amino acid metabolized by brain tissue. Observed results however are equivocal.

4. Gonadotropic hormones

Gonadotropic hormones have been used because of their supposed anabolic effect in tissue.

5. Ephedrine

Some investigators have felt that ephedrine given for short periods of time have a beneficial effect on the cardiovascular system.

6. Vitamin B

As mongoloids age their skins become rough, dry and exzematous. Fissures are frequently seen on the lips and corners of the mouth. Vitamin B has been noted to have a beneficial effect in such cases.[14,20]

7. Miscellanous Specific Measures

Of course those meausures used in the care of the normal child are employed with the mongoloid as well.

Congenital heart defects may now be repaired surgically as can the frequent orthopedic defects.

VI. The PREVENTION OF MONGOLISM

No specific measures have been developed to prevent mongolism. One can only advise people to have their family while the mother is young, preferrably under 30-35 years of age. It might be pointed out that a woman becoming pregnant after she is 40 runs a statistical chance of about 1-6 per cent of having a mongoloid child. Also if a woman has had a mongoloid child she runs a risk of having another mongoloid which is 40 times greater than the average for all ages.(4)

SUMMARY

Mongolism is briefly discussed with special emphasis on the diagnosis and theories of etiology of the syndrome. One of the first to describe the mongoloid individual was J. L. H. Down of London. He thought mongolism was the result of a degenerative process and that it was constantly associated with tuberculous parents.

The incidence of mongolism varies with ethnic groups. In people of Northern European extraction the incidence is reported as 0.16 per cent of live births. As far as we now know it is about 10 times less common in Italy and among the negroes of America.

One of the most striking features observed is the variation in the number of mongoloid children born to mothers at different age levels. From age 30 years to the end of the child bearing age there is a rapid and progressive increase in mongoloid births. Ten per cent of mental defectives in institutions are mongoloid. No sex difference in the incidence of mongolism has been consistently reported.

Usually the diagnosis of mongolism is quite simple, especially if enough stigmata are present in the individual. The most diagnostic stigmata are the flattened occiput and the muscular atonicity. Histologic abnormalities have been found in almost every body system. Some of the more common and striking changes seen are enlarged upon.

Growth is very slow in the first few years of life. The adult has arms and legs which are short compared to the trunk. Sexual activity, as are many other physiologic functions, is almost absent though the female may menstruate for a few years. Some mongoloid females have born children.

The largest percentage of mongoloids develop I. Q.'s of 25-49. Their ability to develop socially somewhat exceeds that expected from their I. Q.

A differential diagnosis, though in most cases quite simple, may in the less severe case of mongolism or with a coexisting hypothyroidism, in early infancy be confusing from the standpoint of differentiating between mongolism and cretinism. This is especially true because the mongoloid is often also hypothyroid.

The most widely acclaimed of the theories of etiology of mongolism, especially earlier, was the environmental theory. It concludes that some often obscure pathologic process acting on the embryo enutero in the fourth through the ninth weeks of pregnancy causes the development of the mongoloid.

Several genetic theories of origin of mongolism have been set forth. The most widely acclaimed theory until recently states that a very commonly occurring recessive gene will in the homozygous individual result in a mongoloid diathesis. Though one of every 25 persons in the general population have this diathesis less than 4 per cent with the diathesis develop

into mongoloids. The rest of the homozygous individuals apparently are effected by some kind of protective maternal influence which seems to diminish rapidly after the age of 30 years.

Dominant gene and sex-linked gene theories have not proved satisfactory to most men's thinking.

Recently investigators seem to have established that the chromosomal number in the mongoloid is not 46 as has been found in a normal person but is 47. The extra chromosome, which seems to appear in the ovum during reduction division, apparently is an autosome. This extra chromosome is considered responsible for the profound effect on the development and physiology of the mongoloid.

Numerous biochemical studies have been carried out, revealing several abnormalities in the mongoloid. Among the findings are abnormal vitamin absorption, metabolism, and excretion, a relative lack of gonadal sex hormone production, an increased serum gamma-globulin level, abnormal glucose metabolism and decreased serum calcium.

The life expectancy of the mongoloid, which twenty years ago was 10-15 years, has since the advent of antibiotics and other specific measures increased considerably though no absolute figures are yet available.

The general consensus of opinion is that the mongoloid child is better off with his parents during the first years of his life. His education should stress personality and emotional development.

Later on he may be trained or permanently placed on an institution. The notion that his presence in the home will endanger the emotional tone of the rest of the family is, generally speaking, unfounded.

Specific measures, including thyroid extract and vitamins, may be of some benefit to the child. Certain of the proposed measures have had questionable and disappointing results.

No means of preventing mongolism has yet been discovered aside from having the family early. i.e. before the mother is 35 year old.

CONCLUSIONS

A. Diagnosis

The diagnosis of mongolism is usually easy from the numerous physical stigmata that result. In certain instances in infants, cretinism must be differentiated from mongolism. Moreover, cretinism is frequently found in association with mongolism.

B. Incidence

1. The incidence of mongolism is definitely increased with a maternal age over 30 years. This tendency progressively increases from the age 30 until the end of the child bearing age. The chance of having a mongoloid before that age is about one in 500 whereas at age 45 it is about one in 25. Good prenatal care does not seem to influence the incidence of mongolism.

2. The Negro and Italian groups seem to have an incidence 10 times less than do those observed in groups of Northern European extraction.

C. Etiology

1. Mongolism, it now appears, is not due primarily to certain early prenatal environmental influences.

2. The evidence seems to indicate that the genetic factor is extremely important in the etiology of mongolism.

3. The theory that mongolism is due to a simple recessive gene has merit but fails to explain adequately certain

features among which are: (1) the nature of the maternal protective influence and why it might diminish with advancing age; (2) why the incidence of mongolism remains unchanged in spite of the loss of genes with the death of every childless mongoloid.

4. The presence of an extra autosome in the chromosome compliment of the mongoloid child could well explain the profound anatomic and physiologic variation seen in mongolism. Recent, though limited, studies would indicate this to be a likely etiology of mongolism.

D. Biochemical Studies

No common factor of a biochemical nature unique to mongolism has been yet derived which can adequately explain the physical and physiological deviation from normal seen in mongolism. No particular enzymatic system defect, for example, has been as yet demonstrated. However, biochemical abnormalities which have been discovered are best explained on the basis of some kind of genetic influence.

E. Care of the Mongoloid

1. During the early years the mongoloid is generally best cared for in the family group. Later insitutionalization may be desirable.

2. No specific measures of therapy have been found to help mongoloids in general, although certain measures such as thyroid and vitamins may be helpful in individual cases.

F. Prevention of Mongolism

The only measure now known to effectively decrease the possibility of having a mongoloid in the family is that of having children when the mother is young, preferably under 35 years of age.

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