Mongolism and cretinism / by Clemens E. Benda.

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MONGOLISM AND CRETINISM

CLEMENS E. BENDA

SECOND EDITION

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WITH 104 ILLUSTRATIONS

BY

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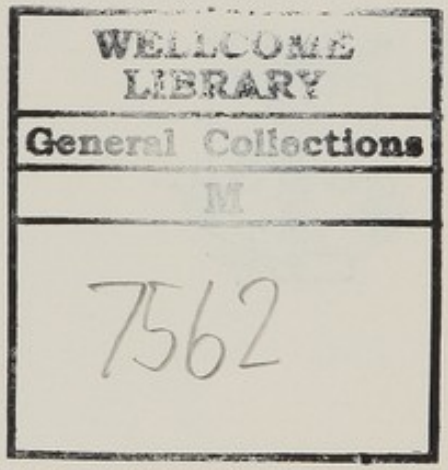

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Dedicated to

My beloved wife, Elizabeth Benda, M.D.

The original research in mongolism was done at the Wallace Research Laboratory for the Study of Mental Deficiency, Wrentham State School, Wrentham, Massachusetts in the Years 1936 to 1946. I wish to thank Dr. C. Stanley Raymond, Superintendent of the Wrentham State School and founder of the Wallace Research Laboratory for the help and support this research received.

I wish to acknowledge with gratitude the collaboration of my co-workers in the Laboratory on whose devotion to their work and reliability depended the outcome of this research

Edward Roosen-Runge, M.D., Pathology of Liver
Emily May Bixby, Ph.D., Biochemistry
Marjorie Baker, Tissues
Robert Sharp, X-ray and Photography
Florence Pease, A.B., Blood Studies
Ruth Prouty, M.A., Psychological Testing

Since 1947, research has been continuing in the Research Laboratory of the Walter E. Fernald State School, Waverly, Massachusetts, whose Superintendent, Dr. Malcolm J. Farrell, and whose trustees have most generously aided in further progress by providing funds and adequate facilities.

C.E.B.

PREFACE TO THE SECOND EDITION

Indicative, beyond doubt, that there has been an urgent need for a new scientific approach to the problems of mongolism and cretinism is the fact that in less than three years a second edition has become necessary. The friendly response to the data presented in this book is encouraging. During the last two years a steadily increasing number of publications have dealt with mongolism and suggest that this long neglected chapter of human pathology seems finally to be coming into its own.

A number of reviewers have cited the author's theory of mongolism as stating that it results "from pituitary deficiency of the mother and embryo" or that mongolism is "caused" by congenital hypopituitarism. A well-known author of books on child psychiatry quotes the writer as attributing "a causal role to a dysfunction of the hypophysis and more particularly of the hormonal secretion of the basophilic cells."

Since similar statements are repeated by numerous reviewers—reading apparently other reviews rather than the original source—it seems advisable to orient the reader by a brief statement on the present status of research as presented in this book.

The name "mongolism" is unfortunate and misleading. The condition encompasses an abnormal fetal development which varies in its physical manifestations and in intensity of mental retardation. The mongol- "like" features are frequently not conspicuous and the absence of certain physical signs often prevents the diagnosis early after birth. Moreover, in some instances, mental deceleration is outstanding with not too marked physical aberrations; in other cases, physical stigmata are conspicuous, but mental capacity is only moderately impaired. The Langdon Down syndrome (congenital acromicria, [Benda]) should be conceived like other syndromes, for instance, Hurler's syndrome (gargoylism), as a congenital symptom complex, characterized by a specific deficiency of physical and mental growth and endocrine metabolism. Such a concept would help gradually to eliminate the term "mongolism."

In the etiology of this condition, two problems must be distinct: first, the causes leading to the abnormal development of the embryo; and, secondly, the abnormal factors operating in the mongoloid child that prevent it from maturing in a normal way. Since mongolism is present at birth and the faulty development takes place in the early stages of fetal growth, the causative factors are either of a genetic nature, or environmental, operating in the mother during gestation. The author believes that his data, which encompass now a study of around 500 families, provide evidence that mongolism is not due to genetic factors. He considers mongolism as the result of a deceleration of the developmental rate due

to noxious agents interfering with proper blood supply and nutrition of the growing fetus. The most critical time seems to be the end of the organogenetic period from the sixth to the fourteenth week, when the maternal corpus luteum regulates fetal development and nutrition of the fetus is gradually transferred to dependency upon the placenta. The data at hand seem to indicate that mongolism can be potentially the outcome of any pregnancy if a constellation of factors occurs which produces a threshold condition of sterility. The various factors which seem to be responsible are discussed at length in chapters X and XI.

A deceleration of the fetal growth rate, due to abnormal hormonal and nutritional conditions, may explain why the newborn is an "unfinished" or "ill-finished" child, but it cannot explain why the mongoloid does not develop normally after he is born. Children with other congenital anomalies show, in general, a much better physical growth rate.

Clinical and anatomic studies of children with mongolism produce evidence that all endocrine glands like the thyroid, adrenals and gonads, which depend on the stimulating action of the tropic hormones of the pituitary, remain dormant. As the result of a faulty metabolism, changes are evident in the bone cartilage, liver, brain and other tissues. These observations point toward a basic deficiency in the function of the pituitary, the "master gland," that maintains a key position in the regulation of tissue metabolism. This book offers evidence that the abnormal prenatal condition creates a congenital hypopituitarism. Pituitary function, on its part, depends on the brain, which receives the stimuli from the outside world and primes the organism as a whole for proper responses. Extensive studies of the nervous system reveal that the nervous system is immature at birth and develops at a much slower rate than necessary. The vicious circle between brain and endocrine systems keeps the mongoloid child constantly out of tune with normal development, and if left to its own resources, the mongoloid child falls consistently further back in its mental and physical growth. This situation is similar, *though not identical,* with that of cretinism, where the deficiency of the thyroid results in the arrest of physical growth and of mental development. The brain becomes edematous, like other organs, and the nervous system degenerates progressively if no steps are taken soon after birth. The arrest of brain development in cretinism, on its part, leads also to a degeneration of the pituitary, which terminates physical growth.

In understanding the factors which operate in the mongoloid child and which prevent its normal development, the author is convinced that science will develop ways of coping with this situation. The treatment of the mongoloid child has to break into the vicious circle somewhere, and since at present the endocrine deficiency is easier to control than the

retarded brain maturation, consistent attempts should be made to correct the physical growth disorder. Later on, science may provide means to cope more effectively in a direct way with abnormal brain maturation.

The present edition is revised where further research offers new data. As far as the original research is concerned, new observations have confirmed the facts presented in the first edition, and the first nine chapters needed only minor corrections.

Chapter X, "Relationship of Mongolism to the Maternal Condition," presents the basic data as to the etiology of mongolism. The material seems to provide definite evidence that mongolism develops in the fetus under a constellation of certain adverse factors which operate in the maternal organism and deprive the growing embryo of a proper nutritional environment. The chapter has been thoroughly revised, and the accumulated evidence lays the foundation for a preventive approach briefly outlined in Chapter XI.

The experience gathered from the treatment of mongoloid children during the last eight years makes it possible to strike a somewhat more optimistic note and to outline a new program based on observations collected from the community as well as from institutions. Chapter XII, "Principles of Treatment," has been accordingly revised and enlarged.

CLEMENS E. BENDA

ARLINGTON, MASSACHUSETTS
JUNE, 1949.

PREFACE TO THE FIRST EDITION

A few years ago a speaker at the Royal Society of Medicine in London referred to our ignorance of the condition known as mongolism as a "disgrace to the medical profession." His charge was irrefutable, and the situation today is little changed. Textbooks and standard medical publications refer to mongolism as a "mysterious" or "unknown" disease and treat it as briefly as possible. Most of the current thinking about it dates back to opinions expressed forty or fifty years ago. These facts are all the more startling since mongolism is the most frequent growth disorder of infancy—at least ten times more prevalent than cretinism in America. The number of living mongoloids in the United States is estimated at 60,000. Of about 8,650 daily births in this country, at least 17 are probably mongoloids. Seventeen babies born daily into normal families, often babies, as observations show, who have been more deeply desired by their parents than many of their more fortunate brothers and sisters.

The purpose of this book is to rid mongolism of the mystery clouding its proper medical recognition and to publish data which were collected in the Wallace Research Laboratory, devoted to the study of mental deficiency, during ten years of continuous research. The collected facts may guide the physician in his management and treatment of the condition. Mistaken notions of a heredity factor with consequent feelings of disgrace at having produced a feebleminded child have ruined the lives of many a family. Doctors who think of mongolism as a "regression to the Mongolian race" or a pathological "racial mutation" scarcely ameliorate the situation. Efforts to treat these children are often met with skepticism or delayed until nothing can be done.

In the course of this study of mongolism, more than three hundred different patients of all ages were examined, and many were observed for a period of almost ten years. Repeated measurements, radiological observations, biochemical and psychological studies rendered a wealth of data which indicated an endocrine deficiency disease of a particular character. Through the performance of fifty autopsies, it was possible to study every aspect of this disease from the time of birth to death, the occurrence of which ranged all the way from two days to over thirty years. Much gratitude is due the many parents who co-operated freely, furnishing all required personal information and giving autopsy permission "in order that future generations may benefit." The co-operation of members of some other hospitals in furnishing material which was not available at our place is also greatly appreciated.

The material collected should be of broader interest than just to those concerned with this particular problem. In the mongoloid, nature has

provided mankind with one of her strangest experiments—creating a human being without proper function of the pituitary, the "master gland." Countless experiments have been made as to the effects of pituitectomy in animals, but so far scientists have taken little advantage of their unique opportunity to study this striking endocrine disorder in man. Actually, the philosophical aspects of mongolism, which so greatly impressed the first investigators, have beclouded its interesting biological aspects. The frequency of the condition furnishes endocrinology, pathology, physiology, and radiology with an unequaled opportunity. Although the endocrine material is mainly collected from mongoloid patients, the findings on the thyroid, pituitary, adrenals, and gonads offer the opportunity of studying the general relationship between the various endocrine glands in man. The influence of pituitary deficiency upon the other endocrines is as well demonstrated as, conversely, the reaction of the pituitary to thyroid and gonadal deficiency. The findings in mongolism offer practical demonstrations for the pathology of all known growth disorders.

The relationship between the birth of a mongoloid and the condition of the mother during pregnancy throws new light on the importance of the health of the pregnant woman. Although suspected for many centuries, the relationship between the prenatal condition of a mother and the birth of an abnormal child has never been clarified. This material presents some evidence on this subject which is of general significance and may provide means of preventing the occurrence of such disaster.

When it was decided to include cretinism in this book, it was with the idea of comparing mongolism, the unknown disease, with cretinism, the well known one; of contrasting a complicated growth disorder of unknown origin with a growth disorder produced by a single gland. Since there are hundreds of contributions dealing with cretinism and the various aspects of experimental thyroidectomy, it felt like safer ground. But, in the course of the study, it turned out that cretinism, too, is generally less understood than the writer realized. Some readers may feel that cretinism does not receive a fair deal, being less extensively discussed than mongolism. The author did not attempt to cover the whole field. The physiological studies on thyroidectomy and the chemical aspects of iodide metabolism are omitted. The books of Means, Salter, and Hertzler, to mention only three, discuss with competence and authority the clinical, chemical, and surgical aspects of thyroid disease.*

* Hertzler, Arthur E.: Diseases of the Thyroid Gland. Paul B. Hoeber, Inc., New York and London, 1945.

Means, J. H.: The Thyroid and Its Diseases. J. B. Lippincott Co., Philadelphia, 1937.

Salter, William Thomas: The Endocrine Function of Iodine. Harvard University Press, Cambridge, 1940.

On the other hand, the writer felt that the large amount of clinical, pathological, anatomical, and x-ray observations which he was able to collect made it possible for him to present some aspects which have not been too well covered previously. Gaps may be filled and emphasis placed on those angles which need more attention. The condensed treatment of cretinism is due to a conscious effort to avoid repetition.

For almost a thousand years, mongoloids and cretins have been confused with one another and considered brethren. Only during the last half century have differences between the two become increasingly appreciated. Now, with the recognition of the etiological factors operating in each, the time has come to compare the thyroid cretin and the "pituitary cretin" and to place emphasis on similarities as well as differences. Both conditions have given rise to wilder speculations than any other diseases. It is to be hoped that thorough study of them will benefit not only the unfortunate patients, but medicine as such.

Wrentham, Massachusetts
June, 1946

Clemens E. Benda

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CHAPTER I

HISTORY, FREQUENCY, TERMINOLOGY

Mongolism

Historical Introduction

When Langdon Down published his classic paper on *Ethnic Classification of Idiots* in 1866, which described mongolism for the first time, he was influenced by a dogma, prevalent in his day, that pathological phenomena were frequently retrogressions into earlier types in the history of man. Mongolism, he believed, is "an example of the retrogression which furnishes some argument in favor of the unity of the human species." In spite of his philosophical speculations, Down's observations on the mongoloid are very accurate in many ways. He considered the condition as one type among various ethnic groups of idiocy. Although he did not mention cretinism in this paper, several years later he gave an accurate description of the sporadic cretin. He described some aspects of both types in almost identical words, but he never expressed an opinion about their mutual relationship.

John Fraser and Arthur Mitchell deserve the credit for giving the first scientific report on this type of mental deficiency, in a meeting of the Medico-Psychological Association held at the Royal College of Physicians, Edinburgh, December 14, 1875. Their report was published in the *Journal of Mental Science*, July 1876. It is interesting to note that when Dr. Mitchell first called Fraser's attention to the case which he presented, he was not aware of any literature on the subject. Mitchell, who was then Commissioner of Lunacy, said that this condition was known by the name of "Kalmuc idiocy," which he described as "a form of idiocy rarely met with in asylums, but nevertheless not really uncommon." Dr. Ireland, who discussed Fraser's paper, and the chairman of the meeting rejected the term. Fraser defended it "on account of the form of the eyes and the size of the head." His report dealt with a 40 year old woman of whose skull he had made a fine reproduction. His description is a masterpiece of clinical observation, and he covered every aspect of the condition very thoroughly. Mitchell presented notes on 62 cases arranged according to age groups, emphasizing the short life span and brachycephaly, which he considered "almost invariably found." He noticed no hereditary factor, and no kinship of the parents, but observed bad health during pregnancy in a great number of cases. "The mental state is as distinct, as peculiar, and as steady as the physical. If the patients were brought together, they

would be found to resemble each other strikingly in personal appearance. But more than this, they would also be found to resemble each other in character, in capacity, in likings and dislikings, in habits, in defects, in aptitudes." Mitchell recognized that these cases were not cretins but that they had some aspects in common with the "cretinoid" idiot.

In 1877, Ireland included the mongoloid as a special type in his book on *Idiocy and Imbecility*. Shuttleworth, in 1886, pointed out that these patients are in fact unfinished children, and that their peculiar appearance is really that of a phase of fetal life. "I do not mean that they are necessarily prematurely born, but that some cause has depressed the maternal powers, and there has been a defect of formative force. It is remarkable that, in my experience, nearly one half of these children are the last born of a long family. . . ."

The knowledge of mongolism increased steadily through a number of Anglo-American publications which dealt with such characteristics as the mouth and jaws (Robert Jones), the eyes (Oliver, 1891), the hands (Telford Smith, 1896), and the heart (Thomson and Garrod, 1898). In America, Wilmarth carried out extensive work on the pathology of idiocy as early as 1885, 1886, and 1890, when he published a survey on the examination of 100 brains of feebleminded children.

It is interesting to note that Bourneville, whose great pioneer work on mental deficiency began in 1881, did not deal with mongolism until 1900, after which his publications on this subject followed each other at yearly intervals.

In the same year Kassowitz, in Vienna, took up the subject and studied the relationship of mongolism to infantile myxedema. In the following decade much interest was centered on the differentiation of mongolism and cretinism, an enterprise from which the knowledge of cretinism greatly benefited. Mongolism was not so fortunate as cretinism, which attracted the attention of outstanding medical authorities. Without the help of surgeons of the fame of Horsley, von Eiselsberg, Reverdin, and Theodor Kocher, cretinism would still be among the less well known diseases.

It is surprising to note how little progress has been made in the knowledge of mongolism since it was definitely divorced from sporadic cretinism and myxedema. Although the number of contributions is fairly large, the reports usually deal only with a few cases or with a single aspect of the condition. Considerably more material has been collected regarding the relationship between mongolism and maternal age, but even on this subject the interpretation is still a matter of argument.

In 1928, Brousseau's careful American monograph presented the collected available material for the first time. The book offers a thorough review of the literature and the many aspects of the condition. However, it does not attempt to underline the medical problems which are involved.

Almost at the same time, in 1929, van der Scheer published a German monograph that summarized his studies carried out in Holland. The book abounds in personal experience. Unfortunately, van der Scheer committed himself to an interpretation of the whole pathology, which he explained on the basis of a narrow amnion sac which prevents the fetus from full development. The "amnion sac theory," which is now associated with van der Scheer's name, is little supported by facts. It has obscured the merits of this publication, which rest on the abundance of clinical material that the author collected.

Frequency

The frequency of mongolism has attracted attention from the very beginning. Langdon Down claimed that the mongoloid type of idiocy occurred in more than 10 per cent of mental cases presented to him. Later calculations range from 5 to 25 per cent of the feebleminded, the variations being due to the fact that the age factor is rarely taken sufficiently into consideration. Bleyer, in 1932, calculated the occurrence of mongolism on the basis of a study involving almost 50,000 children in the out patient department of the St. Louis Children's Hospital. Among these, 777 mentally deficient children were found, or approximately one mentally defective child in 60 dispensary cases. Among the mentally deficient there were 150 mongoloid idiots, which gives a percentage of 0.3 per cent of the total enrollment and 19.4 per cent of the mentally defective. On the basis of these figures, one might expect at least 2.3 mongoloids among 1,000 newborn infants. As a matter of fact, this figure is too small, because Bleyer has shown that among 30,000 children between the ages of 4 and 14 years, 45 mongoloid idiots occurred; but among 20,000 admitted in the first three years of life, 70 mongoloids occurred. Hence, in the younger group one mongoloid appeared in about 285 dispensary children. Bleyer estimated the number of mongoloid children in the United States to be at least 28,000. This number indicates impressively the importance of this condition, and the fact that among every thousand newborn babies two or three mongoloids may be found shows the great toll which this disease takes from the health of the population. The calculated percentage of at least two to three per thousand births seems to be correct for all countries of the white race, as various publications from different places demonstrate. Lahdensuu reviewed the frequency of mongolism in Finland. He encountered 40 mongoloids among 8,517 patients of the University Children's Hospital, Helsinki, in the period from 1925 to 1936, which gave him a percentage of 0.47. Hellsten figured 0.63 per cent mongoloids from statistics in the Children's Hospital of the University at Lund. Among a studied group of 34,494 children in Italy, Gallo found 94 mongoloids, which represented a percentage of 0.27.

As far as the proportion between the mongoloids and other groups of mental defectives is concerned, the calculations are not uniform because some investigators used statistics from institutions for the mentally defective, while others calculated the percentage from outpatient material. From the many different statistical studies, however, it appears definite that mongolism accounts for 6 to 10 per cent of all mental deficiency.

Van der Scheer found 500 mongoloid persons among a general population of 8,000,000 in Holland, which represents one mongoloid in 16,000 or 0.0625 per thousand. Penrose reported one in 10,000 in the eastern counties of England. These numbers indicate the proportion between the mongoloid patient and the whole population, including all age groups, but they do not give a fair idea of how many mongoloids live in our midst. Such a number can be estimated from the actual birth rate of mongoloids. A recent report by Beidleman, based on observations in the Lying-in Hospital of Boston, states that for the last fourteen years an average of 3.4 per thousand mongoloid births was observed with surprising uniformity. This shows a higher birth rate of mongoloids than expected. Since the Boston Lying-in Hospital represents an average maternity hospital, and since it is increasingly common for all women to give birth at a hospital rather than at home, there is no reason to assume that this rate does not represent an average for all births. Possibly as many as 50 per cent of all mongoloid babies are not recognized at birth. The babies are considered as normal, and a child's peculiarity is discovered only after several months have passed. If other statistics should show a lower average of mongoloid births, the factor that some cases were not recognized has to be taken into consideration. With a birth rate of almost 3,000,000 for the year 1943, a conservative estimate would be that at least 6,000 mongoloids were born in that year, but the number may well be as high as 9,000. With a life expectancy of only ten years for this group of patients, there are 60,000 mongoloid persons among the general population in the United States. A life expectancy of only ten years is based on the high mortality rate in the first year of life. Warner reported that half of her subjects died when she was making a study of mongolism, the average age of death being 12.6 months. Tredgold mentioned a loss of at least 25 per cent between birth and the age of 5 years. With improved health conditions and infant mortality on the decline, the number of living mongoloids will, however, increase considerably during the next decade.

Terminology

The time-honored name of "mongolism" is so well established that the term will never disappear, but the attempt should be made to reach some uniformity of terminology and to eliminate expressions which are inaccurate

and misleading. The name "mongoloid" refers to the mongol-"like" appearance of these patients. It cannot be denied that a superficial resemblance to the Mongolian race exists in a number of cases, especially at a certain early age. But to term these children Mongolians is incorrect, since a Mongolian is a member of the Mongolian race. Even less appropriate is the term "Mongol," for this refers to a limited group of people, the inhabitants of Mongolia.

The early members of the Medico-Psychological Association in London objected to "nick-naming an idiot by calling him a Kalmuc or mongolian" because he is "no more a Kalmuc than any other human being."

Shuttleworth introduced the name of "unfinished children," which John Thomson improved upon by changing it to "ill-finished." R. Bennett Bean described the mongoloid as a "hypomorph white type."

Since mongolism has been recognized in Negroes and Indians and is not rare in Chinese and Japanese children, the need for a better scientific expression is urgent. Chinese doctors point out that they can distinctly recognize the condition in their population, but are at a loss because the term "mongolism" is certainly inadequate in describing a Chinese child of that type.

When in the course of studying the growth disorder of mongolism it became evident that mongolism represents the opposite condition of acromegaly, I introduced the term "congenital acromicria," which would permit a broader application of the term to all races, including the Chinese, Japanese, Indian, and Negro patients. At that time I was unaware of the fact that this term had been used before by Schüller* and by W. Clift. In 1922, Clift reported roentgenological findings in mongolism. He found the name "acromicria" appropriate because of "the disproportionate developmental deficiency" of the nose, maxilla, and other bony structures, whose development was "in opposition to acromegaly." The simultaneous agreement of three independent investigators regarding the character of the growth deficiency indicates that the name of "congenital acromicria" is well chosen.

The term is not only descriptive in the characterization of the specific growth disorder, but it includes an important clue to the essential pathology. When, in 1886, Pierre Marie discovered the relationship between acromegaly and a "dysfunction" of the pituitary gland, he freed acromegaly

* Arthur Schüller, whose name is well known from the "Hand-Schüller-Christian's disease," wrote in an article on "Infantilism," with regard to mongolism, in 1907: "Die für diesen Typus characteristische Wachstums-anomalie bildet gewissermassen einen Gegensatz zur acromegalen. Die Gesichtsknochen und die Endteile der Extremitäten sind nämlich auffallend verkürzt, sodass man von einer Acromicrie sprechen kann." Wien. med. Wchnschr. **57**, 629, 1907.

from a concept similar to that which overshadowed the study of mongolism, namely, that acromegaly represented an atavism. Acromegaly has long been removed from the field of speculative mythology, and the pathogenesis of hyperpituitarism is firmly established.

The overwhelming clinical and pathological material which was available for this book provided evidence that mongolism is a congenital hypopituitarism. Not only do the patterns of growth deficiency follow the patterns of experimental and clinical hypopituitarism, but the study of the endocrine glands has accumulated evidence that mongolism is a polyglandular deficiency, in which all glands that depend in their function upon the tropic hormones of the pituitary are at fault. The pituitary itself is a hypoplastic organ incapable of providing efficient stimulation to the organism. The relationship between mongolism (congenital hypopituitarism) and the so-called pituitary dwarfism is the same as that between congenital thyroid aplasia and childhood myxedema ("acquired cretinism").

The pituitary dwarf is a patient in whom pituitary deficiency develops after birth, usually not before several years have elapsed. The mongoloid's pituitary is hypoplastic or damaged in fetal life, and the mongoloid is born with a pituitary deficiency which he is never able to overcome.

Growth and development of the mongoloid resemble conditions which are seen in animal experiments after pituitectomy. With the recognition of mongolism as congenital acromicria, this condition is freed from the stigma of mysticism and racial mutation. As hypopituitarism, mongolism offers a wide field for endocrine research, and the discovery of its pathogenesis prepares the way for a more effective therapeutic approach.

Cretinism

Terminology

Turning from mongolism to cretinism, one feels on comparatively firm ground as so much more clinical and experimental work has been done in this field. The most illustrious names in surgery, medicine, and pathology are connected with the exploration of cretinism.

The name "cretinism" is so old that its origin is in doubt. According to one theory the word is a twisted form of the French *chrétien*, meaning a Christian, considering the fool as a kind of blessed person similar to the epileptic, but this interpretation seems rather far-fetched and has little to support it. A much sounder tradition links the word "cretin" to the Latin *creta*, which means chalk, pointing to the grayish white, pasty color of the skin characteristic of this condition. Some link the expression simply with the word "creature," but other terms used in the Austrian-Swiss regions of endemic cretinism, such as *Kreidling* from the German *Kreide*,

meaning chalk, suggest the etymologic interpretation of the cretin as a "cretean." In the Rhaeto-Romanic language the word *cret*, cretin, means dwarf or little, and it is likely that the term "cretin" refers simply to the dwarfs of those sections. The cretins have been known as goiterous people since the days of the ancient Romans. The use of the term "cretin" seems to date back to Felix Plater's writings in 1614. The name was also used by Wolfgang Hoefer, a Viennese physician, in 1655, and by Fodéré, a Savoyard physician, in 1792. Napoleon I in 1811 opened the line of dictatorial health measures by taking a census of the cretins in the Canton Wallis, with the purpose of transplanting the goiterous population into healthier sections—an attempt which was defeated by the conservative adherence of the people to their homes, while Napoleon's defeat on the battlefields ended the first dictator's dream of happiness by decree.

Occurrence

With regard to the frequency of cretinism, distinction has to be made between sporadic cases and endemic cretinism. Sporadic cases of congenital and acquired athyroidism occur outside of goiterous areas in every country. Sporadic cretinism is not frequent, although not rare, and many milder cases may still be overlooked. Murray B. Gordon, in 1922, discussed 340 cases which he collected from the American literature or which came to his personal attention. There is no indication how many of these patients were congenital thyroid aplastic cretins or how many were cases of childhood myxedema. The most interesting observation in Gordon's report is that none of the cretins came from an area in which goiter is endemic (Canada along the St. Lawrence River, Pennsylvania, the Great Lakes, and the Rocky Mountains).

It is impossible to offer exact statistics or estimates on the frequency of sporadic cretinism because no census registers these cases as a separate category. Moreover, the term "cretin" is used by some writers for varieties of thyroid deficiency, many of which are discovered before the full picture of cretinism has developed. These cases form a part of the routine of any pediatrician. Myxidiocy, Bourneville's term for the severe form of sporadic cretinism or thyroid aplasia, seems to occur in less than 1 per cent of the feebleminded population. They are at least ten times less frequent than mongoloids, but the successful treatment which is possible in hypothyroidism makes the knowledge of this condition a fundamental medical requirement.

Although endemic cretinism has been investigated statistically in many countries, it is impossible to obtain an accurate over-all picture. Goiter and endemic cretinism occur in the same areas, but, of course, they are not identical. Goiter has been the subject of many large-scale investigations,

and several countries, including the United States, England, Austria, Switzerland, have appointed special goiter commissions that have studied the subject with great care. Maps of the distribution of goiter in the world have been prepared by Robert McCarrison and by H. Eggenberger. These surveys have demonstrated that goiter increases in proportion to the distance from the ocean or, more exactly, with the distance from sea level. The flat plains bordering the ocean coasts have little cretinism. Wherever mountains rise, near or far from the ocean, cretinism increases on the slopes up to a certain level, which is thought to be 1,400 m. or 4,200 feet, above which level no cretinism is encountered (Kutchera). Where the mountains are near the ocean, as in some sections of Italy, Southern France, and in Chile and California, cretinism occurs relatively near the ocean. The same is true for the Asiatic mainland, Formosa, and Japan. It is beyond doubt that the common denominator for such a great variety of geographical areas is the low concentration of iodine in soil, water, and air.

Endemic cretinism is thought to occur in a goiterous population as a "cretinoid degeneration." If we analyze available statistics regarding the frequency of this condition, we find that the number of cretins in Switzerland is estimated at about five thousand in a population of about four million people, or 1.25 per thousand. According to Eggenberger, these five thousand are cases who need to be cared for by the State. A. Koller has made an inquiry for the Kanton Appenzell on two occasions and has estimated the number of cretins at 2 per cent of the population, including all degrees of mental retardation. A study made by Endvay on the Danube Island Schütt, in Hungary, found an incidence of 1.3 per cent. In Austria cretins were found in 0.24 per cent in Kärnten and in 0.19 per cent in Salzburg. In the United States about six centers of endemic cretinism are recorded on Eggenberger's map, where the actual number of cretins is said to surpass several hundred. On the other hand, goiter runs in some of these places as high as 90 per cent of the population.

These figures are somewhat startling. Any expert on mental deficiency knows that mental deficiency, as such, runs between 2 and 4 per cent in any given population. We are, therefore, entitled to expect the same percentage of feebleminded persons of varying degree in any of the areas reported as homelands of endemic cretinism. Since at the same time goiter runs as high as 75 to 90 per cent of the population, the same percentage of enlarged thyroids has to be expected among feebleminded. Anyone who has traveled or studied* in countries with endemic cretinism, like Switzerland,

* The author of this book had the privilege of working in Switzerland for several years. One year was spent on research in the Kantonal Asylum of the Kanton Appenzell, in Herisau. This community is a center of endemic cretinism. The valuable studies of Eggenberger and Koller were made in Herisau.

Austria, or Southern France, knows that in these areas any feebleminded idiot or imbecile or simpleton is considered a "cretin" and the name is synonymous with the term "imbecile." The suspicion that many feebleminded with goiter are included in statistics on cretinism is more than justified if one sees the clinical descriptions and pathological records published from those areas and often illustrated by pictures. Any type of mental deficiency and endocrine disorder may be found included in these statistics as occurring on the basis of endemic goiter. If one reads that cretinism occurs "with goiter, hypothyroidism or normal [?] thyroid" and if one further learns that it runs through all degrees of mental retardation from full cretinism to borderline intelligence while the physical development varies from dwarfism to measures of 5 feet 6 inches and more in height, then there can be no doubt that these reports include many cases familiar to any expert working in regions where no endemic goiter exists. It is not surprising that some critics have come to the startling conclusion that, in contrast to sporadic cretinism, endemic cretinism is not due to a thyroid disease, or if thyroid deficiency develops, it is only in the course of a general degeneration. According to their preferences, authors emphasize heredity, infections, pluriglandular disorder, or general degeneration. There can be no doubt that many feebleminded persons who grow up in areas with goiter have enlarged thyroids, but their feeblemindedness occurs independently of thyroid disease. The observation that the majority of feebleminded persons tends to be undersized in stature makes a distinction even more difficult. We have, therefore, to postulate that the term "cretinism" be restricted to those cases in which a thyrogenic physical growth disorder is associated with a specific mental deficiency. If this definition is adhered to, it becomes evident that cretinism, sporadic or endemic, represents a rather uniform morbid entity. Working in a sea-border state, one encounters cases of athyroidism and hypothyroidism, but one also meets cases which resemble the true endemic cretin in every respect. A committee on endemic cretinism should include not only experts in goiter, but experts in mental deficiency as well, in order to screen out the familial mental defective from the true cretin.

Historical Notes

We owe the knowledge of cretinism to a large extent to the nineteenth century. With its interest in natural science and its progressive optimism, such a striking picture as the cretin could not escape attention for a long time. Cretinism became the subject of many scientific studies, and numerous attempts were made to improve the fate of its victims by changing their environment. At that time cretinism was considered the only form of idiocy with distinct characteristics, a concept which one finds now, one

hundred years later, applied to mongolism. The Swiss physician Guggenbühl is credited with the first and most persistent attempt to improve the life of cretins. In a series of publications from 1835 on, Guggenbühl succeeded in attracting world-wide attention to his enterprise. Rudolf Virchow's yearly reports to the Physiological-Medical Society of Würzburg on his pathological studies in cretinism laid the scientific basis for an understanding of the growth deficiency, but not until experimental and clinicopathological studies discovered the key position of the thyroid gland did cretinism become a well-established morbid entity. In the brief period of thirty years between 1858 and 1888, the pathology of the thyroid emerged from the darkness that had enveloped it for more than a thousand years. So closely do the discoveries of the rôle of the thyroid follow each other in the various European countries that every historian gives a somewhat different story, according to his background and allegiance. While Moritz Schiff, in Geneva, experimented to determine the rôle of thyroid in animals as early as 1858, Curling published the first two autopsy reports of cases of sporadic cretinism, in which he established for the first time absence of thyroid tissue as the cause of a peculiar condition similar to that seen in endemic cretinism. Curling is also the originator of the name "sporadic cretinism," which he coined in contradistinction to endemic cretinism. In 1870, Hilton Fagge published a case of acquired cretinism in a girl who developed the symptoms after measles and erysipelas at the age of 8 years. Two more autopsies were made by Fletcher Beach, in 1876, who included a report on a 15 year old girl, the finding of large fatty tumors which he considered especially characteristic. Better known are the merits of Sir William Gull (1873) and of W. M. Ord, who made an autopsy report on an adult patient with myxedema in 1878. There has not been a single year since without an important contribution by one of these leading medical figures: Charcot, Osler, Thompson, Telford Smith, Bourneville, Horsley. As early as 1888 the London Myxoedema Commission, with Ord and Barlow as heads, was able to summarize the situation in the following way: "There is strong evidence that myxoedema, sporadic cretinism, endemic cretinism, cachexia strumipriva and the operative myxoedema of animals are species of one genus, and that the one pathological fact common to all these conditions is the occurrence of morbid processes, involving destruction of the thyroid gland." The knowledge which was gained and the rapid progress during the years before 1888 has been well established now by countless clinicopathological observations and animal experiments. With the knowledge of the rôle of the thyroid, interest has shifted away from cretinism as such to a study of the various degrees of thyroid deficiencies. Some clinicians would like to abandon the name "cretin."

It is, however, not generally realized that the cretin, whose almost legen-

dary family resemblance has induced some writers to consider him as a descendant of the Goths who fled into the mountain hideout of the Alps (Ramond de Carbonnières) or as a degenerative form of the Malayan race (Damerow), is the patient with congenital thyroid aplasia. If this condition represents a morbid entity as closely as does mongolism, one may well restrict the name "cretinism" to that condition and exclude the acquired forms of athyroidism and hypothyroidism with and without myxedema. The term would then refer to a clinical and pathological entity, while postinfectious, posttraumatic hypothyroidism would require a different classification. Many arguments would be irrelevant, and the prognosis would be a matter of accurate calculation.

As matters stand, the following classification appears appropriate:

1. Endemic Cretinism
2. Sporadic Cretinism: congenital thyroid aplasia, idiotie myxoedemateuse (Bourneville), congenital myxedema (Gordon), angeborene myxidiotie (Siegert), congenital athyroidism
3. Acquired Hypo- and Athyroidism: postinfectious, posttraumatic, degenerative infantile myxedema, juvenile myxedema

It may be wise to remember that the increased knowledge of cretinism has not simplified the situation. This view is well expressed by one of the most recent writers on this subject. It may sound disappointing to those who prefer simplicity to truth, but for those who are not only concerned with practical application, but study the general principles in each disease, W. Salter's words represent a great advance. Salter writes:

> Discovered and rediscovered by several investigators, the paradoxical truth has dawned finally that man or beast may suffer less from the loss of several glands than from losing a single one. For each of the precious juices the other secretions supply a partial antidote, so that health and personality may be preserved, delicately poised. Henceforth the practicing consultant and the laboratory investigator, both, must think in terms of integrated hormonal effects and must look to precise chemical mechanisms whereby the parent organs react upon one another. No longer will it suffice to describe in romantic or in clinical terms the superficial results of imbalance.

BIBLIOGRAPHY

Mongolism

Bean, R. Bennett: Some Anatomical Characters of the Mongoloid, a Hypomorph White Type. Am. A. Study of Feebleminded. Proc. Forty-ninth Ann. Sess., May 8–11, 1925.

Beidleman, Barkley: Mongolism. Am. J. Ment. Def. **50**: 35–53, 1945.

Bleyer, Adrian: The Frequency of Mongoloid Imbecility. Amer. J. Dis. Child. **44**: 503, 1932.

Bourneville: Idiotie du Type Mongolien. Recherches sur Epilepsie, e.c. **22**, Paris, 1902.

Brousseau, Kate: Mongolism. Baltimore, 1928.

Clift, W.: Roentgenological Findings in Mongolism. Amer. J. Roentgenol. **9:** 420, 1922.

Down, J. Langdon: Observations on Ethnic Classification of Idiots. London Hospital Reports **III:** 259, 1866.

Fraser, John: Kalmuc Idiocy. J. Ment. Sc. **98:** 169, 1876.

Gallo: Quoted by Lahdensuu, Acta pædiat. **21:** 256, 1937.

Hellsten: Quoted by Lahdensuu, Acta Pædiat. **21:** 256, 1937.

Ireland, W. W.: Idiocy and Imbecility. London, 1877.

Jones, Robert: The Mouth of Backward Children of the Mongol Type. J. Ment. Sc., 1890.

Kassowitz: Myxödem, Mongolismus und Mikromelie. Wien. med. Presse **43,** 1902.

Lahdensuu, Sakari: Über Vorkommen und Ätiologie der Idiotia mongoloidea im Lichte des in Finnland gesammelten Materials. Acta pædiat. **21:** 256, 1937.

Mitchell, Arthur: Notes on Kalmuc Idiocy. J. Ment. Sc. **98:** 174, 1876.

Oliver, Ch. A.: A Clinical Study of the Ocular Symptoms Found in So-called Mongolian Type of Idiocy. Tr. Ophth. Soc., 1891–93.

Penrose, Lionel S.: Mental Defect. Farrar & Rinehart, New York, 1934.

Proc. Medico Psych. Assoc. *in* J. Ment. Sc. **97:** 157, 1876.

Schüller, Arthur: Infantilismus. Wien. med. Wochnschr. **57:** 629, 1907.

Shuttleworth, G. W.: Mongolian Imbecility. Brit. M. J. London, 1909.

Smith, Telford: A Peculiarity in the Shape of the Hands in Idiots of the Mongolian Type. Ped., 1896.

Thomson, John: Notes on Peculiarities of the Tongue in Mongolism. Brit. M. J., May 4, 1907.

Tredgold, A. F.: Mental Deficiency. Wm. Wood, Baltimore, 1937.

Van der Scheer, W. M.: Beiträge zur Kenntnis der mongoloiden Missbildung. S. Karger, Berlin, 1927.

Warner, E. N.: A Survey of Mongolism. J. Can. M. A. **33:** 495, 1935.

Wilmarth, A. W.: Report on the Examination of One Hundred Brains of Feeble-minded Children. Alienist & Neurologist, October, 1890.

Cretinism

Barr, Martin W.: Mental Defectives. P. Blakiston's Son & Co., Philadelphia, 1913.

Beach, Fletcher: Notes on a Case of Sporadic Cretinism. J. Ment. Sc. **22:** 261, 1876.

Bourneville: De l'idiotie avec cachexie pachydermigue (idiotie myxoedemateuse). Assoc. franc. pour l'avancement des sciences, Paris, 1889.

Curling: Sporadic Cretinism. Med. Chir. Transact. 303, 1860.

Damerow, H.: Zur Cretinen und Idioten Frage. Allg. Ztschr. f. Psychiat. **15:** Berlin, 1858.

DeCarbonnières, Ramond: Voyage dans les Pyrennées françaises et espanioles. Strasbourg, 1789.

Eggenberger, Hans: Kropf und Kretinismus. Handbuch Innere Secretion. Leipzig, 1928, Bd. 3: 684–955.

Fagge, Hilton: Med. Chir. Transact. **54:** 159, 1870.

Fodéré, Franz Em.: Essai sur le goître et crétinage où l'on recherche particulièrement, quelles sont les causes de ces deux maladies des habitants des vallées, et quelles sont les moyens physiques et moraux, qu'il convient d'employer pour s'en préserver entièrement à l'avenir. Turin, 1792.

Gordon, Murray B.: Childhood Myxedema or So-called Sporadic Cretinism in North America. Endocrinology **6:** 235, 1922.

Guggenbühl: Die Heilung und Verhütung des Cretinismus. Berlin, 1835.
Gull, William: On a Cretinoid State Supervening in Adult Life. Transact. Clin. Soc. London, 1874: 180. Brit. M. J., 1873.
Hoefer, Wolfgang: Hercules medicus, 1655.
Horsley: The Pathology of the Thyroid Gland. Lancet, 1884.
Hoskins, R. G.: Endocrinology. W. W. Norton & Co., New York, 1941.
Kocher, Theodor: Über Kropfexstirpation und ihre Folgen. Arch. Klin. Chir. **29,** 1883.
——: Zur Verhütung des Kretinismus . . . D. Ztschr. Chir. **34,** 1892.
Koller, A.: Zählung geistig gebrechlicher Kinder im Kanton Appenzell in 1907. Zt. Erf. jugd. Schwachs. **4,** 1911.
Kutchera, A. v.: Beiträge zur Ätiologie des Kropfes und des Kretinismus. Prag. Med. Wo. **13,** 1914.
McCarrison, Robert: "Etiology of Endemic Goiter." John Ball Sons & Danielsson.
——: Observations on Endemic Cretinism. Proc. Roy. Soc. Med. 1908, 2, 1.
——: Recherches récentes sur l'étiologie du goître. Presse méd. **41:** 1612, 1933.
McClendon, J. F.: Iodine and the Incidence of Goiter, Univ. of Minnesota Press, Minneapolis, 1933. J. Biol. Chem. **102:** 91, 1933.
Ord, W. M.: On Myxoedema. Med. Chir. Transact. **57:** 43, 1878.
—— and Barlow: Report of a Committee of the Clin. Soc. to Investigate the Subject of Myxoedema. London, 1888.
Osler, W.: On Sporadic Cretinism in America. Transact. Am. Physiol. Soc. **8:** 380. Philadelphia, 1893.
Plater, Felix: Observationum in hominis affectibus plenisque. Libri tres, Basel, 1614.
Reverdin, J. L.: Note sur vingt-deux opérations de goître. Rev. méd. de Suisse Rom. **4–6,** 1883.
Salter, William T.: The Endocrine Function of Iodine. Harvard Univ. Press, Cambridge, Mass., 1940.
Schiff, Moritz: Résumé d'une série d'experiences sur les effets de l'ablation des corps thyroides. Rev. méd. de la Suisse Rom. **2 & 8,** 1884.
Scholz, Wilhelm: Cretinismus. Berlin, 1906.
Virchow, Rudolf: Über die Physiognomie der Cretinen. Verhandl. d. phys.-med. Gesellsch., Würzburg, 1856. Ges. Abh. 974. 24 Mai, 21 Juni 1851, 9 V, 13 XI; Verh. II S. 230; Verh. III S. 247. Virch. Arch. VII 133.
Wagner, Jauregg V.: Über die Folgen der Exstirpation der Schilddrüse nach Versuchen an Tieren. Wien. med. Bl. **25 & 30,** 1884.

CHAPTER II

PHYSICAL CHARACTERISTICS AND DIAGNOSIS

Mongolism

Physical Characteristics

In 1866, when J. Langdon Down gave the first description of mongolism as a morbid entity, Edouard Séguin, in his famous book on *Idiocy and Its Treatment by Physiological Method*, gave a precise description of the same type, which he considered as a subgroup of cretinism. He wrote:

> The lowland cretinism of Belgium, Virginia,—with its discrete goiter, its grey and dirty straw-colored skin, bears the same relation to idiocy and imbecility as the more extensive alpine variety. So does the Furfuraceous Cretinism with its milk-white rosy and peeling skin; with its shortcomings of all the integuments, which give an unfinished aspect to the truncated fingers and nose; with its cracked lips and tongue, with its red, ectropic conjunctiva, coming out to supply the curtailed skin at the margin of the lids.

It is worth mentioning that this description contains, in a few words, the essentials of the mongoloid features and includes an observation which has escaped attention for more than half a century. It is interesting that Séguin describes the epicanthal fold of the mongoloid child as caused by curtailment of "skin at the margin of the lid." Had this observation received greater recognition, the idea that the mongoloid is a kinsman of the Mongolian race would not have found general approval, and many contributions dealing with the strange "retrogression" to that race would not have been written.

Langdon Down described the mongoloid as

> a representative of the great mongolian race: When placed side by side it is difficult to believe that the specimens compared are not children of the same parents. 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 prominence. 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. Tongue is long, thick and 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.

This description covers well the appearance of many mongoloid children between about 5 and 15 years of age, but it does not apply to the mongoloid

newborn. Many a mongoloid baby would escape proper recognition if the diagnosis were too strictly based on stigmata given above.

The tabulation of signs of mongolism does not indicate the relationship of the symptoms to each other. Such a description looks too much like the accumulation of various stigmata linked together by chance, and one cannot conceive what pathologic process may produce such a variety of unfortunate imperfections. Admitted that mongolism is a physical deviation which defaces the unlucky person stamped with this condition, why is mongolism of such serious importance that the child is doomed to idiocy or imbecility? It is obvious that the collection of physical stigmata does not suggest the character of the disease which is apt to exercise such an influence upon the growing individual.

In order to make a diagnosis at any age in any race under any condition, one has to recognize the essential growth disorder that characterizes this deficiency. What is it that makes mongoloid children so much alike that most of them look like brothers and sisters? Other constitutional defects do not obliterate the individual differences due to race and family. Even idiots vary as much from each other in appearance as normal persons. The physical characteristics of mongoloids cannot be, therefore, the result of idiocy or of any mental defect. After years of measuring and comparative studies of the skeletal features of mongoloid children, it became evident to the writer that the so-called "mongoloid" appearance depends upon a growth disorder of the skull which is invariably encountered in every mongoloid child. The mongoloid skull, including the facial bones, deviates from the normal in its proportions, and it is this malproportion of the skull that will decide the diagnosis in doubtful cases. Of course, not only the skull is affected in mongolism; the condition is a general growth disorder which involves the whole skeleton, and this fact is a cornerstone in the understanding of the pathology.

What is mongolism at birth? If mongolism is a kind of general "fetalism," what is the difference between a newborn mongoloid and a premature baby of 7 months? If mongolism is merely a delay or absence of normal growth, why do not all premature babies look "mongoloid," at least for a transitory period? These are indeed questions of interest, and an analysis of the mongoloid features at birth and shortly thereafter seems desirable.

The mongoloid skull at birth has not yet a definitely brachycephalic shape, but the fronto-occipital diameter (normally 11.5 to 12 cm.) appears somewhat shortened, though not in all cases. The width of the skull (biparietal diameter, normally 9.5 cm.) is normal or slightly subnormal. The circumference of the skull is, therefore, within normal range but below average (34 cm., or $13\frac{1}{2}$ in.). Four mongoloid skulls which I had the opportunity to measure within the first two weeks after birth had a circumference

of 34 cm. or less. Lahdensuu has presented measurements of 11 mongoloid babies who were observed within the first five days after birth.

There were only 2 girls out of 11 patients who had a skull length above 11.5 cm. One boy had a skull length of 11.5 cm., but all the other patients were below the average, some of them definitely below normal. In most cases, the biparietal diameter was small. In one case only, that with the largest length, the diameter was past the average of 9.5 cm. Measurements of several mongoloids during the first half year after birth indicate that the skull of the mongoloid infant does not grow in the first few months. The brain, however, increases somewhat in size, and as a compensatory measure the parietal and temporal parts of the skull protrude, producing a

TABLE 1

	FO Cm.	Bip. Cm.	Circum. Cm.	Index
Boys				
1	11.5	9.0	34.0	78.3
2	11.0	8.4	33.0	76.6
3	10.9	9.4	33.0	86.3
4	10.6	9.3	33.0	87.7
Girls				
1	10.1	8.5	33.5	84.2
2	10.5	9.0	33.5	85.7
3	10.6	8.6	32.0	81.1
4	11.9	9.7	35.2	81.5
5	11.6	8.5	34.0	73.3
6	10.4	8.6	32.0	82.7
7	11.4	9.4	34.0	82.5

"rounding out" of the mongoloid skull which is sometimes so marked that length and width are equal. The face of the mongoloid child appears short in contrast to the large forehead. The bridge of the nose is flat and sunken. Craniologic studies indicate that the nasion is absent or underdeveloped. Although the nasion is rather small in every newborn baby, the mongoloid shows such an obvious underdevelopment of the root of the nose that this is a very conspicuous sign. Another item is the malproportion of the facial development. The distance between acanthion (anterior nasal spine) and prosthion (alveolar point) is so short that there is only a small crest between the lower border of the nasal cavity and the alveolar edge. The vertical diameter of the orbit holes is definitely larger than the distance from the lower orbit margin to the alveolar crest.

The condition of the skull sutures is of great diagnostic value. It is known that in mongolism the anterior fontanelle is unusually large and

closes after great delay. It has, however, not yet been noted that all sutures may be separated and that, in palpating the skull bones, one may find that the sagittal suture is not in approximation and the parietal bones are separated $\frac{1}{2}$ cm. or more. The frontal suture, which is normally not present at birth, may be palpated down to the nasion even several months after birth. The same delay is recognizable about the posterior fontanelle and the sutures which cross the sides of the skull. That this delay or absence of union of sutures may last throughout childhood is shown in Greig's three skulls, which showed incomplete union of sutures, defects of ossification, and persistent crevices. Normal growth of the flat skull bones proceeds

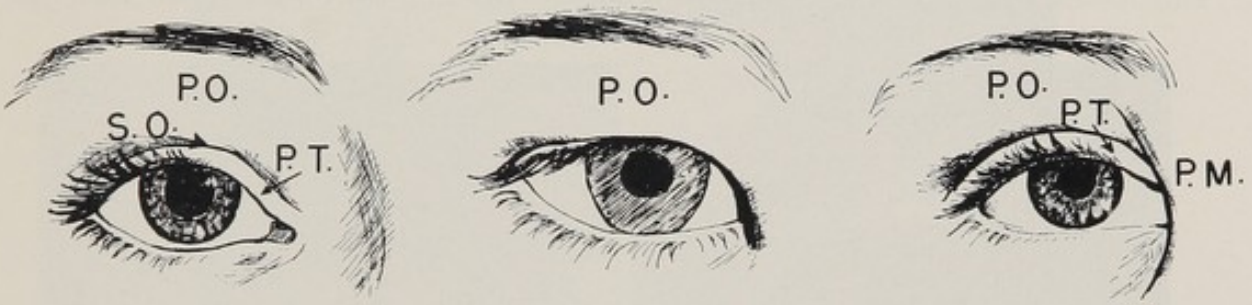


FIG. 1. Formation of external eye in (A) European races, (B) Mongolian races, (C) mongoloid patients.

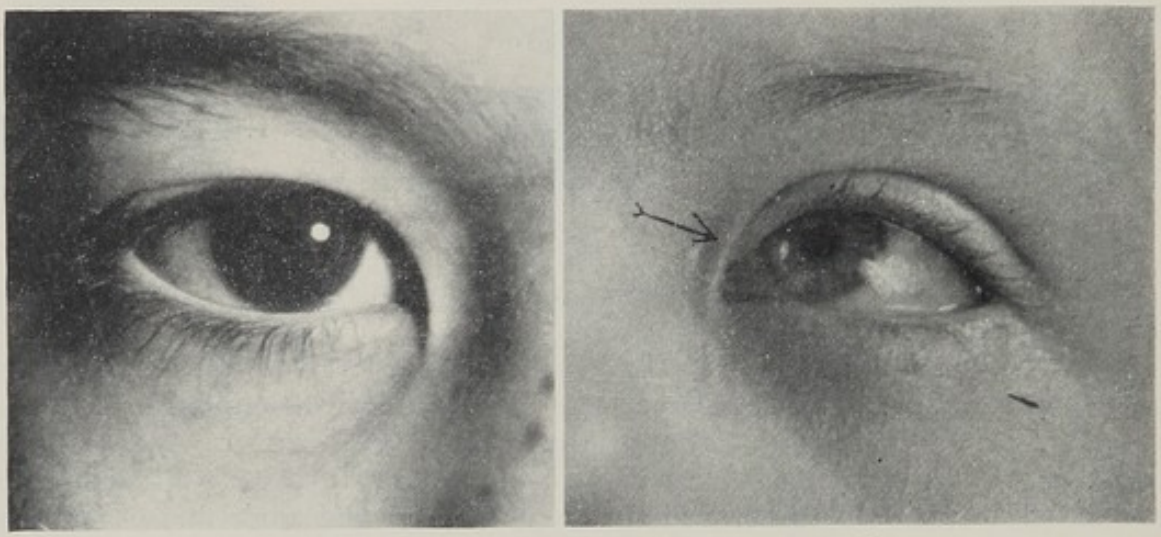
The superior palpebra is divided into the pars orbitalis (p.o.) and the pars tarsalis (p.t.), which are separated by the sulcus orbitopalpebralis superior (s.o.).

In European races the pars tarsalis is exposed. In Mongolian races (B) the pars orbitalis overlaps the pars tarsalis with a skin fold; the pars tarsalis is, therefore, not visible. The skin fold turns medially around the medial angle and covers partly the caruncula lacrimalis (epicanthus). In the mongoloid patient (C) the upper palpebra is formed as in A, exposing the pars tarsalis of the upper lid. But the medial angle of the eye is covered by a skin fold, plica marginalis fetalis (p.m.), which crosses from the skin of the pars orbitalis over to the skin of the sulcus infrapalpebralis, covering the medial angle, forming also an epicanthal fold. This plica is a fetal feature, which normally disappears before birth, but persists in mongoloids for two to ten years.

in proliferative ossification. The delay of closure of the fontanelles and the open sutures are due to insufficient growth activity at the margins of the flat bones.

Eyes. From the viewpoint of diagnosis, in contrast to cretinism, the formation of the eyes is the most conspicuous anomaly. The mongoloid has short, slanting palpebral fissures which slant upward toward the lateral edge. At the medial corner the angle is covered by a skin fold, the "epicanthus" (*epi*—above, *canthus*—angle). It is, however, interesting to note that this epicanthal fold is entirely different from the Mongolian epicanthus which is due to overlapping of the eyelid fold above the margin of the eyelid (Fig. 1). The eyelid of the mongoloid child is formed as in

every European person. The mongoloid has a skin fold, plica marginalis fetalis, which runs sickle-shaped around the medial angle of the eye and ends beneath in the skin of the sulcus infrapalpebralis. This fold has no relationship to features found in the Mongolian race, and, as I said before, if the essential difference had been recognized from the very beginning, as Séguin did, the theory of racial retrogression could never have attained such general recognition. This plica marginalis of the mongoloid is a fetal feature, a residual, still present at birth, related to the underdevelopment of the nasion. This type of epicanthus is not rare in normal newborn babies, especially in races with rather flat nose bridge like the eastern European races. It is, therefore, not surprising that in Russia and the



A B

FIG. 2. (A) Eye of a feebleminded child of Chinese ancestry. Note true Mongolian eye with overlapping pars orbitalis over pars tarsalis and sharp, sickle-shaped curvature of epicanthus.

(B) The eye of a mongoloid child with plica marginalis fetalis covering the caruncula.

Baltic states and eastern and central Germany, between 30 and 40 per cent of newborn babies have these folds. In normal children they disappear usually within one to three months. In mongoloids they also disappear, but at a much slower rate. I was, however, not able to find a single mongoloid with epicanthus above the age of 12 years, while the majority of mongoloids have an epicanthus below 5 years of age. After 10, the mongoloid eye has more a birdlike appearance. While the epicanthus is not a sign to rely upon, the peculiar smallness of the orbit holes is absolutely pathognomonic. As my x-ray studies show, the orbit holes are egg-shaped and lack the size seen in normal children or even cretins.

There are several more anomalies connected with the eye. The skin of the eyelids is abnormally thick, and the conjunctivae are susceptible to inflammation and chronic changes, which lead to thickening and tumifica-

tion. The ciliary body of the lower lid is frequently enlarged. The eyelashes are short and sparse. There is frequently chronic blepharitis, and ectropion is not rare. The distance between the eyes is short.

There are numerous anomalies of the eyeball and its structures. The iris shows speckling and heterochromia, unilateral or bilateral. The lens is apt to form cataracts, which develop in childhood or are present at birth.

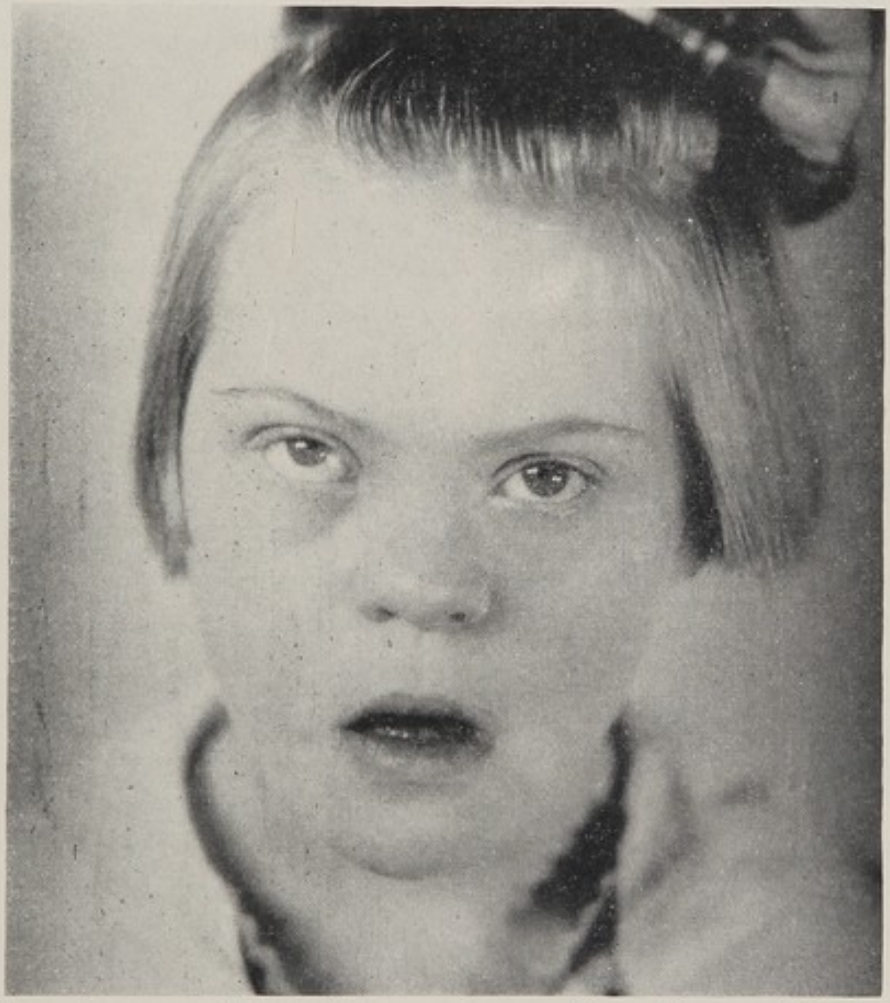


FIG. 3. Face of a mongoloid girl, 10 yrs. of age. Note thin, straight hair; upward-slanting almond-shaped eyes; strabismus; medial marginal fold almost disappeared; flat nose bridge; fissured, dry lips and tongue.

The lens opacities of mongolism have attracted some attention, and Ormond and van der Scheer have made a detailed study of these. The cataracts are progressive and develop as a result of changes taking place in the lens after its formation. This would suggest a progressive disease of possible endocrine origin rather than a malformation. The relationship between cataract formation and endocrine disorders has become increasingly established.

Eye movements are frequently abnormal, strabismus is almost a constant feature, and nystagmus not rare.

Ears. Anomalies in the formation of the external ear are so frequent that they form a part of the picture. This is not surprising in view of the fact that ear anomalies are frequently associated with all types of mental deficiency, and abnormal ear formation seems a rather sensitive indicator for developmental anomalies. The type of pathology is not constant. The various shapes of the ear have not yet been properly classified, and the terminology is inadequate. In infancy and early childhood, the mongoloid ear is frequently very small and gives the impression of fetalism. The upper helix is more overlapping than usual, and the margin forms a right angle with the descending part of the ear (Fig. 6). The tragus may be flattened and borders the entrance to the ear in a straight line. Later in life many mongoloids have extremely outstanding "lop" ears, with flat or absent helix. The ear may then resemble the Darwinian "pointed" ear. Similarities with the ears of some macacus species or cats, with large posterior helix, may also be found. The site of the ear is frequently low.

Mouth. The mucosa of mouth and lips becomes abnormal in early life. The lips then appear fissured and dry. The tongue undergoes fissuration and hypertrophy of the papillae. The fissuration of the tongue is frequently referred to as "scroted." The tongue may protrude but is not unusually large, with the exception of some cases where hypertrophy may be present. Protrusion is due to the smallness of the oral cavity rather than to the size of the tongue.

Voice. Of special interest is the voice of these patients. Many a small mongoloid child has a very deep voice, and the diagnosis of mongolism can be made by hearing the voice without even seeing the child. The voice is raucous and of a low pitch, almost masculine, which is in striking contrast to the infantile appearance of these patients. I was not able to find any definite explanation for this disorder. I have made a study of the larnyx of several cases and found the mucosa thickened and fibrotic. The position of the larynx appears very high in the neck. It may also be possible that the absence of sinus formation in the skull has something to do with the deep voice and the lack of resounding.

The same type of voice is common in cretinism, and, since only a restricted number of mongoloids have such a voice, which disappears under thyroid treatment, the most likely explanation is myxedema of the pharynx.

Nose. The nose of the mongoloid is characterized by flatness of the nose bridge, owing to absence or underdevelopment of the nasion bone. The cartilagenous part may be fairly large in later life, which produces a pug-shaped nose; many mongoloids, however, have small, short noses with broad nose bridges all their life.

Dental Development. Observations on the teeth are of special interest because they permit some insight into the disturbance of bone formation.

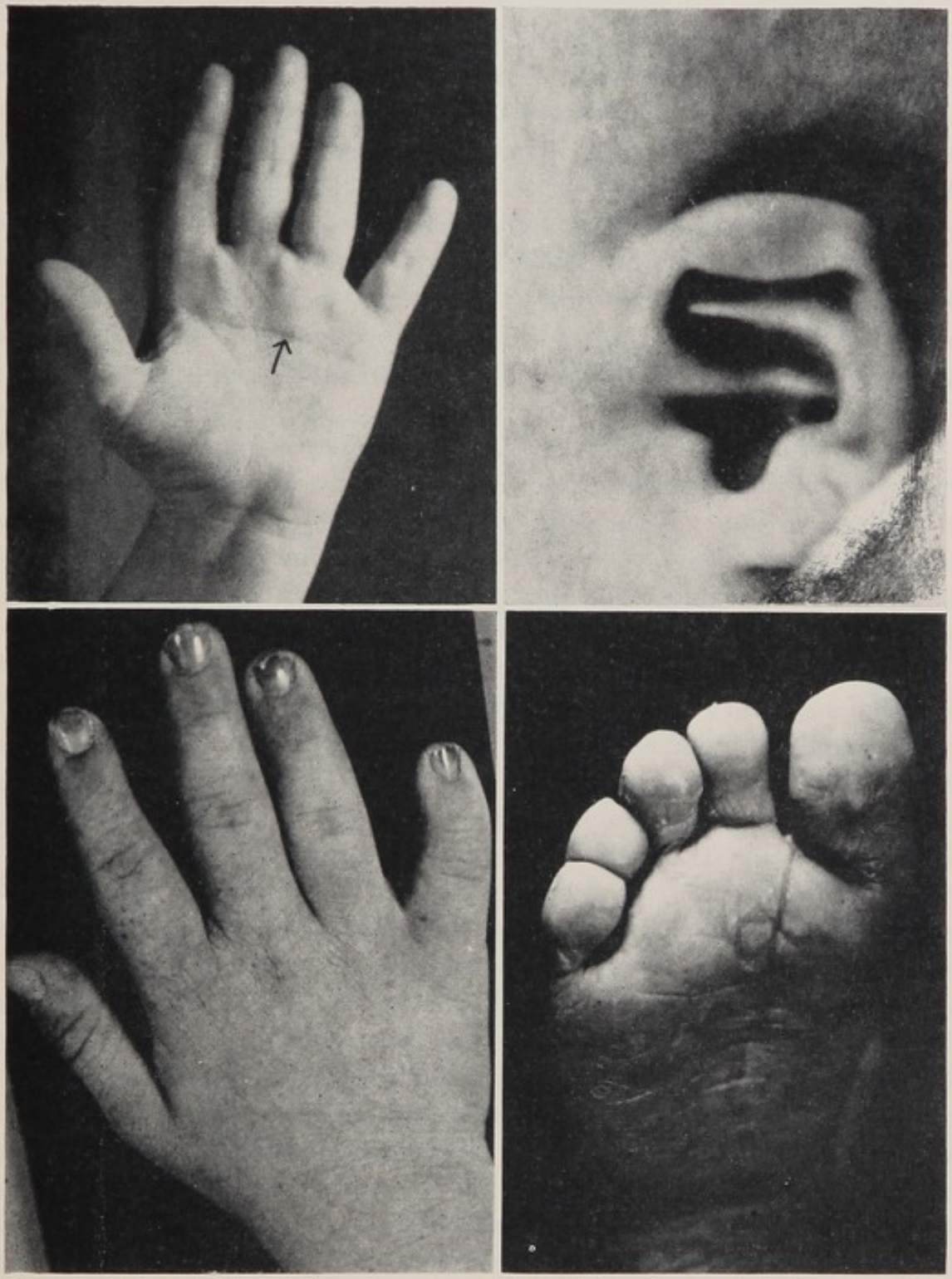


FIG. 4. (Upper left) Palm of a mongoloid child. Note straight "four finger line," shortness of little finger and low set thumb.

FIG. 5. (Lower left) Hand of a mongoloid child, dorsal view. Note curvature and shortness of little finger; marmorated, thick skin.

FIG. 6. (Upper right) Ear of a mongoloid child. Note overlapping, straight upper helix and abnormal formation of concha with outstanding crus helicis crossing in the middle through cavum conchae.

FIG. 7. (Lower right) Foot of a mongoloid child. Note gap between first toe and second toe and skin crevice crossing the foot sole from the gap.

It has not escaped attention that the eruption of the first teeth is usually retarded. Brousseau has studied the exact time of their appearance. Eruption was rare before the ninth month, while normal children have their first incisors usually at six months. A large number of mongoloids had their first tooth at an age of 12 months or between 12 and 20 months. There were a considerable number of cases in which the first tooth appeared at the age of 2 years or more. Dentition was usually not completed before the fourth or fifth year and was frequently even more delayed. Eruption of teeth did not follow the usual patterns, and the molars appeared before the incisors in many instances. The second dentition begins somewhat more regularly, but completion is again irregular and frequently never takes place.

The size of the jaws is abnormal, the upper jaw being too small and the lower jaw showing prognathism. This is due to the absence of counteraction from the upper jaw under the stress of abnormal muscle pull. These anomalies of the jaws are not without influence upon the development of the teeth and especially their alignment. The teeth are crowded or sometimes abnormally widely spaced, and normal alignment is rare.

Some aspects of the tooth development in mongolism have been the subject of a special study by Dr. John A. Nash, who, after having examined several hundred mongoloid patients, registered his findings in 84 cases ranging from 3 years to 35 years. This study covered the following items: alignment, mucous membranes, caries, paradentosis, and eruption of teeth. The results of this study, grouped according to age, are given in Table 2.

Some points are worthy of special emphasis. Abnormal alignment was seen in 68 cases, the majority having crowded conditions and a small number of widely spaced teeth. The most conspicuous fact is the absence of caries. Extensive caries was found in only one case of the whole group; moderate and very moderate caries was present in 44 cases; and 39 cases were completely free. This is the more striking if one considers the rather poor dental hygiene which is present in these children, even with the best supervision, owing to their mental shortcomings. An equally important observation is the frequency of paradentosis, which was present in at least 78 out of 84 cases. Although differing in degree, gingivitis was local in 33 and general in 45 instances. Pocket formation was present in 45 cases, recession in 59.

Eruption of teeth was considered retarded in 18 cases, while teeth were missing in at least 28 but possibly 30 instances. It was not always possible to decide whether eruption was merely delayed or the teeth were completely missing. In several instances x-ray examination was made and the absence of teeth definitely established.

It goes without saying that the mongoloid teeth are smaller than normal

and are frequently abnormally shaped, in addition to showing moderate hypoplasia. This growth deficiency is a part of the general growth disorder which I have already emphasized.

The study reveals two factors which have not been recognized before and which are of great biological interest. In spite of the fact that other investigators felt that the mongoloid teeth are predisposed to caries, this study has established that caries is practically absent even in the age group above 16, where most of the normal children show a considerable amount of tooth caries. At the same time paradentosis is present from the very

TABLE 2.—*Dental Development*

Age in Years	Sex	No. of Cases	Irregular Alignment	Caries		Paradentosis	Retarded Eruption	Missing Teeth
				Moderate	Severe			
3– 5	M	—	—	—	—	—	—	—
	F	5	4	—	0	5	5	0
6–10	M	10	9	6	0	7	1	1
	F	6	5	—	1	6	2	1
11–15	M	13	8	7	0	13	5	3 poss. 4
	F	16	14	8	0	14	4	7
16–20	M	9	8	4	0	9	1	4
	F	7	5	5	0	7	1	4
21–30	M	7	4	4	0	7	4	2
	F	9	9	8	0	8	—	6
31–35	M	—	—	—	—	—	—	—
	F	2	2	2	0	2	—	1 (?)
		84	68	44	1	78	18	28 poss. 30

beginning, and each of 5 girls below an age of 5 years showed a marked degree of paradentosis. It is generally agreed that paradentosis suggests the presence of abnormal metabolic factors and is a result of endocrine dysplasia. If we consider the relationship of the observed anomalies with better known endocrine disorders, the hypoplasia and the irregularity of dentition point toward a thyroid deficiency. It is well established that in infantile myxedema dentition is never normal: it is retarded and irregular, and the size of the teeth is below normal. Studies of the thyroid in mongolism have provided evidence that thyroid deficiency is a part of the picture, and it is not surprising, therefore, that the teeth share some of the characteristics seen in cretinism. The strange association of lack of caries

and frequency of paradentosis points, however, to still another endocrine system, the gonads. It is known that there is increased susceptibility to caries during puberty, pregnancy, and lactation, all periods which are associated with increased pituitary-gonadal activity. On the other hand, after castration the teeth remain smaller than normal, especially in males. The relationship between gonadal activity and increased caries is further supported by observations reported by Büttner and Bacherer, that after menopause caries does not proceed with the same speed as during the time of greatest gonadal activity. Teeth which are in good condition after 50 are likely to stay so, if no other factors, such as vitamin deficiency or senile changes, come into play. The observations on mongoloid patients seem to add new evidence to the close relationship between gonadal activity, caries, and paradentosis. Increased gonadal activity is associated with increased caries and decreased paradentosis, while absence of gonadal function stops caries but increases the susceptibility to paradentosis.

Neck. The neck of the mongoloid is short and appears unusually broad, apparently owing to two factors: (1) the straightness of the vertebrae and (2) the flatness of the occiput. There may be great laxity of the skin.

Trunk. The trunk is relatively long in comparison to the shortness of the extremities; absolutely, however, the length of the trunk shows definite signs of growth deficiency. The chest appears rather round. The spine does not show the normal curvature and has a tendency to straightness or dorsolumbar kyphosis.

Abdomen. The abdomen is pear-shaped, distended, with insufficient tone of the abdominal muscles. Umbilical hernias are frequent, distention of abdominal muscles not rare. The pelvis is small and infantile. Mongoloids are likely to suffer from constipation. In two autopsies I observed microcolon, which involved the whole of the transverse and descending colon. Thompson reported a case of "congenital stenosis" of the large intestines, which probably refers to the same condition.

Genitalia. The male sex organs are retarded in development. In about 50 per cent of cases the testicles are not descended at the time of birth and never will descend. Frequently only one is found in the scrotum, but even if both are descended, they are small and never of normal size. If they appear of a fairly good size to palpation, this does not indicate normal development. Fibrosis and fat tissue usually replace the parenchyma. The penis is mostly infantile and short, but may sometimes be long and thin. Pubic hair is long and silky and of female distribution. Axilla hair is absent. The secondary sex characters of mongoloids offer some indication of hermaphroditism. The breasts may show hypertrophy of fat, and the fat distribution of the abdomen is female. If hair appears on the face it is spotty and grows along the margin of the lower jaw. It is short, straight, and silky and does not resemble a normal beard.

Female Sex Organs. The major labia in mongoloid infants are frequently oversized. Bleyer has made the same observation and thinks that the anomaly is so characteristic that "it affords another sign." The skin is full, and the labia form round cushions, whereas the minor labia are underdeveloped or absent. In older mongoloids they may be apron-like and protruding. The clitoris protrudes and is frequently hypertrophic. Menarche is delayed. About 70 per cent of mongoloid girls menstruate between the years of 18 and 30. Menstruation is irregular and menopause early. The breasts remain infantile during puberty but become large, owing to hypertrophic subcutaneous fat tissue. The nipples are frequently tiny and flat, and the glands of the areola may be missing. Adiposogenital dystrophy is present in the majority of cases. In the slender type hair growth is increased and hirsutism is marked.

Extremities. The extremities are short, with special emphasis on the hands and fingers as well as feet and toes. The growth deficiency is so characteristic that the name of "acromicria" is well justified. The fingers are short and slightly cone-shaped, with the end phalanx most markedly retarded in growth. The little finger shows curvature in about 60 per cent. The second phalanx of the little finger is rudimentary. Another anomaly may be noted in the position of the thumb, which is lower set and shorter than usual. The hand, as such, is flat and flabby. Owing to the shortness of the bones, the skin is wrinkled like gloves which are of too large a size. Of special interest is an abnormal hand line, a flexion-furrow, which is described in the literature as "four finger line" or "macacus line." In the normal hand the furrow which crosses the palm from the side of the thumb above the so-called "life line" does not meet the line which starts beneath the little finger and ends between the second and third fingers; in a certain number of mongoloid cases, however, these two flexion furrows form one straight line. This anomaly is sometimes present in one hand only. It is not pathognomonic for mongolism, but is rare in normal persons. The minute skin ridges of the hand, which form certain constant patterns that are the basis of every governmental identification service, are also the subject of considerable scientific interest. The patterns are laid down in the third and fourth fetal months, and they remain unchanged throughout life (Cummins, Bonnevie, Evatt). N. Ford has studied these ridges in mongolism and found that the dermal patterns show a disturbance in growth, indicating retardation as early as the third and fourth fetal month. Interestingly enough, N. Ford studied siblings of mongoloids and found that those born to older mothers had normal dermal patterns, while those born to younger mothers showed indications of retardation. I assume that in the former group the siblings are older than the mongoloid, who is the last child, while in the latter group the mongoloid is born at the beginning of the birth line and the normal siblings are born afterwards. If the observa-

tion that these siblings show slight signs of retardation in growth should prove true, it would add further evidence to the theory that the occurrence of a mongoloid child indicates some "depression in the reproductive faculty" of the mother (see Chapter X).

The observations may turn out to be of considerable importance for the diagnosis of mongolism in stillborn babies and abortions which occur in the latter half of pregnancy. Mongolism has so far never been diagnosed in stillborn babies, but one may expect that quite a number of abortions and stillbirths involve a mongoloid fetus.

The toes and feet show malformations similar to those of the hands. There is a big gap between the big toe and the second toe, and a deep line may extend from this gap into the sole of the foot. The third toe is frequently longer than the second, and two toes may be grouped together in a forklike position. Sometimes webbing is present. The foot soles show many transverse wrinkles. The foot is round and lacks the formation of an arch.

Skin. The condition of the skin is a subject of some disagreement. This will be readily understood when the pathology of the thyroid is discussed. There is no doubt that the skin of the mongoloid baby is soft, thin, and velvety, which is distinctly different from the skin of the cretin. The subcutaneous tissue contains much fat and is puffy. The skin at the trunk and thighs appears marmorated, because the capillaries are marked and congested. The skin of the cheeks is frequently strikingly red. This redness is sometimes circular or spotty and is quite different from the normal color of children's cheeks. When the mongoloid grows older his skin rarely retains the characteristics just described. According to the degree of thyroid deficiency, the skin becomes thick, dry, and rough, and various degrees of myxedema may be found. The skin tends to be wrinkled and is susceptible to eczema.

Hair. The hair of the mongoloid is generally fine, silky, and straight. Most mongoloids of mixed Anglo-Saxon stock have fair hair with definite lack of pigmentation. Mongoloid children of Mediterranean stock have dark hair and more pigment, but it is noteworthy that they too show less pronounced characteristics than those of northern races. The hair becomes dry with increasing age, and partial or complete alopecia is not rare. I have seen three Negro patients with mongolism whose hair was black and rather strong and curly.

Heart. The most common anomaly of the heart is a congenital septum defect. With regard to the frequency of this anomaly, statistics vary because of the different material that has been accessible to various investigators. Children with a severe septum defect are likely to die early, and if autopsy material of children's hospitals is examined, congenital heart

defects may range as high as 75 per cent. If, however, survivors beyond the first decade are examined, a septum defect is found in about 25 per cent. This defect is clearly audible, but it does not interfere with the activities of the child. It is rare to see a mongoloid child suffer from acute heart failure, although during their frequent infectious diseases the heart may give reason for concern. Even more important than the septum defect is the general infantilism of the vascular system. The aorta is thin and narrow, and all the main trunks are definitely undersized. One wonders how the mongoloid child can display so much activity. The peripheral vascular system appears distended and congested. A great variety of other heart anomalies may be found, such as abnormal distribution of the vessels, congenital pulmonary stenosis, aortic stenosis, open ductus botalli, dextrocardia. The variety of defects is great, and almost every heart of a mongoloid reveals at least one.

The deficiency of the vascular system is not restricted to the heart. The whole system is inadequate, narrow, thin, and the peripheral capillaries are underdeveloped. It never has been thoroughly investigated whether the hypoplasia of the vascular system forms an important link in the chain of functional inadequacy. The vessels of the brain are thin and less numerous than in control cases, even of mentally deficient persons. The same is true for the endocrine organs and practically the whole body. The capillaries are found congested and enlarged—another symptom of significance. Some insight into the pathology can be gained by capillary microscopy, a method which is easily used and deserves a greater clinical application. Studies in cretinism have provided evidence that in this condition hypoplastic capillaries are frequently found, developmental anomalies which point to the prenatal period. The same is true for mongolism. Many mongoloids have abnormal capillaries. Pototzky has utilized the experience gained in cretinism and thinks that one can distinguish between mongoloids with thyroid or pituitary deficiency and those without. In view of the pathological material which will be presented in a later chapter, Pototzky's conclusion seems to overshoot the goal, however. I was not able to find any correlation between capillary hypoplasia and degree of mongoloid deficiency. Capillary microscopy is not reliable enough to permit such a specific statement, but the method is useful in diagnosis and rechecking of therapeutic progress and deserves, therefore, more general application.

Measurements

The growth of mongoloid children results finally in a stunted growth or dwarfism. In the following table a list of one hundred and twenty measurements is given which shows the height of patients of various ages.

TABLE 3.—*Clinical Data in 120 Cases of Mongolism*

Age	Case	Sex	Height		Weight, Lb.	Length of Skull, Cm.	Width of Skull, Cm.	Circumference of Skull		Sexual Development
			Cm.	Inches				Cm.	Inches	
Mo.										
2	1	M	45	17.75	7.5	12.4	9.8	36.4	14.5	
3	2	F	59.8	23.5	8.8	11.6	10.8	36.5	14.6	
5	3	F	59	23.25	10.2	12.6	11.8	39.2	15.6	
5	4	M	56.5	22.25	9.4	12.5	11.2	37.3	14.12	
7	5	F	65	25.5	11	13	10.5	38.3	15.3	
13	6	F	75.4	29.75	22	13.6	11.7	41.8	16.8	
Yr.										
2	7	F	79	31	25	13.5	12.9	44.6	17	
2	8	M	83.2	32.75	19.75	12.7	12.5	48	18.14	Testes not descended
2	9	M	80	31.5	25	13.8	13.7	46	18.2	Testes not descended
3	10	F	87.5	34.8	28	14.8	12.9	45.4	17.14	
3	11	F	84	33	23	15.4	12.6	44.5	17.9	
4	12	F	86	33.75	34	15.2	13.8	46.2	18.3	
4	13	F	96.2	37.75	31	16.2	13.4	48.5	19	
4	14	F	92	36.25	29	15.5	12.3	44.8	17.12	
4	15	F	93	36.75	40	14.8	14.8	47	18.8	
5	16	F	97	38.25	38	15.8	13	45.9	18.2	
5	17	F	89.5	35.25	36	16.2	13.9	49.9	19.1	
5	18	M	98.8	38.75	34	17	13.4	47.6	18.1	Testes not descended
5	19	M	86.5	34	32	15.1	13.1	46.3	18.4	
5	20	M	81	32	28	13.5	1.3	44	17.4	
6	21	F	106	41.75	46	15.5	14.3	48	18.14	
6	22	F	97	38.25	36	15.9	13.3	46.5	18.4	
6	23	F	100	39.10	37	15.8	13.1	46.3	18.3	
6	24	M	109.5	43.6	56	15.5	14.7	48.5	19	Testes not descended
6	25	M	107	42	36	15.2	13.5	44.6	17	One testis descended
6	26	M	99	39	42	16	13.5	47	18.8	One testis descended
7	27	F	100	39.10	37	15.3	13	45.6	17.15	
7	28	M	117	46	54	16.5	14	50	19.1	
7	29	M	108	42.5	47	16.3	13.4	48	18.14	Testes not descended
7	30	M	108	42.5	41	16.1	13.7	48.6	19.1	Testes not descended
7	31	M	119.5	47	51	16.3	13.7	48	18.14	Testes not descended
7	32	M	109.5	43.2	41	15.5	12.4	44.7	17.11	
7	33	M	110.5	43.5	42	15.8	13.9	48	18.14	Testes not descended
7	34	M	117	46	49	15.7	13.4	46.4	18.4	
8	35	F	103	40.5	42	16.5	13.5	48.5	19.2	
8	36	F	109.5	43.5	39	15.1	13	45	17.12	
8	37	M	117	46	52	15.9	14.5	48.5	19.2	
8	38	M	112.5	44.25	48	16.9	14.7	50.1	19.11	Testes not descended

TABLE 3.—*Clinical Data in 120 Cases of Mongolism—Continued*

Age	Case	Sex	Height		Weight, Lb.	Length of Skull, Cm.	Width of Skull, Cm.	Circumference of Skull		Sexual Development
			Cm.	Inches				Cm.	Inches	
9	39	F	125.5	49.7	59	16.5	14.2	49	19.5	
9	40	F	109	43	41	14.8	13.2	45.8	18.1	
9	41	F	104	41	37	15.5	13.2	46.8	18.17	
9	42	F	104.5	41.3	40	14.5	13.4	45.5	17.15	
9	43	F	126	49.5	51	16	14	48.5	19.2	
9	44	F	106	41.75	41	15.6	13	46.5	18.5	
9	45	F	121	47.1	56	16.5	13	47.7	18.13	
9	46	F	105.5	41.5	39.5	15.8	13.3	46.4	18.4	
9	47	M	117	46	51	15.8	14	48.5	19.2	One testis descended
9	48	M	118	46.5	52	15	14.2	46	18.2	
10	49	F	126.5	49.75	69	15.4	13.8	47.5	18.12	
10	50	F	120	47.25	52	16.4	13.3	47	18.8	
10	51	M	120	47.75	52	15.1	15	48.6	19.2	Testes not descended
10	52	M	129	50.75	60	15.7	14.6	48.7	19.3	Testes not descended
10	53	M	111.5	44	68	16.9	14.2	49	19.5	One testis descended
10	54	M	129.2	50.14	64	15.6	13.4	47	18.8	
11	55	F	123	48.5	53	16.8	13.2	48	18.14	
11	56	F	128.5	50.1	69	16.2	13.9	49.5	19.8	
11	57	F	123.3	48.9	69	16	13.5	46	18.2	
11	58	M	139.5	55	70	17.4	13.7	48.5	19	
11	59	M	128.5	50.1	58	15.8	13.8	47.5	18.9	
11	60	M	127.7	50.25	76	16.6	14.1	49	19.5	
11	61	M	124.5	49	61.5	17.4	13.8	49.4	19.7	
11	62	M	124.5	49	54	17.7	14.2	49.5	19.8	Testes not descended
12	63	F	133	52.6	72	16.7	13.8	49.3	19.6	
12	64	F	124	49	53	15.9	13.2	46.7	18.5	
12	65	M	136	53.9	76	18.5	14.5	53.8	21.3	One very small testis
12	66	M	120.5	47.5	58	16	13.7	49	19.5	
12	67	M	150	59	71.5	16.4	14.6	50.5	19.15	
13	68	F	137	54	88	16.4	15	49.8	19.1	
13	69	M	136	53.9	78	16.5	14.4	50.5	19.15	Testes not descended
13	70	M	131	51.5	62	15	14.4	48	18.14	
13	71	M	137.5	54.9	77	17.8	13.8	50.5	19.15	
13	72	M	124	48.13	66	14.9	13.1	45.6	17.15	Testes not descended
14	73	F	142	56	93	16.1	14.5	49	19.5	
14	74	F	141.5	55.75	78	17.5	13.4	49.5	19.7	
14	75	F	141	55.5	93	16.5	13.7	49.2	19.5	
14	76	F	135.5	53.6	90	17	13.8	48.7	19.3	Irregular menses
14	77	F	133	52.6	70	15.3	14.4	46.5	18.5	No menses

TABLE 3.—*Clinical Data in 120 Cases of Mongolism—Continued*

Age	Case	Sex	Height		Weight, Lb.	Length of Skull, Cm.	Width of Skull, Cm.	Circumference of Skull		Sexual Development
			Cm.	Inches				Cm.	Inches	
14	78	F	136	53.9	95	16.7	14.2	50	19.1	
14	79	F	140	55.1	80	16.5	13.6	48.5	19.2	
14	80	M	129.5	51	82	16.6	14.4	50.5	19.15	
14	81	M	135.5	53.6	74	16.7	14.9	50.3	19.13	
14	82	M	137.3	54	84	16.5	13.9	48.6	19.2	
15	83	F	145.5	51.5	99	16.8	14.3	49.2	19.5	
15	84	F	134	52.75	78	16	14	48	18.14	No menses
15	85	F	130	51.25	109	17	14.8	50.5	19.15	
15	86	M	123.5	48.1	81	17.3	14.5	51	20.1	
15	87	M	139	54.75	101	17.2	14.3	50.5	19.14	Small testes
16	88	M	160	63	129	18	15.1	53.5	21.1	Small testes
17	89	F	145	57.2	83	16.4	13.3	49	19.4	Irregular menses
17	90	F	135	53.3	105	16.9	13.4	49	19.4	
17	91	F	146	57.5	105	17	14.8	50.8	20	
17	92	M	151	59.1	126.5	17.3	14.8	51	20.1	
18	93	F	142	56	98	16.9	14.3	53	20.14	
18	94	M	152.5	60.1	102	17.7	14	51	20.1	
18	95	M	151	59.7	127	17	14.3	50.5	19.14	
19	96	F	144	56.75	93	17.2	14.7	50.6	19.15	
19	97	M	148.5	58.8	109	16.9	14.2	49.3	19.5	
19	98	M	148.2	58.6	124	17	16.5	51	20.1	
20	99	M	157	61.13	116.5	16.7	15	55.1	20.1	
21	100	F	135.5	53.6	104	17.5	14.6	50.7	19.16	
21	101	F	126	49.1	98	16.1	14	49	19.4	Irregular menses
21	102	M	152	59.14	137.5	17	14.5	51.5	20.4	Very small testes
22	103	F	137.5	54.3	84	17.5	15	49.4	19.6	
22	104	F	140	55.8	118	15.8	14.2	49	19.4	
22	105	M	152.5	60.1	111	18	14.6	52	20.8	
22	106	F	134.4	52.13	90	16	14	48.6	19.2	Regular menses
23	107	F	131	51.1	90	16.2	14.4	49.2	19.5	
23	108	M	143	56.25	130.25	18.4	15.7	52	20.8	
23	109	M	149	58.12	98	16.1	14.7	50	19.1	
23	110	M	157.5	59	136	18.2	14.4	53.4	21.1	
23	111	M	149	58.12	114	17	15	51	20.1	Very small testes
24	112	F	138.5	54.9	92	16.7	15.2	49.6	19.7	

TABLE 3.—*Clinical Data in 120 Cases of Mongolism—Concluded*

Age	Case	Sex	Height		Weight, Lb.	Length of Skull, Cm.	Width of Skull, Cm.	Circumference of Skull		Sexual Development
			Cm.	Inches				Cm.	Inches	
25	113	F	136	53.9	99	17.2	13.5	49.7	19.8	
25	114	M	141	55.5	99.75	17	15	50.7	19.16	
27	115	M	157	61.13	134	16.7	14.3	51.7	20.5	One testis descended
28	116	M	143	56.25	138	17.2	15.3	50.5	19.14	
28	117	F	141	55.25	106	17.2	14.5	51	20.1	
28	118	F	148	58.5	104	15.5	13.8	47.5	18.9	
33	119	F	143.6	56.5	98	16.6	13.9	50.7	19.16	Regular menses
34	120	F	138.5	59.4	94.5	16.7	13	49.5	19.8	No menses

The measurements show that at birth the height of the mongoloid child is within the normal range, although a large number of cases is below average. At the Children's Hospital, in Boston, I examined records of mongoloid patients in the first months of life in order to increase the number of measurements and found similar conditions in these children, as illustrated in Table 4.

TABLE 4

Age	Height Cm.	Age	Height Cm.
9 days	46	9 mos.	65
9 wks.	49	13 mos.	70
3 mos.	52	18 mos.	72
6½ mos.	60		

It may be said that retardation of growth is most conspicuous during the first three years, when complete arrest may last sometimes for a period of many months. In the following ten years the growth rate may be temporarily normal, but the children have a delayed start and appear, therefore, always smaller than normal. Growth comes to an early standstill. After thirteen years the retardation becomes increasingly apparent, and at the end of the period of growth few persons with mongolism exceed 150 cm. in length of body. Only 8 boys in my material reached a height of over 150 cm.; it is interesting that these boys represented borderline cases, with only some mongoloid stigmata. No mongoloid girl exceeded the height of 150 cm.

Most mongoloids in their late teens appear like children between 9 and 14. This biological retardation is well shown in Figures 74–77. The irregularity of the growth rate is noticeable when the same child is measured at different times.

There is no relationship between early growth and final height. Some children who had at 6 years a height of more than 3 feet, which would be within normal range, ended in being dwarfs of 4 feet. Other children who were very much retarded in early childhood picked up finally and reached a height of almost 5 feet. A. Werner and collaborators studied the growth in children with mongolism over a period of several years. They concluded that the growth rate was almost normal and that medication had no influence upon the growth. Their results are well in line with my observations if one observes mongoloid children for an interval of a few years. However, they did not measure the growth in babies or patients between 12 and 18 years. If they had included these age groups, the pathology of growth could not have escaped their attention.

The weight at birth and during the first year is lower than normal. During the following three years the weight is within the normal limits. At the age of 5 years the increase in weight becomes more noticeable, and most mongoloid children are overweight after that time. This is especially striking when the weight is compared not with that of a normal child of average height, but with that of a child of the same length. Many adult persons with mongolism, especially women, appear to be of the dystrophia adiposogenitalis type. Only a few mongoloid adults are underweight. They frequently show pituitary cachexia.

Mongolism represents a specific growth deficiency which differs from cretinism, achondrodysplasia, and other types of dwarfism. Details of the skull development and bone pathology will be discussed in a later chapter.

In mongolism, growth at the distal ends of the long bones is insufficient, resulting in a shortening of the femur and humerus; but even more pronounced is the growth deficiency toward the distal ends of all extremities, that is, hands, fingers, feet, and toes. Each bone shows increasing hypoplasia the more peripheral it is. Each center seems to be laid out fairly normally, but since growth proceeds in the periphery, away from the center, we see a true "acromicria" (*acros*—end, point; *micros*—small).

The mongoloid at birth is an infant who suffered from a deficiency of skeletal growth before birth. The prenatal deficiency involves the same structures which are affected in the postnatal period. The deficiency is a "hypomorphy" (Davenport) with a well-defined pathology in which the growth of the distal parts is predominantly involved, giving rise to what I comprehend in the term "acromicria." The difference between a mongoloid and a normal premature baby is that the latter is proportionate in its

TABLE 5.—*Measurements of Mongoloid Patients Taken at Different Ages*

Case No.	Ages in Years																
	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
	Height in Centimeters																
1	102.5									129.5							
2	96.2										123.5						
3		110															137.5
4		100											135				
5		107			122												
6			95											140			
7			109			124.1											
8			119.5			135							151			155	
9			110			123.5											
10			120										146.5				
11			105														141
12					97.5												152
13						125											131
14								116									136
15								100						152.5			
16								121.5									126
17								140									148
18									132.5								149
19									125								143
20									102								149

features according to the stage of development which it has reached at the time of birth. The mongoloid is not proportionate; it shows a "rounding" of the features because of delay of distal growth.

In a condition which represents the opposite of mongolism—namely, acromegaly—the same structures are involved in a different way. In this condition the whole skeleton does not increase in size indiscriminately. The skull reveals abnormal pneumatization, which leads to extension of the sinus system. The mandible increases in size by osseous deposits upon the mental process. In the flat skull bones the diploe is chiefly involved. The cartilagenous disks react by renewed proliferative activity. Mongolism is associated with a deficiency of cartilage proliferation, absence of diploe development, nonextension of the sinus system, and deficient osseous proliferation about the skull sutures and the protruding parts of the face.

There are degrees of growth deficiency. It is not infrequently stated in the literature that mongolism is either present or not, that no gradations of mongolism are to be found. Fanconi emphasized this idea by stating, "There are no transitional forms between mongolism and the normal." However, there are gradations, and mongolism is not a malformation or pathologic mutation of a definite degree.

After birth the abnormal features of the mongoloid child become more conspicuous with each passing week. In some cases it may, therefore, be well advised to refrain from judgment until several weeks have elapsed, when the diagnosis can be established without doubt. The fact that mongolism becomes more conspicuous is not due to an increasing development of the pathological features, but to lack of normal development. Everybody who is familiar with the growth of a newborn baby knows the tremendous amount of development that takes place immediately after birth and continues for the first four years. The appearance of a baby changes with every passing week. In the mongoloid this process of molding is absent or strikingly delayed, and the unfinished appearance of these patients becomes, therefore, increasingly more evident.

I have described the physical characteristics which are present in every case to a greater or less degree. Mongolism is also frequently associated with a number of other malformations which have to be taken into consideration when the prognosis is discussed. The malformations indicate abnormal fetal development of a more severe degree than is present in the average mongoloid. The more malformations are found, the less promising is any therapeutic effort.

Almost every type of malformation has been observed in mongolism, and it is of little value to report each single case. In the following I present a list of the more frequent anomalies which may be found in addition to features discussed before.

Cataracta zonularis, polaris anterior, centralis
Ectopia lentis
Coloboma lentis
Panophthalmia
Optic atrophy, deficiency in myelination
Exophthalmus
Blepharitis
Strabismus
Nystagmus
Occlusion of external ear
Septum defects of nose
Hydrocephalus (rare), possibly due to rickets
Congenital clubfoot, hemiplegia, paraplegia
Syndactyly of fingers or toes, fork position, irregular length of toes
Heart: Defects of intra-auricular septum, patent foramen ovale, intraventricular septum defects, pulmonary stenosis, Fallot's tetralogy (pulmonary stenosis, defective intraventricular septum, hypertrophy of right ventricle, dextroposition of aorta), patent ductus arteriosus botalli
Umbilical hernia, diastasis of abdominal muscles, splanchnomicria, microcolon, colon stenosis
Hypospadia, undescended testicles, fimosis, infantilism; hypertrophy of clitoris, absent minor labia, long, apron-like labia, hypoplasia of uterus
Hirsutism, alopecia

Summary of Observations

The collected material provides evidence beyond argument that mongolism is a growth disorder with specific patterns which are manifest at the time of birth and become more definite as life goes on. Mongolism is not a stationary malformation, but the mongoloid child may be affected with a number of malformations like heart defects (very frequently), abnormal hands or toes (syndactyly), and others.

The patterns of abnormal growth which are present at birth reveal a deceleration of bone development. The skull sutures are less united than expected, the crevices are larger, including the fontanelles. The orbit holes are smaller, the nasion is underdeveloped, the maxilla and mandible are undersized. The long bones are slender and delicate. Ossification centers are frequently normal (in contrast to congenital thyroid aplasia) but undersized, and eruption of new ones is delayed.

We see that at birth the patterns of deficiency show certain characteristics which differ from the patterns of thyroid aplasia, but are well known as the patterns of hypopituitarism. This condition produces proportional gen-

eral retardation of the type of infantilism and fetalism, but at the same time it is apparent that harmony is not complete: the distal protuberances (acra—ends of any structure) seem to have slowed down in growth more than the central parts. This is conspicuous in the skull formation but present in the whole skeleton.

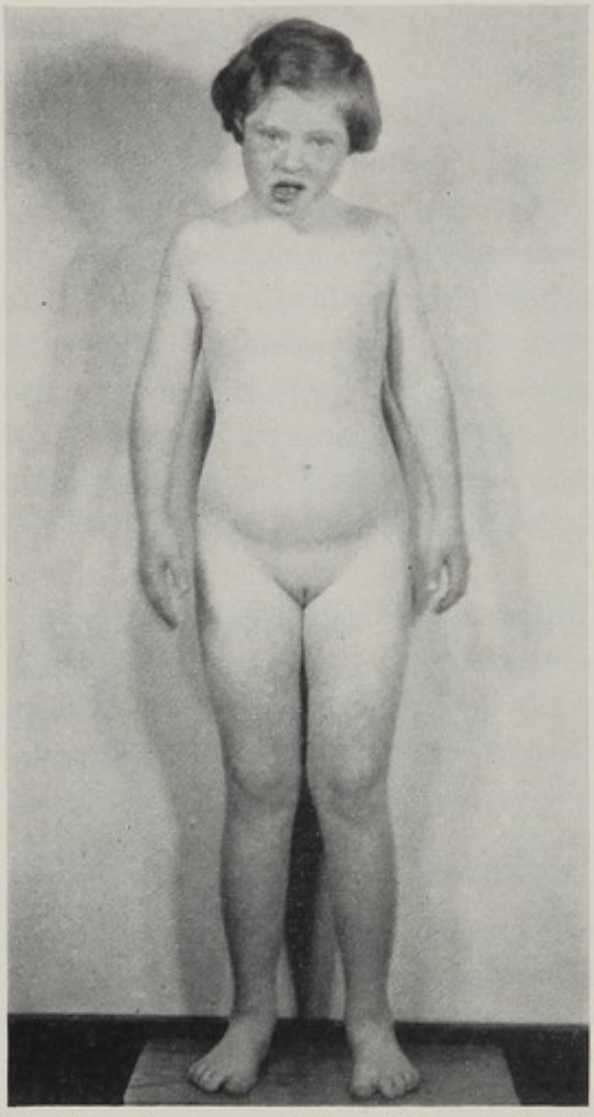


FIG. 8. General infantilism in mongolism. Mongoloid girl almost 15 yrs. of age, height 52 in., developmental age 9 yrs., developmental quotient about 60 per cent. Note length of trunk and shortness of neck, arms, and legs, especially feet; gap between big toe and second toe; marked marmoration of skin of thighs and lower legs; shortness of hands; breasts still completely undeveloped; no pubic or axillary hair.

The acromicric patterns of growth deficiency become more apparent in infancy and childhood and are most conspicuous in the skull and face. The patterns remain fetal and lack the normal molding of the head, although some increase in size is recognizable. The face remains small, and sinus formation (sphenoid, frontal, and paranasal) is absent or rudimentary. The maxilla is undersized, the mandible infantile, and the distal relation

disturbed through underdevelopment of the mandibular condyles and the mental process. Anomalies in the teeth are conspicuous. Eruption is retarded but keeps pace with the biological age of the organism. The vertical height of the jaws is undersized, teeth are crowded, and some remain submerged.

The body of the mongoloid appears fairly proportionate in childhood, but the mongoloids are children who are three to five years behind their chronological age, and the hands and feet are short out of all proportion. Later in life general acromicria becomes more conspicuous. At a time when the maturation of the gonads manifests itself in normal children, the mongoloids are not participating in sex maturation. The mongoloids are a castrated "race" deprived of the adrenal-gonadal activity which dominates the three decades from the middle of the teens to the end of the forties. After a prolonged babyhood and infancy, these unfinished children become old people and manifest all symptoms of old age. The skin becomes dry and wrinkled, the vessels show fatty degeneration and arteriosclerosis, and all functions are sluggish. After puberty they lose their "mongoloid" appearance, and nobody would have thought of that expression if these patients had been studied only during adult life.

While the hypogonadal deficiency in mongolism is conspicuous, hypothyroidism is not always clinically manifest. As the pathological studies which are presented in Chapter V show, about 12 to 20 per cent of the mongoloids have a hypoplastic colloid-free thyroid incapable of producing colloid. The picture is identical with that of cretinism. In 80 per cent, however, thyroid function is on the level of hypopituitarism and the deficiency stops short of myxedema. Clinically, retarded ossification and appearance of ossification centers, constipation, and dry skin indicate hypothyroidism.

Hypo-adrenalism in mongolism has not yet been generally recognized. The adrenal deficiency is more striking than has been suspected by previous investigators. The recognition of this factor makes an understanding of several clinical features possible. The symptoms of chronic adrenal insufficiency appear a few weeks to months after birth. The mongoloid baby little resembles those heavy, rather fatty mongoloid infants whom one may see after the second year has passed. The mongoloid baby is likely to lose weight and is not able to regain it easily. Most mongoloid babies weigh between 12 and 15 pounds at the end of the first year. This is due not only to their susceptibility to infectious diseases, but to a chronic marasmus which seems uninfluenced by any dietary measure. Temperature studies show that heat regulation is insufficient. If the outside temperature is low, mongoloids have subnormal temperatures. If infection takes place, temperature regulation gets out of control and low and high temperatures

may change within a few hours. The mongoloid has a low blood pressure and suffers from capillary dilatation. The skin appears marmorated. The peripheral organs are found congested with dilated capillaries at autopsy. Although the musculature seems well developed, asthenia and muscular weakness are outstanding, but when excited and under powerful stimuli mongoloid infants display an amazing amount of muscular strength. Many mongoloids hang limp in the arms of their mothers and are not able to hold their heads up.

The features which are listed below indicate chronic adrenal insufficiency.

1. Asthenia in early life
2. Hypothermia
3. Low blood pressure
4. Abnormal circulation
5. Susceptibility to infections
6. Low metabolism
7. Specific alterations in blood and biochemistry

The great resemblance to each other of all mongoloids rests upon the fact that their racial and familial differences are obliterated by a uniform deficiency which encroaches upon the individual differentiation. As a group, mongoloids appear as the victims of an experiment by nature to produce human beings without adequate endocrine function. The result is an ill-finished child, eternally deprived of maturation in body and mind.

Cretinism

Physical Characteristics

In a discussion of the physical characteristics of cretinism it is customary to separate sporadic and endemic cases. This distinction is indeed necessary because both varieties show certain differences. It is, however, not the endemic cretin who is the prototype of that morbid entity, and even in countries with endemic cretinism it has been recognized that the most extreme degrees are found in those persons who have no goiter or a palpable thyroid and who, therefore, approach most closely the features of sporadic cretinism.

"The cretin," as known all over the world, is the sporadic cretin who has attracted the curiosity of laymen and scientists. It is the uniformity of his appearance which impressed R. Virchow, as early as 1851, who wrote: "Their similarity has attracted the attention of many observers for a long time; so much has the pathologic form obscured the ethnic differences." This idea has been reiterated time and again. In 1936, J. H. Means emphasized: "The various characteristics give cretins a strong resemblance

one to another. As a class they appear like one big family of brothers and sisters." When Murray B. Gordon writes that "the condition in this country [America] is not the condition which is recognized as cretinism in Europe" and that the term "sporadic cretinism" should be dispensed with and replaced by "childhood myxedema," he is correct in underlining the difference between sporadic and endemic cretinism, but "the" cretin is the same all over the world; the classical treatises have dealt with sporadic cretins rather than with endemics.

Congenital Thyroid Aplasia

"The" cretin is the patient with congenital thyroid aplasia. He represents a type of so striking a uniformity that it is only equaled by the mongoloid, and it is certainly no coincidence that statements identical to that of Means have been made with regard to the family resemblance of all members of the group in both types.

If I describe the cretin in the following, I am choosing the thyroid aplastic cretin as the prototype for them all. Any other thyroid-deficient patient should be graded according to the degree in which he approaches the prototype of that morbid entity.

Cretins are rare nowadays, because most of them are treated for at least a short interval and they readily lose some of their characteristics under treatment. In institutions, however, one finds some of them, and the following description is based on a study of 10 patients, several of whom reached adulthood without too much medical interference.

The adult cretin is a dwarf. When standing, his height may hardly surpass 3 feet, but if the actual body length is measured in a lying position, the length is usually 4 feet with a few inches' variation above or below. The shortness of stature is accentuated by a curvature of the spine and the laxity of the hip joints. The legs are slightly bent.

The cretin walks with a shuffling, waddling gait, the sound of which is so typical that one may recognize his approach without looking up.

The head is large, measuring at least 21 to 22 inches (55 cm.) in circumference, which is a good-sized head for any woman but is impressively large when the body is that of a dwarf. Measurements of 22 to 23½ inches are not uncommon. The head is round or slightly dolichocephalic. Extreme brachycephaly, as in mongolism, is absent. The skull appears heavy, and the bones are thick. A calvarium, which I had the opportunity of weighing at autopsy, weighed more than 500 grams, while the normal weight would be around 300 grams. The head does not resemble hydrocephalus, because in the latter condition the forehead is bulging above the orbits and the upper orbit margin is rounded out through internal pressure. Moreover, the hydrocephalic skull appears thin and translucent and the hair is sparse

and fine. The cretin has abundant black, wiry hair, strong like that of a wire-haired terrier. In all the material there was no cretin with blond hair, though there was one with a reddish tinge. The black hair is apparently a

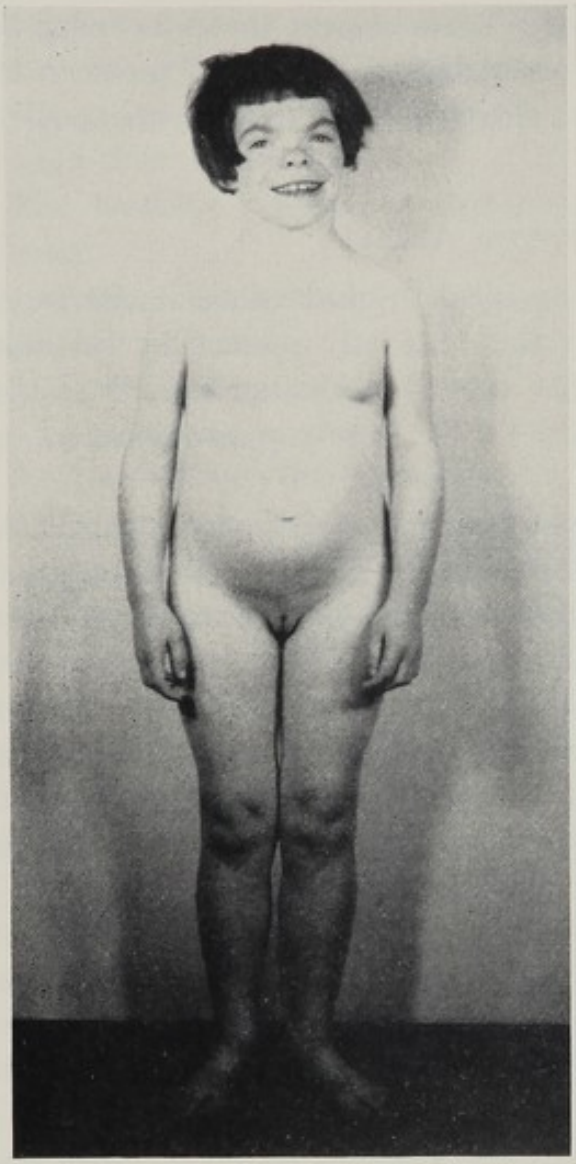


FIG. 9

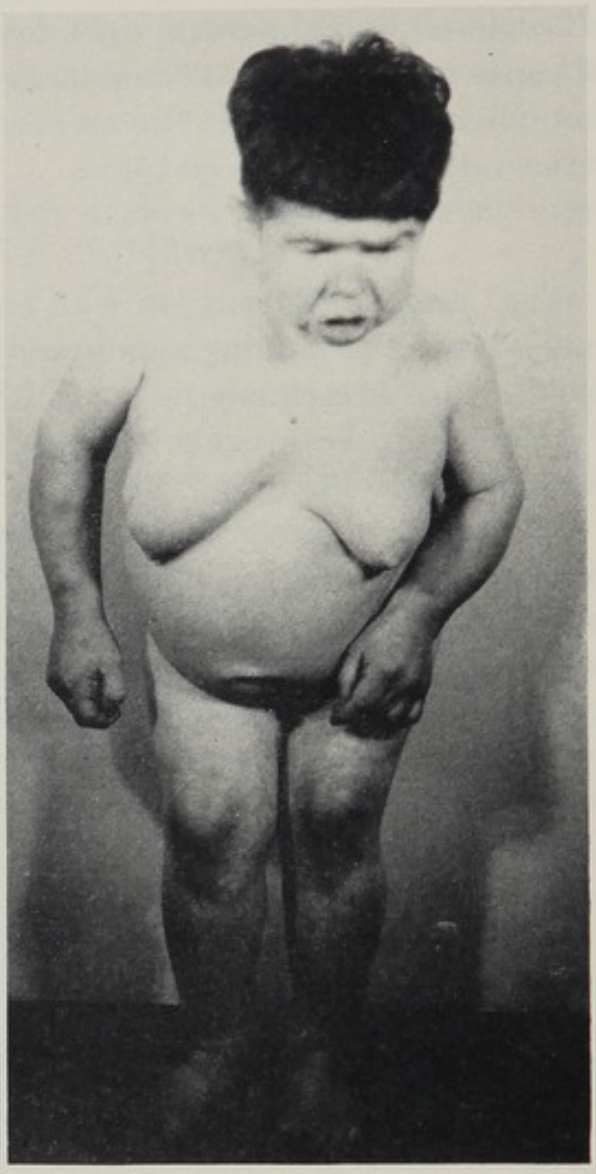


FIG. 10

FIG. 9. Thyroid aplastic cretin, age 15 yrs., height 45 in., developmental age 7 yrs., developmental quotient 50 per cent. Note rather large head, depressed nose bridge, prominent cheek bones. Note general infantilism of body. Breasts slightly better developed than in mongoloid (see Fig. 8). Normal formation of eyes.

FIG. 10. Thyroid aplastic cretin, age 38 yrs. Standing height 3 ft., body length about 4 ft. Note large skull with heavy black hair; protruding lip; short neck; pendulous breasts; protruding abdomen; umbilical hernia; short, slightly curved legs; short arms; spade-like hands. Typical posture.

part of the picture, and a cretin with fine blond hair would suggest either a case of acquired thyroid deficiency or early, effective treatment of at least several months' duration. In case 1 of my material the cretin was treated in early infancy, and it was noted at that time that the black, curly hair was

gradually replaced by fine, silky hair much lighter in color. In contrast to myxedema of adult age, where all writers agree that the hair becomes thin and sparse or disappears, the patient with myxidiocy of infancy, or thyroid aplasia, has strong, black hair.

The structure of the face bones is of great significance. The orbit holes are large, and the eyes are set in a horizontal (normal) position. The palpebral fissures are long. No cretin has the anomalies of the eye set which are typical of mongolism. The eyelids are swollen, thick, and puffy, which narrows the palpebral fissures and forces the cretin to look through a small slit. This gives him a sleepy appearance, and one may notice the effort to keep the eyes open.

The nose is broad and flat. The bony part is underdeveloped and retracted and the cartilaginous part flabby and flexible. One can move the tip of the nose to both sides. The striking flexibility of the nose is a helpful diagnostic sign.

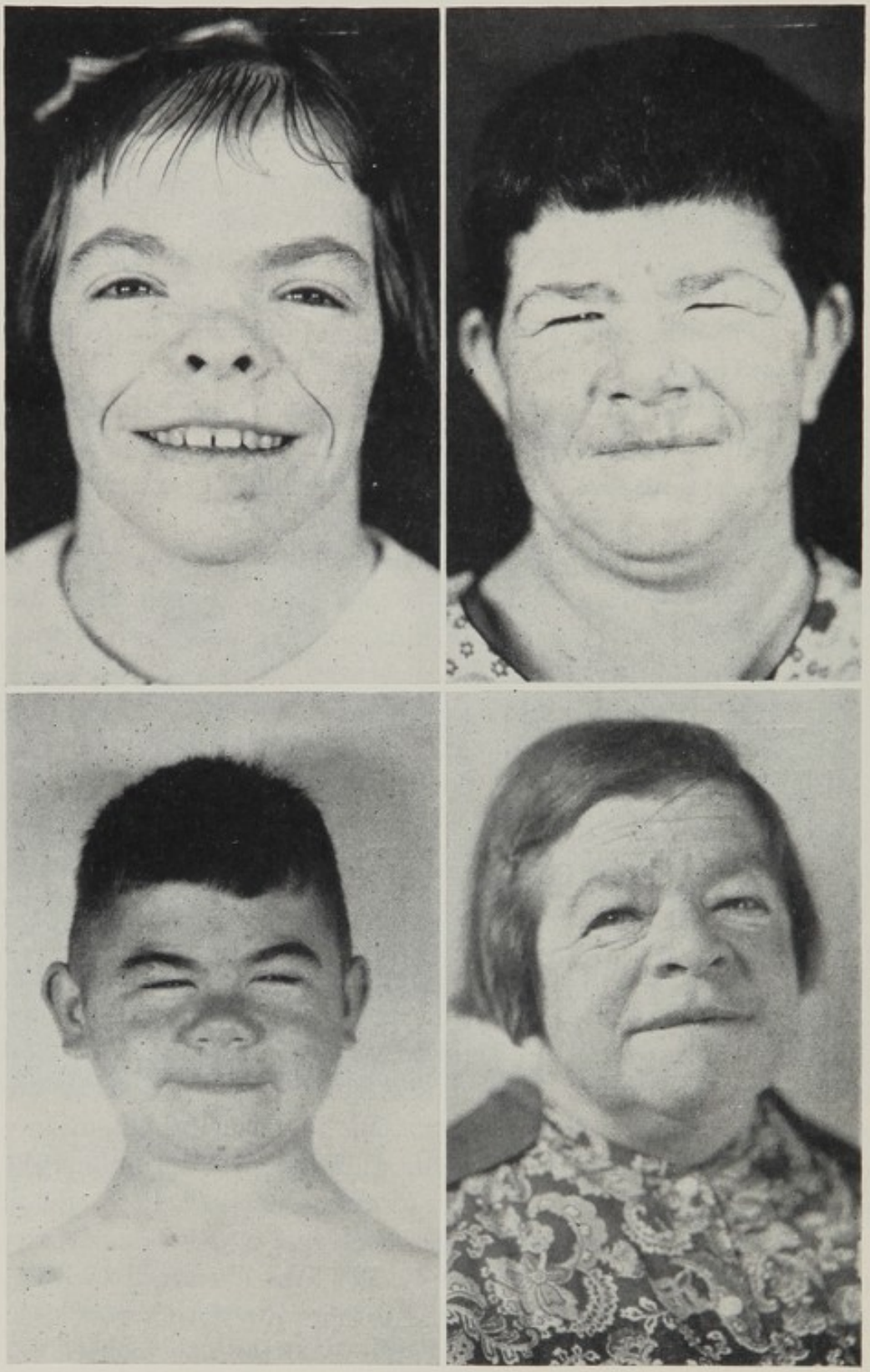
The ears are large and flabby. Their flexibility is as marked as, or more so than, that of the nose. The lower part of the face appears heavy on account of the thickness of skin and subcutaneous tissue, but the bony parts of the face are small and delicate.

The thick skin forms pouches above and beneath the eyes and around the jaw. It is pale, grayish, and wrinkled. Since the puffiness of the subcutaneous tissue limits the mobility, the expression of the face is dull and apathetic. In true untreated myxidiocy there may be no reaction to friendliness or stimulation, but under treatment the cretin is ready to smile "with a childlike benignity, which spreads after a latent period very slowly over his countenance" (Means).

The neck is short and broad. The subcutaneous tissue in the supraclavicular cavities and at the sides of the neck is pouchy, and under palpation one gets the impression of tumors or cysts, which have been described in the literature as lipomas, cysts, and tumors. One may easily think that goiter is present, and it is indeed impossible to decide by palpation whether these pouches are parts of the thyroid or are independent lipomatous structures. As we shall see in the chapter on endocrine pathology, these "cysts" may be persistent pouches of the ultimobrachial pouch (a derivative of the fourth brachiogenic body). They may even form cysts, filled with a colloid-like albuminous fluid, and yet these structures are not thyroid tissue at all and are therefore no "goiters." In other cases the pouches are lipomas or merely an accumulation of myxedematous infiltration of the skin.

The trunk is short, but compared with the extremities it is relatively long. The shortness of the trunk is accentuated by the laxity of the spine, which will curve in upright position but straighten out in bed.

The breasts are small and infantile up to an age of 20 to 30 years. Some



FIGS. 11 (Upper left), 12 (Lower left), 13 (Upper right), 14 (Lower right). Sporadic cretinism in America. Note great resemblance of all 4 patients, born in America but descendants of Italian, Canadian, German, mixed American stock. Note squint of eyes; long palpebral fissures; depressed nose bridge; short neck. The head is relatively large in all patients. The same types could be found easily in any Swiss or other alpine community.

females apparently retain the infantile breasts throughout life, but many cretins eventually develop huge, pendulous breasts, which rest on the protruding belly. The nipples are small, sometimes retracted, and the surrounding area has an indistinct demarcation.

The abdomen is round and protruding, and umbilical hernia is common. The belly is filled with hard masses. Chronic constipation is common, and spontaneous bowel movements may be as rare as once weekly. Urinary output is small. Under slight thyroid doses a tremendous amount of diuresis commences at once. The concentrated urine of untreated cases usually contains traces of albumin.

The external sex organs have few pubic hairs. Infantilism remains present for a long time, but finally the sex organs may appear large in males and not abnormal in females.

The extremities are short and broad, as can be readily seen in x-ray pictures. The hands are broad, the fingers short and cone-shaped, cool to touch, flabby and wrinkled, as if one were touching a toad. The toes are short but not malformed;* the feet are short, like those of a child.

Although the skin is cool, wrinkled, and thick, the dryness is not apparent all over. There may be large areas of smooth, normal skin about the chest and belly, and dryness may be restricted to the inside of the legs and arms. There is no general pitting on pressure, but the skin may pit above the ankles and about the foot as in ordinary kidney edema.

The nails are thick, brittle, and short.

Body temperature is usually one to two degrees lower than normal, running in the morning around 96 and in the afternoon around 97. Temperature depends upon the outside temperature to some degree, and cretins are happiest on hot summer days.

The pulse is slow in some cases, but in others the opposite is true. This observation is quite important when a cretin is under thyroid treatment. I discontinued treatment several times because of irregular, accelerated pulse rate until I learned that this was not due to overdoses of thyroid,

* In the well-known book *Endocrinology and Metabolism* (D. Appleton & Co., New York and London, 1922), volume 1, chapter on cretinism, five photographs are published to illustrate the various physical aspects of cretinism. Four of the pictures may have been taken of mongoloid patients and not of cretins. Fig. 2, "Typical Cretin" (p. 399); Fig. 3, "The Cretinic Stare"; Fig. 4, "Cretinic Feet: note stubbiness and space between great and second toe" (p. 400); Fig. 5, "Hypothyroidism in a girl of ten years. Notice Hertoghe's eyebrow sign, myxedematous swollen eyelids, saddle nose and spade-like hands." The cretin has neither the cretinic stare nor is there a big space between the great and the second toe. Although several publications have dealt with the differential diagnosis of cretinism and mongolism, the illustrations show that the diagnosis may still be difficult in quite a number of cases.

but to inadequate treatment. The following chart of two myxedematous congenital cretins demonstrates clearly how the temperature rises and the pulse rate falls under thyroid administration—an experiment which could be repeated ad libitum.

The heart is usually enlarged, and the sounds are feeble. In congenital thyroid aplasia, the systolic blood pressure is low. The capillaries reveal certain anomalies of retardation, which indicate general infantilism of the vascular system.

Menarche is delayed but may be established after 25, and menstruation may occur at irregular intervals for a period of about ten years.

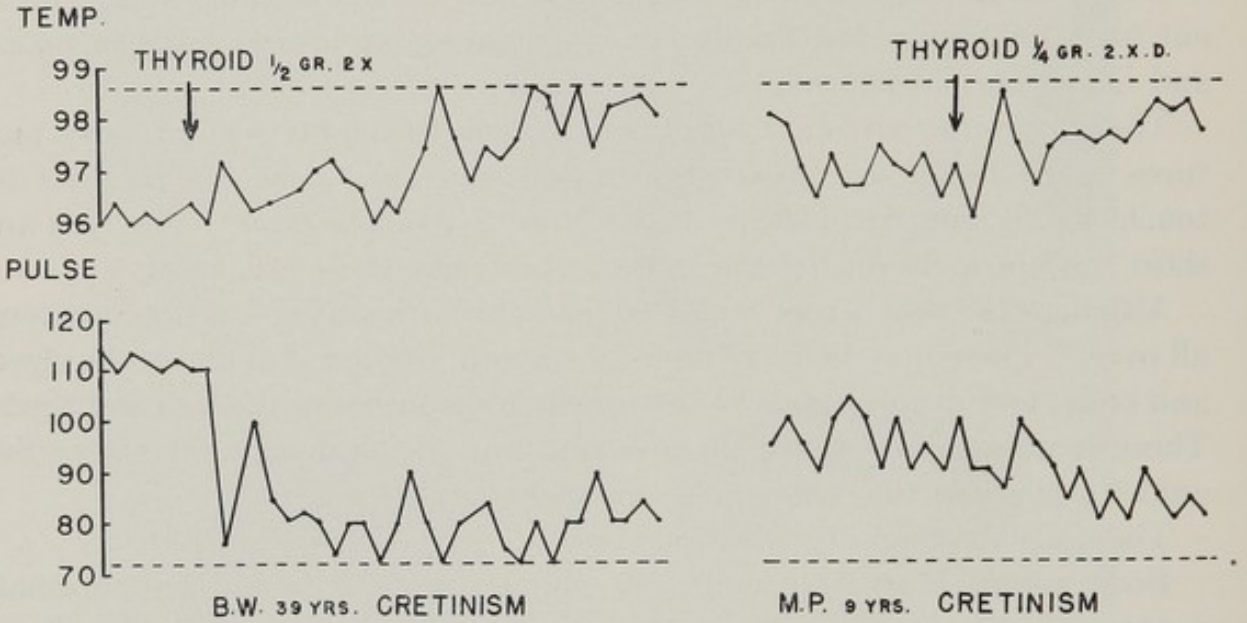


FIG. 15. Temperature and pulse charts of two cretins at the beginning of thyroid treatment. B. W., 39 yr. old cretin never adequately treated with thyroid before. Note low temperature running between 96° and 96.4°, and high pulse rate running between 110 and 114 per minute. With the beginning of thyroid treatment the temperature rose gradually to normal and the pulse rate fell to a level between 70 and 90. P. M., 9 yr. old cretin. Note also rise in temperature and paradoxical fall in pulse rate under thyroid treatment.

The untreated cretin will not learn to speak. He will utter some indistinct sounds in a low-pitched, harsh voice. The thick lips and the heavy tongue make even the treated cretin sound tongue-tied and muttering, like a drunkard.

All movements are slow and awkward. Most typical is the waddling and shuffling gait, broad based, with bent knees and feet apart.

Are these phenomena merely due to low mentality, lax joints, and myxedema, as earlier writers seem to have taken for granted, or are they manifestations of a neurological involvement? This question has attracted some attention in recent years and has led to the establishment of a separate syndrome, the "thyroneural dystrophy," or "neurono-cretinism."

A number of investigators—F. Langmead; Kraus, Brock, and Sloane; De Quervain—have observed the association of congenital myxedema with mental and neuromuscular disorders. In several studies De Quervain found increased knee jerks in 50 to 60 per cent of the cretins, an observation which can be easily confirmed in any neurological examination. This is the more noteworthy as mongolism shows decreased or absent knee jerks. But in addition to the knee jerks, cretins display a number of neurological symptoms. Many walk with arms and legs bent and stiff. A neurological examination reveals rigidity, increased reflexes, and ataxia—symptoms which are not explained by mere mental retardation. The stiffness may be so great as to suggest spastic paraplegia, but the symptoms are alleviated by thyroid therapy, though not eliminated. Tremors are not too rare. These symptoms indicate involvement of the central nervous system beyond repair and are of value in making a prognosis. If more severe neurological complications are present, such as paraplegia or hemiplegia, one may hesitate to attribute these disorders to mere thyroneural complications. I would suspect, rather, that malformations or birth injuries play an additional rôle.

Thyroid aplasia produces a clinical picture which is indeed most uniform, making every patient a member of one great family, that of the "sporadic cretin." The appearance of these patients differs in many points from the patient with acquired thyroid deficiency, even if the loss of thyroid occurred in early infancy. It is, therefore, possible to distinguish the various types of athyroidism by clinical observations.

The literature contains frequent statements that, in contrast to mongolism, sporadic cretinism is not present at birth and can, therefore, not be recognized before several months have passed. In view of the fact that earlier writers have not properly distinguished between the various forms of congenital and acquired athyroidosis, the statement may be correct that the majority of their cases were not recognized at birth, but as far as congenital thyroid aplasia is concerned, the observation is not correct. Thyroid aplasia is present at birth and offers a morbid entity which deserves proper recognition.

The cretin seems to be heavy at birth. Four out of five cretins whose birth weight I was able to obtain weighed between 8 and $10\frac{1}{2}$ lbs. at birth, and the fifth was said to have been a heavy baby also. Although such a birth weight is frequently a matter of special maternal pride and is certainly a symptom of health in the great majority of cases, in association with other symptoms the heavy weight is worth noticing.

The cretin baby has a large head with a wide open anterior fontanelle. Moreover, he shares the open frontal suture with the mongoloid, whose condition I have described before. The nose is flat, broad, and depressed

with retracted root, the forehead slightly protruding. The cheek bones are prominent, the eye fissure straight and horizontal but narrow, owing to a relative heaviness of the lids. The forehead is unusually wrinkled, giving the child the look of an old person. The skin is dry and scaly, and the extremities are short, leaving the skin in loose folds about wrists, hands, feet and neck. The color of the skin is grayish white, and the small vessels are not recognizable through the skin. The baby is quiet and slow from the very beginning and pays little attention to feedings. When nursing or at the bottle, he will stop after a few minutes and fall asleep. The abdomen is large and pear-shaped, and the umbilicus remains protruding. Constipation is also present from birth on.

In such a child x-ray examination of pelvis and legs is indicated. The wrists, which serve usually as objects for determination of the bone age, cannot be used because the first metacarpal bones are not present before three to six months after birth, in the majority of cases. The distal epiphyses of the femur, however, and the pelvic bones have reached a stage of maturation at birth which can easily be checked. These ossification centers are not fully developed in cretinism. G. B. Dorff pointed out that, in using this observation, thyroid aplasia makes itself manifest before birth, because otherwise bone development of the fetus could be expected to be normal up to that term. X-rays of the skull also show indications which make a diagnosis possible at the time of birth. Further details will be discussed in a later chapter (VIII).

A few months after birth the syndrome of congenital thyroid aplasia assumes full proportion and will attract the attention even of inexperienced relatives. The baby is quiet and unresponsive, although it was expected to be so healthy on account of its heavy weight. The color of the skin is pale and ash gray, the tongue large and protruding. Breathing may be slow and difficult, and yet pulmonary infection is absent. Temperature is subnormal, around 96° in the morning and 97° at night. Feeding is a slow, laborious business, and the child does not gain in spite of all efforts.

With each passing month, the general growth deficiency will become more prominent and will be eventually the outstanding symptom of athyroidism. Growth is practically at a standstill for several years, and the cartilages remain infantile. Ossification centers fail to appear. In addition to these features, which are striking and readily discovered in any examination, there are certain hematological and biochemical changes which are of great significance. More details on the blood picture and biochemical data are offered in Chapter IX.

Representative Case Histories: Congenital Thyroid Aplasia

Case 1 (5805). Family history not contributory. There were three older children who were supposedly normal.

Pat. was born full term, instrumental delivery, birth weight 9½ lbs. At three months it was noted that the child was unusually quiet and unresponsive and that the tongue was large and protruding. It was also noted that she had difficulties in breathing and feeding. Although no respiratory infection was present, her breathing was stertorous. When put on the bottle soon after birth, the baby would suck well for two or three minutes and then stop. At the age of 3 months she weighed about 9 pounds six ounces, the same as her birth weight. At that time respiration was rather rapid, and there was a slight loose cough. When she was first observed in a hospital she was pale and did not have the rosy color seen in healthy children. Her skin was unusually dry, inelastic, and loose. The hair was dark and curly; the tongue large, covered with a yellowish fur, and dry. Respiration was labored, regular, but of unusual depth. The heart showed a soft systolic murmur. Hands and feet were thick and slightly cyanotic, the hands shovel-shaped.

The baby's temperature remained below the base line practically all the time. Blood showed Hgb. 10 Gm. per cent, R.B.C. 4,280,000, W.B.C. 11,400, Differential normal. Blood cholesterol 134 mg. per cent (Dec. 1936), 171 mg. per cent (March 1937). The baby was unusually quiet and lacked movements seen in infants of the same age. Basal metabolic rate on basis of weight was −31 per cent, on basis of height −27 per cent. The baby was put on thyroid ⅛ twice daily increasing to ¼ twice daily. A metabolism test repeated March 1937 showed +27 on basis of height and +43 on basis of weight.

There was an impressive improvement of the child under thyroid administration. The hair was replaced by fine normal hair, the skin lost its thickness and showed normal turgor, body temperature increased to normal, and the child gained in weight. One year later her metabolism was +14.5 on the basis of weight and +19 per cent on the basis of height. At that time she had a normal number of teeth (namely, nine) and a mental age of 4 months with a chronological age of 16 months. Head circumference 16¼ inches.

The child escaped medical control until the age of 7 years, 5 months, when she was again admitted to a hospital. At that time her height was 3 feet 10 inches; weight was 43 lbs. Respiration 22. Pulse 92. The child had a head of 19 inches circumference, measuring 16 cm. in length and 12.5 cm. in width. The neck was short; there was curvature of the lumbar spine. The nose was broad, puggy, very soft, and flexible; ears asymmetrical, soft cartilage, flexible; the mouth thick, tongue large, rough. Abdomen protruding, pear-shaped, umbilical hernia. Heart sounds decreased, systolic murmur. Appearance pale, hair dark brown, skin pasty, dry, not elastic. The hands were wrinkled, thick, like those of an old woman. The child would not speak, made only funny noises. The gait was waddling, slow, spastic. Neurological examination revealed spasticity of arms and legs with increased reflexes. Arms and legs slightly bent. The mental age was 10 months; I.Q. was .11. She could not retain her balance either sitting or standing but was able to walk slowly, shuffling. She said no words, but made loud sounds, and drooled.

Blood count Hgb. 73 per cent, R.B.C. 4,940,000, W.B.C. 8,950. Segmented polys 79 per cent, small lymphs 16.5 per cent, eosinophils 1 per cent, basophils 1 per cent, slight achromia. It was stated that the patient had been on thyroid all the time, but it was quite obvious that she had conspicuous signs of hypothyroidism. Diagnosis: Cretinism, congenital thyroid aplasia, thyroneural dystrophy.

Serum cholesterol 134 mg. per cent, Dec. 1936. No treatment.

Serum cholesterol 171 mg. per cent, March 1937. Thyroid treatment.

Serum cholesterol 374 mg. per cent, August 1944. 1¼ grain thyroid.

Serum cholesterol 530 mg. per cent, July 1945. Without treatment.

During the last year of observation the child remained on a low mental level,

with a mental age of not more than 2 years. Under thyroid treatment she was active, smiling, friendly, and affectionate. When thyroid was taken away, she slipped gradually into a typical state of cretinism, becoming completely apathetic, motionless, stupid, with a dull expression, protruding tongue, and without any interest even in food.

Case 2 (5392). Family history not contributory. Father Italian immigrant, mother American born. There are two siblings who are said to be normal. A child a year previous to our patient had been delivered by cesarean section necessitated by toxemia. The patient was also delivered by cesarean section. At the age of 7 months she was admitted to a hospital because of lack of progress, and the diagnosis of "mongolism" was made and in addition malnutrition was noticed. X-ray of the skull showed a rather large A.P. diameter. A year after discharge she was again admitted to the hospital with the diagnosis of upper respiratory infection, mongolian idiocy. At the age of 2 years and 7 months she was admitted to the Wrentham State School. On admission the child had a chronological age of 2 years and 8 months, with a mental age of 10 months and an I.Q. of 31. She could not stand without support and would not talk. She had a friendly smile and was co-operative but slow in her motions. Her height was 2 feet 5 inches, weight 22½ lbs. Head 45.5 cm. in circumference, length 15 cm., width 11.2 cm. Forehead prominent. Skin wrinkled. Eyes: palpebral fissures narrow, upper lids heavy. Nose: flat bridged, puggy. Mouth: open. Thick lips. Neck short, heavy pouches around neck. Belly protruding, pear-shaped, umbilical hernia. Legs short and flabby. Skin dry. Hair thick, brown, curled. Heart: sinus arrythmia. Pulse 104. Knee jerks very active.

Blood picture Hgb. 80 per cent, R.B.C. 4,970,000, W.B.C. 5,900, polymorph 40.5 per cent, small lymphs 55 per cent, eosinophils 1.5 per cent, serum calcium 10.6 mg. per cent, serum phosphorus 5.47 mg. per cent, serum phosphatase 7.46 Bodansky units, serum total cholesterol 128 mg. per cent, blood N.P.N. 30 mg. per cent, blood sugar (Folin-Wu) 69 mg. per cent, chloride (NaCl) 538 mg. per cent.

Six months later serum total cholesterol was 182 mg. per cent after the child had been on ¼ grain twice daily for one month. Before treatment was started serum cholesterol had been consistently low on three different occasions, 103 mg. per cent, 102 mg. per cent, 128 mg. per cent. After four years of continuous thyroid treatment serum cholesterol was 189 mg. per cent, almost the same as it had been after one month of treatment.

Serum cholesterol $\left.\begin{matrix}103\\128\end{matrix}\right\}$ mg. per cent, 1940. No treatment.
Serum cholesterol 182 mg. per cent, 1941. ½ gr. thyroid.
Serum cholesterol 189 mg. per cent, 1944. ½ gr. thyroid.
Serum cholesterol 188 mg. per cent, 1945. ½ gr. thyroid.

Case 3 (2876). Father born in Russia, said to be in good health; 43 years of age at birth of child. Mother, born in Russia, 35 years of age at birth of child. Said to be in good health, but very nervous. Patient is the eighth child. There is one other child younger than patient. One sister is insane and one died, cause unknown.

Patient was born in 1906. Birth was normal. Her peculiarity was noticed two weeks after birth. She was unresponsive, had protruding tongue, and was stout. Patient did not have medical attention until 1924, when she was 18 years of age. At that time she measured 3 feet 2 inches, weight was 84½ lbs. Pulse was slow, around 60, and the body temperature 96.4°. Patient did not talk or walk. She could take

a few steps with a waddling gait. Her expression was dull, vague, and she took no notice of things going on around her. The hair was black and thick, forehead wrinkled, nose bridge depressed, shape puggy, palpebral fissures narrow, cheeks thick and pendulous, mouth large, lower lip protruding, tongue protruding. Her skin was anemic, waxy, and flabby. She had many deposits of fat, "suggestive of lipomas," in front and on the sides of her neck, in her armpits and sternal notch. Hands and feet were broad and short. There was marked scoliosis.

Patient was placed on thyroid, half a grain twice daily, which was gradually increased to one grain, three times daily. This dose was continued three weeks and was reduced again to half a grain twice daily. During the first month of treatment she lost 13 pounds, during the second month 9 pounds. Her skin became less dry and flabby, her color improved. The deposits under her skin disappeared and she started to walk a little. When, a year later, some x-ray pictures were taken, the epiphyses were still open and the soft tissues were much thicker than normal. The patient learned to walk around and moved with a slow, waddling gait. She learned to feed herself. When, however, no further mental development was noticed, some doctor stopped thyroid treatment and the patient became again increasingly myxedematous. In 1937 a physical examination showed a height of 3 feet 8 inches (111 cm.), weight 94 lbs. Head circumference was 56.5 cm. (22⅛ in.), length of skull was 18.7 cm., width 15.7 cm. The hair was black, thick, and coarse. The neck was short and smooth, with large tissue deposits on both sides. The breasts were overdeveloped, the pubic hair normal. The feet were flat, toes short; the fingers short, spadelike. The skin was wrinkled (cutis laxa) and could be lifted in large folds. Abdomen protruding, umbilical hernia. Another eight years later, the patient had not gained in height but had gained in weight to 103 lbs. The axilla was hairless, the pubic hair scanty. The breasts were huge and pendulous. Patient was slow and myxedematous. Serum total cholesterol 417 mg. per cent, in 1945, without treatment.

Case 4 (126) A 43–112). Both parents born in Italy. Three older children, said to be normal. Patient was born in 1896. When 5 years of age she did not walk or talk. Height at that time was 2 feet, weight 30 pounds. Diagnosis of cretinism was made at that time and thyroid treatment started. She improved gradually and learned to talk and walk. In those years she was a rather active girl, happy, fond of music, and could do simple errands. In 1910 she was admitted to the Wrentham State School, where thyroid treatment was apparently not continued for some time. In 1915 she had a height of 4 feet 6 inches, a weight of 120 lbs. She was very short and stout, skin dry and myxedematous. The circumference of the head measured 22½ inches. She menstruated regularly. Intermittent courses of thyroid treatment were carried out, and each time her condition improved greatly. She brightened up and became more active, her gait improved, and her appearance was better. When thyroid was withdrawn she began to gain weight, became myxedematous, and her waddling gait was conspicuous. When she died, at the age of 48 years, in 1943, she was extremely obese and myxedematous. Length of body was 4 feet 7 inches, weight 145½ lbs. Her weight had been as high as 150 and 165 lbs. There was no axilla hair, the pubic hair sparse. The extremities were short, the hands and feet small and short. An autopsy did not reveal any thyroid remnants whatsoever. The skin is shown in Figs. 78 and 79. The pituitary is described on page 138.

Case 5 (3666). Father alcoholic. Patient was born full term, normal delivery. She was a very slow baby and very fat and was over 2 years of age when first attempts

were made to walk and over 2½ years when she started to talk. The patient did not come to medical attention until the age of 8 years, when a full picture of cretinism had developed. Patient measured 36½ inches in height and weighed 34¾ lbs., which corresponds to an age of about 3 years. The nose was depressed, broad, flabby. The arms short and broad, the legs the same. The skin was dry, and general dystrophy of skin and genitalia (gerodermia) was noticed. The patient had a good disposition, was obedient and complacent. Comprehension was slow. She tested on the Merrill-Palmer test: M.A. $3\frac{11}{12}$ years, I.Q. 48. She was put on thyroid therapy with immediate response. The skin, which had been pale, became rosy and the patient became quite active. She ate faster, where she used to dawdle, and finished her meals now at the same time as the rest of the family. She ran around and took an interest in her surroundings. About three months after the beginning of thyroid treatment, her weight was 34½ lbs., her height 3 feet 2 inches. The hair was thick. The head circumference measured 19¾ in.; length 17.3 cm.; width 13.3 cm. The nose was depressed and broad, the palpebral fissures narrow. The pulse was irregular, temperature 96°. There was a tendency to cyanosis. The tongue was slightly coated. During the following years the child was kept on small doses of thyroid and made slow progress. At the age of 17 she was subjected to more careful studies, with the following results: Height 45 inches. Weight 52 lbs. Head circumference 20½ in. Length 18 cm.; width 14.2 cm. Total cholesterol 294 mg. per cent. I.Q. 42. Basal metabolism −24.

Thyroid treatment was not continued, for unknown reasons, and another eight years later the patient showed the following measurements: Height 49¼ inches. Weight 75.4 lbs. Circumference of head 21 inches, length 18 cm.; width 14.4 cm. Pulse 60. Skin fine, marmorated, of infantile texture, no myxedema present. Hair black and straight, rather thin. Ears small, flexible; nose depressed, pug-shaped, very flexible. Mouth infantile, small. The breasts huge and pendulous, nipples inverted, no pigmentation of areola. The area around the nipples was pink and of irregular outline. Heart beats regular, no abnormal sounds. Fingers short, small, and childlike; feet childlike (shoe size 1). Knee jerks hyperactive, enlarged area of elicitation (whole shin). Menstruation fairly regular. In the neck some tissue is palpable, which suggests cystic tumors.

Acquired Athyroidism and Hypothyroidism

While congenital thyroid aplasia represents a well-defined clinical and morbid entity, for which the name "sporadic cretinism" should be reserved, loss of thyroid function may occur at any time of development. Children with athyroidism differ from each other as much as other patients, according to race and family, but, a uniform pathological process exercises a unifying influence upon its victims, and the earlier the onset the more uniform the "cretinoid" appearance of a child. Acquired athyroidism resembles experimental thyroidectomy and postoperative myxedema and differs, therefore, in certain features from the congenital variety. The hair becomes sparse and thin. The color will be the child's natural hair color, and blond cretinoid patients are as frequent as brown or dark haired. The skin becomes dry and scaly. The color is pale and anemic, suggesting anemia, which indeed is present. The appearance of the skin is puffy and may suggest heart or kidney disease. This mistake is further facilitated

by the fact that pitting on pressure may well be present about the shin and ankles.

In the course of time, arrest of physical growth will be conspicuous. X-ray examination of the metacarpal bones may shed light on the time when the condition developed, since no new metacarpal bone centers appear, while the condition of those which are present before the onset of symptoms may serve as an indication of the age of the disorder. The presence of "normal" metacarpal bones can, therefore, serve to rule out congenital cretinism but can by no means be used to rule out a present state of hypothyroidism, which may have developed after an acute infection. It is not sufficiently appreciated that hypothyroidism may develop after acute infectious diseases of infancy. There are not only Curling and Fagge's original cases of sporadic cretinism, which were cases of post-infectious athyroidism, but a large number of case reports have been published since, establishing this fact beyond doubt.

Measles apparently ranks first among the causes. Several reports have been published in the French literature (Combe, Comby, Bouchaud). Breitel discussed twelve cases of Comby's. Siegert described a case after measles and whooping cough, and H. Fagge's famous first case occurred after measles and erysipelas. Scarlatina (Parker) and diphtheria (Acker and Williams) are also of importance.

Siegert collected 56 cases of acquired athyroidism and discussed the onset of symptoms according to age. He found an age of 6 to 12 months in 14 cases. The onset fell into the second year of life 18 times, into the third year 8 times, and the fourth year 3 times. The sixth year is mentioned 7 times. Seven further cases are recorded for the ages between 7 and 12 years.

It is worth remembering that, besides infectious diseases, trauma may also be the cause of athyroidism. Birth injuries with bleeding into the thyroid (Siegert: 2 cases) or traumata in infancy (Bourneville, Fuchs, Schmidt) point toward the fact that the development of cretinoid symptoms after birth injuries or accidents is worth attention. A number of birth-injured children show endocrine symptoms, but the fact of a cerebral birth injury makes the examiner unwilling to take athyroidism into consideration as an additional factor.

It need hardly be repeated that the older the child, the less will be the mental retardation and the thyrogenic growth deficiency. On the other hand, a traumatic or infectious factor at birth or shortly afterwards may produce a clinical picture of cretinism which cannot be distinguished from the thyroid aplastic case. Moreover, to complicate matters even more, congenital thyroid hypoplasia may not manifest itself until years after birth, when growing up puts an increasingly heavier tax upon thyroid

function. A small hypoplastic thyroid may carry an infant through the first two years but be entirely inadequate to fulfill the requirements of the period between 4 and 10 years or before and at puberty.

Case 6 (3510). Family history not contributory. Father is said to have an unusually large head. W. R. was born at full term, normal birth. He walked at the normal age of 15 months and started to talk in the second year. When he fell ill with influenza and pneumonia at the age of 3½ years, he was able to talk fairly well. After his illness his appetite became poor, he became slower, and at the age of 4 years it was noticed that he did not grow and was untidy. At the age of 6 years he was admitted to the public school, but he could not make any progress and was sent to special class. At the age of 10 years his mother finally took him to a clinic, where cretinism was suspected. He was, however, not admitted to a hospital before the age of 13 years. At that time a typical picture of cretinism was present, although he was somewhat brighter and more active than a child in that condition usually is.

Physical examination revealed a quiet, shy boy, poorly developed but rather fat. Height 3 feet 1 inch, weight 67 lbs. Hair brown, coarse, and sparse. Face flushed. Skin dry and rough; slight cyanosis of feet. Depressed nose bridge. Teeth in poor condition. Blood pressure systolic 80, diastolic 40. Abdomen protruding, large. Heart appeared slightly enlarged. Pulse 66 per minute. Heart sounds faint. He was put on thyroid treatment and improved considerably.

A basal metabolism test done four years later showed a rate of −20 per cent. Total serum cholesterol done at the age of 24 years was 262 mg. per 100 cc. At that time the boy had a height of 4 feet 7 inches (137.5 cm.) and weighed 119 lbs. The head circumference measured 57 cm. The head was egg-shaped, he had a saddle nose, and the cartilage of the nose was very flexible. Ears large and protruding, the neck short. Skin rough and dry. The male sex organs were unusually large, but the pubic hair showed a feminine type of distribution. There was very little axillary hair.

Case 7 (M. S.). Patient is an illegitimate child. The mother is a borderline case with an I.Q. of 88. The child was born at full term, normal delivery. Birth weight was 7½ lbs. On the third day after birth jaundice developed and lasted for ten days. The child developed slowly, but retardation did not become conspicuous before the second year of life. At the age of 14 months the child was taken to a hospital, where a diagnosis of cretinism and secondary anemia was made. Basal metabolism was −29 per cent, cholesterol 352 mg. per cent. The baby was placed on thyroid and iron therapy, first on ¼ of a grain, and the dose was gradually increased to 3 grains daily. The dose was later decreased to 1½ grain because basal metabolism went up to +36 per cent. When the child was again admitted to a hospital at the age of 20 months, she measured 2 feet, 5 inches and weighed 23 lbs. The eyes were rather wide-spaced, the nasal bridge flat and broad; the hair was fine, slightly wavy, of light brown color. The abdomen was round and protruding. The texture of the skin was fine and no myxedema present. The head was rather large, round, measuring 46 cm. in circumference. The child was playful and alert but resistive to examination. She could not walk. In the course of the next few years the child learned to walk; she walks around slowly with a waddling, shuffling gait. The belly is protruding and the posture that of an old woman. Although it is not clear whether the jaundice had anything to do with the present state of cretinism, it is felt that the child is not a thyroid aplastic cretin. She is in many respects better developed than thyroid aplastic cretins usually are. The athyroidism is, however, complete, and if thyroid is taken away the child slips into a condition of myxedema and complete apathy.

Endemic Cretinism

Historically the term "cretinism" has been associated with a certain type of dwarfism and mental deterioration found in some geographical areas of mountainous character. The feebleminded dwarfs of these sections vary to some extent in degrees of physical and mental retardation, and in studying a large group of persons who are called "cretins" by their compatriots, it is not easy to define a common denominator. Having also studied feeblemindedness in areas where no endemic cretinism exists, I suspect that many feebleminded patients born in goiterous areas are considered cretins in spite of the fact that this diagnosis does not apply to them. A comparison of a large group of cretins in a Swiss institution or a Swiss community with a group of feebleminded patients in an American institution would show that in the former group numerous patients are regarded as cretins whose equivalent and likeness can be found in the American institution where no cretinism exists. At the same time, many endocrine disorders are considered sequelae of cretinism which can well be found in areas without cretinism. The confusing variety of types, including dwarfs as well as persons of average size, and idiots as well as borderline cases, has led several European writers to the belief that thyroid deficiency is not the essential factor in endemic cretinism. But this statement is only correct when the term endemic cretin is applied to any goiterous or nongoiterous patient in an area of endemic goiter. The many valuable studies of endemic cretinism are lacking in one point, they are done without knowledge of the problem of mental deficiency as it exists all over the world, regardless of geographical distribution. Not only are 2 to 4 per cent of the people feebleminded in every country, but mental deficiency is associated with physical inferiority of varying degree. It is rare to find a tall feebleminded person except when the mental defect was clearly due to traumatic or infectious factors. But taking a group of 200 familial imbeciles and low-grade morons, there is hardly a single person taller than 5 ft. or 150 cm. and most of the women are less than that. The skin is wrinkled and dry, posture is poor and sex development frequently retarded. If the population of an American seaboard state institution would be exchanged with a similar group of a Kantonal institution and vice versa, more than 50 per cent of the patients could not be correctly diagnosed without autopsy. But, as autopsy reports from Switzerland, Austria, Tyrol indicate, "cretinism" can be found associated "with goiter, without goiter and a normal [!] thyroid." One has to admit that this use of the term endemic cretinism is not too satisfactory.

Many writers dealing with endemic cretinism write about endemic goiter. Careful studies on the normal thyroid and the thyroid in areas of endemic goiter have provided sufficient evidence to show that thyroid hypertrophy is the "normal" reaction of the thyroid to chronic want of iodine. In areas

in which the water, air, salt and soil are poor in iodine, goiter develops and is present in 40 to 90 per cent of the population. Increase in iodine by feeding and supplying iodine rich salt can prevent goiter. The endemic cretin—and all experts have agreed on this point—is the patient who has no goiter (p. 118). This observation gives an important clue to the solution of the problem.

Since discovery of the thyroid aplastic sporadic cretin, the clinical and pathological features of cretinism are fairly well known. The endemic cretin is the patient who participates in the main features of chronic thyroid deficiency. All those patients who are feebleminded due to other than thyrogenic factors are not cretins regardless where they live. In this way a large number of patients ought to be excluded from the diagnosis, but the rest would reveal such an impressive uniformity in every respect that their pathological kinship would not be subject to doubts.

I mentioned that the general incidence of feeblemindedness is about 4 per cent. The incidence of endemic cretinism is not higher than 2 per cent, including all degrees from idiocy to slight mental retardation. It is, therefore, difficult to estimate how many cretins remain after elimination of all hereditary cases of mental deficiency. Complete thyroid aplasia is apparently not too frequent in areas of endemic cretinism. The same number of cases can be expected anywhere as seen in nongoiterous areas. Gordon's observation mentioned before, that not a single case of congenital thyroid aplasia seen in the state of New York came from an area of endemic goiter, is worth mentioning and supported by other observations.

It is not the purpose of this book to discuss the features of endemic cretinism in detail. In postulating the identity of all cretinism as thyroid aplasia or chronic thyroid deficiency, regardless of geographical distribution, the great variations seen in endemic cretins do not afford a separate theory for endemic cretinism. After excluding all feebleminded persons of other etiology, the real variations are due to remaining familial traits smothered under the same all-prevailing deficiency.

The clinical features of endemic cretinism resemble those of sporadic acquired athyroidism and hypothyroidism. Endemic cretinism shares with this group the variations in onset and degree. Instead of the vague terms of full cretin, half cretin, and borderline cases, psychological testing provides the exact classification of idiot, imbecile, and moron. The clinical diagnosis rests upon the recognition of growth deficiency, mental retardation and changes in skin and internal metabolism. Each of these syndromes can be studied to effect an exact diagnosis in order to differentiate the type from other similar disorders. With regard to the somatic retardation, arrest of growth at the level when athyroidism commenced, the open sutures and epiphyseal lines, the retardation of appearance of ossification centers, the dental anomalies have to be present.

The list of twenty measurements of cretins in Table 6 shows impressively not only the underdevelopment in length, but at the same time the extreme degree of underweight. In this point the endemic cretin differs from the thyroid aplastic individual with his tendency to increase in weight. It seems suggested that thyroid remnants which prevent the development of myxedema bring about a clearer picture of the general dwarfism (splanchnomicria) which is obscured by myxedema in congenital myxidiocy. Experimental studies in thyroidectomy have demonstrated that the growth of all organs (including the brain) depends on thyroid function. The dwarfism is accentuated by anomalies in posture, by the weakness of the

TABLE 6.—*Height and Weight in Endemic Cretinism*
(After Scholz)

Age	Sex	Height Cm.	Weight Kgm.
64	M	134	54
20	M	129.5	34.5
14	F	116	22.5
15	F	125	25.5
21	F	119	29.0
25	F	115	23.5
26	M	103	25.0
18	M	125	34.5
18	F	138	43.0
16	F	107	22.5
23	F	136	54.5
45	M	132	41.5
48	F	125	42.5
18	F	85	—

spine and the laxity of the joints. The posture, together with the protruding abdomen and the shuffling gait, reveals the cretin in any group of feebleminded children.

The mental deficiency, which will be discussed in the next chapter, is a specific one. The diagnosis rests on the slowing down of all psychosomatic manifestations—that is, the disappearance of mental alertness, the slowness of response, slow speech, and the change in the voice, which are thyroneural manifestations. Reduction in mentation runs parallel to the physical manifestations and develops according to the age at the time of onset. One can state safely that an idiot of 170 cm. height is not a cretin.

The third factor, which is thoroughly influenced by athyroidism, is the development of secondary sexual characteristics, hair, beard, the condition of the skin, and general maturation. The cretin does not enter puberty with such dramatic changes as take place in normal children within two to

three years. The cretin, however, may slowly change within the course of ten years and finally display large breasts and pubic hair, although axillary hair is always sparse. The skin is usually not myxedematous, but it is dry, wrinkled, cold, and scaly, and perspiration is absent.

The transitional period from rudimentary thyroid function to complete inadequacy may last several years and is likely to produce a variety of symptoms, including toxic ones, which may change the features of the endemic cretin and give him a different appearance from that of sporadic cretinism. These toxic symptoms of a "dysthyroidism" have promoted the widely accepted theory that, in endemic cretinism, no thyroid is better than a degenerated one. This view of many leading surgeons is well supported by facts.

BIBLIOGRAPHY

Mongolism

Bacherer: Innere Secretion und Zahnheilkunde. Berlin, 1923.

Bonnevie, K.: Studies on the Papillary Patterns of Human Fingers. J. Genetics. **15:** 1, 1924.

Bourneville: Idiotie du type mongolien. Recherches sur epilepsie, e.c., 22, Paris, 1902.

Brousseau, Kate: Mongolism. The Williams and Wilkins Co., Baltimore, 1928.

Cummins, H.: Dermatoglyphic Stigmata in Mongoloid Idiocy. Anat. Rec. **73,** 1939.

Davenport, C. B.: Influence of Endocrines on Heredity. Proc. Am. A. Ment. Deficiency, 48th Ann. Session, Washington, D. C., 1924.

Down, J. Langdon: Observations on Ethnic Classification of Idiots. London Hospital Reports. **III:** 259, 1866.

Evatt, E. J.: The Development of Papillary Ridges and Patterns on the Volar Surface of the Hand. J. Anat. **41:** 66, 1906.

Fanconi, G.: Mutationstheorie des Mongolismus. Schweiz. Med. Wchnschr. **43:** 995, 1939.

Ford, Norma: Evidence of Disturbance of Growth in Mongoloid Children during Their Early Fetal Development and a Comparison in This Respect with Their Parents and Siblings. Proc. Am. Neurol. A. Meeting Cincinnati, June 1940.

Greig, David M.: The Skull of the Mongolian Imbecile. Edinburgh M. J. **34:** 253, 1927.

Jones, Robert: The Mouth of Backward Children of the Mongol Type. J. Ment. Sc., 1890.

Oliver, Ch. A.: Clinical Study of the Ocular Symptoms Found in So-called Mongolian Type of Idiocy. Trans. Ophthalmol. Soc., 1891–1893.

Pototzky, Carl: The Classification of Mongolism with the Aid of Capillary Microscopy. Am. J. Ment. Deficiency **47:** 167, 1942.

Séguin, E.: Idiocy. New York, 1866.

Shuttleworth, G. E.: Mongolian Imbecility. Brit. M. J., London, 1909.

Smith, Telford: A Peculiarity in the Shape of the Hands in Idiots of the Mongolian Type. Ped., 1896.

Thomson, John: Notes on Peculiarities of the Tongue in Mongolism. Brit. M. J., May 4, 1907.

Werner, August A., Lewald, James, Johns, George A., and Kelling, Douglas: Growth in Children with Mongolism: a Four Year Study of Eight Patients. Am. J. Dis. Child. **57:** 554–63, 1939.

Cretinism

Acker: Fall von erworbenem Myxoedem. Arch. f. Ped., May 1904.
Bouchaud: Crétinisme spor. compliqué de nanism. J. Sci. Med. de Lille, 1883.
Bourneville: Fin de l'histoire d'un idiote myxoedémateux. Arch. de Neur. **16,** Paris, 1903.
Breitel: Du myxoedème spont. chez l'enfant. Thèse de Paris 1903.
Combe: Un cas de myxoedeme infant. Rev. Méd. de la Swisse Rom. **669,** 1895.
Comby: Myxoedème. Arch. Med. des enf. 1, 1899.
De Quervain, F.: Crétinisme. Schweiz. Arch. Neurol. **14:** 3, 1924.
Dorff, G. B.: Sporadic Cretinism in One of Twins. Am. J. Dis. Child. **48:** 1316, 1934.
Fuchs: Vier Fälle von Myxoedem. Arch. Kinderh. **41:** 60, 1903.
Gordon, Murray B.: Childhood Myxedema or So-Called Sporadic Cretinism in North America. Endocrin. **6:** 235, 1922.
Kraus, W. M., Brock, S., and Sloane, P.: Association of Congenital Myxedema with Mental and Neuromuscular Disorders. Am. J. M. Sc. **178:** 315, 1929.
Langmead, F.: Neurono Cretinism. Proc. Roy. Soc. Med., Sec. Dis. Child. **6:** 149, 1913.
Means, J. H.: The Thyroid and Its Diseases. Lippincott, 1937.
Parker: Acquired Cretinism or Juv. Myxoedema. Brit. M. J. **1:** 1339, 1897.
Siegert, F.: Athyreose im Kindesalter. Handbuch Innere Secretion 3. Leipzig, 1928.

CHAPTER III

MENTAL DEVELOPMENT

Mongolism

Mental Age

In 1928, Brousseau and Brainerd wrote that "mentally we find that mongol infants show no peculiar defect or perversion that distinguishes them from other aments." The present writer, however, wishes to emphasize that the mental development of the mongoloid is as characteristic as is the physical. The statement quoted above shows how little was known about the psychological peculiarities of the different groups of the mentally deficient even fifteen years ago. While the mental retardation of other infants and children of a mental level comparable to the mongoloid is usually the result of a brain injury or encephalitis or a developmental disorder of the nervous system, the mongoloid represents the clearest example of infantilism. Psychologically the term "unfinished children" is even more appropriate than with regard to the physical development. Shuttleworth, who was a great expert on mongolism, felt that "the mental condition of defectives of this type is almost as characteristic as the physical."

Numerous psychological papers have dealt with the question of whether the mongoloid is an idiot or an imbecile, and many tests have been made to determine on which psychological level the majority of mongoloid patients remain.

Speaking in statistics, the mental age of an average group of mongoloid patients including all age groups ranges between 2 and 5 years. L. Grant Tennies found that the majority of cases remain on a low imbecile level. J. E. Wallace Wallin reported on a large number of cases from St. Louis and Ohio and found that the St. Louis cases varied from Binet age 2 to 7.8 and the Ohio cases from 2.6 to 6.8. M. W. Kuenzel reported on mental ages ranging from 1 to 7. The highest tests were recorded by C. Pototzky, who reported mental ages up to 10.8.

These studies merely demonstrate the inadequacy of psychological routine testing to reveal certain peculiarities of the feebleminded. The most characteristic trends of the mongoloid development are not recognized because tests determine the limitations in language, vocabulary, counting, and solving certain experimental assignments, but they do not take account of the inherent potentialities and capacity to make social adjustments. Figure 16 demonstrates the mental development of mongoloid patients in a

state institution on the basis of 329 tests on 132 persons. The diagram shows the mean of different tests on different patients for each age group. The values were corrected to avoid unreasonable ups and downs of the curve due to single tests which were far out of line. It may be said, however, that the variations were relatively slight, and no mongoloid in this study was far outside of the average range for the group. The average mental age ranged from $2\frac{1}{2}$ to $3\frac{1}{2}$ years. This study, however, is not representative of all mongoloids and does not consider their "social maturity." Children of this type develop much better if they have individual care and

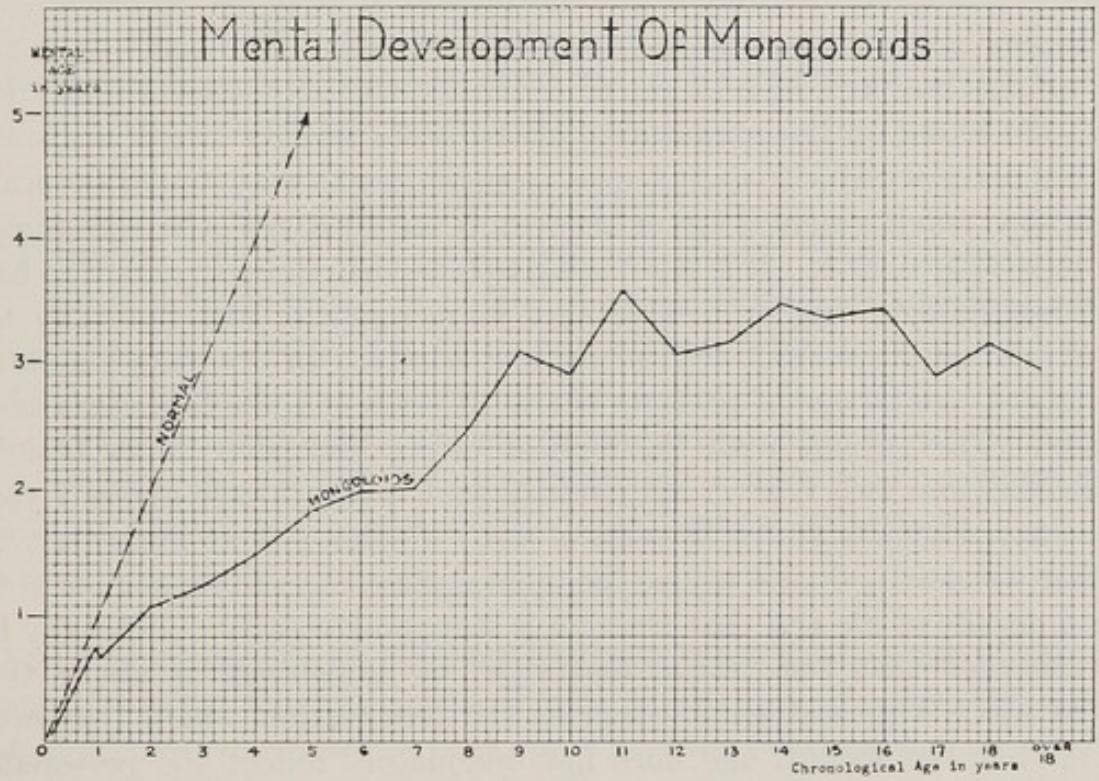


FIG. 16. Mental development in mongolism. Punctured line, normal development; unbroken line indicates mental age found in 132 mongoloid patients based on 329 tests.

attention at home or in private schools where they live in small groups. In large institutions, where the mongoloid is placed with other types of mental defectives, no emphasis can be put on his special needs, and the majority remain on a lower level of achievement than can be attained under special attention. The chart, however, reveals one startling aspect: it shows that between 1 year and 10 years of age the mongoloid child passes through mental levels of from 1 to 3 years. The mongoloid is an infant for the first ten years of his life; in other words, it takes him ten years to accomplish what the normal child accomplishes in two years. With this approach, one can easily understand why the mongoloid shows special

character and psychological traits which are entirely different from those of other types of mental defect. In the "ordinary" idiot or imbecile, mental development is arrested at a certain mental age. These patients are not able to do more than an infant of an equivalent chronological age, and the psychological tests reveal the limitation. The mongoloid is not really arrested at any mental level before puberty, but his psychological development is so extremely slow that he is not capable of absorbing more than an infant during childhood and adolescence and he is still a child when his faculty of development comes to an end.

It may be stated that the potential mental development depends on the degree of biological maturity which was present at birth and on the amount of training and therapy given during infancy and childhood. It is true that no one has been able as yet to overcome the pathological limitations which are based on the immaturity of the brain and its arrest of growth, but it is not justifiable to deny that a mongoloid who may, under favorable conditions, reach a mental age of between 6 and 10 might otherwise remain on a mental level of 4. It is interesting to note that those writers who have published data on higher mental ages in mongolism, like Pototzky and A. M. Gordon, have dealt with mongoloid adults. In Pototzky's material the highest mental age of patients below 10 years of age was 5 years and 7 months. The patient with the highest rating had been under training for the previous two years. All patients with a mental age above 7 years were chronologically above 18 years of age. I think it is an important factor that we usually do not utilize the mental plasticity of mongoloids in the second decade of life and that training is stopped too early. Pototzky has also observed that the "social maturity" of mongoloids is above their mental age. This statement confirms the observation which I reported above, that 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. It is in contrast to the dullness of other imbeciles or the destructive overactivity of postencephalitic or psychotic children. The low opinion of the potentialities of mongoloid persons is based on observations in large institutions or on single cases who have had little attention. Reports and observations on those mongoloids who remain in the community or are pupils of smaller institutions show that the number of mongoloid children who maintain an I.Q. of 60 to 70 when growing up is not so small as one would expect from earlier publications. This statement is based on personal communications from psychologists and parents from all over the country and on some observations made in the community outside of institutions. It is, therefore, of greatest importance, that medical treatment and educational training are continued over a long period. Many physi-

cians discourage the parents with their skepticism and unwillingness to take proper steps. Of course, from the viewpoint of the average and students above average, the mongoloid will always remain retarded and needs special attention. But for any family as well as institution, it makes a considerable difference whether a child of 10 years has to be cared for like an infant of 2 or 3, wetting himself and needing permanent supervision, or if a child of that age acts like a child of 6 or 7, is able to attend at least kindergarten and first grade and can easily mix with other children of that age. This goal is by no means beyond reach and as long as humanity feels the obligation of taking care of the weak and feeble in body and mind, the treatment and care of mongoloid patients is as gratifying as that of cretins whose care has made very satisfactory progress.

The mongoloid child has two great assets, his emotional response to his surroundings and his gift of mimicry.

Emotional Response

Mongoloid children, if treated well, are lovable little creatures full of affection and tenderness. A visitor of an institution summarized her observations: "As playmates, they are always hugging and kissing one another with vague but genuine smiles of 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-naturedly answer yes to any question, hoping that will please."

Gift of Mimicry

The astounding gift of mimicry has been considered as one of the most conspicuous psychological traits of mongoloids, and yet, everyone familiar with child psychology knows that mimicry is the outstanding characteristic of a normal child between 2 and 4. Time and again parents are delighted and proud to see their infant child observe certain peculiarities of his surroundings and copy them with the greatest of ease and correctness, only to experience that the child is unable to do the same thing a year later. The faculty of mimicry is a most important psychological asset in early childhood, and no normal infant would learn to talk or eat and behave without an inborn aptitude for mimicry. The faculty of mimicry in the mongoloid is, therefore, not a character trait of this condition, but a manifestation of his protracted infancy. For each developmental step, the mongoloid needs so infinitely much more time than the normal child that one may say he represents a slow motion picture of human development. Since, in the majority of cases, the film is broken either by premature death or by progressive deterioration, the mental capacities are never fully utilized.

Stubbornness

A word should be said about a very characteristic behavior pattern of mongoloid patients: their stubbornness. Although the meaning of the word is familiar to everybody, the underlying behavior has not attracted attention as an elementary psychological trend. Defined as "inflexible in opinion or intention, unreasonably obstinate, characterized by perseverance or persistence," the behavior has nothing to do with perseveration, which term psychiatry uses as a terminus technicus. This indicates a persistence of associations, thoughts, and words from which the patient is unable to depart. As a behavior pattern stubbornness is the inflexibility in intentions. Stubbornness can be observed in very young mongoloids and seems to depend upon their inability to shift quickly from one object to another and to react to new impressions. With great patience, the stubbornness may be overcome in a certain test condition, but it remains a fundamental trend of the patient in all new situations. Contrasted with the lack of attention and the distractibility of many subnormal patients, I venture to suggest that the stubbornness of mongoloids is a psychological manifestation of the peculiar discrepancy in the development of the nervous system, in which the central subcortical areas serving emotional responses are fairly well developed, while the "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.

Motor Development

We may now consider the mental development in its special phases and aspects. The mongoloid baby is usually very quiet and sleeps most of the time. Even at feeding times it is not restless and will seldom reveal its wants by vigorous crying. In this respect many mothers remark that the mongoloid was "the best baby we ever had. It never made any trouble." The retardation manifests itself more in this general lack of attention and responsiveness than in conspicuous shortcomings. When awake and exposed to adverse conditions, the mongoloid who appeared weak and apathetic a minute ago may display a great amount of strength and resistance. For instance, when we attempted to take x-rays of babies of 4 to 6 months, we frequently encountered a surprising resistance; sometimes three people were needed to hold such a small child. It is not lack of strength or muscle power which makes these children lax and limp at that age, but the immaturity of their nervous system which calls, apparently, for powerful stimuli to reach the threshold level. In psychological tests done in the first year of life, some mongoloids have I.Q.s from 45 to 70.

At an age when the normal child may start to sit up and keep his body erect, the mongoloid will not make such an attempt, and in the second half of the first year the motor retardation becomes more conspicuous with every passing month. It is rare that a mongoloid sits up before the end of the first year, and attempts to crawl will hardly be made before the first year has long passed. As pointed out before, each step in the development is stretched over a long period. Years may elapse between learning to sit up and to stand and again between standing up and learning to walk. It is very hard to determine the exact date at which any child starts to walk, and it is even more difficult to state when such an attempt is made by a mongoloid infant. Roughly speaking, these attempts are rare before the beginning of the second year, and the majority do not start to walk before they are 3 years of age. It is not unusual to see the first steps undertaken at an age of 4, 5, or even 6 years. It may, however, be said that every mongoloid child learns to walk unless it is handicapped by club feet or a neurological condition.

Acquisition of motor control in normal children takes from one to two years. At the age of 2 most infants walk on a broad base, and even at 3 motor control is not perfect. According to the slowness of development, the mongoloid child reveals the same patterns up to about 10 years of age, when his gait is still conspicuously infantile. Many mongoloids always walk on a broad base, and their arm movements are clumsy and awkward. Motor control rarely assumes great accuracy, and even mongoloids of high mental age are clumsy from the viewpoint of motor perfection.

Speech

Speech lags behind walking one to two years, and again pronunciation and articulation are clumsy and indistinct. Many mongoloids have difficulties in pronouncing certain letters all their lives, and many speak so indistinctly that only their near relatives are able to understand them. The vocabulary is limited but depends much on the type of surroundings. Since the speech development is slowed down, the speech will be on a 2 to 3 year level in a large number of children who have a chronological age of 10 years or more. Others, however, acquire a fairly large vocabulary and any generalization is wrong. A peculiarity which has been mentioned before, the low and guttural voice, is not so general as might be expected from the literature. Since in myxedema also the voice becomes raucous within a short time after onset, even in persons who had a perfectly normal voice before, and returns to normality after thyroid treatment, it is suggested that the guttural voice in mongolism is due to myxedema and swelling of the mucous membranes, which are dry and thickened. The harsh voice is

rarely found in patients who have undergone a varying amount of treatment.

Sensory Development

It goes without saying that sensibility examination meets with great difficulties on account of mental retardation, but most textbooks seem to take it for granted that the sensory examination is negative. This seems not to be borne out by clinical observations and the pathology of the nervous system. Moreover, sensory acuity is partly a motor phenomenon, and clumsiness and high sensory accuracy rarely go hand in hand.

The vision seems impaired by strabismus. The lack of myelination of the optic nerves does not suggest very accurate perception. Moreover, many mongoloids are short-sighted and astigmatic. The sense of smell is poor, owing to several factors, one of which may be of a central nature and another due to the chronic rhinitis with alterations of the mucous membrane. It is impossible to form judgment about the accuracy of hearing. Although true deafness seems to be rare, nothing suggests very accurate hearing discrimination. Mongoloids are fond of music and enjoy music more than anything else. It is, however, apparently the rhythm which carries them away; they do not care so much about the melody.

Very few studies have been made on sensory discrimination, because of the difficulties pointed out above. One promising effort has been made by A. M. Gordon. He studied visual and tactile discrimination and compared the results with those found in normal children of the same mental age. It is interesting that the studies were made on mongoloids with a mental age of 5 years and 3 months to 6 years and 8 months. All these patients were adults. The mongoloid patients proved to be inferior in tactile discrimination to the group of normal children equated with them for mental age. It is interesting to note that all mongoloid patients, with one exception, tested higher on visual discrimination than on tactile tests, while the normal controls tested higher on tactile discrimination than on visual tests, with two exceptions. It may, however, be said that all mongoloids tested lower than the normal controls on the visual tests in spite of their having the same "mental age." In addition to the Stanford-Binet form L, the Arthur performance test and the Vineland social maturity and educational achievement tests were used. All tests showed a high intercorrelation, and those mongoloids who ranked first in one test were likely to top also in the other competitions. Only slight changes in rank place were observed. There was, however, no correlation between any of these tests and tactile discrimination. The patient with the lowest mental age scored the highest tactile discrimination, and the poorest show was seen in a patient with a mental age of 5 years and 10 months. The conclusion to be drawn from

this study is that mongoloids are poor in tactile and fine motor discrimination, both of which are probably two aspects of the same somesthetic system.

Clinical observations suggest that touch and pain as well as heat and cold discrimination are poor. The children feel little pain when operated on for minor boils and sores, and they are likely to acquire many skin disorders without calling attention to them, while other children of the same mental level would show discomfort.

With these facts in mind one may ask to what purpose a mongoloid child may best be trained. The highest mental age of children below 10 is usually around 5 years. This means that under most favorable conditions the mongoloid child would not be able to enter public school or kindergarten before an age of 10 years, but by that time the child would be too old and not acceptable. On the other hand, further mental development can be expected in the period from 10 to 20 years, and education should not stop too early. In considering training facilities, mongoloid children should not be trained with other low grade mentally deficient children, unless necessary, because most of the imbeciles of other types are not capable of much further progress, while the mongoloid has dormant possibilities of improvement. Mongoloids profit best in a kindly surrounding with older children of established patterns, because the mongoloid learns by association with other people.

Most mongoloids are unable to help in any trade requiring skilled motor control. They are rarely capable of doing industrial work, sewing, or carpentry. This limits their usefulness, even when the mental age would permit employment in such lines of occupation. The mongoloid girl is best used in housework and may learn to do routine work in a routine manner. She may lead an inoffensive life around the house, because these children learn to stay at home, do little errands, respect traffic rules, and keep out of mischief. Mongoloid boys will be best used in garden or farm activities, where not too great accuracy is required. The question of useful employment is not urgent in the majority of patients, as, under present conditions, they seldom live beyond 15 years of age. But there is a certain relationship between survival time and higher mental ages.

With regard to the question whether or not a mongoloid child should be kept at home with older and younger siblings around, the well-being of the normal siblings should be considered first. Brothers and sisters are frequently embarrassed by the presence of their mongoloid sibling. It is of utmost importance to provide a favorable upbringing for the normal members of the family. It is, therefore, not justifiable to expose the growing children constantly to the presence of an abnormal child. Mongoloids need special facilities for education and will thrive best if such are offered.

At the same time, their management and treatment need constant medical supervision.

Cretinism

Experimental Behavior

Before the mental development of cretins is discussed, it may be worth while to register the psychosomatic syndromes which develop a few weeks to months after operative thyroidectomy in adults. Intelligent patients have observed these symptoms themselves. The experience is worth recording, because spontaneous thyroid deficiency may stop at a level on which only "psychoneurotic" symptoms are present. The patients feel a heaviness of their arms and legs, which may be swollen for intermittent periods in the beginning of the disease. Pains in arms and legs and the abdomen are not rare. The patients feel tired and cold. They are more comfortable near the oven and feel better in summer than in winter. They notice heaviness in their eyelids, swelling of the cheeks, hands, and feet, and gain in weight. Abnormal fat is deposited on the lower parts of the trunk. The patients notice that their mental reactions become slower and that they have a hard time grasping the meaning of a sentence. They talk slowly, in a low voice, and feel too tired to concentrate on any special subject. They lose interest and initiative and are contented to sit around and do nothing. Since many of these patients are aware of their slowness and lack of responsiveness, they avoid company.

In congenital athyroidism or endemic cretinism, one has no opportunity of hearing patients complain of such symptoms, but in children who develop a thyroid deficiency after infectious disease or for other reasons, complaints of that kind may be heard and they should be considered alarming enough to call attention to a possible thyroid failure.

Psychological experiments on thyroidectomized dogs have been reported by O. D. Anderson and others. Anderson's observations are of special interest, because in contrast to other workers who compared the behavior of thyroidectomized animals with normal controls, in Anderson's investigation each animal served as his own control. Behavior in the preoperative period was directly compared with behavior after operation. Anderson has pointed out that experience shows that the behavior of one animal may not only differ in many noticeable ways from that of another at a given moment of comparison, but that each animal may pursue strikingly diverging courses during different periods of time. Thus, the characteristic behavior undergoes a continuous reorganization. Alterations in response to environmental changes are a consequence of education or conditioning. Thus, each animal is his own best control. In a study of conditional reflexes after thyroidectomy it became obvious that the efficiency

of the positive condition reflexes, C-R, salivary and motor responses, decreases, while the negative C-R increase. Positive responses were greatly decreased in efficiency and magnitude. Decrease in general alertness was shown by lengthening of the latent period. On the other hand, the percentage of correct responses to negative condition stimuli increases not on account of improved discrimination, but on account of general lack of alertness and response. A lowering of the general level of excitability was most conspicuous.

Mentality

Clinical and experimental observations indicate that the thyroid is the most essential gland with regard to the proper functioning of mental processes. To make it clear, the thyroid does not determine the amount of intelligence or genius which any person possesses, but thyroid function provides the essential internal environment for any brain function. Removal of the thyroid or lowering of its action is immediately followed by a lowering of excitability, responsiveness, and alertness. It is impossible to speak of mental development in cretinism, because there is no development if thyroid function has stopped. Any development which takes place in cretinism occurs on the basis of how much thyroid function is left. In congenital aplasia of the thyroid the child remains an idiot unable to take care of himself. Even sounds are not uttered in cases of complete absence of thyroid. If a cretin under thyroid treatment has reached a certain mental level and thyroid is taken away, the level goes down at once, and one can observe the loss of mental function from day to day, until every response is eliminated and the child will starve in front of plenty of food. As pointed out in the chapter on the nervous system, adequate thyroid therapy cannot improve mental achievements beyond the developmental level which is determined by heredity and was reached at the time of onset of thyroid deficiency. It must be emphasized that results of proper thyroid treatment cannot be judged by the mental level alone. A misunderstanding of this fact has led to the statement in literature that it matters very little whether thyroid treatment is started very early in infancy or later in life. One has to remember that the thyroid is not only necessary for mental function, but is needed for the development of the brain, and absence of thyroid hormones will inhibit further progress.

Congenital thyroid aplasia and unrecognized thyroid deficiency of infancy interfere with the brain development as an organ, and the resulting mental deficiency cannot be corrected in later life.

In juvenile myxedema and endemic cretinism cessation of thyroid function occurs usually after the child has reached a certain level of intelligence. With the onset of athyroidism the patient will remain on that given level. Most of these patients are happy, good-natured, and clean, but shy and

afraid of company. In this respect they differ from the mongoloid child. The cretins are said to be moody, unpredictable, and mischievous at times, but this depends apparently upon surroundings which lack understanding.

These few remarks reveal that there is no uniform psychology of the cretin, but there is a very uniform change in mental behavior under thyroid deficiency. Other glandular disorders or mental defects associated with dyspituitarism are likely to produce symptoms of a certain degree of thyroid deficiency, which explains the improvements that are sometimes observed from thyroid treatment, although the condition is not that of cretinism.

BIBLIOGRAPHY

Anderson, O. D.: The Role of the Glands of Internal Secretion in the Production of Behavior Types in the Dog. Am. Anat. Memoirs **19:** 647–746, Oct. 1941.

Gesell, A.: Infancy and Human Growth. Macmillan, New York, 1937.

Gordon, Alan M.: Some Aspects of Sensory Discrimination in Mongolism. Am. J. Ment. Def. **49:** 55, 1944.

Hammett, F. S.: Thyroid and Growth. Quart. Rev. Biol. **4:** 353, 1929.

Kuenzel, Myra: A Survey of Mongolian Traits. The Training School Bull., June 1929. Vineland, N. J.

Pototzky, C., and Grigg, A. E.: A Reversion of the Prognosis in Mongolism. Am. J. Orthopsychiat. **12:** 503, 1942.

Shuttleworth, G. E., and Potts, W. A.: Mentally Deficient Children. P. Blakiston's Sons & Co., London, 1922. Fifth edition.

Tennies, L. Grant: Some Comments on the Mongoloid. Am. J. Ment. Def. **48:** 46, 1943.

Wallin, J. E. Wallace: Mongolism among School Children. Am. J. Orthopsychiat. **14:** 104, 1944.

CHAPTER IV

THE NERVOUS SYSTEM

Mongolism

Twenty-five years ago, in his introduction to a large-scale study in mental deficiency, E. E. Southard, speaking of the general aspects of the brain anatomy of the feebleminded, expressed an idea which is still of importance:

> One of the most fruitful distinctions of feeblemindedness of the present day is that of Tredgold, who, seeing the inadequacy of the distinction of the feebleminded into congenital and acquired cases has replaced this dichotomy with a new and different one, namely, with a division into what he calls primary and secondary amentia. The primary aments are victims of what is sometimes termed "germinal blight," whereas the secondary aments are victims of some cause working from outside the brain. The primary ament, according to Tredgold, has cells with an intrinsic vital deficiency—cells which are unable to develop. The secondary ament is the victim of arrest, due to some external cause. One might say that the cells of the primary ament, if this distinction of Tredgold can be upheld, have "run down" or ceased to develop at a certain point, whereas the cells of the secondary ament have not run down of themselves, but have run counter to some agent; that is, the cells have not ceased to develop, they have been stopped. . . . One deals with a plastic impotence, an agenesia, in the case of the primary ament; one deals with a sort of plastic arrest of aplasia in the case of the secondary ament.

If this is applied to mongolism, the problem can be condensed into three theories which express the possible relationship between the physical disorder and the mental defect.

1. The first conception, which is held by Roessle, van der Scheer, and several other authors, considers mongolism to be due to a primary inferiority of the brain with a secondary growth disorder. Roessle, in 1923, introduced the term "dyscerebral dwarfism" in order to distinguish those cases in which the physical growth disorder depends on the pathology of the brain from those in which a primary deficiency of the endocrine glands is present. Through the recent work of Ranson, it is well established that in some instances the dysfunction of the endocrine system may depend upon a primary destruction, for instance, of the hypothalamic region.

2. The second concept, which is expressed by Tredgold, doubts the existence of a mongoloid type. Tredgold is inclined to consider mongolism as a coincidence of several factors in which a physical growth disorder is linked with a mental deficiency by chance.

3. According to the third concept, the mental deficiency is dependent upon the same factors as those which produce the malformation of the skull

and the general growth disorder. In this case, mongolism would not be a primary mental deficiency, but a mental defect secondary to extrinsic agents acting upon the brain.

Although the late E. E. Southard was not able to reach a final conclusion, he expressed the opinion that in mongolism the question of "functional" feeblemindedness arises and "one might logically ask what role endocrinopathy might play in these cases." It will become evident that the collected facts do indeed point in that direction.

Few investigations of the central nervous system of mongoloids have been made. In the last twenty years only four papers have dealt with the brain, and in no case has the spinal cord attracted interest.

As early as 1890, A. W. Wilmarth, in his report on the examination of one hundred brains of feebleminded children, included five cases of mongolism. His observations are interesting enough to be quoted in his own words:

> In all these, the brains are of good size for imbecile brains, the pons and medulla alone being very small, weighing in each case about one-half ounce, whereas the usual weight is nearly twice as much. The cerebral vessels are inclined to be much thinner than in healthy brains. In some places, evidences of old arteritis were discovered. In one instance the vessels showed a tendency to form angiomatous groups, four or five different vessels in a bunch, having somewhat the appearance of erectile tissue. The defective nutrition and circulation of these children lead one to suspect that the defective condition of the vessels may be a general condition. From the small size of the pons and medulla in every instance, there seems to be a strong probability that the low nutrition and possibly the other anatomical peculiarities of this group may be due to the imperfect development or absence of certain cell-groups in this region.

In 1902, Bourneville mentioned the smallness of cortex and white matter. Some authors have noted deficient development of the frontal lobes and suppression of the temporal convolutions. H. Vogt considered the deficiency of the mongoloid brain as an arrest and incomplete development in the last stage before birth. The smallness of the white cores was also noted by Hellemann, who observed retarded myelination, diminished amount of white matter, and lack of cytoplasm in the nerve cells.

Van der Scheer's collaborator, Gans, published several studies in the microscopic anatomy of the brain without reaching conclusions which were generally accepted by subsequent investigators.

A study by Sergio Levy, in 1936, dealt with five mongoloid brains but was restricted to an examination of the convolutional and fissural patterns. Higgins summarized Levy's observations as follows:

> (1) No gross abnormality, no inflammatory factor, and no abnormal character of the brain substance, either diffuse or localized, was found to explain mongolism. (2) The weights of the brains were less than those of normal individuals of the same age and sex. (3) The relative development of the frontal lobes was less than normal.

(4) The cerebral cortex showed a diminished development and differentiation from normal. (5) The brains suggested a biological reversion toward those seen in lower primates.

The most basic study in the microscopic anatomy of the brain in mongolism was carried out by Leo M. Davidoff, in 1928. Davidoff studied ten brains—four of which were recorded in more detail. He concluded:

I have found few morphologic changes which are constant, with the exception of: a small cerebellum and brain stem, the embryonic convolutional pattern, and my own observation of the small content of the ganglion cells of the third cortical layer. The process by which the latter defect arises cannot be determined with certainty from the appearance of the preparations.

He summarized that the brain in mongolian idiocy shows:

(1) Agenesis—as evidenced by cell poverty and failure of gyral development (there probably is also a degenerative process in very early life, increasing the paucity of the ganglion cells in the cerebral cortex); (2) aplasia—as shown by its small size in comparison with that of children of corresponding age; (3) paragenesis—as demonstrated by the frequent occurrence of anomalies.

The result of this study was not too satisfactory, and in 1937 Meyer and Jones wrote: "So far the results of histologic examination of mongol brains have not been too satisfactory, as can be seen from recent reviews given by Davidoff, 1928, Schob, 1930, Kreyenberg, 1936, Weygandt, 1937." The paper by Meyer and Jones is of interest because these authors placed their emphasis on a study of the fibrous glia. They observed the same foci of demyelinization as were present in my material and pointed out:

The occurrence in mongols of a patchy gliosis often around blood-vessels, of circumscribed sub-ependymal softening, and in one case, apparently uncomplicated with epilepsy, of a typical sector sclerosis of the cornu ammonis, makes one think that a vascular factor or other interference with the oxygenation of the tissue might be instrumental in the production of these changes.

In the Waverley research in the pathology of the feebleminded, five cases of mongolism are included. In Case 1 (13 of the series) there was a moderate increase in neuroglia fibers throughout the subpial areas wherever examined, but there was on the whole very little increase of neuroglia cells either of a general distribution or of a perivascular or pericellular distribution. There was also a moderately extensive, somewhat locally variable diminution in the number of nerve cells. In Case 2 (19 of the series) there were some minute cysts of softening in various areas (frontal, temporal), and the pia mater was slightly hazy and thickened over the entire brain and over the cerebellum. The neuroglia tissues showed a tendency to an increase of cells. There was a widespread loss of nerve cells. Case 3 (21 of the series) showed more variable alterations, heterotopia of nerve cells,

vacuolization, and gaps in the cell layers. No consistent change in any given cell layer was found. In Case 4 (27 of the series) a smaller number of glia cells in the white matter was seen, and the vessels looked more numerous and had thicker walls than usual. Slight gliosis in some areas and loss in clear staining power in the Purkinje cells were present. In Case 5 (29 of the series) the myelin of the frontal and parietal region was only faintly stained. Considerable fat was present in the larger nerve cells and in the vessel walls in all sections. The heterotopia mentioned in other cases was striking, as seen in the number of nerve cells in the white matter. Again, the most general findings in the analysis of the cortex were gaps between cells in the seventh, sixth, fourth, and third layers and the pale cells in the deep layers. The rounded contour of the cells in the second layer was outstanding and widespread. There was a slight increase of glia in the first layer.

In a recent paper on alterations in the hypothalamus in mental deficiency, L. O. Morgan reported observations on six mongoloid brains. He succeeded in making exact cell counts and found a normal appearance of the hypothalamic nuclei proper, but found reduction in the number of cells in the nucleus supra opticus. The reduction ranged from 13 to 60 per cent, the tuber lateralis was affected to a greater degree, ranging from 29 to 74 per cent, and the substantia grisea was less affected. These observations indicate strongly that hypothalamic lesions do not precede a pituitary disorder, and the assumption that the main trouble in mongolism must be sought in the brain is not supported by facts.

Spinal Cord

Studies in the spinal cord of mongoloids have not been published, to my knowledge. For the present discussion more than a dozen spinal cords were available. They revealed a most characteristic picture. Similar alterations were not found in any case of a large control material of other types of mental deficiency, although myelodysplasia as such is fairly well known and is frequent in oligo-encephaly. The spinal cord is never what one would call "normal," but the degree of pathology varies. The alterations may be divided into two groups: (1) mere retardation, ranging from hypoplasia to true fetalism, and (2) arrest of development with pathological differentiation.

1. Retardation and Fetalism.—It is a common feature in mongolism that the central canal remains open and forms a well-outlined tube or a sagittal slot. At many levels the central canal appears enlarged and presents the picture of hydromyelia. The enlargement may not involve the whole length, and at some levels a shaft ependymosis may be found. The tendency to irregular proliferation of the ependyma is great, and in several cases a true wedge formation was found in place of the original roof plate.

In the best developed cases, pathology was restricted to a slight infantilism consisting of a large central canal, enlargement of the gray commissure,

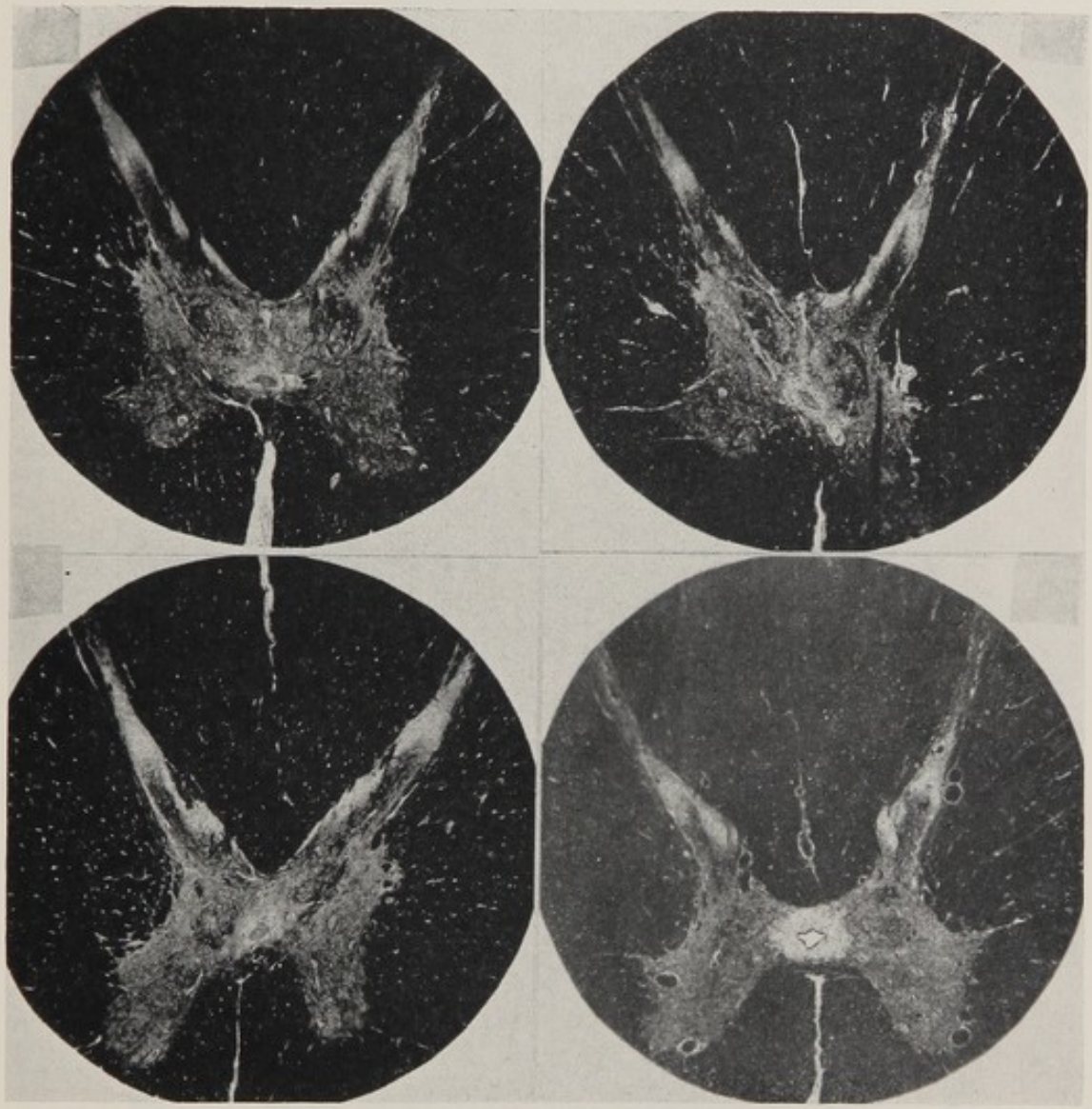


Fig. 17. (Upper left) Spinal cord, twelfth dorsal segment, 18 yr. old mongoloid boy. Note asymmetry of anterior horns; the left is underdeveloped; gliosis around central canal; absence of separation of Clark columns.

Fig. 18. (Lower left) Third dorsal segment, same case. Note asymmetry between right and left sides, with underdevelopment of all structures on the right.

Fig. 19. (Upper right) Eighth dorsal segment, same case. Note seam between central canal and white matter; lack of separation of Clark columns; persistent fetal configuration of gray matter with persistent roof plate.

Fig. 20. (Lower right) Upper dorsal segment, 28 yr. old mongoloid female. Note hypoplastic gray matter with enlarged, persistent central canal; moderate hydromyelia; gliosis of central commissure.

and hypoplastic gray matter with fairly well outlined anterior horn cells, in which the Nissl substance is clearly recognizable. The white matter was spongy, and the vessels were congested.

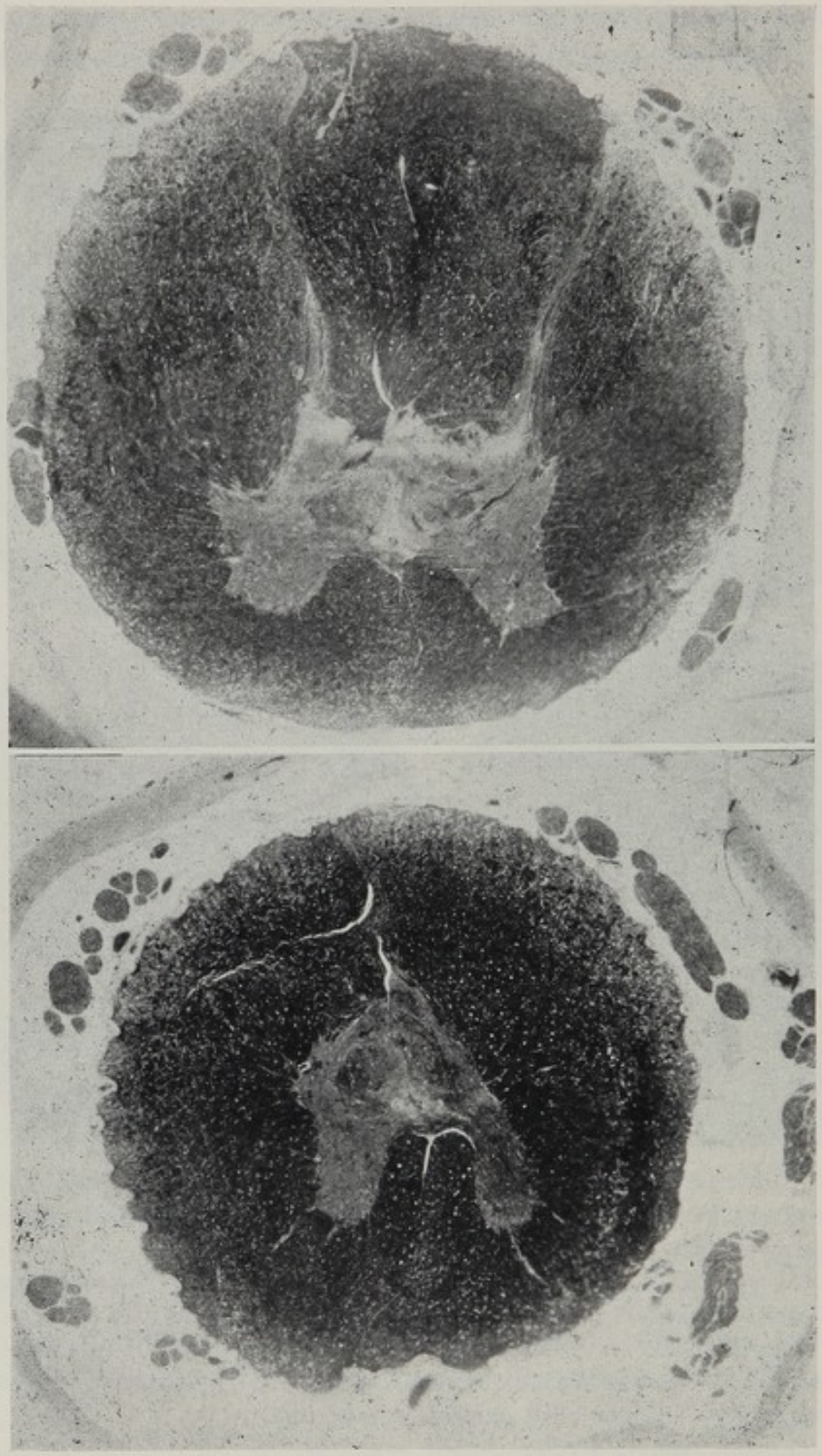


Fig. 21. (Upper) Spinal cord, upper lumbar segment, 16 yr. old mongoloid boy (41/58). Note thread-like, partly missing posterior horns; fetal configuration of gray matter with persistent roof plate and lack of separation of Clark columns.

Fig. 22. (Lower) Spinal cord, lower dorsal segment, same case. Note complete absence of both posterior horns; abnormal configuration of gray matter with persistent roof plate; lack of separation of Clark columns; asymmetry of anterior horns.

Cases with only minor degrees of developmental retardation are not too frequent, but there is another, more common type of developmental arrest

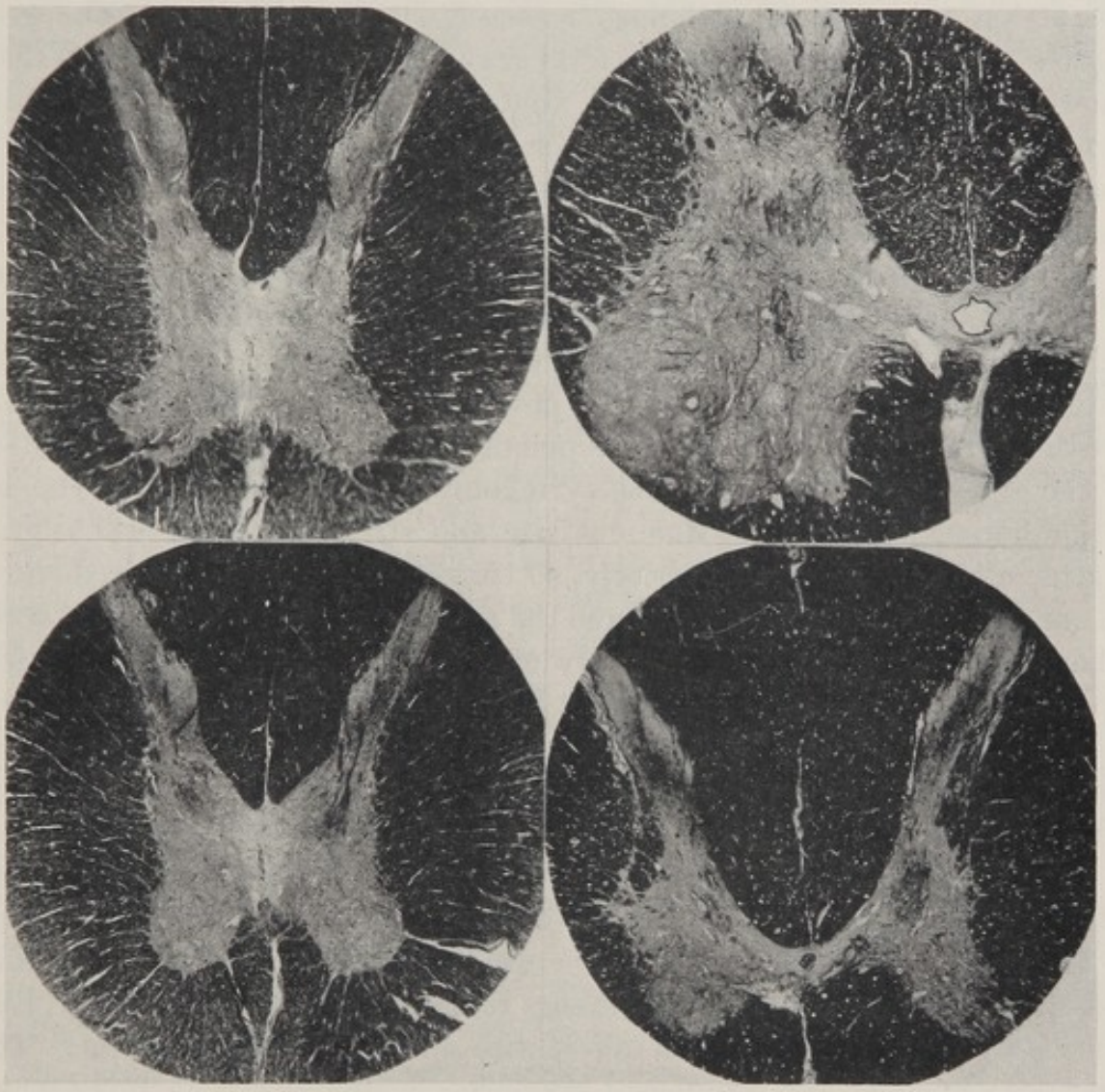


Fig. 23. (Upper left) Spinal cord, lower dorsal segment, $1\frac{8}{12}$ yr. old mongoloid baby (44/140). Note fetal configuration of gray matter with lack of separation of Clark columns.

Fig. 24. (Lower left) Spinal cord, upper dorsal segment, same case. Note fetal configuration with sagittal, slot-shaped central canal and persistent roof plate; asymmetry of anterior horns.

Fig. 25. (Upper right) Spinal cord, cervical level, 15 yr. old mongoloid girl (43/100). Note enlarged central canal—moderate hydromyelia.

Fig. 26. (Lower right) First dorsal segment, same case. Note striking asymmetry of anterior horns.

which seems to be unique with mongolism. This is the lack of separation of the Clark columns. In these cases, which represent the majority, the gray matter behind the central canal forms a broad mass in which the cells of the Clark columns are embedded without being separated by white

matter, as they normally are. The central canal appears slotlike in a sagittal direction. The anterior horns are round and short. If the picture is compared with the embryological development of the spinal cord, it appears that this type of pathology represents a true fetalism. The gray matter preserves the shape of the fetal gray matter. The ependymal shaft shows abnormal proliferation and abnormal differentiation. The ependymal lining is also abnormal in the brain. We see, therefore, in mongolism an abnormal differentiation of the whole ependymal shaft throughout its length from its caudal end to the lateral ventricles.

2. Fetalism with Abnormal Differentiation.—Only in about 50 per cent of the cases may the pathology be considered as a moderate or severe arrest. In the other half, arrested development is associated with abnormal differentiation, certain structures fail to develop, and true malformations are present. Such pathological development consists of gliotic proliferation of the ependymal shaft with true syringomyelia and anomalies of the anterior horns, which are of different size and structure. The whole gray matter may be displaced anteriorly, so that the anterior sulcus is shallow. In one case the gray matter bordered the anterior surface of the spinal cord. The posterior horns were frequently abnormal, asymmetrical, and a few times completely missing. The most conspicuous malformation was found in a mongoloid of 16 years with congenital club feet. In this case a myelodysplasia of severe degree with absence of the posterior horns and abnormal differentiation of the whole gray matter was present.

Study of the spinal cord provides evidence that the pathological factors which influence the development of the fetus act from a very early period in fetal life. They interfere with the differentiation of the whole nervous system. The developmental anomalies range from moderate degrees of infantilism to severe degrees of fetalism with abnormal differentiation. The pathology includes also insufficient myelination, spongy edema of the white matter, vascular stasis, and insufficient myelination of the peripheral nerves. Various degrees of hydromyelia, shaft ependymosis, and true syringomyelia are not rare. The most unique developmental defect is an abnormal persistence of the roof plate with junction of the Clark columns, which are found embedded in a broad band of gray matter that forms the posterior gray commissure.

The Brain

Half a hundred brains of patients ranging from birth to 40 years of age were examined. The material is divided into two groups. The first group comprises those cases in which the infant died within the first two years of life, the majority being observations on infants who died a few days to months after birth. The second group presents all cases of patients who had sur-

vived four years. There was no child who had died between 2 and 4 years of age.

The study of the material of the first two years seems of special importance, because it is only such material that can throw light on the question of whether the central nervous system of the mongoloid is abnormal from the very beginning or whether the changes seen in later life are due to degenerative processes occurring after birth.

Group 1: Mongoloid Brain in Infancy

In the following table the brain weights of 24 cases are recorded. The first case, with a given age of 2 days, appears very much underweight, but the child had not only a brain weight which corresponded to the eighth fetal month but had a body length of 40 cm., a weight of the liver of 44 Gm., a weight of the spleen of 4 Gm., of the kidney 10 Gm.—all measurements which indicate that the child was about 2 months premature. In correlation with the other organ weights the brain was normal for the eighth fetal month. The next three brains have also to be considered as normal if the age is corrected and the prematurity taken into consideration.

In the last column of the table, the weights are compared with the average normal, and it is evident that quite a number of weights are within normal range for the first eight months. It is interesting to note that during the second year, all cases have remained on a level which is normal for the first year with the exception of the last case, whose brain weight of 1,050 Gm. may be considered within normal range. Although the brain weight gives only a limited idea of brain development, the observations seem to indicate that the brain development suffers a severe setback during the first year. It will be seen from Table 7 that the arrest is not complete.

The brain of the mongoloid baby is essentially immature, but it rarely shows true malformations. The convolutions are small and are not broad like those seen in older cases. Myelination is not up to date, and the brain appears softer and of a different color. It is frequently yellowish and wax-like. Most outstanding is the smallness of the cerebellum, the retardation of which seems more pronounced than that of the cerebrum.

Concerning the shape of the brain, Fig. 27 shows the brain of a mongoloid infant, 22 months of age. The original fissural and convolutional patterns are not abnormal, but there is flattening of the convolutions and compression of the frontal and temporal poles. All brains of that age group show a more or less pear-shaped outline viewed from above. The basis of the brain shows some peculiarities which are noteworthy. The gyri recti are flattened, having been pressed against the cribriform plate, whereas the lateral parts of the inferior frontal lobes are compressed and slant upwards from the steeply arched orbit roofs; the frontal poles are markedly flattened;

the temporal lobes are distorted and twisted. The cerebellum is pushed forward, and the brain stem originates almost anteriorly from the center of the brain (Fig. 29). In the lateral view the upward push of the frontal poles is striking. The brain convolutions anteriorly from the vertical branch of the sylvian fissure are compressed. There is also striking dis-

TABLE 7.—*Weight of the Brain in Mongolism*

First Two Years of Life

No.	Age	Sex	Body Length Cm.	Weight of Brain Gm.	Corresponds to Chron. Age
1	2 days	F	40	218	8 fetal mo.
2	6 weeks	F	49.5	432	6 weeks
3	2½ months (2 mo. prem.)	M	47	388	2 weeks
4	3 months (1 mo. prem.)	M	52	409	5 weeks
5	2 months	M	—	315	birth
6	3 months	F	—	500	3 months
7	5 months	—	—	352	birth
8	5 months	M	56.5	650	5 months
9	6 months	M	—	760	7 months
10	6 months	F	60	770	8 months
11	7 months	F	65	650	7 months
12	7 months (3 wks. prem.)	M	58.5	550	4–5 months
13	8 months	M	63	790	8 months
14	11 months	F	—	650	7 months
15	12 months	F	—	836	11 months
16	12 months	F	—	730	7½ months
17	13 months	M	70	722	7 months
18	18 months	F	72	678	7 months
19	18 months	M	—	940	12 months
20	18 months	F	—	725	7 months
21	21 months	F	—	820	11 months
22	21 months	M	—	850	11 months
23	23 months	M	—	880	11½ months
24	23 months	M	—	1,050	21 months

tortion of the temporal lobes. The superior and medial temporal fissures are pushed upward. The anterior pole of the temporal lobe is twisted and the superior temporal gyrus compressed.

On horizontal sections the impact of the operculum into the sylvian fissure is conspicuous. The insula is compressed and the anterior part of the sylvian fissure partly fused. The frontal poles appear markedly fused. The frontal poles appear markedly compressed. It is worth mentioning

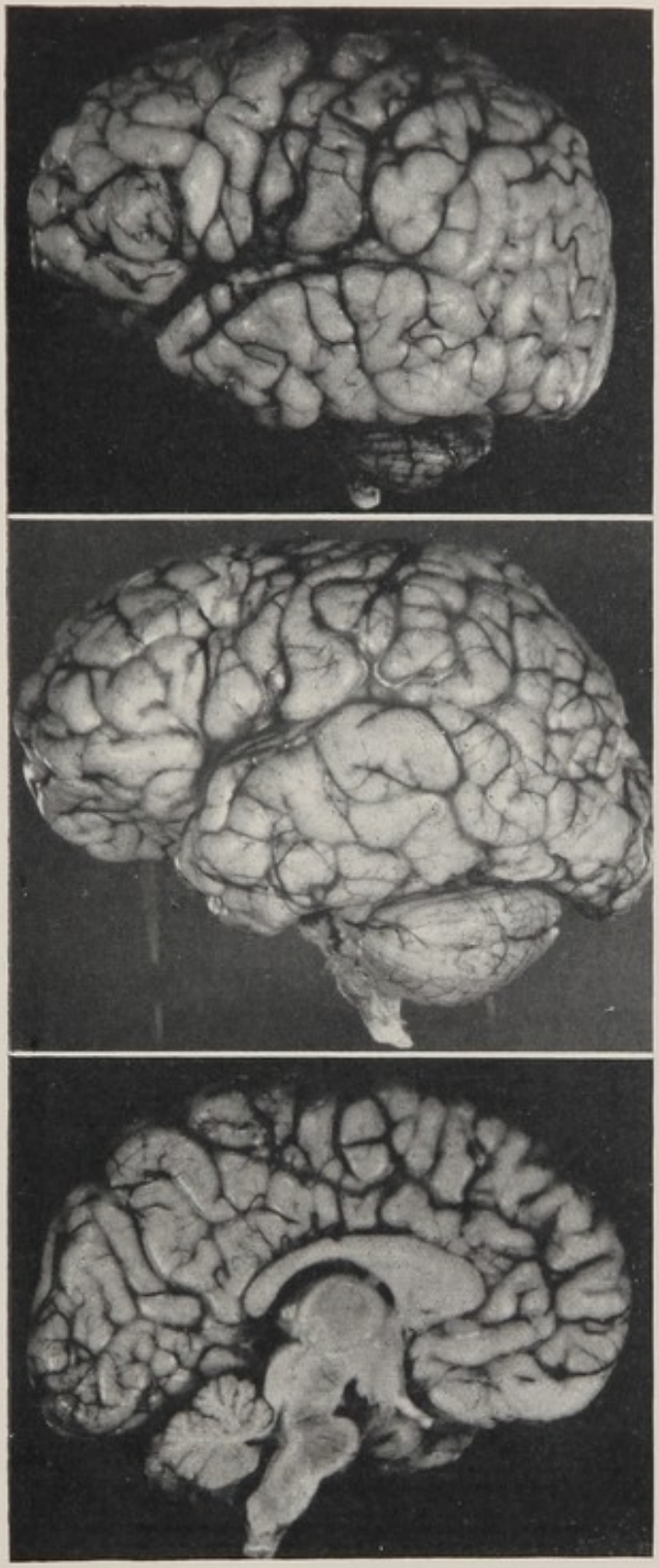


FIG. 27. (Upper) Lateral view of brain of $1\frac{10}{12}$ yr. old mongoloid baby (42/102). Note distortion of fissures of lower temporal lobe; accordion-like coronal fissuration with deviation of all fissures which run normally in a sagittal direction; underdevelopment of frontal poles with retroflexion. Hypoplasia of cerebellum.

FIG. 28. (Center) Lateral view of brain of $4\frac{5}{12}$ yr. old mongoloid girl (40/57). Note hypoplasia of frontal poles with retroflexion; compression of temporal poles with deviation of fissures; compression of occipital poles; hypoplasia of cerebellum. Some of the temporal convolutions are flattened.

FIG. 29. (Lower) Medial aspect of brain seen in Fig. 27. Note short corpus callosum and hypoplasia of brain stem and medulla; marked hypoplasia of cerebellum which lay partly in the foramen magnum.

that at that age the ventricular system is not yet compressed. The pia-arachnoid is more adherent than normal, and the stripping off produces decortication of the convolutions because of adhesion of the pia to the first cortical layer. The microscopic examination revealed that the first layer was thinned out and the margin of the convolutions roughened. In the frontal, temporal, and occipital lobes many convolutions are tightly pressed against each other, and there are many points where the roughened walls of the fissures form glia bridges which close the fissures either partly or completely. The phenomenon of beginning fusion is recognizable on many slides. The tips of many convolutions are tilted, and the surface is flattened.

A microscopic study of the cellular and myelin structures is of great interest. The nerve cells of the cortical layers are dense, but the tissue appears mottled, and stripes devoid of nerve cells run through the cortical layers along the vessels. The loss of nerve cells is not restricted to one layer and is obviously dependent upon the vascular system. Figure 36 shows the dense cortical architectonics of the occipital lobe, but in the center of the picture there is a patchy necrosis around a capillary. Figure 38 gives a high power picture of the cortical cells stained by the Heidenhain iron hematoxylin method. At the right, the ground substance has a pepper and salt appearance. The nuclei of the cells are dark and swollen and are surrounded by a bright halo of watery cytoplasm. At the left, these halos appear larger, and confluence of the edematous areas is recognizable. In the upper part, confluence of the halos is striking and the nerve cells have more or less disappeared. This picture is typical for almost every section from infants below the age of 9 months. In every case, edema of the fibers and loss of cells were recognizable. The cells of the substantia nigra, which is not pigmented at that age, appear well developed but are in a stage of swelling or shrinking.

The myelin fibers show striking pathology (Fig. 37). Under low power the white matter appears "moth-eaten," the fibers being interrupted by numerous small patches of necrosis. The vascular system is hyperemic. Around many vessels, deposits of darkly stained corpuscles are recognizable (Fig. 39). Fractions of myelin and fat substances are frequently encountered. The demyelination of the centrum semiovale is striking; especially involved is the white matter of the frontal, occipital, and temporal lobes; less involved are the optic radiation and the radiation of the corpus callosum in contrast to the patchy demyelination of the association fibers.

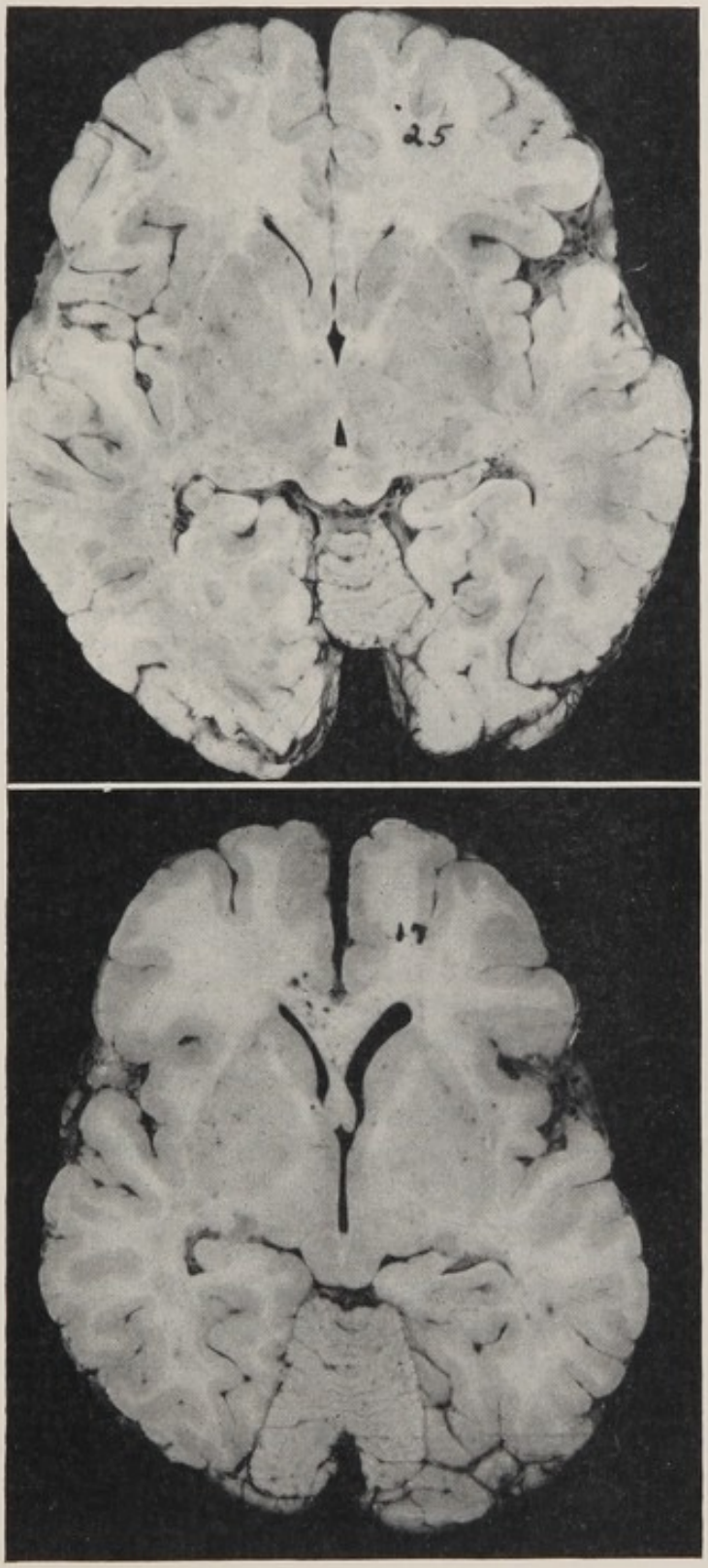


FIG. 30. (Upper) Horizontal section through brain (8 yr. old mongoloid). M. A., $2_1^6_2$. Note large size of basal ganglia with compression of lateral ventricles. The walls of the right ventricle are partly fused. Several areas of ectopic gray matter in occipital lobes.

FIG. 31. (Lower) Horizontal section through brain ($9_1^8_2$ yr. old mongoloid). M. A., 9 mos. Note smallness and asymmetry of lateral ventricles; primitive brain with "simple patterns." Note underdevelopment of frontal lobes. Convolutions broad. Gray matter wider than normal; irregular outline.

Five Case Reports

Case 1. CH 40/137. Female mongoloid, 2 months of age. Body length, 49 cm. Brain weight, 376 Gm. Weight after fixation, 249 Gm. Consistency soft. Length of right hemisphere, 9.9 cm.; length of left hemisphere, 9.7 cm.; width of brain, 7.8 cm.; height, 5.5 cm. The brain was asymmetrical; the right hemisphere appeared smaller and was more compressed, particularly in the frontal region. Temporal width of right hemisphere 4.1, of left 4.75 cm. The right occipital pole was separated from the parietal lobe by a deep fissure. The parietal lobe overlapped the right occipital lobe, which protruded markedly beyond the left occipital pole. The cerebellum was very small and covered only partially the lower facies of the occipital lobes, leaving almost a centimeter of the poles uncovered.

The brain was dissected in frontal sections. The convolutions were tightly pressed against each other, leaving no space between the convolutions, and no vessels were found within the sulci. The sections appeared of uniform color, and there was no demarcation between gray and white matter. The lateral ventricles were narrow and compressed, leaving only a slitlike opening, the walls of which touched each other. Toward the occipital pole the compression of the convolutions was even more marked, but the posterior horns of the ventricles were slightly larger.

Microscopic examination: Cerebral Cortex.

Most outstanding was the mottling (focal necrosis) of gray and white matter and congestive stasis of the small capillaries in the tips of the white cores. The "moth-eaten" appearance was so marked and widespread that it could be recognized with the lowest magnification in myelin preparations. The foci of necrosis showed thinning out of the tissue, a vessel being frequently in the center of necrosis. Myelination was little advanced and hardly up to the level of a newborn baby. The internal capsule showed some myelinated fibers, but the peduncles were almost free of myelin. The nerve cells in the cortex were in a state of severe Nissl's disease. The large Betz cells showed little granules of dustlike appearance displaced toward the periphery of the cytoplasm. The smaller ganglion cells showed large, round, vesicular nuclei with only a brim of cytoplasm around. The various stages of disintegration suggested that the small brim was a result of cytoplasmic degeneration and not a primary cell dwarfism. There was a severe degree of cell loss involving especially the third layer. The white matter was retarded in myelin formation, but more conspicuous was focal necrosis of severe degree. The capillaries appeared congested. There were numerous ganglion cells in the white cores.

Cerebellum: Marginal layer still present, consisting of three to four layers of round cells. The Purkinje cells showed large vesicular nuclei. The cytoplasm was reduced to a small brim, which had frequently a round shape and contained little granules.

Cross sections through brain stem, pons, and medulla showed a remarkable picture. The sections were almost 50 per cent smaller than control cases of the same age.

Myelination was well advanced in the tegmentum. The medial lemniscus, seventh nerve, and trapezoid body showed well-advanced myelination. In contrast to the tegmental area, the pontine part showed little myelination, and even the pyramidal bundles were almost free. In the medulla, the decussation of the medial lemniscus, the internal arcuate fibers, and the tractus solitarius were well myelinated, but pyramidal myelination was scanty. The reduction in size was conspicuous and appeared due to underdevelopment of the white matter.

Case 2. CH 40/102. Two months, male. Brain weight fresh, 362 Gm.; after fixation, 440 Gm. Volume, 415 cc. Brain in fairly good shape, dolichocephalic; no

distortion recognizable. Cerebellum very small, definitely undersized. The cerebellar convolutions were covered by the embryonic marginal layer, consisting of four to five layers of small round cells which surrounded evenly the whole arbor vitae, following each convolution into the depth of the sulcus. The distribution of the Purkinje cells was very irregular; they were missing in many areas and crowded in others. There was duplication, and many cells were found arrested in the granular layer. The cells themselves varied in shape. The majority was small and the Nissl substance dustlike. Myelination of the white cores was only fragmentary, and the tips were free of myelinated fibers. The white matter was congested, edematous, and loose.

Pons and medulla were very tiny, myelination was in the very beginning, and only the medial lemniscus appeared dark blue. The olive showed some myelination in the hilus, but little intraganglionar. The olivary cells were small and pyknotic.

On sections through corpus callosum, caudate nucleus, and pars basilaris metencephali, the most conspicuous fact was the lack of myelination in the corpus callosum and the basal ganglia. Only a small part of the fibers of the internal capsule had any myelination. The optic nerves were well myelinated. In the sulcus thalamostriatus, a deep wedge of ependymal matrix was found separating the caudate from the internal capsule for 6 millimeters by a width of 1 millimeter. The ependymal lining was abnormal. There were areas with extensive proliferation, others devoid of any lining. The nerve centers of the basal ganglia were large and crowded with cells, but many appeared immature or faintly stained.

The nerve cells of the cortex showed extreme degree of Nissl's severe cell disease, presenting a textbook picture of this condition. The cells were foamy, vacuolated, the nuclei round; the cytoplasm had lost the Nissl substance, and only a small margin was present, giving the cells a crustaceous appearance. In many nerve cells a single large fat vacuole was present.

Case 3. 35/173. Three months, male. The cerebellum was underdeveloped, the marginal layer still present but only about one to two cell layers thick. Purkinje cells were irregularly distributed and in a state of vacuolation. The white matter was congested and myelination very much retarded.

In the cortex, all cells were in a state of severe cell disease with widespread vacuolation. The small capillaries of the white matter were congested and enlarged. There were many small hemorrhages present. The appearance of the white matter was moth-eaten with multiple necrotic foci. Myelination was fragmentary, the U-fibers were unmyelinated and were outstanding as a light zone meandering beneath the gray matter.

Case 4. 37/6. Five months, male. Weight of brain, 650 Gm. Length, 11.4 cm.; width, 8.9 cm.

The convolutions were small. There was slight flattening upon the parietal lobes. The fissural patterns appeared normal, with the exception of the frontal lobes, which were compressed and pushed upwards with the fissures distorted. The temporal poles were tilted upward, and the direction of the fissures deviated; instead of a horizontal furrowing a vertical, accordion-like fissuring was present. The cerebellum was small, medulla and pons appeared straighter than normal. The microscopic picture was identical with that described in the two previous cases, with the moth-eaten appearance of the tissue outstanding. All nerve cells were in an acute state of disintegration.

Case 5. 40/113. Six months, female. Head was unusually large, 41 cm. circumference. Brain weight, 690 Gm.

The lateral ventricles were definitely enlarged. The ependymal walls were interrupted by nodules of ependymitis. The subependymal layers were gliotic in the occipital lobes. The white matter showed large areas of a demyelinating process. The ganglion cells in the cortex were in a state of degeneration, and in some areas there was definite loss of cells. In the cerebellum the vessels were congested, and there was some venous telangiectasis. The lack of myelination was conspicuous.

Diagnosis: Ependymitis, with one ependymal polyp floating in the enlarged lateral ventricle. Corpus callosum unmyelinated. Very active degenerative process in nerve cells and white matter.

It seems unnecessary to record more cases in detail. Ten cases of this age group were studied in hundreds of microscopic sections, and every case showed essentially the same picture, with the exception of the last recorded one, where the enlargement of the ventricles and extensive ependymitis indicated another pathological process which was not frequently seen in mongolism. In the majority of cases, the ventricles were rather small and narrow. The most outstanding factor in all cases was the presence of degenerative processes in the cortex and white matter. The cortex and white matter were congested and the small vessels enlarged. The tissue had a moth-eaten appearance, with many small foci of softening and necrosis.

Group 2: The Mongoloid Brain in Children and Adults

The weights of brains after the second year of life are shown in Table 8. According to all statistics, the normal brain weight exceeds 1,000 grams at the end of the second year. A large majority of normal children reach this weight at the beginning of the second year. The table shows that with two exceptions, all mongoloid brains weighed below 1,000 grams up to an age of 8 years. In that age group the weight remained on a level equal to the first year of life. After 8 years, practically all cases had a brain weight above a thousand grams, ranging from 1,025 to 1,295 grams. There are four exceptions to that rule: one girl of 12 years, two girls of 16 years. and one male adult of 23 years, whose brain weights ranged from 910 to 990 grams. The table suggests that the brain development is very much retarded, but that some development takes place, although it never reaches the level of a normal person. The brain weight corresponds to the mental development, which remains on the level of children below 6 years of age. I may mention an observation which is of histochemical interest and has certainly some significance, although it is not possible to evaluate it at present. Normal brains gain slightly in weight during fixation and remain stationary after an initial increase. The mongoloid brains often lose more than 100 grams during fixation.

Out of thirty-three cases, ranging in age from 4 years to 40 years, more details are given in Table 9. Six of these cases are fully described.

Case 1. (40/47). 8 year 7 months female. The brain weighed 1,120 grams, which is the average weight of the brain in a 3 year old child. The shape of this brain was

TABLE 8.—*Weight of the Brain in Mongolism*
Above Two Years of Age

Age Yrs.	Sex	Weight	Age Yrs.	Sex	Weight
$2\frac{1}{2}$	M	750	13	M	1,070
$2\frac{1}{2}$	F	983	14	M	1,220
4	M	920	$14\frac{5}{12}$	M	1,100
$5\frac{1}{2}$	M	1,045	15	F	1,184
6	F	875	15	M	1,290
6	—	855	16	F	980
7	M	845	16	—	985
7	M	1,065	17	M	1,140
8	M	800	18	—	1,058
$8\frac{5}{12}$	—	1,290	18	F	1,160
$8\frac{7}{12}$	F	1,120	$20\frac{5}{12}$	M	1,295
$9\frac{8}{12}$	F	1,044	22	—	1,248
10	M	1,225	23	M	910
10	M	1,295	24	—	1,034
10	F	1,025	24	M	1,275
11	M	1,124	26	—	1,120
12	F	1,110	30	—	1,260
12	F	990	37	M	1,080
13	—	1,105			

TABLE 9

No.	R. No.	Age	Sex	Body Length Cm.	Circum. of Head Cm.	Brain Weight Gm.	Developmental Age of Brain Yrs.
1	40/47	$8\frac{7}{12}$	F	$113\frac{1}{2}$	47	1,120	3
2	38/25	$8\frac{8}{12}$	M	113	48.9	1,290	5
3	38/17	$9\frac{8}{12}$	F	116	46.4	1,044	2
4	Met. 1	10	F	108	46.2	1,025	$1\frac{1}{2}$
5	37/10	12	F	126	48	1,110	3
6	38/23	$14\frac{5}{12}$	M	137.3	49	1,100	3
7	Met. 2	14	F	125	45.7	980	1
8	38/32	15	M	134	49.5	1,290	5
9	38/22	$20\frac{6}{12}$	M	160	50.8	1,295	5
10	37/8	$30\frac{8}{12}$	M	142	50.2	1,215	4

typical of every monogloid brain. The frontal lobes were pushed upward, and only the gyrus rectus had kept a somewhat horizontal position. The orbital gyri were compressed by the slanting orbital rocfs. The temporal lobes appeared short, and the fissures, which usually run in a sagittal direction, were distorted, "S"-shaped, or

accordian-like. The occipital poles were flattened, and their outline reflected the upright direction of the occipital squama.

Case 2. (38/25). 8 years 8 months male. The weight of the brain after removal was 1,290 grams. After some weeks' fixation, it weighed 1,192 grams. The color of the brain was yellowish white, instead of the gray color usually seen in a normal brain. It did not have the pronounced waxlike appearance, however, that is sometimes found in mongolism. The shape of the brain was similar to that described in Case 1, but the bulging toward the top and the parietal poles was even more pronounced. The convolutions were flattened upon the convexity, the frontal lobes were displaced upward and backward, the occipital poles were compressed, the temporal lobes distorted. Externally the convolutions appeared broad and primitive. The central parts—the basal ganglia and hypothalamic region—were large and corresponded in size to the normal. Van der Scheer's statement that the hypothalamic region is underdeveloped could not be verified in any case.

Microscopic Examination: The convolutions were irregular and flattened. The first layer was thinned out, roughened, and covered by a thick fibrotic pia-arachnoid membrane containing enlarged congested vessels. Inflammatory signs were absent. Many ganglion cells were pathologic; they showed shrinkage and the axons were swollen. There was marked patchy edema of cells, most marked near the vessels. The cells showed a round unstained halo. In some sections these halos showed confluence and the cells were degenerated within the necrotic area. Myelin stains showed a thin radiation; the tangential fibers were completely absent in the second layer and almost absent in the third and fourth layers. A few association fibers were present, but their number was obviously decreased. In the central and parietal lobes the convolutions were flattened and thinned out, the first layer was atrophic, and the surface rough. Many convolutions had tilted tips, and their cells were piled irregularly. The cells were small and atrophic. A most irregular picture was noticeable in the occipital poles. While the structural patterns were normal upon the top of the convolutions, the structure was confused in the depth of the sulci. Some sulci were indicated by the U shape of the gray matter, but a fissure was not present. From the outside those convolutions appeared broad and simple because of absence of secondary fissures, which were sometimes hidden beneath a tilted top. In the cerebellum the alterations were marked. On a section through the rostral end of the lobus quadrangularis anterior, the convolutions were found flattened and the inferior part compressed. The myelination was incomplete, and many convolutions were without myelinated white matter. In all convolutions the radiation was short, and the intraganglionar fibers were absent. The Purkinje cells were irregular, sometimes piled up and lined in several rows; many cells were degenerated and shrunken. The granular zone was less dense than normal. Capillaries were hyperemic, and perivascular spaces were enlarged. On a sagittal section through the lobus biventer, the peripheral convolutions were stretched and thinned out. Large areas were without white matter because myelination was incomplete. The whole cerebellum appeared compressed, and its shape was different from the normal.

The brain stem measured 24 mm. in width and 19 mm. in height, which is only slightly below normal. The medulla near its rostral end measured 20 mm. in width and 12–13 mm. in height, which corresponded to the normal. The pons measured 20 mm. in width and 20 mm. in height, which was within expected range. It is noteworthy that the substantia nigra was almost without pigmentation, although those cells which were preserved were well developed. The condition corresponded to an age below 4 years, when the substantia nigra is without pigment. Edema and ne-

crosis were present. Special attention had been placed upon a study of the hypothalamic region, and a series of horizontal sections had been made. Although the child was only 9 years of age, the size of the sections corresponded to the size of a normal adult brain. The sections encompassed the nucleus ruber, the medial geniculate bodies, the rostral end of the substantia nigra, the mammillary bodies, the tuber cinereum with the nuclei tuberalis lateralis and the nucleus tubero mammillaris. All these structures and fiber systems were recognizable and most of the cells well developed. There were edema and necrosis of the cells of the oculomotor nuclei. As a whole, the hypothalamic region was better developed and preserved than any other part of the brain.

Case 3. (38/17). 9 year 8 months female. This child was much retarded. The mental age was only 9 months. The brain weighed 1,044 grams, which corresponds to 2 years. The convolutions of this brain appeared simpler than in any other case. They were flattened, and the shape of the brain was markedly piriform, with bulging of the parietal lobes. In a lateral view the brain shape was similar to that of Cases 1 and 2. In horizontal sections simplicity of the convolutions was obvious because of the absence of secondary fissures. The outline of the cortical layer was arcade-shaped and showed many loops toward the white matter. The convolutions were atrophic and pia-arachnoid fibrotic. The occipital lobes showed compression. Microscopic examination revealed the same principal alterations: irregularities in fissural patterns, distortion of convolutions with thinning of the first layer, rough ening of the surface, edema of the cells, and marked edema of the white matter. Some hemorrhages into the gray and white matter were noticed. It might be mentioned that the basal ganglia and the hypothalamic region showed again relatively good development, while the brain mantle was undersized.

Case 4. (M. I.) Ten year old female mongoloid. Brain weight, 1,025 grams. Convolutions were markedly flattened; the consistency of the brain was soft. The frontal and temporal lobes were distorted and short. The temporal lobes showed an increase in vertical fissuration. The furrows divided the temporal lobe in parallel lines, while the main sulci were "S"-shaped. The frontal lobes were displaced upward, and the brain was markedly bulging toward the upper part of the convexity. The occipital poles were compressed; the cerebellum appeared small. From above, the convolutions appeared extremely flattened and broad, sometimes measuring more than 2 cm. in width; the fissures appeared shallow and ran in an irregular course upon the convexity. The occipital poles appeared atrophic. From below distortion of the temporal lobes was most conspicuous; the fissures were irregular and the poles pushed upward and outward. The pons and medulla were normal in size, although the color was whiter than usual. In a horizontal section through the whole brain, the flattening of the convolutions was marked. The tips were "T"-shaped and pressed into every available space. Irregularity of the gray matter was most outstanding. It formed large loops around the bottom of sulci, and sometimes the fissures were entirely missing and the gray matter alone formed an arcade-shaped band. In some sections the gray matter of different convolutions was confluent and formed piles of irregular cells. The basal ganglia were large and well developed.

Microscopic examination revealed the disturbance of the architecture of the gray matter in the depth of fissures. Huge piles of undifferentiated dwarf cells were recognizable. The tops of many convolutions were tipped over and flattened, the first layer thinned out, and the edge rough. Areas 18, 19, and 7 showed a marked degree

of atrophy with irregular surface and fibrotic leptomeninges. Hyperemia and small hemorrhages into the gray matter were seen. A study of the myelination revealed that the medullary cores were scarce. The tangential radiation was in most regions insufficient. It did not penetrate into the more superficial layers, and large sections of the gray matter appeared to be without myelinated fibers at all. The radiation of the corpus callosum and the deeper layers of the white matter disclosed patchy demyelination. The fibers appeared moth-eaten and interrupted, and the tissue was thin and necrotic. The cells of the gray matter were shrunken or edematous. There was extensive, patchy loss of cells, not restricted to any particular layer.

In the cerebellum the scarcity of the myelinated fibers was conspicuous. The distribution of the Purkinje cells showed irregularities; sometimes the line was duplicated. Many Purkinje cells were arrested within the granular layer on their way toward the borderline. The brain stem, pons, and medulla were normally developed; the substantia nigra was almost without pigmentation, while the locus caeruleus was pigmented.

Case 5 (37/10). This mongoloid girl died at the age of 12 years. Brain weight, 1,110 grams. Brain volume, 1,080 cc. The shape of the brain was similar to those previously described. The occipital poles appeared flattened, the frontal lobes pushed upward, and the convexity of the brain was bulging. Color of the brain was yellowish white and waxlike (color of pons, white). The blood vessels were small and scarce.

On microscopic sections there was a sharp contrast recognizable between the white and gray matter, which appeared broader than normal. In sections near the frontal poles the fissuration appeared normal, and the differentiation of the gray matter showed few anomalies. On sections through the superior frontal gyrus and the central gyri, the convolutions were broad and the fissures shallow and incomplete. The stratum corticale appeared unusually broad and showed many loops bulging into the white matter. The white cores were short and stout, the tips of the convolutions tilted, and the cortical layers flattened. The surface of the first layer was rough and thin. In this case the irregularities of the fissural patterns were most marked upon the occipital lobes. Here tilting of convolutions was especially frequent, and areas of gray matter without medullary branches were conspicuous. Some submerged microgyri were recognizable, and many secondary fissures were not separated. The temporal lobes were flattened at the base of the brain; the superior temporal gyrus was pressed against the insula, which was flattened. Sections through the basal ganglia and the hypothalamic region revealed that the central parts of the brain were large and well developed; the nuclei of the hypothalamic region were distinct, and no abnormality was noticeable in these regions. Brain stem, pons, and medulla showed a normal development, but the cells of the substantia nigra—which were well developed—were without pigmentation. The myelination of the cortex appeared retarded. In the frontal lobes, tangential fibers were almost absent, and even the association fibers were very little developed. The radiation penetrated only into the deep layers of the gray matter. The incomplete myelination was most conspicuous in the cerebellum, where the medullary radiation was scarce and thin; no infraganglionar fibers were myelinated, and large areas of cerebellar gyri appeared without myelinated fibers. The arrangement of the Purkinje cells was irregular, with many piled up or with rows of them duplicated. In other sections the Purkinje cells were rare. Their development appeared unequal. Many were found without axons, and others were sclerotic.

Case 10. (37/8). 30 year 8 months male. At autopsy the brain weighed 1,215 grams. Convolutions were fairly well preserved but flattened out, especially upon the convexity. The cerebellum appeared small. In sections the brain revealed a high degree of atrophy with fibrosis of the pia-arachnoid and marked sclerosis of the convolutions. The nerve cells were scanty. Myelination appeared thin and corresponded to that of a child of 2 years.

Summary of Observations

In spite of the fact that previous investigators were not able to reveal consistent pathology of the central nervous system in mongolism, the available material indicates that mongolism is associated with a particular neuropathology which is as typical as the clinical picture itself.

For the sake of distinction, the alterations may be divided into two groups: (1) pathology of development, (2) pathology of brain metabolism.

The developmental disorder is most readily understood from a study of the cases beyond 4 years of age.

Every brain of that group had the same shape, which is distinguished by an upward position of the frontal poles, the short, distorted temporal poles, and the steep occiput. The cerebellum also had a peculiar shape: it was not only smaller in most instances, but almost triangular, with the apex pointing in a downward direction. From a study of mongoloid brains there can be no doubt that the outline of the frontal lobes, the distortion of the temporal lobes, and the compression of the occiput are the result of the impact of the pathologic skull. It seems, therefore, impossible to accept van der Scheer's idea that the skull formation is due to brachycephaly. The brain is so soft and variable in shape that, even post mortem, it is difficult to preserve its original shape and special attention has to be paid to conservation. Moreover, the distortion of the gyri and fissures, the compression of the basis, and the extension of the convexity are obviously of mechanical origin. The same form can easily be reproduced by experiments with rubber balloons. The bulging of the brain toward the top and toward the sides, with the typical rounding out, is due to the fact that the membranous bones over the convexity yield more readily to pressure than the firm skull basis.

Related to the distortion of the brain is the confusion of the convolutional and fissural patterns. It has not escaped the attention of previous investigators that the mongoloid brain seems to have especially broad and simple convolutions. I mentioned the opinion of Sergio Levy, who considers the brain of mongoloids as a "biological reversion toward those seen in lower primates." This view was also expressed by Comby, who found that "secondary fissures are rare and shallow, in fact the brain is, so to speak, simplified, it recalls the brain of an animal, a monkey or a ruminant." My observations indicate that this explanation is not correct.

It has been one of the main subjects of my studies to clarify the discussion about the convolutional and fissural patterns. If the pia-arachnoid is stripped off the brain and the leptomeninges are entirely removed from the sulci it becomes obvious that the main fissural patterns are normal, and a similarity to patterns of lower animals was in no case present. All fissures which are in a sagittal direction appear distorted; they are either "S"-shaped or deviate upward, accordion-like. About the inferior and lateral parts of the frontal lobes and about the occiput, the folding is increased through upward thrust, while the convexity is stretched like an arch by shortening of the basis. It is true that the convolutions upon the convexity appear simple and broad, but an analysis of these convolutions reveals that the dividing fissures are either distorted or submerged beneath the convexity. The flattened convolutions have a drumstick shape, and fissures have disappeared by fusion of their walls. This phenomenon of fusion of the fissures is, to my knowledge, not mentioned by previous investigators, but it is one of the most characteristic features of the mongoloid brain. There was not a single brain beyond an age of 4 years in which this fusion of fissures was not present. New evidence for this phenomenon has recently come from L. O. Morgan, who restricted his work to a study of the hypothalamic region in mental deficiency. He observed fusion of the walls of the third ventricle. In one of his cases "the ependyma was obliterated in the center of this fused area, allowing the hypothalamus to become continuous across the midline."

The question of whether submergence and fusion of the fissures which are seen in older mongoloids are present in the mongoloid infant was of special interest. Their presence in the latter would indicate that the broadening of convolutions and the fusion of fissures is a prenatal abnormality. If they were not present, it might be due to a pathologic process which obliterates the original fissural patterns. A study of the brains of mongoloid babies showed that none of these brains revealed the broadening and simplification. In all of them the fissural patterns were normal and the convolutions were not broad, although some flattening upon the convexity was noticeable.

Microscopic examination decided the question of whether the abnormality of convolutional patterns was a malformation or the product of disease. It was obvious that in the young mongoloids no abnormality of fissural patterns was noticeable. A study of the walls of the fissures and convolutional edges, however, revealed that in mongoloid infants beginning fusion is noticeable. Especially in the frontal lobes, many convolutions showed a roughening of the margin, and both walls of fissures showed felt-like proliferations of fibrous glia. Even complete fusion could be noticed. In infant brains one finds flattened convolutions with the top of each mush-

room-shaped and the margin pressed upon the neighboring convolution. The tissue reacts with a proliferation of glia at the edges and degeneration of ganglion cells in the cortical layers. These pressure marks resemble warts. In older mongoloids these warts are frequently fused with the neighboring convolution, and tissue bridges are formed which overlap the fissures.

Summarizing the disorder of convolutional and fissural patterns, there are three factors which account for the pathology: First, submerging of fissures through flattening and distortion of convolutions; second, fusion of fissures which were previously separated; third, suppression of secondary fissures through arrest of development. In this instance, one may observe an arcade-shaped outline of the architecture, but invagination of the surface did not take place.

This disorder of the "perigenesis" is not without influence upon the cortical tectonics and myelination. The different cortical areas are well differentiated. The disorder of the fissures, however, is associated with a confusion of the cortical strata, and the cortex reveals irregularities of the gray matter. The pathology consists of piles of small nerve cells, which were considered "embryonic cells" by some investigators (Weygandt). These cells are more numerous in older mongoloids. It is hard to believe that embryonic cells would remain in the same condition for an indefinite period of life. I consider them as cells stunted through degeneration. Sections which are grossly normal show a rather dense arrangement of nerve cells, which correspond in their architecture to the normal after birth. The infantile cortex is denser in cells and appears somewhat broader. With increasing differentiation, the space between cells becomes larger while the individual cell appears more developed. In mongolism the cortex shows infantile patterns, with a broader cortical stratum and denser cell arrangement, not to speak of the cell loss, which will be discussed later.

The pathology of myelination is conspicuous in every case. Tangential fibers are either absent or poorly developed. The gray matter is almost without myelinated fibers because tangential fibers are not present and the radiation does not penetrate into the superficial layers. In the younger mongoloids, lack of U-fibers is conspicuous, leaving a bright band between the dark medullary core and the gray matter. Especially conspicuous is the disorder and underdevelopment of myelination in the cerebellum. The fibers are scarce and end far away from the tip of the folia, therefore leaving a rather large area of the stratum granularis without myelinated fibers. Supra- and infra-ganglionar myelination is absent. It is of interest to note that the disorder of cyto-architectonic and myelination is more obvious in the cerebellum, the pons, and the medulla than in the pallium. Purkinje cells are lined up in several rows or are absent, and many are found arrested

within the stratum granularis. A "tuber flocculus" described by Gans was not seen in my material, but irregularities in the flocculus were frequently found.

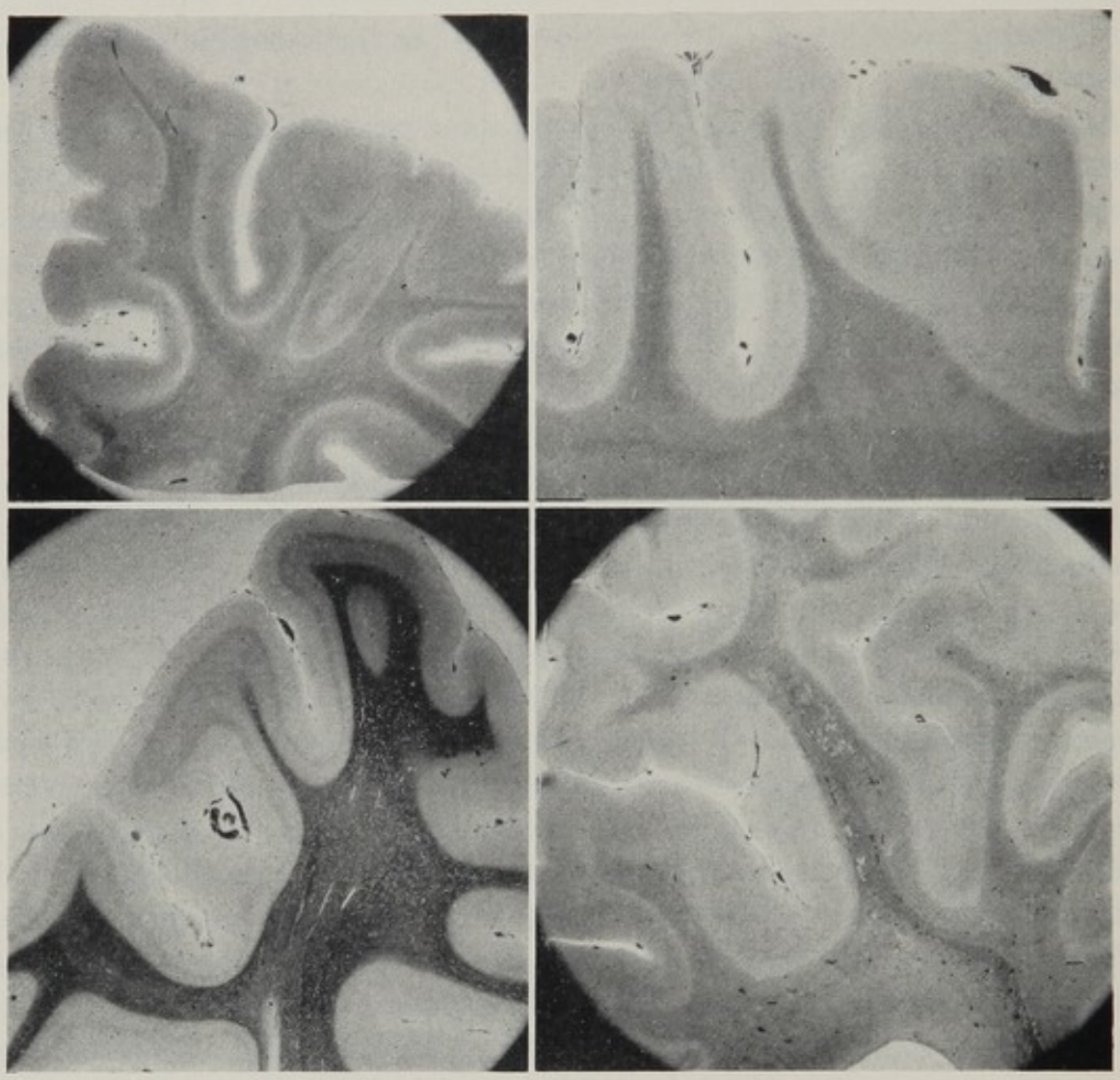


Fig. 32. (Upper left) Frontal lobe (7 mos. old mongoloid male). Note complete absence of myelination of U fibers; unusually broad gray matter; absence of myelin radiation; white cores poorly myelinated.

Fig. 33. (Lower left) Occipital lobe (14 yr. old mongoloid male). Note absence of U fibers and deficient myelin radiation in gray matter; poorly developed white cores; tipping over and flattening of convolutions with submergence of others.

Fig. 34. (Upper right) Parietal lobe, myelin stain. Note deficiency of white cores and unusual size of gray matter.

Fig. 35. (Lower right) Occipital lobe, myelin stain, low power (15 yr. old mongoloid). Note moth-eaten appearance of white matter and focal devastation of gray matter; extremely underdeveloped myelination and lack of U fibers.

Pathologic changes of a general character include in the first place the absence of nerve cells in the cortex. Davidoff, who put emphasis upon this observation, felt that the loss was most marked in the third layer, but other observers (Waverley research, Meyer-Jones) indicate that the loss

of cells is not restricted to any layer. The main problem is whether absence of cells is due to a degenerative process or to a primary failure of development. Davidoff found evidence of degenerative processes only in

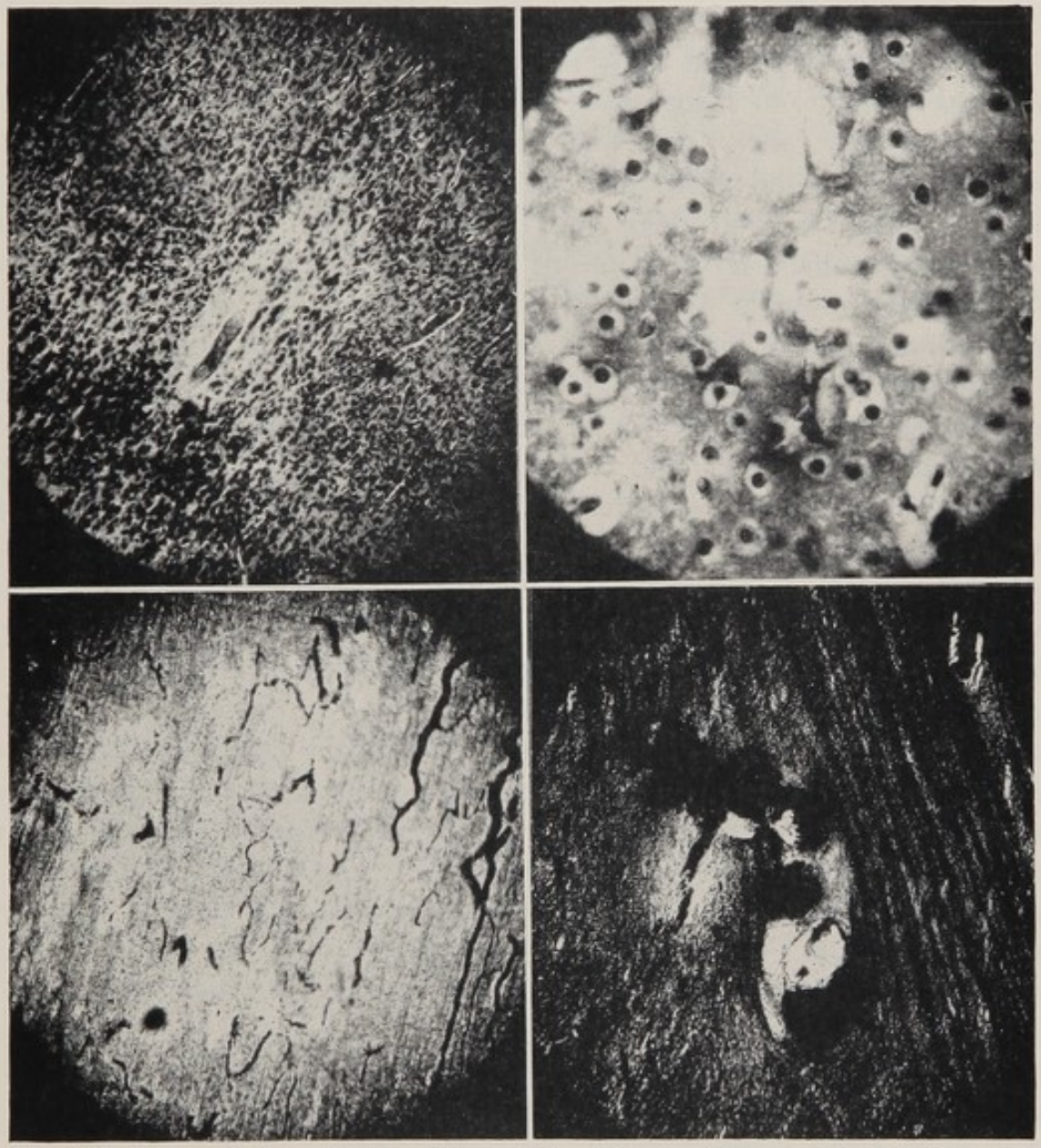


FIG. 36. (Upper left) Cortex, Nissl stain; 7 mos. old mongoloid baby. Note crowding of nerve cells; marked perivascular necrosis and loss of cells.

FIG. 37. (Lower left) White matter, myelin stain; 7 mos. old mongoloid baby. Note marked perivascular demyelination with loss of myelin and oligodendro glia.

FIG. 38. (Upper right) Watery dissolution of nerve cells in cortex, Heidenhain iron hematoxylin stain; 5 mos. old mongoloid baby. Marked brain edema.

FIG. 39. (Lower right) Perivascular necrosis with heavy calcification in white matter; a 5 mos. old mongoloid baby. Weigert myelin stain.

his first and second cases, in which myelin-bearing granular corpuscles were found, and he noticed that it may be of significance that those two brains were both from patients under 1 year of age:

It is not unlikely, therefore, that a degenerative process affecting the ganglion cells, particularly those from the third cortical layer, occurs very early in life, and that in my youngest patients the last traces of this are still in evidence in the form of granular corpuscles filled with the remains of the myelin from the axons belonging to the degenerated cells.

This degenerative process is by no means completely at an end after the first year of life. In many cases degenerative processes are present and still in progress. Meyer and Jones also observed those degenerative processes and emphasized that older and very recent alterations were always found, refuting Davidoff's view that the degeneration was at an end. Even Bourneville's collaborators (Philippe and Oberthur), who studied a number of mongoloid brains in 1902, 1903, and 1904, observed those degenerative processes and gave a marvelous description which is still worth reading.

From a study of mongoloid brains through all age groups it is, therefore, evident that degeneration of brain tissue, loss of nerve cells, and atrophy of the cortex with gliosis and pachymeningeal fibrosis are always present. In some of my cases a coagulation necrosis was marked with older and recent hemorrhages into the tissue. Although this extreme degree of deterioration was not seen in all cases, minor degrees of the same alteration were frequently encountered. By demonstrating the ground substance, the speckled pepper and salt appearance of the tissue is impressive. Under lower magnifications the tissues appear mottled, thinned out, and necrotic. Islands where the ground substance seems still intact alternate with necrotic patches. On the tissue islands, nerve cells in all stages of degeneration are noticeable. The cytoplasm of many nerve cells forms a bright halo around the nucleus; the more edematous the cells are, the brighter and larger the halo. In many patches these halos are confluent and form a large area of necrosis. It is suggested that the dropping out of cells, which is recognizable in every case, is due to a continuous edematous submerging of nerve tissue in which cell after cell meets death by suffocation. In Nissl preparations various stages of misplacement of Nissl substance to the edge, formation of vacuoles, and chromolysis are present. Many cells are loaded with fat. Similar observations are mentioned by Meyer and Jones, Canavan, and Philippe and Oberthur, who noticed vacuolated cells also. It seems of importance to trace degeneration of nerve cells into its early stages, and in young mongoloids below 1 year we encounter, indeed, the first stages of this pathology. At that age the loss of cells is associated with cell changes of varying severity. Acute degeneration is general and occurs within a rather densely piled cortical stratum. Almost every necrosis can be traced to a vessel in the center. The material indicates that edema of the nerve tissue with asphyxiation of the cells is one of the most important pathologic features. It is, therefore, evident that the loss of ganglion

cells in mongolism is due to a continuous dropping out of cells, owing to a pathologic condition of the brain. The remaining nerve cells are in a stage of severe disease, either ischemic or sclerotic, with all those changes described by Nissl, Spielmeyer, Cobb, and recent investigators of asphyxiation. In regard to the localization of cell destruction, the frontal, temporal, and occipital lobes seem mainly affected, but in older mongoloids there is no part without involvement. It is, however, worth mentioning that the degeneration of the basal ganglia and the hypothalamic region is less conspicuous than the cortical destruction. Especially in the mongoloid infants below 1 year, the cells of the hypothalamic region were well preserved, while at that age the dentate nucleus and the fascia dentata of the hypocampus showed a marked degree of disintegration. In six cases of Morgan, whose patients were between an age of 6 and 28 years, "a very striking feature in most of these cases was the normal appearance of the cells in the nuclei of the hypothalamus." This adds new evidence against the view of van der Scheer and the opinion of those authors who assume that the endocrine disorder in mongolism may be due to a primary degeneration of the hypothalamic region.

Similar changes of a "metabolic character" are also seen in the white matter. Patchy necrosis, with softening and loss of myelination, was evident. It was, again, of interest to determine whether these changes are consistent with the pathology of mongolism and are present in infants below 1 year. Meyer and Jones included in their material one case of a mongoloid male infant, aged 10 months. They noticed some rarefaction in the myelin. There was also glia proliferation in subependymal areas and perivascular sclerosis throughout the white matter as far as it could be ascertained. Davidoff included two cases of infants in his description. The first was a mongoloid female child of 11 months. In the white matter he noticed

> several areas of demyelination affecting at times only a few fibers, which could be followed for a considerable distance in myelin sheath preparations. Along the path of these degenerating fibers were granular corpuscles, either singly or in groups, staining brilliant red in preparations for fat and also taking the deep blue tone of the myelin fibers. These areas were almost wholly confined to the neighborhood of the ventricular system. A somewhat larger collection of granular corpuscles [his Figure 5] seemed to differ in character from the others; the cells, in addition to vacuoles representing fat, also contained pigment which gave the iron reaction and showed a pseudocalcareous reaction in hematoxylin and eosin preparations.

In the second case, a male infant of 6 months,

> numerous small areas of absent myelination were present. Here also, as in Case 1, the path of the absent myelin was strewn with granular cells staining deeply for fat as well as the hematoxylin in the myelin sheath preparations.

Those areas were also described by Philippe and Oberthur.

A histologic analysis of the alterations in the white matter reveals that under low power the changes are best described as "moth-eaten" and are areas of focal softening. That the enlargement of the perivascular spaces is not artificial is clearly indicated by homogeneous masses which fill the spaces or fat corpuscles or calcium. A network within the spaces is frequently preserved. The concrements are frequently referred to as calcium or pseudocalcium on account of the staining reactions. Davidoff and Meyer and Jones have analyzed those areas of necrosis and have demonstrated that they are filled with granular corpuscles and fractions taking the fat stain. Meyer and Jones applied the Holzer stain and demonstated that there is a definite scarring around the vessels. The glia fibers were increased.

A study of the vascular system indicates that the vessels of the brain are generally small. There is no striking pathology, but in Nissl preparations the intima stands out as a broad, translucent, jelly-like band, undoubtedly swollen. The intima stains deeply black by the tannin-silver method, the muscularis appears homogeneous, and cells are difficult to recognize. The venous system generally shows enlargement and congestion; stasis is marked in the capillaries of the white cores and gray matter. In some cases the vascular walls are entirely homogeneous or degenerated. Intima proliferation and arteriosclerosis were not found, although perivascular calcification was frequently seen. Small hemorrhages into the necrotic tissue were not rare.

Synopsis of Observations

The study of the central nervous system indicates that mongolism is not a "primary" mental deficiency or agenesis in the sense which was explained in the introduction. The disorder is dependent upon a number of pathologic processes which interfere with development and produce arrest of growth and differentiation. The histology of the central nervous system indicates circulatory deficiency, asphyxiation, edema, and brain swelling. These factors produce a widespread disease of the nerve cells, which react with ischemic changes and complete loss, a demyelination of myelinated fibers and arrest of new myelination, signs of pressure upon the convolutions with disorder of the convolutional and fissural patterns, internal pressure with compression of the ventricular system and frequently fusion. Eventually general atrophy, sclerotic changes, and degeneration are found.

The alterations reported above—focal necrosis, demyelination, ischemic cell changes, and Nissl's severe cell disease—are well known through a number of experimental studies and clinical observations. All recent investigators agree that hypoglycemia, carbon monoxide poisoning, asphyxia, and ischemia—in short, all conditions associated with central anoxia—

produce the same type of histologic alterations in the brain, varying according to the duration of exposure and time of survival.

The important conclusion which we may draw from the study of the mongoloid brain is that the mental deficiency is the result of a chronic deficiency of oxygenation or sugar metabolism. The brain reveals the results of chronic anoxia, most marked in those babies who died in the first few months after birth. In older patients more evidence of devastation and atrophy is present without the acute signs of metabolic deficiency. Some of the deficiency of brain metabolism seems to date back to the stages of prenatal morphogenesis, and we observe some indications of interference with normal brain differentiation. The disorder of brain metabolism during the most important period of development results in dwarfism and stunted growth of the nervous system according to the same biological laws which govern the arrest of physical growth.

Cretinism

Alterations in the Central Nervous System

The pathology of the nervous system of cretins is less well known than that of mongoloids. Not only is cretinism rare, but few cretins succumb to acute infections in infancy and childhood. If an adult cretin dies, the observations collected at autopsy are difficult to evaluate because alterations which developed later in life are likely to obscure the original developmental disorder. It must be expected that the pathology is not uniform, and proper consideration must be given to the type of cretinism—thyroid aplastic, postinfectious, endemic. It is unfortunate that little use has been made of the experimental material of thyroidectomies, despite its abundance, to investigate the changes which take place in the nervous system after removal of the thyroid. Observations on endemic cretinism are more numerous. Most of the studies, however, were made many years ago, when relatively little was known of the general neuropathology of mental deficiency and growth disorders.

From the available material one may say that the effect of thyroidectomy is a metabolic one, acting through channels of blood supply and lowered brain metabolism. Since intelligence may be restored in myxedematous adults, even after a considerable lapse of time, we may assume that the alterations are reversible, if hypothyroidism has not lasted too long a time.

The first changes which are observed in the brain are vascular stasis, enlargement of the small vessels, and edema. The white matter becomes spongy, and the fibers are separated by fluid. Similar changes, though of less extent, are recognizable in the gray matter, and the nerve cells react with alterations similar to those seen in experimental asphyxiation. If

hypothyroidism continues, these changes become irreversible, according to duration and degree of metabolic disorder. The result is severe cell loss and severe cell disease. In the end stages the cortex will be found devoid of nerve cells, with cell shadows and stunted nerve cells as the only remnants.

From observations on a few experimental animals which the writer has studied, and a few autopsies, it may be said that the various regions of the brain are affected in the same sequence that is seen in anemic or anorexic asphyxia. The cerebellum, especially the dentate nucleus, and the Purkinje cells are very vulnerable. The fascia dentata of the hippocampus and the large Betz cells suffer severely and are reduced after longer lasting hypothyroidism. As a whole, one cannot expect to find too many changes in persons or experimental animals exposed to athyroidism for a limited period of time and previously in good condition.

The brain of the thyroid aplastic cretin shows variations according to the severity of the prenatal developmental disorder. The congenital condition can be associated with agenesis or hypoplasia of the brain, and the observations resemble those reported in mongolism. The spinal cord reveals asymmetry and a large central canal or ependymal proliferations. The white matter is deficient in myelination, and in children myelination is delayed. As a whole the brain is larger than in mongolism. Severe neurological complications are seen in as many as 50 to 70 per cent of the congenital cretins. Lesions in the basal ganglia are apparently similar to those which are found in severe anemias of childhood (erythroblastosis), and one may wonder whether the anemia which is frequently associated with cretinism does not have bearing on this type of pathology.

If athyroidism develops after birth the development of the brain is arrested at a corresponding age level, and the condition of the brain reflects the developmental age at the onset of the disorder. In contrast to mongolism, a certain degree of hydrocephalus is common with myxidiocy. The cretin tends to have a large head. Brain swelling and edema alone do not produce enlargement of the skull cavity, but the skull yields readily to even a moderate degree of internal hydrocephalus.

If cretins are adequately treated, their mentality is restored to the mental level with which they are endowed by heredity. This means that treatment cannot improve the level of achievements beyond heredity. Many a cretin will remain feebleminded in spite of early and efficient treatment. At autopsy such cases reveal brain patterns which are bestowed upon the cretin by his ancestry and not by cretinism. In areas of endemic cretinism every feebleminded person is likely to be considered a cretin, and the great variety of observations which are reported is due to the fact that so many

anomalies are described which have no relationship to cretinism. De Quervain has pointed out that

> if only the most extreme cases are seen, the problem appears simple and uniform, but if there is opportunity to observe cretins by the dozens and hundreds, ranging in degree from creatures below the level of animals up to somewhat simple citizens who are able to vote and involving all the variations between dwarfism and normal growth, then the problem appears extremely complicated, and one is inclined to ask what is the common denominator for all these conditions.

The common denominator is a metabolic brain pathology produced by the effect of chronic anoxia (anemia, histotoxic, and neurohumeral). The lowered brain metabolism leads to stunted growth, if it is present during the period of brain development. It leads to arrest of growth, if acting upon a brain after organogenesis has been completed. The great variations in structure are due to individual variations upon which the metabolic disorder has encroached, but which are not completely leveled by the extrinsic factors.

BIBLIOGRAPHY

Benda, Clemens E.: The Central Nervous System in Mongolism. Am. J. Ment. Def. **45:** 42–47, 1940.

Bourneville, Philippe, and Oberthur: Idiotie du type mongolien. Recherches cliniques et thérapeutiques sur l'epilepsie, l'hysterie et l'idiotie. **22:** 137–51, 1902; **23:** 1–23, 1903; **24:** 149–75, 1904.

Brousseau, K., and Brainerd, H. G.: Mongolism. Williams & Wilkins, 1928.

Davidoff, Leo M.: The Brain in Mongolian Idiocy. Arch. Neurol. **6:** 1229–57, 1928.

De Quervain, F.: Cretinisme. Schweiz. Arch. Neurol. **14:** 3, 1924. Über die Veränderungen des Zentralen Nervensystems bei Experimenteller Cachexia Thyreopriva. Virch. Arch. **133:** 1893.

Gans, quoted by Davidoff.

Gildea, Edwin, and Cobb, Stanley: The Effects of Anemia on the Cerebral Cortex of the Cat. Arch. Neurol. **23:** 876–903, 1930.

Higgins, H.: Am. J. Dis. Child. **53:** 1129, 1937.

Hoff, E. C., Grenell, R. G., and Fulton, J. F.: Histopathology of the Central Nervous System after Exposure to High Altitudes, Hypoglycemia and Other Conditions Associated with Central Anoxia. Medicine **24:** 161, 1945.

Isenschmid, Robert: Histologische Veränderungen im Zentralen-Nervensystem bei Schilddrüsenmangel. Frankf. Ztschr. Path. **21:** 321–336, 1919.

Levi, Sergio: Studio sulla Morfologia cerebrale nella Idiozia Mongoloide. Riv. Clin. Pediatr. **34:** 769, 1936.

Lewey, Frederic H., and Drabkin, David L.: Experimental Chronic Carbon Monoxide Poisoning of Dogs. Am. J. M. Sc. **208:** 502–11, 1944.

Lotmar, F.: Histopathologische Befunde in Gehirnen von endemischem Kretinismus Thyreoaplasie und Kachexia thyreopriva. Ztschr. ges. Neur. **146,** 1933.

Meyer, A., and Jones, J. B.: Histological Changes in the Brain in Mongolism. J. Ment. Sciences **85:** 206–21, 1939.

Morgan, L. O.: Alterations in the Hypothalamus in Mental Deficiency. Psychosomat. Med. **1:** 498, 1939.

Ranson, S. Walter: Edward K. Dunham Lectures, Boston, 1940.

Roessle, Robert: Wachstum und Altern. Lubarsch-Ostertag: Ergebnisse d. allg. Path., 1923, 20, II Teil.

Scholz, Wilhelm: Cretinismus, Berlin, 1906.

——, and Zingerle, Herm.: Über Gehirnveränderungen bei Kretinismus. Ztsch. Jugndl. Schwachsinns. **3:** 307, 1910.

Southard, E. E., Fernald, Walter E., and Taft, Annie E.: Waverley Researches in the Pathology of the Feebleminded. Memoirs of the Am. Acad. Arts & Sciences **14:** 2, 1918.

Stewart-Wallace, A. M.: A Biochemical Study of Cerebral Tissue and of the Changes in Cerebral Oedema. Brain **62:** 426–38, 1939.

Tredgold, quoted by Penrose: Mental Defect, p. 100, Farrar & Rinehart, New York.

Van der Scheer: Beiträge zur Kenntnis der mongoloiden Missbildung, S. Karger, 1927, Abhandl. Neurol. & Psych. **41:** 1–162.

Waverley Researches in the Pathology of the Feebleminded. Research Series, Memoirs Am. Acad. Arts & Sciences: 1, May 1918; 2, Dec. 1921; 3, 1938; 4, 1940; 5, 1941.

Weygandt, W.: Der jugendliche Schwachsinn Ferd. Enke, Stuttgart, 1936.

Wilmarth, A. W.: Report on the Examination of One Hundred Brains of Feebleminded Children. Alienist & Neurologist, October 1890.

CHAPTER V

ENDOCRINE PATHOLOGY

The Thyroid Gland

In Mongolism

When, at the end of the last century and at the beginning of this one, mongolism was recognized as a morbid entity and separated from cretinism, some interest was centered on the pathology of the thyroid. Several of the earlier reports mentioned a "normal" thyroid, apparently in contrast to the thyroid in cretinism, which shows conspicuous signs of pathology. These earlier reports had few facts to rely on as to the structure of the normal thyroid and the general patterns of endocrine pathology. In the light of present day knowledge, those reports are of little value. Bourneville, however, reported definite changes, mostly of a degenerative nature. In recent publications Gordon and Pennacchietti have reported pathology. The latter called attention to the similarity between goiter in childhood and the alterations which he saw in his mongoloid material. All these reports were based on few observations only. Thyroid therapy had been tried, but on the whole with little success, and the thyroid as a problem in mongolism had been discarded. In 1939 I first gave a report on the thyroid in mongolism based on a study of 14 cases. In the meantime, the material has increased to more than 48 cases.

The study of this material establishes beyond argument that the thyroid in mongolism is profoundly abnormal. Although the term "colloid goiter" is used to indicate the histologic appearance, the term does not mean an enlargement of the glands. The weight of the thyroid is far below normal, and if one considers the fact that it is impossible to separate correctly the glandular tissue from the surrounding connective tissue, the given weights are still too high. The weights of 24 cases are given in Table 10.

The hypoplasia is impressive at autopsy, and it is sometimes difficult to find the gland at all. The location is rather low around the trachea, and thyroid and thymus are frequently separated incompletely.

There are few careful observations on the weight of the thyroid of normal persons. Hertzler in his recent book writes of "the gland weight 2.5 Gm. at birth and 10 Gm. at an age of fourteen years. The remainder of weight, say 15 grams, develops after puberty up to twenty-five grams average weight at twenty-eight years of age." For the adult thyroid, a weight of 20 to 30 Gm. is generally considered normal, and a weight of between 2 and 3 Gm. is normal at birth. I am not aware of any data on the normal

thyroid weight during infancy and childhood in the sea border states of the United States. For this reason I collected the weights of 40 control cases of children, and found the weights which are given in Table 11.

This table gives a reliable minimum which may be expected in the average child, although the weights it contains are probably low, because some feebleminded children were included. However, the table reflects fairly well how much one can expect in the average. Comparison with a weight table prepared by Eggenberger for several European countries shows that the weights given above can be generally accepted.

TABLE 10.—*Weight of Thyroid in Mongolism**

Case No.	Age	Sex	Weight Gm.	Case No.	Age	Sex	Weight Gm.
	Mos.				Yrs.		
1	1.5	F	1.0	13	12	F	9.0
2	2	M	2.3	14	14.5	M	7.0
3	5	M	1.1	15	15	M	6.0
4	6	F	0.5	16	16	M	7.7
5	7	M	2.5	17	16	M	11.0
6	7	F	2.0	18	17	M	5.0
7	19	M	2.0	19	17	M	11.0
	Yrs.			20	18	M	3.5
8	4.5	F	1.0	21	20	M	23.0
9	8.7	F	5.0	22	20	M	19.0
10	8.8	M	2.5	23	28	F	5.5
11	9.8	F	4.5	24	31	M	3.5
12	10	F	9.8				

* Including capsule and connective tissue.

These tables demonstrate that the thyroids of mongoloids are extremely underdeveloped. The hypoplasia varies in its extent, but it was present in all cases with the exception of two described later. The most extreme degree of hypoplasia was seen in four patients. One mongoloid girl of 4.5 years of age had only two small nodules with a total weight of 1 Gm. In one mongoloid baby the thyroid was absent, but some abnormal thyroid tissue was found within the thymus. One 9 year old boy had a thyroid weighing 2.5 Gm., and in one 18 year old boy the gland weighed 3.5 Gm. In several cases thymus and thyroid were connected with each other, and it was impossible to separate the two without use of a microscope.

The pathology of the thyroid can be understood only through microscopic study. It may be useful to start with a brief discussion of the normal thyroid in infancy and childhood. Such a report may be the more welcome because of the lack of studies at hand.

The glandular tissue develops from solid epithelial nests during fetal life, which gradually form lumina and secrete colloid. In fetal thyroids many acini are already well developed in the last four months before birth and contain colloid. After birth the thyroid is composed of acini which

TABLE 11.—*Average Weight of Thyroid of 40 Control Individuals*

Age in Years	Thyroid Weight Gm.
2–5	2–4.5
8	6
12	8–14
14	12–14
15	12–20
19	17–24
20 and above	12–27.5

TABLE 12.—*"Normal" Thyroid Weights in Childhood*

Author: Place:	Isenschmid Bern, Switzerland	Wegelin North Germany	Eggenberger Rome, Italy	Castaldi Florence, Italy
Age	Gm.	Gm.	Gm.	Gm.
Newborn	4–6.6	1.9	1.5–3.0	1.1
1 year	5.0	2.4	1.9	1.7
2 years	7.5	3.7	2.2	2.8
4 years	14.5	6.1	—	3.4
6 years	17.0	7.4	4.4	3.6
11 years	25.0	11.2	7.0	—

"Normal" Thyroid Weights in Adults

Author: Place	Marine & Kimball U. S. A.	Huck, Wegelin North Germany	Marchand France
	Gm.	Gm.	Gm.
	25	20–25	22–24

are lined by cuboid or high columnar epithelium. Wetzel states that the thyroid of infants shows a uniform picture. The acini are of almost equal size, and the diameter gradually increases from 50 to 100 microns during the first year. The colloid is thin and liquid. Concerning the uniformity of the size of acini in the so-called normal thyroid, my observations are more in line with Hertzler's, who stressed that throughout infancy and

childhood there are solid epithelial nests and small new-formed acini to be found beside the well-developed acini which contain colloid. It is, however, true that the acini gradually increase in size and that an average of 250 microns is not to be found before 4 years of life. Greater distention with flattened epithelial walls and brittle colloid is not common before an age of 8 to 12 years. The normal epithelium is cuboidal, with a vesicular nucleus and a clearly demarcated cytoplasm. The adjacent acini walls do not crowd each other and are separated by a large capillary system and fine connective tissue fibers. Hertzler mentions that "the colloid in very early life is so thin that it is not stained at all by eosin and only faintly by Mallory's trichrome methylene blue. It does not stain normally as compared with that of the adult until the fourth to sixth year. When it does stain, it is uniformly acidophilic with eosin." Normal colloid stains red with eosin and blue with the trichrome Mallory. Hertzler and others use the term "acidophilic," but this term reminds one too much of the acidophils of the pituitary gland, which stain red both with eosin and with Mallory's trichrome stain, while normal colloid of the thyroid stains light blue with the latter. If colloid becomes abnormal, thick, and stagnant, the color is darker. Abnormal colloid stains with the hematoxylin of the H & E stain, while it stains orange by Mallory's trichrome. Brittleness is clearly indicated by wavy appearance and splintering.

One may approach the problem by establishing the main patterns of pathology which can be found in infancy and childhood. The so-called Basedow thyroid is not included.

1. Distention of acini beyond normal size, with flattening of epithelial walls, disappearance of cytoplasm border lines, and pyknosis of nuclei. Acini tightly filled with colloid which stains dark pink or dark blue and orange and is wavy and brittle. The epithelial walls touch each other, and there is little interstitial tissue: Colloid goiter, "resting."

2. Absence of colloid formation. The acini are small and empty, or no lumina are formed at all. Parenchyma consists of solid epithelial nests: Fetal gland, developmental arrest or retardation.

3. Increase in connective tissue separating the acini and encroaching upon them: Replacement fibrosis.

4. Inequality of acini, most of them abnormally distended by colloid. Solid epithelial nests and small acini with thin colloid between. Proliferation of epithelial cells in the epithelial walls, duplication of walls, and papillation: Colloid goiter with possible toxic activity.

These four standard alterations may occur in various combinations. The pathologist is not able to make a statement about toxicity or mere hypofunction. Until recently observations of pathologists and clinicians were so little in accord with each other that it seemed almost impossible to

come to any agreement. Recent research, however, gives a lead for a sounder approach to correlating histology and physiology. The cells of the thyroid are a secretory epithelium with the task of discharging their secretion into the lumen of the acini, in which the incretion is stored as colloid. The colloid is viscous, but it is a fluid that is in permanent exchange with the epithelial wall, which absorbs certain agents as well as produces new material. It is easily understood that in order to function there has to be a normal epithelial wall, colloid in a correct state of liquidity, and sufficient vascularization. If colloid is stored and petrified to such an extent that the epithelial wall is flattened and the cells are unable to secrete, the gland is no longer sustaining normal function. If no acini are formed and no colloid is produced at all, the gland is then unable to carry out its assignment. The deduction that new growth of epithelium may have a toxic influence upon the organism is taken from observations in Graves' disease, where epithelial proliferation and papillation dominate the picture. The type of toxicity and its extent cannot be determined by histological means.

A study of forty-eight mongoloid thyroids provides evidence that the mongoloid child has an abnormal thyroid, which is not suited for adequate function.

1 (CH 60). Two days, female: Advanced development with beginning colloid stasis.

Peripheral acini enlarged, filled with dark red, brittle colloid. Some papillation. Epithelial walls high columnar. Many smaller acini empty or with colloid thin and granular. Center of gland contains many interacinal cell nests without lumina. Glandular age seems advanced. Distention of acini and dark colored, brittle colloid indicate stasis.

2 (CH 31–76). Nine days, male: Beginning colloid goiter with replacement fibrosis and degeneration. Fetal nodule in center. (Fig. 40.)

Small nodules separated by thick strands of connective tissue, especially on one side of the trachea. Peripheral acini enlarged, irregular in shape, filled with thin colloid. Many epithelial nuclei pyknotic; cells degenerated. Center of gland congested. Increase in connective tissue separating the fetal cellular columns without formation of acini and conspicuous cell degeneration.

3 (CH 35–94). Six weeks, female: Colloid stasis, replacement fibrosis, fetal cell nests in degeneration.

Connective tissue separating parenchyma into smaller nodules. Acini of varying size and shape. Majority of acini with no or little colloid. Epithelial walls show pyknotic nuclei and degenerated cells.

4 (CH 29–162). Two months, male: Beginning colloid stasis, replacement fibrosis, fetal cell nests.

Peripheral acini greatly enlarged, filled with pink, crenated colloid. Epithelial walls columnar. Center of gland congested. Acini small, empty, or filled with thin colloid. Shape of acini irregular. Increase in interacinal connective tissue.

5 (CH 30–181). Two and a half months, male: Undeveloped fetal gland with fibrosis.

There are only small nests of undeveloped fetal tissue interspersed among thick connective fiber bands. Few acini in the periphery enlarged, ill shaped, contain some colloid.

6 (CH 35–173). Three months: Beginning colloid goiter, replacement fibrosis.

Interacinal fiber tissue increased, acini irregular in shape, lined by columnar epithelium with many pyknotic nuclei. Colloid pink, retracted, and crenated. Acini in periphery greatly enlarged and lined by flattened epithelium. Colloid dark in periphery and slightly brittle.

7 (CH 29–95). Four and one half months, male: Fetal gland colloid-free. Degenerative replacement fibrosis. (Fig. 42.)

Irregular strands of connective tissue separating parenchyma. Acini irregular in shape, compressed, empty, or filled with thin colloid. Epithelial walls lined by small degenerated cells with pyknotic nuclei. Fibrosis conspicuous.

8 (CH 37–6). Five months, male: Colloid goiter with replacement fibrosis.

Acini distended and filled with dark colored, brittle colloid, crenated, vacuolated. Epithelial walls columnar or thinned out, and partly destroyed colloid in interacinal spaces. Conspicuous fibrosis in some areas.

9 (CH 31–62). Six months, female: Fibrosis of old degenerated colloid goiter. (Fig. 44.)

Conspicuous fibrosis with nodular separation of parenchyma. Acini narrowed by proliferated fiber tissue. Shape of acini irregular. Acini filled with colloid, vacuolated, dark pink. Epithelial walls lined by pyknotic degenerated flat cells.

10 (CH 43–120). Six months, male: Replacement fibrosis of undeveloped fetal goiter.

Acini almost empty, lined by small, dark, nucleated epithelial cells. Borderlines indistinct. Conspicuous increase of connective tissue encroaching on the irregular sized acini.

11 (CH 37–1). Seven months, female: Colloid goiter, resting.

Acini greatly distended, lined by thin layers of epithelium partly destroyed. Colloid thick, vacuolated, brittle. Interacinal tissue absent. Epithelial walls of adjacent acini pressed against each other. (Fig. 49.)

12 (CH 45–152). Eight months, male: Within normal range.

(Treated with thyroid since first month of life.) Acini fairly regular, medium sized, but distended in periphery. Colloid pink, slightly brittle. Epithelial walls well preserved, but many nuclei pyknotic. Interstitial connective tissue increased.

13 (CH 31–30). Nine months: Colloid goiter with replacement fibrosis.

Conspicuous increase in interstitial tissue encroaching on the acini. Acini filled with dark staining, crenated, and vacuolated colloid. Epithelial walls flattened and degenerated. The small acini are lined by columnar epithelium, partly degenerated. Much of the colloid stains orange with Mallory stain.

14 (CH 30–13). Ten months, female: Fetal cell nests, colloid-free. Thyroid and thymus not separated.

Thyroid-like tissue found within thymus nodule. Thyroid without colloid. Small, irregular, epithelial strands compressed by fibrous tissue.

15 (CH 32–207). Thirteen months, male: Colloid goiter with fibrosis.

Acini with flat epithelial walls, irregular in shape. Colloid brittle, crenated, and vacuolated. In center of gland small areas with acini little distended and almost empty. Increased connective tissue.

16 (CH 45–154). Eighteen months, male: Colloid-free, degenerated fetal gland.

Acini irregular in shape, compressed by fibrous tissue. Walls partly destroyed. Cell nuclei pyknotic. Congestion.

17 (CH 33–80). Eighteen months, female: Colloid goiter with replacement fibrosis.

Distended acini, filled with dark, brittle colloid. Epithelial walls flattened. Cell nuclei pyknotic. Tremendous increase of connective tissue encroaching on the smaller acini, which are irregular in shape, compressed, and filled with thin granular colloid.

18 (CH 43–102). Twenty-two months, male: Colloid goiter.

Acini lined by flat epithelium partly destroyed. Acini distended. Colloid vacuolated, slightly brittle. Increase in connective tissue. Smaller acini compressed. Few solid epithelial nests without formation of acini.

19 (CH 24–102). Two years, four months, female: Colloid goiter with replacement fibrosis.

Acini irregular, distended, filled with granular, pink colloid. Epithelial walls partly destroyed. Nuclei pyknotic. Interstitial connective tissue increased.

20 (CH 40–57). Four years, five months, female: Colloid goiter with fetal cell nests and replacement fibrosis.

Acini in periphery enlarged, lined by flat epithelium. Most nuclei pyknotic. Colloid pink, vacuolated, and partly brittle. Large area of gland shows undeveloped fetal epithelial nests with little development of acini and no colloid. Nests are separated by thick strands of connective tissue.

21 (CH 42–99). Four years, five months, male: Colloid goiter with fetal cell nests and fibrosis.

Small acini greatly distended and filled with brittle colloid lined by flattened epithelium with pyknotic nuclei. Rest of gland consists of fetal tissue with solid cell nests surrounded by increased connective tissue.

22 (CH 43–103). Six years, seven months, male: Colloid goiter.

Some areas tightly filled with colloid, dark pink, and crenated. All walls flattened and epithelial nuclei pyknotic. Some areas without colloid degenerated.

23 (CH 43–124). Seven years, seventeen days, male: Colloid goiter resting.

Acini distended, colloid brittle, epithelium flattened. Little epithelial activity.

24 (CH 40–47). Eight years, seven months, female: Colloid goiter.

Majority of acini distended, filled with colloid. Flattened epithelial walls.

25 (CH 38–25). Eight years, eight months, male: Colloid goiter.

Acini greatly distended, filled with brittle colloid. All epithelial walls flattened. Majority of cells pyknotic. Many walls destroyed. Interacinal spaces filled with colloid. Some irregular cell columns dispersed among fiber tissue. (Fig. 45.)

26 (CH 43–125). Eight years, nine months, male: Degenerated thyroid with fibrosis.

Majority of acini empty. Epithelial walls thin. Cells small, pyknotic nuclei. Increased connective tissue, encroaching on the irregularly shaped and compressed, empty acinal tubes.

27 (CH 44–134). Nine years, seven months, female: Degenerated thyroid with fibrosis.

Majority of epithelial walls irregular and partly destroyed. Large acini filled with thin colloid. Many smaller acini empty. Increase in connective tissue.

28 (CH 38–17). Nine years, eight months, female: Simple colloid goiter, resting. (Fig. 46.)

All acini greatly distended, filled with brittle colloid. All epithelial walls flattened and compressed.

29 (CH 44–141). Ten years, nine months, male: Degenerated colloid goiter with increased fibrosis and numerous undifferentiated cell nests.

Small groups of acini, separated by broad bands of faintly staining connective tissue. Acini filled with pinkish colloid, partly vacuolated. Walls are compressed, flat, and partly destroyed. Much cell desquamation. Numerous solid cell nests without formation of lumina.

30 (CH 44–139). Eleven years and one month, male: Colloid-free fetal gland. (Fig. 43.)

The gland is free of colloid. The parenchyma consists of solid epithelial strands or narrow, ill-shaped acini filled with epitheloid elements.

31 (CH 37–10). Twelve years, female: Old diffuse colloid goiter.

All acini extremely distended, filled with dark blue or orange colloid (Mallory stain). Walls of acini flattened, pressed against each other. Almost no interstitial tissue. There is a moderate amount of small sized acini, but no undeveloped fetal tissue.

32 (CH 42–82). Thirteen years, ten months, female: Old colloid goiter, resting.

Majority of acini distended, tightly filled with colloid. Epithelial walls flattened. Cells moderately degenerated, nuclei pyknotic.

33 (CH 38–23). Fourteen years and five months, male: Degenerated, exhausted, colloid goiter.

Acini partly distended and filled with colloid. Epithelial walls flattened. Much degeneration of walls and exfoliation. Majority of acini colloid-free or filled with some faintly staining granular material. (Fig. 48.)

34 (CH 38–32). Fourteen years and eleven months, male: Old colloid goiter with some evidence of toxic activity. (Fig. 47.)

Acini distended, filled with pinkish, brittle colloid. Vacuolation. Epithelial walls extremely flattened. Cells show no borderlines. Nuclei pyknotic. There is some evidence of epithelial cell proliferation and papillation.

35 (CH 43–100). Fifteen years and eight months, female: Old colloid goiter with slight indication of toxicity.

Acini distended, filled with dark pink colloid. Epithelial walls flattened, cells compressed. Nuclei dark stained. There is moderate formation of solid epithelial nests and new small acini. Papillation in few larger acini.

36 (CH 44–148). Fifteen years, ten months, male: Degenerated colloid goiter, fibrosis, undifferentiated fetal cell nests or fetal acini.

Connective tissue greatly increased, encroaching upon the acini, which vary greatly in size and shape. The large acini are distended, filled with crenated colloid. Epithelial wall flat, compressed. Nuclei dark stained. Many smaller acini contain little or no colloid and show cell desquamation. There are solid epithelial strands and proliferating epithelium nests.

37 (CH 42–85). Sixteen years, male: Colloid goiter with some fetal activity and possible toxicity.

Acini distended and filled with pink colloid. Vacuolated and crenated. Epithelial walls flattened in some areas, in others of medium columnar size. Acini separated from each other by enlarged congested capillaries. Some epithelial walls degenerated and exfoliated. Cells are suspended in interacinal colloid and connective tissue. There are numerous smaller solid epithelial nests.

38 (CH 41–58). Sixteen years and three months, male: Colloid goiter, degenerated, fibrosis.

Acini filled with brittle colloid. Irregularity of shape and size. Increased fibrosis, encroaching upon acini.

39 (CH 42–90). Seventeen years, male: Colloid goiter with fetal epithelial nests. New formation of rather high epithelium, possible toxic activity.

Acini greatly distended, filled with brittle colloid. Flat epithelial walls. Epithelial cells do not show borderlines, and nuclei stain darkly. Numerous solid fetal cell nests and areas of epithelial proliferation.

40 (CH 42–81). Seventeen years, male: Colloid goiter with large remnants of undeveloped epithelial nests and columns with increased fibrosis. Possible toxic activity.

Increase in connective tissue encroaching upon the acini and separating them from each other. In periphery some distended acini filled with colloid. Epithelial walls flattened. Cells without borderlines. Capillaries enlarged and congested. In center, majority of acini of small size and filled with thin, faintly staining colloid, or empty. Numerous epithelial cell nests and strands without formation of lumina embedded in fiber tissue.

41 (CH 43–126). Seventeen years and one month, female: Diffuse colloid goiter resting.

Numerous acini distended and tightly filled with colloid. Acini in small groups separated from each other by faintly staining connective tissue. Large acini surrounded by smaller acini and some solid cell nests without lumina.

42 (CH 42–83). Seventeen years and nine months, male: Colloid goiter with degeneration and some possible toxic activity.

Few extremely distended acini, filled with colloid, are recognizable by naked eye. Walls thinned out. Epithelial layers partly destroyed. Colloid within connective tissue strands. Other medium sized acini tightly filled with colloid. Cell borderlines indistinct. Nuclei darkly stained. Considerable amount of epithelial proliferation and defoliation.

43 (CH 44–146). Eighteen years and four months, male: Colloid goiter with possible toxicity.

Acini distended, filled with colloid. Walls flattened, borderlines of epithelial cells indistinct. Nuclei darkly stained. In some areas acini show exfoliation, and epithelial walls are partly destroyed. Moderate amount of small epithelial nests.

44 (CH 38–22). Twenty years and six months, male: Hashimoto's thyroiditis. (Fig. 41.)

Few islands of greatly distended acini, filled with orange colloid (Mallory stain). Rest of the gland shows epithelial cells in strands without lumina. Dense infiltration with lymphatic cells.

45 (CH 43–111). Twenty-six years and four months, male: Colloid goiter with possible toxic activity.

Majority of acini greatly distended and filled with colloid. Epithelial walls flattened. Moderate amount of small solid epithelial nests and new formation of acini.

46 (CH 41–71). Twenty-eight years, female: Old colloid goiter with possible toxic activity.

Majority of acini greatly distented, tightly filled with colloid. Epithelial walls flattened, cell borderlines indistinct, and nuclei pyknotic. Some solid epithelial cell nests and interacinal cell proliferation.

47 (CH 37–8). Thirty years and eight months, male: Colloid goiter with some possible toxic activity.

Many acini distended, filled with colloid. Epithelial walls flattened, capillaries congested. Smaller acini show columnar epithelium and contain little granular colloid. Some solid epithelial nests.

48 (CH 44–129). Forty years, female: Old colloid goiter with degeneration and no signs of activity.

Acini distended, filled with colloid, considerable destruction of epithelial walls with cell desquamation and cells floating in colloid.

TABLE 13.—*Pathology of Thyroid in Mongolism*

	Number	Percentage
Colloid goiter, "resting"	10	20.8
Colloid goiter with marked fibrosis	15	31.1
Colloid goiter with signs of possible toxic activity	10	20.8
Fetal glands without colloid formation	6	12.5
Fetal cell nests and nodules with some colloid formation in periphery	4	8.35
Chronic lymphatic thyroiditis (Hashimoto's thyroiditis)	1	2.12
Normal (one prematurely advanced)	2	4.17
Total	48	

By summarizing the observations, the pathology may be indicated as in Table 13.

It is hard to understand that the mongoloid thyroid has escaped its proper classification for such a long time. The main reason seems to be that, in spite of some work on cretinism and Graves' disease, knowledge of thyroid pathology is still little developed. Progress has been greatly retarded by the misconception of many clinicians and pathologists, who think only in terms of plus-minus metabolism or hyper- and hypo-function of a gland. It has been recognized for only a few years that Graves' disease is not a simple hyperfunction of a normal gland and that myxedema is not a mere hypofunction. Neither is endemic cretinism a simple athyroidism.

The mongoloid is endowed with a thyroid which does not function properly. If we take all cases with resting colloid goiter and fibrotic colloid

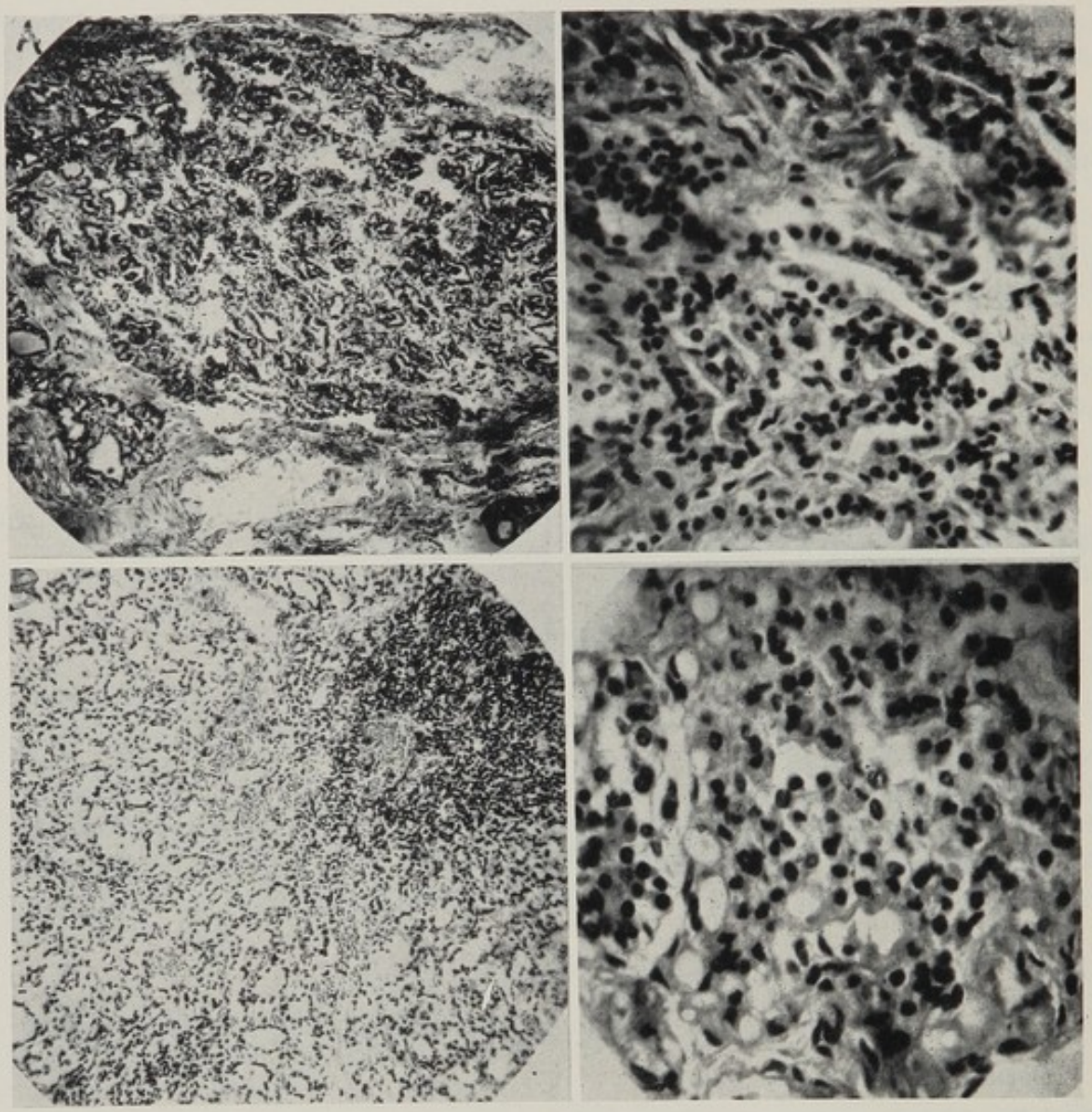


Fig. 40. (Upper left) Colloid-free "cretinoid" thyroid in a 9 day old mongoloid male baby (31/76). Note fetal nodule without formation of acini and colloid; increased connective tissue and irregular epithelial proliferation.

Fig. 41. (Lower left) Hashimoto's lymphoid thyroiditis in a 20 yr. old mongoloid male (38/22). Note lymphatic infiltration; acini small; thyroid without colloid.

Fig. 42. (Upper right) Colloid-free "cretinoid" thyroid in a mongoloid baby 4½ mos. old (29/95). Note irregular epithelial proliferation without acini formation; increased fibrosis.

Fig. 43. (Lower right) Colloid-free "cretinoid" thyroid in 11 yr. old mongoloid (44/139). Note "myxedema" cells without colloid formation in thyroid.

goiters or those with possible toxic activity, we see that 35 of the 48 patients fall in this group. Histologically, the colloid goiter is undoubtedly the

most frequent type in mongolism and may be found even in babies of a few months. Such completely resting colloid thyroids have never been described in infants of such a tender age. It is, however, wrong to consider the colloid goiter as the only type of pathology present in mongolism. It is important to realize that 10 patients, or 20.8 per cent, had fetal glands which were either not developed at all or showed fetal nodules of considerable size. Whether this fetal tissue as such exercises any abnormal toxic influence is impossible to determine. In some of these glands, myxedema cells were present. In all of them the lack of colloid was conspicuous.

As will be seen in the discussion of cretinism, myxedema develops only if no colloid is present at all, and very few colloid-containing acini suffice to prevent its development. This is the reason that myxedema is relatively rare in mongolism. This, however, does not mean that thyroid function is normal and adequate. The available colloid may prevent myxedema, but the parenchyma may be entirely inadequate for all the other functions, especially growth and sex development. The presented material provides evidence that 20 per cent of the mongoloid patients, especially babies and infants, are on the threshold of myxedema and are suffering from inadequate thyroid supply. In all mongoloids, thyroid function is lagging. The only gland which was macroscopically enlarged was a case of Hashimoto's thyroiditis, where practically the whole gland was replaced by lymphatic tissue. Of the so-called two normal glands, one was that of an 8 months old baby who died of pneumonia after having been treated for seven months with thyroid and pituitary injections. The other gland was that of a 2 days old mongoloid. In this case the gland showed well-developed, rather large acini which contained thick colloid. This finding is not exactly what one may consider a normal thyroid and is suggestive, at least, of some abnormal premature stimulation.

I may summarize that the mongoloid baby starts life with an abnormal thyroid gland. Not only is such a thyroid not fit to provide the necessary hormones, but the fact that the thyroid shows profound pathology from the very beginning indicates that the causative factors are operating in the prenatal period. It would be of great interest if one could draw conclusions from the pathology of the newborn as to the maternal deficiency. Observations, however, are still too confusing. It is, therefore, impossible to speculate on a hyper- or hypo-thyroidism of the mother of a mongoloid child. In several papers Clark has stressed the idea that mongolism is "the result of hyperthyroidism ceasing at birth." C. R. Myers and others are inclined to attribute it to hypothyroidism.

My observations on mongoloid thyroids obtained a few days to weeks after birth, where fibrosis and lack of colloid formation were conspicuous in all but one case, do not favor Clark's idea of a "hyperthyroidism ceasing at

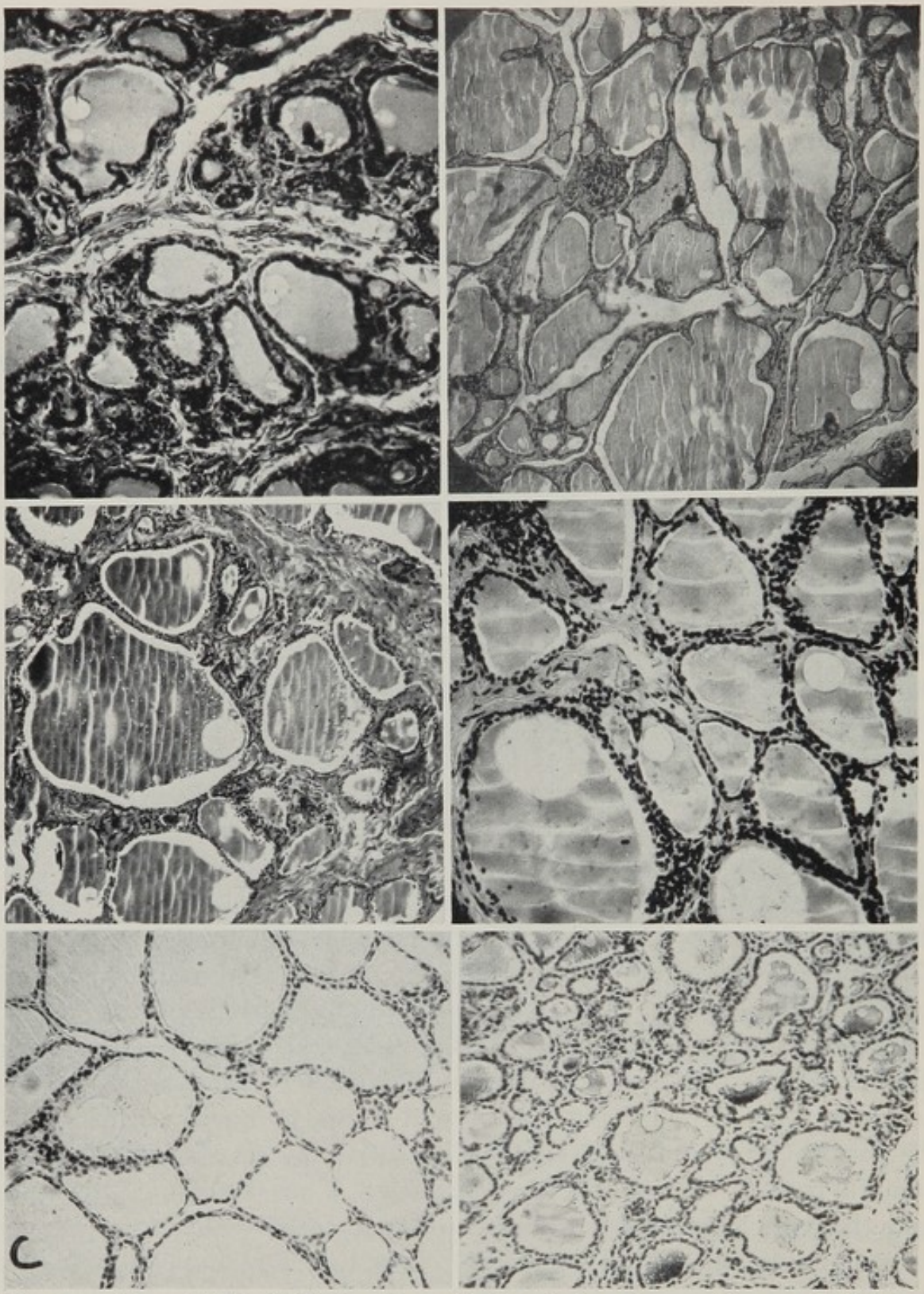


FIG. 44. (Upper left) Colloid goiter with fibrosis in a 6 mos. old mongoloid female (31/62). Note enlargement of acini filled with thick, crenated colloid; flattening of epithelial walls; replacement fibrosis.

FIG. 45. (Center left) Colloid goiter in an 8 yr. old mongoloid male (38/25). Note enlargement of acini up to 500 micra; flattening of epithelial walls; colloid brittle, stagnant; some interstitial fibrosis.

FIG. 46. (Lower left) Resting colloid goiter in a 9 yr. old mongoloid girl. Note flattening of epithelial walls; colloid brittle; no vascularization of interstitial tissue.

birth." My observations are compatible with maternal hypothyroidism, yet not conclusive.

With the discovery of a definite thyroid pathology in mongolism, this condition again takes its place among the thyroid deficiencies or dyscrasias. An argument more than half a century old seems finally settled. The observations, however, do not permit the classification of mongolism as a thyroid deficiency per se. The fact that resting colloid goiter can be experimentally produced by pituitectomy suggests a close relationship between the thyroid deficiency and pituitary pathology. One feels forced to conclude that the lack of thyrotropic action on the part of the pituitary is the main cause for the failure of thyroid function.

In Cretinism

From the viewpoint of pathology, the diagnosis of any type of cretinism depends upon the demonstration of essential thyroid pathology, and a clinical diagnosis of cretinism with a "normal" thyroid at autopsy would be a mistake. It would suggest that the dwarfism was due to other factors or the mental deficiency was a primary one and happened to occur in an area of endemic cretinism.

Three patterns of thyroid pathology are found in cretinism:

1. Thyroid aplasia as congenital defect.
2. Athyroidism due to loss of thyroid function.
3. Thyroid dysfunction on the basis of a degenerated goiter.

Thyroid Aplasia or Sporadic Cretinism

Thyroid aplasia is the main cause of infantile myxedema or myxidiocy. The interesting observations made in these cases permit one to make the diagnosis with great accuracy and to separate the congenital type from acquired loss. Aplasia as a congenital malformation is due to a failure of proper differentiation of the pharyngeal pouches. The thyroid is derived from pharyngeal epithelium, being one of the "branchiogenic derivatives." Thyroid development is related to the differentiation of the branchiogenic organs (thymus, parathyroid, tonsils), and anomalies in this differentiation

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Fig. 47. (Upper right) Colloid goiter with possible toxic activity in a 15 yr. old mongoloid girl. Note extreme enlargement of acini filled with brittle, splintering colloid; some epithelial nests between acini and papillae formation.

Fig. 48. (Center right) Resting colloid goiter in a 14 yr. old mongoloid male. Note enlargement of acini; brittle colloid; flattening of epithelial walls; absence of vascularization.

Fig. 49. (Lower right) Resting colloid goiter in a 7 mos. old mongoloid female. Note flattening of epithelial walls; crenated, brittle colloid; no vascularization of interstitial tissue.

are not rare. One may remember that the five pharyngeal pouches—with the exception of the first pouch, which is involved in the formation of the inner ear—are the source of the important endocrine glands found in the neck. Pouch two forms the tonsils and lymphatic organs of the pharynx. Pouches three and four are the source of thymus and epithelial bodies (parathyroids), whereby, from the third pouch, the thoracic part of the thymus is derived as well as the lower epithelial bodies. Both structures have, therefore, a rather long trail of migration, by-passing structures, which are later found above the thymus. This is the cause of frequent malformations and displacements. I mentioned before that in mongolism, thymus tissue is frequently found in the immediate vicinity of the thyroid or the thymus may remain connected with the cervical region by ducts or epithelial cords. The epithelial bodies may be found displaced or may not be found at all, because they may be buried in some other tissue far away. Their absence seems extremely rare, at least, in autopsies of persons who have attained a certain age.

The thyroid develops medially from a noblike protuberance in the mesobranchial area as a unilateral organ. Division into two lobes occurs later, while the thymus is bilateral from the very beginning. The thyroid "anlage" develops in the oral portion of the area mesobranchialis, anteriorly to the second branchial arch. It forms a stalked vesicle. The stalk persists for some time as an epithelial cord and is obliterated later, while the glandular part has to move downward and divides into two lobes. If this movement is interrupted at any part of the journey, the thyroid may remain undescended below the tongue, or rudimentary thyroid epithelium may be found somewhere in the brachiogenic tissue complex.

The fifth pouch and parts of the fourth form the so-called "ultimobranchial" bodies, which apparently obliterate in man. Remnants of these structures are sometimes found within thyroid tissue, but it is, at present, generally agreed* that they do not participate in the thyroid formation. Their epithelium, which forms tubules and is filled with albuminous fluid

* The fate of the ultimobranchial tissue has been the subject of a number of recent investigations. It seems that the tissue derived from the fifth pouch is of little importance. That derived from the fourth pouch has a different destination in various animal species and man. In some species it is transformed completely into thyroid-like tissue and is called the "lateral thyroid." In man, most investigators believe, under normal conditions the "lateral thyroid" is not of consequence. In thyroid aplasia, however, the tissue may develop a potency for the formation of thyroid-like tissue or lateral aberrant thyroid tumors. In animals, J. H. Van Dyke was able to show that ultimobranchial tissue remnants can be frequently found in the form of small cysts lined by stratified squamous epithelium. I have seen those cysts as described by Van Dyke in mongolism and cretinism. (See J. H. Van Dyke for recent literature.)

like "colloid," may produce the appearance of thyroid tissue or cystic goiter. It may, however, be remembered that all stagnant albuminous fluids in epithelial tubes or cysts give staining reactions like colloid. We observed that in the skin of myxedema; they will be demonstrated in the pituitary and elsewhere.

It is in the nature of developmental disorders that the earlier a malformation starts, the more derivatives are involved, and vice versa. In thyroid aplasia, various branchiogenic derivatives may be found abnormal. On the other hand, if there is only one system involved, it is suggested that local factors are responsible and the damage is less general.

If the thyroid is missing, the derivatives of the fourth pouch, the ultimobranchial bodies, are usually not obliterated and cell nests and cysts are found at the sides of the trachea which are remnants of those tissues that have disappeared in normal individuals. These cysts are easily mistaken for degenerated goiters. Especially during life, many a cretin with myxedema seems to have a goiterous thyroid, while those pouches which are palpable are the ultimobranchial bodies. If cretinism is discovered a few weeks after birth, one may be almost sure that the palpable tissue is not goiter. Conversely, a careful examination of these cysts or tumors has proven that they are not lipomas, as earlier writers thought, but abnormal branchiogenic remnants. Other anomalies—sublingual thyroid remnants, displaced thyroid tissue, and accessory thyroids—may be found far away from their destination. These observations explain the great variety of clinical pictures and throw light on those cases which do not develop myxedema or recover in spite of transitory myxedema by developing some thyroid tissue after birth.

In a large number of cases, displaced thyroid tissue is present. A delayed development may occur even after the first year of life has passed. On the other hand, it may be accepted that complete lack of thyroid will lead to myxedema under all conditions, in any country. Lack of myxedema is no indication of efficient thyroid function, although absence indicates that some colloid-forming thyroid acini are somewhere present in the body.

The variety of clinical pictures is due to differences in the remaining thyroid tissue. Congenital thyroid aplasia is a true malformation, a developmental disorder of the pharyngeal pouches. Its presence is indicated by abnormal fetal tissue in the sublingual-thyrotracheal region. The parathyroids are not derived from the same pouches and are usually normal in thyroid aplasia. The thymus develops independent of the thyroid. It is frequently involved in developmental disorders and found small or aplastic. The thymus is not able to act as a substitute, and thymus development usually runs parallel to thyroid development, the former being small in hypothyroidism and large in hyperplasia.

Loss of Thyroid

Degeneration of thyroid is not rare and may occur at any time before or after birth. In such a case, thyroid differentiation has been normal, but the thyroid has been destroyed by infectious diseases and has been replaced by fibrous tissue.

In these cases the pathologist is not able to find any thyroid at all, and no malformation is seen. In the absence of malformations, one may assume that thyroid differentiation had been normal at some time of development, but the gland had been destroyed by extrinsic factors.

Cases of this type have been reported by several investigators from the very beginning of the discovery of sporadic cretinism. There is little to say about it, except that complete absence can only be proven when the trachea is examined in serial sections from the bottom of the tongue down to the sternal notch.

Goiterous Degeneration or Endemic Cretinism

It should be understood from the very beginning that endemic cretinism is not due to thyroid hyperplasia or "goiter," but to the abnormal degeneration of a hypertrophic thyroid if present or to the simple absence of it. In countries or areas where the iodine supply is far below normal, the thyroid reacts with a compensatory hypertrophy. This is an attempt to compensate for lack of quality by quantity. The average size of the normal thyroid increases with the distance from sea level, and when Oswald gives an average thyroid weight of 60–95 Gm. for Switzerland instead of the 20–25 Gm. seen in goiter-free countries, then general thyroid hyperplasia is well indicated. The patterns of pathological degeneration of hyperplastic thyroids, cystic degeneration, parenchymatous degeneration, malignant degeneration, and vascular goiters are only a part of the pathology of cretinism, if they develop in infancy. If such a degeneration takes place beyond the age of puberty, no cretinism will develop, although myxedema may occur in rare instances.

W. Scholz, in 1906, reported the observation: "It is strange that especially in those individuals who present the highest degree of cretinoid degeneration, there is no goiter present." This extraordinary fact was also noted by other investigators. Roesch writes: "Not all cretins have a goiter and the cretins of most marked degree who present a full fledged picture are not carriers of goiter. It is rare that they have goiter at all." Another important observation was reported by Allara: "The full fledged cretin rarely has goiter, but cretinoid people always have. With the entrance of puberty, goiter becomes conspicuous, but the true cretin does not enter puberty at all." According to Cerise, the degree of cretinism is in reversed proportion to the size of the thyroid, and Wagner V. Jauregg noted:

"The strange fact is that the cretins without goiter are the real ones; they present the typical triad of dwarfism, mental deficiency, and skin manifestations" (myxedema). There is no need to go into further details or to enter into a discussion of all arguments which have been presented by various authors. In view of our present knowledge, most of the objections are now outdated. They were due to a basic misunderstanding of the essential manifestations of athyroidism. When a scientist of the rank of Bircher considered premature synostosis as a characteristic sign of cretinism (an idea first expressed by Virchow) and excluded cases with persistent cartilage disks from the diagnosis, then it is clear that many of his cases would be excluded from the diagnosis today, while the lack of ossification of the cartilages is one of the most reliable signs of hypothyroidism.

And yet Bircher's argument against the relationship between thyroid disease and endemic cretinism turns out to be a most helpful, unintended support. On the basis of a study of numerous cretin thyroids, Bircher concludes that the struma (goiter) in cretinism is found not in early childhood but, if it appears, at the time of puberty. "The development of a goiter can, therefore, not be responsible for cretinism which becomes manifest in infants of three to four years."

With the testimony of so many independent observers at hand, it is evident that the problem of endemic cretinism starts with the deficiency of the cretin thyroid and is, therefore, identical with the general problem of cretinism or hypothyroidism. Many an endemic cretin is a thyroid aplastic individual and would be considered a sporadic cretin outside of his natural surroundings. In the majority, however, a marked difference exists in the fact that myxedema is absent and that thyroid degeneration, though present in infancy, does not necessarily develop immediately after birth. In contrast to the alpine goiter, the cretin thyroid is characterized not by the presence of colloid cysts, but by their absence. The degree of cretinoid degeneration is in proportion to the disappearance of normal thyroid tissue. Presence of some normal vesicles is not sufficient to compensate for the inadequacy of the cretin thyroid as such. From the viewpoint of pathology, it is not the normal thyroid remnants which deserve interest, but the abnormal degeneration of the other parts.

The histology of the thyroid in cretinism is characterized by degeneration of the parenchyma, proliferation of the connective tissue stroma, degeneration and insufficiency of the blood supply, and a deficiency in or complete lack of colloid. It should be emphasized that the cretin struma is usually free of colloid and that only in a small percentage of cases is colloid to be found at all; if present, it is rather brittle and not liquid. As Wydler emphasized, if colloid is present it is sparse and indicates a previous state of functional activity rather than adequate function at the present.

Marine and Leonard describe the changes as follows:

> The colloid is practically absent. The epithelial cells have lost their regular and columnar type and are irregular in size and shape. The nuclei are in general large, often hyperchromatic, and irregular in size and outline. Nuclear figures are still observed but the new formation of cells is not sufficient to offset the cell death and the follicles become smaller from the death of their secreting cells.

Although the amount of cell death, degeneration, and fibrosis may vary from case to case, the common denominator of all functional inadequacies is the loss of the ability of the follicles to form and store colloid.

The clinical and anatomical features of endemic cretinism are manifold on account of the variety of compensatory thyroid hypertrophy. The normal tissue remnants not only retard and alleviate the development of cretinism, but their pathological activity may introduce a new element into the picture. Hypertrophy of epithelium and formation of papillary protrusions may lead to toxicity, which makes the complete removal of the thyroid preferable to leaving an inadequate or toxic thyroid in the body.

The Pituitary Body

Normal Anatomy

Clinical and pathologic evidence presented in this book indicated congenital acromicria as the essential pathology of mongolism, the opposite of acromegaly. Since the pathology of the latter condition is firmly established as a hyperpituitarism associated with an adenoma of a certain type of pituitary cells, the pathology of the pituitary in mongolism is of special interest. When a study of this condition revealed an increase of eosinophilic cells in a large number of cases (Benda, 1939), such an observation seemed hardly compatible with what had been known and taught in the last decades. If the cells of acromegaly are eosinophilic cells and therefore the producer of growth hormones, how can it be possible that such a definite growth deficiency as mongolism is associated with an increase of the same type of cells? A study of other types of dwarfism, however, microcephaly and even cretinism reveals that in these conditions an increase in eosinophilic cells may also be found in spite of evidence that the growth function is strikingly at fault. How can these observations be reconciled with each other? Indeed, many observations indicate that a revision of our present concepts of the interrelationship of the various cell types and their hormonal function is necessary. Although numerous publications have dealt with the cytology of the human pituitary, the majority of studies is solely based on observations on adult glands. Moreover, anatomy and pathology have not kept pace with the great advances in hormonal physiology and the present day concept of the relationship between function and struc-

ture of the pituitary seems out of date. It is beyond the scope of this book to give a detailed description of the cytology of the anterior lobe in infancy and childhood. The following summary of my observations is based on a study of more than 200 control cases of normal persons of all ages and of other growth disorders.

Most anatomists and pathologists attribute three types of cells to the anterior pituitary body. The differentiation is based upon the staining reaction of the cytoplasm to various stains. The main division is that of chromophobes and chromophils, the latter having a great affinity to acid and basic stains while the cytoplasm of the former remains unstained. Chromophils are divided into "eosinophils" or "acidophils," which stain pink with eosin or acid fuchsin, and "basophils," which stain rust-brown with hematoxylin and blue with aniline blue. The chemical description, "acidophilic" and "basophilic," however, does not hold because the aniline blue of the Mallory trichrome stain, which stains the "basophils" blue, is an acid stain. Terms like "alpha cells" for the acidophils and "beta cells" for the other chromophilic type, which reacts to hematoxylin and aniline blue, seem well fitted. While several investigators thought and still maintain (Collin) that both cell types are different stages of the same secretory cycle, several facts indicate that both cell types should be considered separate entities. This view is based on the fact that tumors may be composed entirely of one cell type (alpha or beta cells) and that no other "stages" can be detected in such a gland. If both cells were different stages of a secretory cycle, one should expect to find them in a highly active adenoma at the same time. A. E. Severinghaus has demonstrated a different Golgi apparatus in alpha and beta cells that he considers a significant difference in type. A third argument, in favor of separate secretory cycles rarely mentioned, is the observation that alpha and beta cells have definite areas of distribution in many animals and also in man. Although in man the distribution may sometimes be confused, the main patterns are definite, at least in childhood. The alpha cells occupy mainly both lateral fields in a kidney-shaped distribution, with the hilus of each side facing the other. The chromophobes and beta cells occupy a triangular field in the middle. With an increase in number, the alpha cells tend to penetrate toward the cleft and embrace the middle field from the periphery. The area between the two connective tissue sectors remains chromophobic and basophilic in the majority of cases, with the exception of complete acidophily.

The chromophobes, the third cell type, are considered precursors of the chromophils by most writers. They are also called "chief cells," or "mother cells," although this term seems little suited if the cell is immature and infantile. The assumption that the chromophobes have no secretory function is based on the observation that chromophobic tumors may be present

and attain considerable size without any hormonal effect. A study of such tumors, however, indicates that these tumors are composed of cells which are by no means identical with the chromophobic cells so dominant in infancy and childhood. It is necessary to make a clearer distinction between the various types of chromophobes. The classical description of the cell type is a small cell with an outstanding nucleus and no cytoplasm visible. If the pituitary is not properly fixed and preserved in formalin only, there appear, indeed, numerous nuclei beside the chromophils, which show no further specification. If, however, the fixation is successful, the chromophobes are by no means without differentiation and several types have to be considered. After birth and in the first three years of life, the anterior lobe is mainly composed of smaller secretory epithelial cells, which have a clear cytoplasm brim around the nucleus. The cells are densely piled in small compartments, but frequently in a tubular arrangement with a lumen in the center recognizable. Although the cell borders are sometimes indistinct and the arrangement suggests a cell syncytium, in well preserved cases individual borderlines are distinct. The cytoplasm stains grayish-blue by the Masson and Mallory stains and pinkish in H & E. The cytoplasm is sometimes loaded with mitochondria and in the H & E the cells appear eosinophilic. In the Masson stain, however, the blue of the cytoplasm may prevail. Many infant glands are entirely composed of these chromophobes, for which I am using the term "gamma cells." Interspersed are always a few alpha cells. The number of these may be below 10 for a whole horizontal section. In other cases, the eosinophils are much more numerous, but their number rarely surpasses 50 per cent. With increasing age, the eosinophils increase, but gamma cells remain predominant in the first decade of life. Only after puberty is a decrease in gamma cells conspicuous and they may entirely disappear. Beta cells are not numerous in the infants' pituitary and they are smaller and less deeply stained than in adults. There seems to be a sex difference. Males have a small percentage of beta cells (5–10 per cent) in the majority of cases, while female glands may be found almost entirely without beta cells. At other times, a female gland has a fairly large percentage of beta cells (20–30 per cent). On account of observations which will be discussed later, it is suggested that the inconstant presence of beta cells depends upon the ovarial cycle which is established early in childhood many years before menarche.

The predominance of chromophobic cells of the gamma cell type during infancy and childhood, the period of most intensive growth, makes it highly improbable that these cells have no secretory function, and that production of growth hormones depends upon the small and inconsistent number of alpha cells present during that period. The gamma cells have all properties of a secretory cell, a varying size of cytoplasm and content of mitochondria.

The fluid in the tubules has a faintly blue staining reaction which becomes dark blue when inspissated. Droplets of the same color may be found in the blood spaces. There is no evidence that these secretory gamma cells ever go through all stages of a cell cycle: chromophobic—acidophilic—basophilic. The majority of the cells show a fast turnover which does not permit accumulation and storage of granules.

Within the chromophobic cell tubules and compartments, a certain number of cells have a larger cytoplasm and stain brilliantly pink or red, the alpha cells. Of course, each of these cells has also a juvenile stage when it is small and contains few red granules. Then the cell is similar to a gamma cell. The majority of alpha cells, however, appear tightly packed with eosinophilic granules and show few transitions. These cells apparently produce another fraction of the pituitary secretion which they either add to the incretion as a new element or they just store and inspissate the hormones, produced by the gamma cells. Every secretory cell possesses apparently the property of storage and a certain number of cells has the function of meeting emergencies and guaranteeing an even metabolic level. The storage cells have a slower rhythm of exchange. In a normal gland, all types are present, but the composition undergoes great variations due to requirements of the endocrine milieu. If secretory activity is slowed down, the storage function of the majority of cells becomes conspicuous. If demands are increased, stores are reduced. This gives a great reserve power to the pituitary.

The second type of chromophils, the beta or basophilic cells, appear entirely independent from the alpha cells. There are no transitions between alpha and beta cells, although occasionally, a beta cell may be filled with red mitochondria and has a purple appearance. As pointed out before, beta cells appear usually among the chromophobes of the medial triangle and on higher levels near the cleft. They are arranged occasionally in tubules and are most frequently inside the two hilus or connective tissue sheaths which carry large vessels into and out of the glandular part. The basophils appear to have a similar relation to some of the secretory gamma cells as the alpha cells. The beta cells appear as enlarged and heavier stained storage cells which accumulate some of the incretion of such smaller secretory cells which have a bluish-gray cytoplasm. There are many transitions between juvenile beta cells and large mature cells. The "basophilic" secretion has a higher *p*H than the acidophilic fluid. The particular function of the beta cells is to store certain agents which are connected with gonadotropic activity. It is possible that the beta cells absorb the incretion of gamma cells and concentrate and modify its properties by means of specific activity. The fact that stagnation in the pituitary circulation and activity causes a shift toward basophily indicates that the

basophilic content of the beta cells is probably not the product of a completely independent cell activity, but that the beta cells modify and store certain agents of the incretion to maintain the balance of gonadotropic hormones.

The pool of chromophobes is further increased by a number of degenerating cells of which only nuclei are left and which appear like other gamma cells when fixation and staining are not adequate. There are also sometimes large chromophobes with a great amount of cytoplasm which stains gray or faintly blue. It is evident that these "large chromophobes" which will be called "delta cells" are of different functional significance than the small chromophobes and should not be counted as "chromophobes" only, without further specification.

A Theory of the Relationship between Pituitary Function and Its Glandular Anatomy

1. While some glandular tissue of the organism (stomach, pancreas liver, thyroid) has a number of functional assignments which are uniformly maintained throughout life in each period of the life span, the pituitary has a variety of assignments which change with age and cycle.

2. With a limited number of secretory cell types in the pituitary which remain the same with certain variations throughout life, it is not probable that the production of each pituitary hormone requires a separate cellular unit. It is rather suggested that the various hormonal requirements are met by the combined action of a limited group of cells with one complex incretion with several inherent tropic actions which are activated and utilized by the varying responsiveness of the customer glands and organs.

3. Although a "hormone" may be isolated as a specific action upon other systems and even as a chemical compound, it should be remembered that hormones, like vitamins, have no independent biological existence. A hormone is the result of an analysis, which separates this specific property either by destroying it through acid or alkalic distillation and the existence of that hormone is demonstrated by the appearing deficiency after its elimination. Or a hormone is demonstrated by destroying all other faculties in a compound and isolating one specific action which is left. In both ways, a hormone is deprived of its natural existence. As a part of an incretion, a hormone represents certain faculties of that secretory activity which appear in contact with other cells or organ systems. Whenever such a contact is established an organ will be activated according to its own needs, while other potentialities are suppressed.

4. The relationship between the pituitary as the "master gland" and the other endocrine glands, especially thyroid, adrenals and gonads is, therefore, not a one way traffic, but a closed circulation which depends as much

on the returns from other glands as on the primary production. Even with only one incretion the influence upon the ovary, for instance, would be different whether the ovary is in its follicular or luteal phase.

5. It is, however, evident that the incretion of other endocrine glands, like thyroid or gonads, influences the pituitary incretion itself. The presence of estrogenic substances during the follicular phase in the circulating blood supports the formation of hormonal agents which support in return follicular growth and prevent formation of luteinizing agents while after ovulation, in the luteal phase, the formation of luteinizing agents is possible which maintain a strong corpus luteum phase, while the follicular activity is held back. This is only one example of the delicate interaction which constantly takes place between pituitary and all other organ systems.

6. Cytology of the pituitary anterior lobe indicates that the secretory activity is shared by three cell types, the gamma cells, alpha, and beta cells. Secretory potency depends upon the presence of all three types which contribute to the pituitary incretion in unison. Whether the three cell types produce a precursor which is activated by confluence of the fractions or the chromophils reabsorb some of the incretion and modify its content by specific action in order to release it again to the circulation, as seems indicated by certain observations, is a question of secondary importance. The main fact is that the demand on pituitary incretion is met by a number of secretory cells and that there is a constant storage of products available which gives the pituitary a great reserve power to meet emergencies and maintain an even metabolic level. It is indicated that the faculty of forming and storing alpha granules and beta granules is specified among different cell types, but of the thousands of cells available, only a restricted number take over this function while if not needed, the cells remain in a state of reserve. In this way the pituitary composition can change within minutes to hours after mating, ovulation, exhaustion, excitement, etc.

7. Although cell counts and determination of the percentage of certain cell groups are of great interest and have thrown some light on the faculty of the gland to change the cell composition quickly under experimental conditions, the counts are of little value for clinical pathology as long as all cell types are present at all.

8. The conclusions presented here are drawn from observations on "normal" glands and from those with definite pathological alterations. Under pathological conditions, certain activities of the pituitary are either emphasized or suppressed and observations provide, therefore, insight into certain aspects of the activity which are otherwise not available.

9. The patterns of pathology can be divided in the following groups:

a) Tumor formation.

b) Destruction due to sclerosis, thrombosis, tuberculosis, or gummi.

c) Abnormal shifts in cell distribution and appearance of pathological cell types.

10. Tumor formation: a) The most frequent tumor in the pituitary body is a chromophobic adenoma. These tumors, which may attain a considerable size and produce deficiency symptoms due to compression and replacement, are composed of small epithelial cells of no secretory activity. The cell type is not identical with the gamma cell, the secretory chromophobe of infancy and childhood.

b) The tumor which has attracted greatest interest is the so-called eosinophilic adenoma whose presence is associated with the clinical syndrome of acromegaly. In long lasting instances of acromegaly, the tumor may be completely eosinophilic and this observation has given rise to the theory that the eosinophils produce the growth hormones. At the same time, observations on the presence of "chromophobic" tumors which were also found in acromegaly have been neglected. Since more operative material is available, the number of "chromophobic" tumors has increased. A cytological analysis of these tumors shows that the chromophobes are not identical with the chromophobic tumors of the type described above, but that the cells are identical with the gamma cells of infancy. The cells are also identical with those "chromophobes" or "chief cells" which appear in pregnancy and are called "pregnancy cells." The cells are highly active chromophobes with abundant mitochondria. Such a relationship between the eosinophilic resting or stagnant tumors of acromegaly and the fast growing tumors of chromophobic appearance has been suspected by Carl Benda as early as 1902, when he pointed out that during the time of great activity the cells appear small and chromophobic, while the chronic stages are characterized by heavy eosinophilic staining reaction. He wrote: "If there is an increased degree of malignity, the formation of granules in the cells is missing and the tumor cells retain the characteristics of *chromophobic* cells." It is, therefore, suggested that the adenomas of acromegaly are not composed of normal alpha or eosinophilic cells but of the smaller variety which is present in infancy and during pregnancy in which periods the requirements for growth hormones are greatly increased. By recognizing the cell type of acromegaly as a relative of the pregnancy cell and the gamma cell of infancy, the growth promotion of these cells is well in line with other established facts. Acromegaly occurs most frequently between the ages of 20 and 30, when the gamma cells of childhood become less conspicuous and should disappear from the picture. It develops frequently in connection with pregnancy where slight acromegalic symptoms are not rare but disappear with the end of pregnancy. On the other hand, it is not surprising to see that eosinophilic cells may be present in all types of dwarfism and are conspicuous in mongolism. Eosinophilic cells indicate

increased storage and stagnation of the incretion, due to cessation of active growth or at least a slowing down of metabolic activity. An eosinophilic shift can be observed under many conditions and is correlated to thyroid and gonadal dysfunction but occurs independent from growth.

c) Basophilic tumors occur rarely during the prime of life but are not rare after menopause. If they occur in younger persons, pathology of gonadal function can be expected. The fact that castration and menopause as well as the lutein phase of the cycle are associated with increase of basophils which become larger and heavier stained indicates that their appearance is linked with the ovarial cycle. Tumors of that type are likely to maintain a pathologic metabolism as seen in sterility and hypertension.

11. Destruction of the pituitary by traumatic injury, infarction with necrosis or infection leads to panhypopituitarism with "hypophyseal cachexia," or Simmond's disease. If it is brought about by slower growing processes like tumors, tuberculosis or gummi, the result may be sclerosis of all blood glands and myxedema.

12. Of greatest interest are the cell shifts in the composition of the anterior lobe produced either by pregnancy or by pathological conditions like thyroid disease and castration. The changes in pregnancy are well studied. The pituitary is enlarged and a great increase in small, well outlined secretory cells is observable. The number of eosinophils decreases gradually in favor of the "pregnancy cells," which are equal in number to the beta cells as early as in the second month of gestation and supersede the number of all other types at term. The classification of these cells has been the subject of many arguments. The cell is larger than the classical chief cell and contains a greater amount of fine eosinophilic granules than usually seen in those cells. On the other hand, the cell is smaller than the ordinary eosinophilic cell and has less and more delicate eosinophilic granules. In the Mallory stain the cytoplasm has a gray-blue color with fine granules. With Heidenhain's iron hematoxylin, the cytoplasm is less dark than that of the eosinophils, but more granulated than the average chief cell. There can be no doubt that the "pregnancy cell" is not a separate cell type, indicative only of pregnancy, but is a secretory cell of great activity. The formation of large mature alpha cells is prevented by the accelerated metabolic turnover. In contrast to the slower secretory activity of the pituitary of adults and the insignificant production of growth hormones, the requirements during pregnancy are greatly increased and the cells return to a state usually seen only in childhood or under pathologic conditions in acromegaly. The cells demonstrate the thesis that the secretory cycle of gamma cells does not always lead through all stages of chromophilic maturation and that when production slows down, deceleration of activity leads to accumulation of chromophilic granules and therefore to increase in alpha and beta cells.

13. Although under experimental conditions, castration, thyroidectomy, cell shifts in the pituitary have frequently been observed, these observations have not yet been fully incorporated into human pathology. When I described the changes seen in the pituitary of mongoloids in 1939, I quoted some of the experimental evidence available at that time which suggested that the acidophily is not an indication of increased cellular activity, but is the result of hypothyroidism and hypogonadism. Recently John E. Kraus has collected more material with regard to those cell shifts under pathological conditions and has described these changes as "hyperplastic disease" of the adenohypophysis. By the term "hypophysial hyperplasia" is meant

> a diffuse proliferation of the glandular elements with or without cell enlargement. The disease may involve either one or more cell types, thus leading to enlargement of the organ or the hyperplasia of one cell type may take place at the expense of the other cell types, in which case the hyperplasia need not result in an enlargement of the organ.

Such cell shifts are seen, for instance, in castration. Although the results of castration vary somewhat with the species under observation, one may well adopt Severinghaus' summary:

> The most constant and striking feature in the hypophysis of all castrates is the marked increase in the size and number of large granular basophiles. . . . Acidophiles regress toward the chromophobic state, certainly an indication of reduced secretory activity. Basophils, although they enlarge and increase their granula content, appear to do so more because of a failure to release their secretory stores than because of a greatly increased rate of secretion. Kraus points out: "The histological picture of the hypophysis in castrated animals is not quite uniform, but the increase in eosinophilic cells is common to almost all mammals." Tandler and Gross were the first investigators to examine the hypophysis in eunuchs as well as in castrated women. The examination was performed partially by x-rays, partially by autopsy. The castration in women is followed, as in experimental animals, by enlargement of the hypophysis with multiplication and heterotopy of the eosinophilic cells and with a decrease in the number of the basophilic cells. In some cases, the castration effect of the hypophysis develops in a very short time, whereas in other cases these changes are not found despite the lapse of many years after castration. Castration by x-rays likewise produces, as far as one can tell from the scanty evidence, an increase of eosinophilic cells. There are known only a few cases of congenital absence of the ovaries in which the hypophysis was examined and also in these few cases the increase of eosinophilic cells was demonstrable.

Although some writers put more emphasis on the alpha cell increase, some on the regressive changes of beta cells, all agree as to the reduction of chromophobes and signs of decreased secretory activity.

14. Although the observations in man and in animals after castration are not entirely consistent, my own observations lend support to the conclusion that gonadotropic activity of the pituitary is related to the alpha

and beta cells, the latter being associated with the luteinizing effect. Absence of acidophilic elements is reflected in absence of spermatogenesis and follicle formation; absence of the basophilic elements is reflected in pathology of interstitial cells or corpora lutea and vice versa.

15. Thyroidectomy and hypothyroidism have an effect on the basophils similar to that of hypogonadism. The basophils show vacuolization and resemble "castration cells"; other basophils regress to large chromophobic cells, "delta cells." Severinghaus concludes:

> (1) The acidophiles decrease after thyroidectomy and increase with hyperthyroidism, thus having a consistent relationship to the thyroid. (2) Basophiles react somewhat similarly to both extremes of thyroid pathology, indicating that they may be indirectly influenced by other modifying factors. Among these factors, changes in the gonads conceivably play some rôle.

The statement with regard to an increase of acidophils in hyperthyroidism has to be slightly modified. This observation has been made after experimental feeding with thyroid. It is known that thyroid therapy replaces thyroid action and leads to colloid stasis in the thyroid. It is therefore suggested, that colloid accumulation rather than hyperthyroidism produces increase in alpha cells. In Graves' disease, the alpha cells are decreased.

16. The accumulated facts indicate clearly that there is not such a simple relationship between acidophilic cells and growth promotion as one would expect from a study of most textbooks. After an analysis of the available observations one will hardly be surprised to find that observations on mongoloid patients fall in line with those made in animal experiments and in widely scattered instances of pituitary pathology.

Observations in Mongolism

The observations on 46 cases of mongolism indicate distinctly pathology of the anterior pituitary lobe. The pathology reveals two patterns:

1. Deficiency of the gamma cell system and general inability of formation of chromophilic elements.
2. Chromophilic shift toward eosinophily with absence or deficiency of gamma cells and pathology of beta cells.

Both types reveal a deficiency of gamma cells or those chromophobes which are of a secretory type and dominate in normal cases during infancy and childhood. These cells are missing and instead a small chromophobic cell with little cytoplasm and pyknotic nucleus is present. In addition, chromophilic elements are almost absent in the first group. The glands lack the ability to form secretory granules which are an important indication of functional activity. It is worth mentioning that the functional independency of alpha and beta cells is emphasized by the observation that

of the 18 cases of this group (8 males and 10 females), in two females some alpha cells were present and in 4 males and 4 females, some beta cells were present but no alpha cells.

In the second group a conspicuous shift toward eosinophily was observed with all other cell elements absent or negligible in number (Figs. 51 and 52). In these cases the absence of gamma cells was as remarkable as the alterations found in the beta cell system. The beta cells showed either regression toward a large, stainless chromophobic cell (delta cell, Fig. 53), or were unusually heavily stained and enlarged, revealing vacuolation. This type of beta cell is known as "castration cell" (Fig. 54). Twenty-five cases or 54 per cent of the material showed this type of pathology.

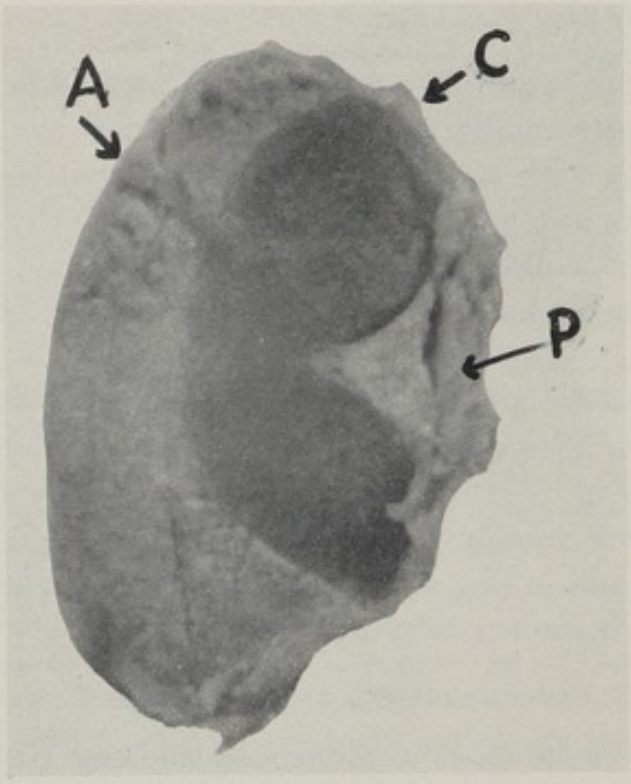

FIG. 50. Photograph of pituitary of a 10 yr. old mongoloid girl. Horizontal section: (A) anterior lobe; (C) colloid accumulation in Rathke pouch; (P) posterior lobe. Note compression of anterior lobe microscopically composed of eosinophilic cells.

In three instances no outstanding alterations could be observed. These three cases showed a fairly normal distribution of the three cell types. The first case is that of a retarded baby who was treated with thyroid and antuitrin and whose diagnosis of mongolism was still not beyond doubt at the time of death. At autopsy thyroid and adrenals were found normal in addition to the pituitary. The next case is that of a mongoloid Negro who was much better developed than most mongoloids and whose thyroid, liver and adrenals were found without changes. The third case was a borderline case with an I.Q. of 56.

The patterns of pathology of the pituitary in mongolism suggest a chronic pituitary deficiency. In this chronic panhypopituitarism all endocrine glands show the effect of this deficiency. It goes without saying that gonads and adrenal cortex are hypoplastic. It is interesting that the thyroid of these cases shows a high degree of deficiency and pictures similar to cretinistic degeneration are observed. It is, however, extremely rare, that full degeneration and myxedema occur.

The observations in mongolism indicate that group 1, the chromophobic regression with or without delta cells, reflects the hypothyroid-hypogonadal type, and group 2, the shift toward acidophily with or without castration cells, is influenced by the colloid stasis of the thyroid. Although the relationship between colloid goiter and acidophily is not 100 per cent, of 35 cases with colloid goiter, 26 showed increased eosinophily. On the other hand, of the colloid-free thyroid cases, only one showed this shift toward eosinophily of the pituitary, and it is quite possible that some parts of the thyroid contained unrecognized amounts of colloid.

The eosinophilic shift which was observed in 25 cases came originally as a surprise. An analysis of the facts at hand reveals, however, that this type of "hypophyseal hypertrophic disease" (Kraus) fits well into observations gained recently by experimental means and clinical observations. The eosinophilic shift is apparently a symptom of thyroid and gonadal dysfunction and associated with colloid stasis in thyroid and pituitary. Not only has this eosinophilic shift been observed in other cases of dwarfism, but it is worth noticing that the only control cases which showed similar alterations in the liver as seen in mongolism showed also extreme colloid accumulation in the cleft and tubules. This stasis has also been observed in some cases of cretinism. We are, therefore, entitled to conclude, that eosinophily as such is not a sign of increased growth hormone production but a sign of secretory stagnation. In this group of mongoloid patients, the deficiency is not a panhypopituitarism, but a deficiency of growth action. The fact that eosinophils and basophils may be present independent from the other type and also without full development of the gamma cells provides further evidence that each of these 3 cell types adds certain agents to the general pituitary secretion. Under pathological conditions this unison of action is split. Normal function requires a delicate coordination of all cell systems not only within the anterior pituitary body but within the whole endocrine milieu.

Emphasis has been placed upon the secretory pathology of the anterior pituitary lobe, because observations indicate the importance of a dysfunction of this system. This, however, does not mean that the posterior lobe is completely normal and the nervous regulation is without importance.

TABLE 14.—*Relationship between Pituitary Cytology and Thyroid Condition*

No.	Age	Sex	Thyroid	Pituitary	Pathology Patterns
36/60	2 days	F	Advanced development, colloid formation	Small, inactive chromophobes predominant. Cell necrosis	1
35/94	6 wks.	F	Colloid thickened, fetal cell nests. Increased fibrosis	Small, inactive chromophobes predominant. Cell necrosis	1
35/173	3 mos.	M	Colloid goiter. Replacement fibrosis	Small chromophobes predominant. Cell necrosis. Few beta cells. No alpha cells	1
37/6	5 mos.	M	Colloid goiter. Fibrosis	Alpha cells predominant	2
31/62	6 mos.	F	Colloid goiter. Fibrosis	Alpha cells predominant	2
43/120	6 mos.	M	Fetal. Colloid-free. Cell nests with increased fibrosis	Small, degenerated chromophobes. No chromophils. Vascular stasis	1
37/1	7 mos.	F	Colloid goiter. Resting	Alpha cells predominant	2
45/152	8 mos.	M	Normal	Normal	Normal
32/207	13 mos.	M	Colloid goiter. Fibrosis	Alpha cells predominant. Congestion	2
45/154	18 mos.	M	Fetal gland. Colloid-free	Fetal gland: no chromophils. Some "large chromophobes"	1
33/80	18 mos.	M	Colloid goiter. Fibrosis	Alpha cells predominant. Congestion	2
43/102	22 mos.	M	Colloid goiter	Small, inactive chromophobes predominant. Delta cells. No chromophilic activity	1
40/57	$4\frac{5}{12}$ yrs.	F	Colloid goiter. Fetal cell nests. Replacement fibrosis	Lateral fields: 95% alpha cells. Trigonum delta cells, dark basophils	2
42/99	$4\frac{5}{12}$	F	Colloid goiter. Fetal cell nests. Fibrosis	Fairly normal distribution. Malformation of posterior lobe	—
43/103	$6\frac{7}{12}$	M	Colloid goiter	Large gland with chromophilic shift. Alpha cells increased. Delta cells, dark basophils	2
43/124	7	M	Colloid goiter. Possible toxic activity	Chromophilic shift. Alpha cells scattered, numerous. Delta cells. Castration cells. Cleft enlarged; colloid	2

43/118	$7\frac{3}{12}$	M	Colloid goiter	Colloid in cleft, enlarged. Delta cells. No basophils. Alpha cells numerous	2
40/47	$8\frac{7}{12}$	F	Colloid goiter. Resting	Colloid in cleft. Small chromophobes predominant. Few heavy stained basophils	1
38/25	$8\frac{8}{12}$	M	Colloid goiter	Chromophilic shift. Alpha cells predominant. Castration cells	2
43/125	$9\frac{9}{12}$	M Negro	Beginning colloid stasis	Large gland, colloid in cleft. Alpha cells scattered. Castration cells. Chromophobes small, inactive. Delta cells	2
44/134	$9\frac{7}{12}$	F	Degenerated, exhausted. Fibrosis	Tightly packed infantile chromophobic gland. No chromophils. No secretory activity	1
38/17	$9\frac{8}{12}$	F	Colloid goiter	Abundant colloid. Alpha cells. Delta cells and few beta cells	2
Mi	10	F	Colloid goiter	Colloid in cleft. Atrophy of anterior lobe. Alpha cells predominant	2
44/141	$10\frac{9}{12}$	M	Degenerated colloid goiter with fibrosis	Small, inactive chromophobes predominant. Delta cells	1
44/139	$11\frac{1}{12}$	M	Fetal gland. Colloid-free	Chromophilic shift. Alpha cells. Delta cells. No colloid	2
37/10	12	F	Colloid goiter	Large gland. Chromophilic shift. Alpha cells, delta cells. Beta cells	2
42/82	$13\frac{10}{12}$	F	Colloid goiter	Colloid in acini. Small chromophobes predominant. Delta cells. Beta cells. No alpha cells	1
38/23	$14\frac{5}{12}$	M	Colloid goiter exhausted	Chromophilic shift. Alpha cells predominant. Delta cells. Castration cells	2
M 2	14	F	Colloid goiter	Chromophobes predominant. Alpha cells. Few beta cells	1
38/32	$14\frac{11}{12}$	M	Colloid goiter with possible toxic activity	Fairly normal distribution	—

TABLE 14.—*Relationship between Pituitary Cytology and Thyroid Condition—Continued*

No.	Age	Sex	Thyroid	Pituitary	Pathology Patterns
43/100	$15\frac{8}{12}$	F	Colloid goiter with possible toxic activity	Large gland. Chromophobes predominating. Alpha cells, violet cytoplasm. No mature beta cells	1
43/116	15	F	Colloid goiter resting	Large gland. Alpha cells. Delta cells	2
44/148	$15\frac{10}{12}$	M	Colloid goiter with fetal nests and degeneration	Infantile gland with dense cell columns. Alpha cells small. Delta cells. Chromophobes degenerated	2
42/85	16	M	Colloid goiter. Some possible activity	Large gland. Tightly packed. Alpha cells in columns, predominant. Beta cells granular, vacuolated. Delta cells. Chromophobes small and degenerated	2
41/58	$16\frac{3}{12}$	M	Colloid goiter degenerated. Fibrosis	Small chromophobes predominant. Chromophils almost absent	1
42/90	17	M	Colloid goiter with fetal cell nests. Possible toxic activity	Alpha cells predominant. Beta cells in tubules	2
42/81	17	M	Colloid goiter. Large fetal cell nests. Possible toxic activity	Chromophobes predominant. Beta cells dark blue, in clusters. Alpha cells almost missing	1
43/126	$17\frac{6}{12}$	F	Colloid goiter. Large fetal cell nests. Possible toxic activity	Small chromophobes predominant. Beta cells dark blue, in clusters. Alpha cells almost missing	1
42/83	$17\frac{9}{12}$	M	Colloid goiter. Degenerative changes	Fetal gland. Small chromophobes. Few chromophils	1
41/65	18	M	Lymphatic infiltration	Alpha cells predominant. Delta cells numerous. Beta cells. Chromophobes almost absent	2

44/146	$18\frac{4}{12}$	M	Colloid goiter resting	Large gland. Tightly packed. Alpha cells predominant. Castration cells. Beta cells. Delta cells. Small, inactive chromophobes	2
38/22	$20\frac{6}{12}$	M	Lymphatic thyroiditis	Alpha cells predominant. Castration cells. Delta cells. No chromophobes	2
43/111	$26\frac{4}{12}$	M	Colloid goiter. Some possible activity	Alpha cells predominant. Beta cells and delta cells. Fetal chromophobes	2
41/71	28	F	Colloid goiter. Some possible activity	Colloid in cleft and spaces. Chromophobes predominant. Small beta cells	1
37/8	$30\frac{9}{12}$	M	Colloid goiter. Some possible activity	Alpha cells predominant. Almost no other elements	2
44/129	40	F	Colloid goiter. Degeneration	Small gland. Large cleft filled with thin colloid. Chromophobes predominant. Almost no chromophils	1

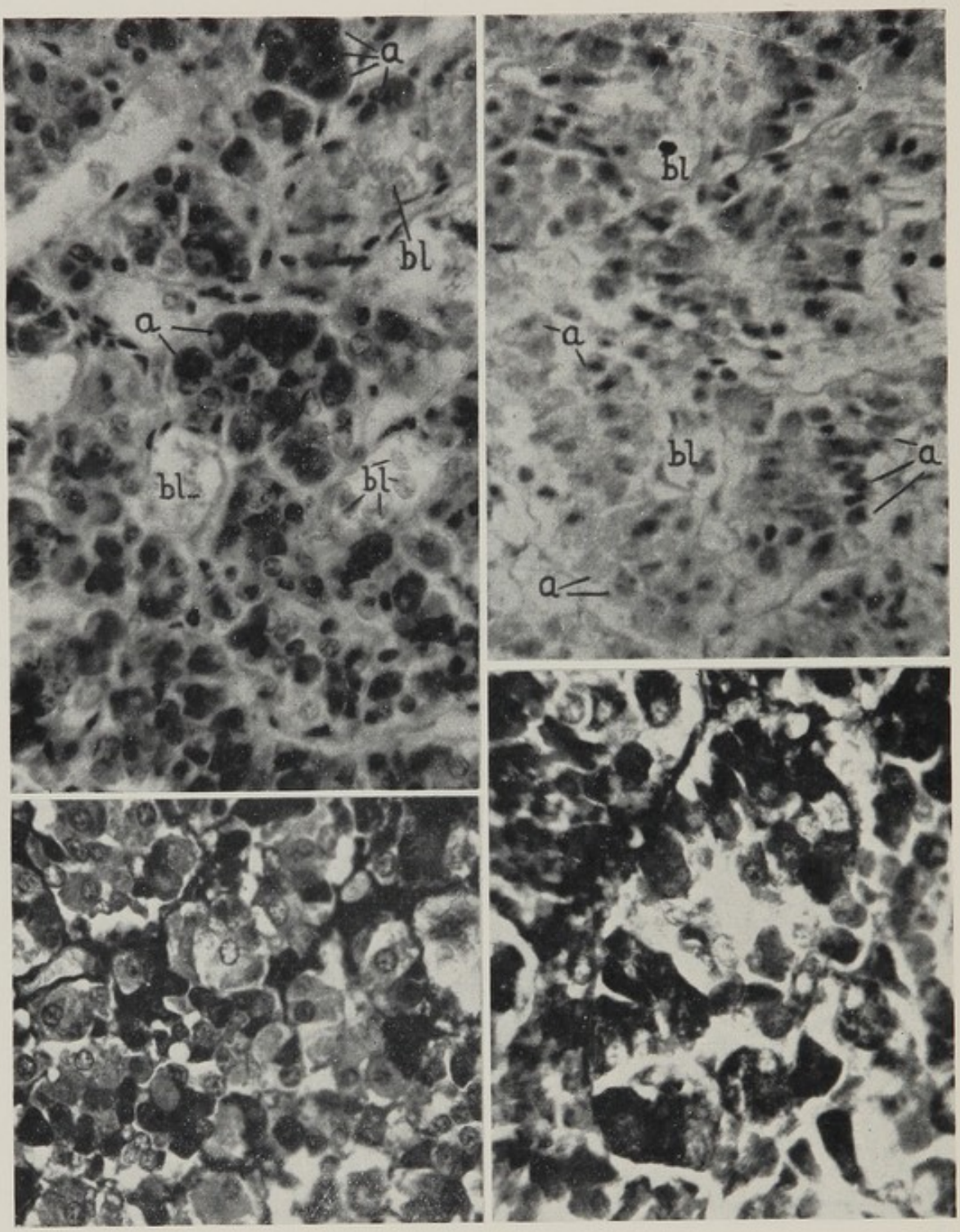

Fig. 51. (Upper left) Pituitary of a 5 mos. old mongoloid male (37/6). Note complete eosinophilic shift with absence of chromophobes. (A) alpha cells or acidophiles, (B) blood in enlarged spaces.

Fig. 52. (Upper right) Eosinophilic shift in a 7 mos. old female baby (37/1). (A) alpha cells or acidophiles, (B) blood. Note absence of chromophobes.

Fig. 53. (Lower left) Pituitary of a 12 yr. old mongoloid female (37/10). Note large chromophobes, "delta cells" also described as struma cells (Romeis), thyroprival cells (Kraus). Cytoplasm grayish-blue, dust-like.

Fig. 54. (Lower right) Pituitary of a 20 yr. old mongoloid male. Heavy basophiles with vacuolation, "castration cells."

Underdevelopment of the posterior lobe has been seen in several cases. As a whole, the nervous elements are poorly developed. Some authors have suggested brain pathology in the hypothalamic region as a possible explanation. Although the brain in mongolism is abnormal and the hypothalamic region is undoubtedly involved, the explanation seems not correct. In cretinism the same changes in the brain are present from birth on. And yet the pituitary of the cretin does not show the pathology seen in mongolism, with the exception of the colloid storage and the "struma cells." If the pituitary changes in mongolism were due to brain pathology, one would expect the same alterations in congenital cretinism. This idea is further borne out by the fact that several other types of mental deficiency show more profuse brain pathology than mongolism, and yet the same type of growth disorder does not develop.

The question of an endocrine function of the central nervous system is still a matter of speculation but, even without postulating such a function, the nervous system cannot be omitted from the endocrine milieu. The significance of the role of psychosomatic interaction is beyond doubt. The importance of psychic factors in Graves disease, for instance, is generally accepted. The interpersonal interaction, transmitted through sensory stimuli and integrated into emotions provides a permanent stimulation of the organism which is constantly forced to take part in its relationship with the surroundings. Emotions are the tides of the organism which bring about a permanent speeding up and slowing down of all physiological functions. A mentally deficient child who lives the vegetative existence of a creature without interpersonal interaction remains infantile in its whole system. The mongoloid, however, reveals much greater emotions than most of its unfortunate companions with whom he may share the same mental age. The relative awareness of mongoloids and their emotional responsiveness indicate further that in this condition the primary disorder is not the nervous system but a specific glandular deficiency.

Conclusions

A study of the pituitary body in mongolism reveals pathology which indicates that this condition is associated with abnormal pituitary function. In contrast to cretinism in which the pituitary tends to be enlarged, the pituitary in mongolism is hypoplastic. Abnormally low secretory activity is indicated by (1) inability to produce secretory cells and granules and (2) by abnormal granule storage (stagnation) and disappearance of signs of secretory activity.

In the first group, there is evidence of hypopituitarism with absence of these granule types which we have seen to be connected with all secretory activity. The gland fails to produce and store potent agents. In the

second group, the secretory elements are filled with one type of granule (alpha granules) while the beta cells regress to castration cells or delta cells (large chromophobes). The secretory chief cells (gamma cells) are underdeveloped.

The endocrine disorder in mongolism is a specific metabolic disorder. Mongolism is the congenital type of hypopituitarism. In the acquired type which develops in childhood and results in dwarfism, the general effect on the body organs, especially the brain, is less conspicuous. The relationship between the mongoloid child and the pituitary dwarf is the same as that between the congenital thyroid aplastic cretin and the myxedematous child. The effect of congenital hypopituitarism is so devastating, because pituitary activity precedes the function of all other endocrine glands which never enter into action on a proper level.

The Pituitary in Cretinism

Alterations in the pituitary in cretinism and experimental thyroidectomy were observed as early as 1888 by N. Rogowitsch. Destruction of the hypophysis in cretinism was observed by Ponfick in 1899. A similar observation was reported recently by Means, who mentions that in one of his cases, in which an autopsy was made, the pituitary was found completely destroyed by what seems to have been a cyst. Such extreme degrees of destruction are the end result of regressive changes which are due to an edematous infiltration and formation of smaller cysts filled with a colloid-like fluid. In experimental thyroidectomy and in most cases of cretinism, one finds an enlarged pituitary body, which appears "hypertrophic." Some writers have spoken of a "compensatory hypertrophy" on account of the increased weight (1.3–2.0 Gm.). The histologic picture shows an edematous gland in which the cell strands are separated and the spaces greatly enlarged. Cysts may be found, or adenoma. A new case of that type may be briefly reported:

Case 43/112. Female, cretin, congenital thyroid aplasia. Age 47 years. Pituitary measured 20 mm. in width and 12 mm. in sagittal diameter. It weighed 1.5 Gm.

The measurements indicate the considerable enlargement of almost 100 per cent, the normal width being 10 to 12 mm. Normal sagittal diameter ranges from 6 to 9 mm., weight from 0.6 Gm. to 1.0 Gm.

Microscopic examination revealed a very peculiar picture. There was one small, round adenoma, measuring 1 mm. in diameter, composed of acidophilic cells of rather juvenile character. The cells were arranged in columns with their length axis in a right angle to the lumen of small tubules with definite eosinophilic granule. This was an "eosinophilic adenoma." A second adenoma was near the posterior-lateral edge of the anterior lobe, measuring 2 mm. in diameter. This was composed of embryonic chromophobic epithelium cells, resembling those near the Rathke pouch. This adenoma had a cyst filled with brittle, albuminous material exactly like the colloid

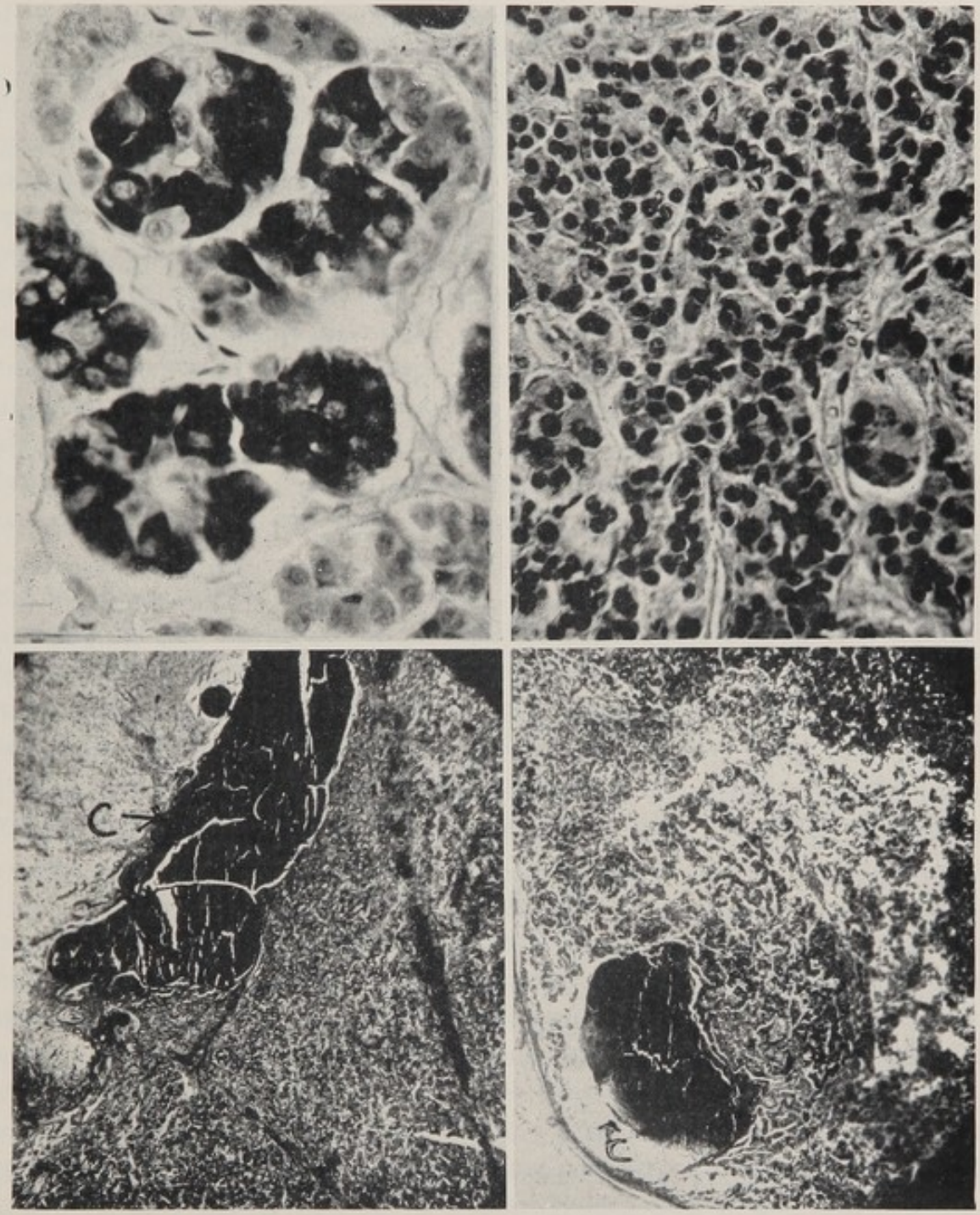

FIG. 55. (Upper left) Hypertrophic basophiles in an 8 yr. old mongoloid male (38/25). Basophilic acini formation.

FIG. 56. (Upper right) Pituitary of a 30 yr. old mongoloid male. Complete eosinophily; irregular cell proliferation.

FIG. 57. (Lower left) Pituitary in cretinism. Rathke cleft filled with brittle colloid (C); at the right side of the picture: the anterior lobe composed of small degenerated chromophobes. The black lines indicate connective tissue strands.

FIG. 58. (Lower right) Pituitary in cretinism. Eosinophilic tumor with colloid cyst in anterior lobe; marked edema.

A few cells in the anterior lobe were acidophils. True basophils were present, but the majority of cells were of the large chromophobic type (delta cells), described as "struma cells" (Romeis), "myxedema cells" (Schilder), or "castration cells" (various authors).

of the thyroid. A third adenoma, also of embryonic cells, was in the middle of the gland. The Rathke cleft was tightly filled with "colloid" and was enlarged.

A pathologist examining this gland without knowing the history or on being told that this was a case of acromegaly would be perfectly satisfied that he had found the obligatory eosinophilic adenoma, which explains acromegaly. For the anatomist familiar with cretinism the above description does not come as a surprise. Similar cases have been reported before.

Enlargement of the pituitary is common and has been reported by Carl Benda, Aschoff, MacCallum and Fabian, Brauchli, Berblinger, and others. Enlargement may not be present in all cases, but it is rather frequent. Histologically, the accumulation of a colloid-like fluid has been seen by Wegelin, Brauchli, MacCallum, and Romeis, who found colloid even in the posterior lobe. Stasis and edema with accumulation of albuminous fluid, giving a colloid reaction, are so typical that they can be considered as indicating thyroid deficiency of severe degree.

With regard to the cell types, the most consistent alteration is the appearance of large stainless cells, which should not be called "chromophobes" because this term obscures their pathological character. They are depleted, decolorized epithelium. The absence of basophils at the same time suggests their origin from the basophils. The fate of the acidophils is not uniform. They are always reduced, but they may be accumulated in small adenomas, as in my case, or they may disappear almost completely.

The Gonads

Anomalies in sex development of mongoloid males and females are common. More than half of the males have undescended testicles and often abnormal sex organs. Females have delayed menarche, the menstrual cycle is often irregular and menopause early. Heterosexual interest is usually little developed in both sexes with occasional masturbation the only sex activity. The pathology of the gonads which is presented here, offers for the first time data indicating hypoplasia in both sexes. Exceptions, however, occur and if sterilization is considered, the case should be thoroughly investigated.

In 1949, Grace M. Sawyer, M.D., reported the first confirmed case of a mongoloid having given birth to a normal child. The mother, short in stature (4′ 7½″), obese, coarse rough skin, eyes slanting with epicanthal folds, I. Q. 25, had been delivered of a female infant, weighing 2532 grams, by Caesarean section in 1937. The pleasant child, now 12 years old, has been tested several times and scored I.Q.s ranging from 120 to 123.

The Male Gonads

Twenty-four cases were available for microscopic study. The age ranged between 2½ months and 31 years. In the age group below 2 years,

there were 7 cases, 3 of which may be considered within normal range for that age group. The seminiferous tubules were filled with Sertoli cells, among which one to three spermatogonia or spermatogenic cells were found per tubule. In one case the interstitial connective tissue was slightly increased, but still within a range in which recovery might be expected. Four of the cases showed no spermatogenic tissue. The tubules were filled with Sertoli cells. The interstitial tissue consisted of more or less coarse fibrous tissue, which was in some instances greatly increased. In no case were interstitial cells found.

The second group of cases comprised 8 patients between the ages of 4 years 5 months and 15 years 10 months. In all these instances the anatomical picture was very uniform. The testicles were very small and undersized, measuring between 10 and 17 millimeters in length and 6 to 8 millimeters in width, on cross sections. The histological picture showed small seminiferous tubules filled with Sertoli cells without spermatogenic cells. The interstitial tissue consisted of coarse strands of fibrous tissue separating the tubules and frequently encroaching upon them. No interstitial cells were found in these cases.

The last group was of 9 patients ranging from 16 to 31 years of age. In this group two patterns of pathology were found. No complete maturation, however, was found in any instance. In measuring the size of the testes, it was obvious that 3 cases showed a better development, which corresponded to about two thirds of the normal size of a male testicle, which is about 5 centimeters in length and $3\frac{1}{2}$ centimeters in width, on cross section. Three testicles measured 3×1.8 cm., 2.8×1.6 cm., and 3×1.6 cm., respectively. In these instances some spermatogenic activity was noticeable. The tubules were lined by Sertoli cells, and numerous mitotic figures were recognizable in the spermatogonia. None of the cases, however, showed mature sperm cells. The interstitial tissue contained a few interstitial cells; it was rather fine and loose and not markedly increased with the exception of the second case, in which a partial fibrosis was noticeable. These 3 cases may be grouped as "almosts." The development, however, lagged definitely behind normal maturation.

The remaining 6 cases showed again a rather uniform picture. The small testicles measured between 20 and 23 millimeters in length and 8 to 12 millimeters in width. The seminiferous tubules were small and filled with a Sertoli syncytium, and little or no spermatogenic tissue was present. In some cases the basal membrane was greatly thickened. The interstitial tissue consisted of more or less coarse masses of fibrous tissue with no interstitial cells. All these cases showed a high degree of testicular hypoplasia and degeneration.

There are several points of considerable interest in the pathology of the male gonads in mongolism. It is noteworthy that in the baby group several

cases were found within normal range, indicating that some mongoloids at least have fairly normal gonadal equipment at birth. The degeneration which is seen in the older age groups seems, therefore, to be due to the absence of those factors which are necessary to develop and stimulate gonadal function to maturity. The absence of spermatogenic tissue in other cases, however, confirms the observation that some of the children are so severely damaged in the prenatal period that germinal epithelium never differentiates. This observation is further confirmed by the large number of mongoloid boys with undescended testicles. It is somewhat surprising to see that in the second age group, in those boys who died before puberty, all testicles showed a great amount of atrophy and degeneration. The infectious diseases to which these children have succumbed may possibly have added to the picture of complete testicular atrophy. The last group of cases offers for the first time the opportunity to study the various patterns of gonadal deficiency in man in connection with the other endocrine glands.

Experimental pathology has collected a huge amount of material on the influence of pituitectomy on sex function. No attempt, however, has been made to establish the relationship between pituitary deficiency and gonadal atrophy in man. In the following table (15) observations on the testes are confronted with the findings in the pituitary body.

Gonadotropic hormones have been fractionated into the follicle-stimulating hormone (FSH) and the luteinizing hormone (LH). Both factors are best extracted from the pituitary tissue by alkaline solvents. Both fractions show definite differences in solubility, the LH fraction being not readily soluble below a *p*H of 5, while FSH is soluble over a wide range of *p*H and is extracted by aqueous solvents whether basic or acidic. This observation probably offers the key to the problem of acidophilic and basophilic granules in the pituitary cells. Although the usual dyes are not strictly acid or basic in a chemical sense, their *p*H differs to some extent.

Experiments in male rats by Greep, Fevold, Hisaw, and many others have shown that the FSH factor stimulates only tubular development, leaving the interstitial elements unaffected. The LH factor, on the other hand, has a definite influence on the interstitial tissue, while the germinal epithelium remains unaltered. Growth of the gonads seems to depend on the presence of both factors. If only FSH is used, a slight increase in size occurs, while the LH factor has little influence upon augmentation. If both hormones are present to a certain degree, normal augmentation will take place.

These observations are of great interest with regard to the pathological patterns of atrophy in man. I have called attention to the fact that the

pituitary in mongolism shows two main types of pathology: (1) a chromophobic shift without development of chromophilic elements, and (2) a chromophilic shift with absence of chromophobic elements. In comparing the pituitaries with the gonads, it is conspicuous that the patients with in-

TABLE 15.—*Relationship between Male Gonads and Pituitary in Mongolism after Puberty*

Case No.	Age	Height of Patient, Cm.	Testicle	Pituitary
42/85	16	126	Size: 3 × 1.8 cm. Interstitial tissue fairly normal. Some spermatogonic activity. No maturity. Some degeneration	Chromophilic shift, alpha and beta cells. Castration cells
41/58	16	138	Size: 2.2 × 1 cm. Solid lumina with Sertoli cells. No spermatogonia. Interstitial fibrosis	Small, infantile gland. Chromophobes, no chromophils
42/81	17	130	Size: 2 cm. × 9 mm. Solid lumina. Sertoli cells, no spermatogonia. Moderate interstitial fibrosis	Chromophobes. No alpha cells. Castration cells
42/90	17	159	Size: 2.8 × 1.6 cm. Mitotic activity, but no maturity. Interstitial tissue normal	Chromophilic shift. Alpha and beta cells
41/65	18	165	Size: 3 × 1.6 cm., 2.5 × 1.3 cm. Some spermatogonic activity, partial degeneration. Moderate interstitial fibrosis	Chromophilic shift. Alpha and beta cells. Castration cells
44/146	18		Size: 2.3 × 1.2 cm. Tubules small but fairly developed. Some spermatogonic activity. Interstitial tissue fairly normal	Chromophilic shift. Alpha and beta cells
M. 3	20		Size: 2.2 cm. × 8 mm. Degenerated tubules. No spermatogenesis. Increased interstitial fibrosis	Chromophobes only
38/22	20	160	Size: 2 × 1 cm. Tubular formation with some activity. No complete maturity. Interstitial fibrosis	Chromophilic shift. Alpha and beta cells
37/8	31	142	Small testes. Some spermatogonic activity. No complete maturity. Great increase in interstitial fibrosis. Fibrosis of basal membranes	Alpha cell shift

ability to form chromophilic elements show definite gonadal hypoplasia and atrophy. None of the cases with only chromophobic cells in the pituitary showed any degree of normal development in the gonads. Conversely, a chromophilic shift warrants a better gonadal development in the majority

of cases, although the presence of chromophilic elements may not prevent degeneration in every case. A rather definite relationship between these factors is observable in patients after puberty, and it is possible to predict the condition of the gonads from a study of the pituitary. Patients with infantile chromophobic cells show gonadal atrophy and hypoplasia, and one may conclude that the chromophobic elements of the pituitary are not able to maintain any degree of gonadal activity. The best development of the testicles was present in those patients in whom alpha and beta cells were fairly numerous. Cases which showed only alpha cells had some activity of the spermatogenic epithelium but, at the same time, increased fibrosis of the interstitial tissue. On the other hand, the presence of beta cells guarantees fair development of the interstitial tissue while tubular activity demands the presence of alpha cells. One may, therefore, conclude that these observations provide evidence of the direct relationship between gonadal activity and chromophilic cells. It is suggested that the alpha cells provide the FSH fraction, while the LH fraction is provided by the beta, or "basophilic," cells. Acromegaly and hyperthyroidism are both associated with an increase in acidophilic cells in the pituitary and a temporary increase in gonadal activity.

Mongolism and cretinism are associated with hypopituitarism. If all chromophilic elements are absent, gonadal hypoplasia is conspicuous. If alpha cells are present, but beta cells are missing, tubular activity is present to a certain degree, but no maturation occurs. If beta cells are present but alpha cells are absent, the interstitial tissue is fairly well preserved, but tubular activity is missing. Thus, a definite relationship between alpha and beta cells and the gonadotropic fractions in man seems established.

This observation, however, is not correct for the age groups before puberty. In the infantile mongoloid, no direct relationship between pituitary cytology and the condition of the testes could be observed.

The Female Gonads

Anomalies in sex development of mongoloid girls are as conspicuous as those of males. They are frequently recognizable in early infancy. The major labia appear sometimes like round cushions or are hypertrophic. After puberty, development of secondary sex characters is abnormal. Mongoloid girls mature late, and menstruation may not start before the end of the teens. The breasts remain infantile longer than in normal children, although they frequently become very heavy and pendulous owing to abundant fat development. The areolar glands are generally missing. Axillary hair is absent. Some mongoloid females show signs of hirsutism. All these irregularities indicate anomalies in the development of those secre-

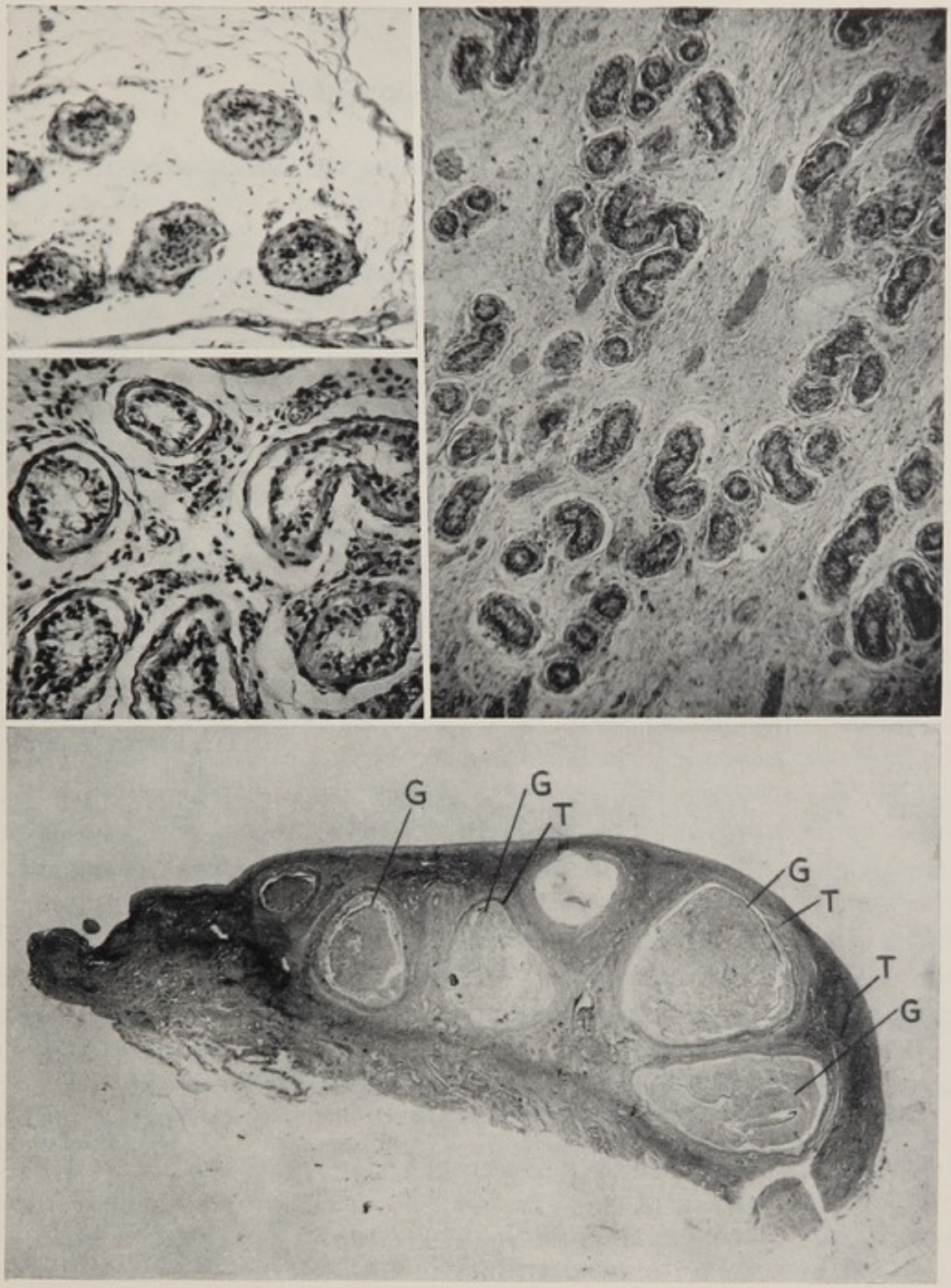

Fig. 59. (Upper left) Gonads in mongolism. Testicular atrophy of a 16 yr. old mongoloid. The seminiferous tubules contain only degenerated Sertoli cells which fill the entire lumen. No spermatogenic cells present. Note increase in interstitial fibrous tissue which is loose and edematous. No interstitial cells present.

Fig. 60. (Center left) Testicle of a 20 yr. old mongoloid adult. Note the thickening of the basement membrane. Tubules filled with Sertoli cells. No spermatogenic cells. No interstitial cells.

Fig. 61. (Upper right) Testicle of a 23 mos. old mongoloid baby. Note the striking increase in coarse interstitial connective tissue separating the tubules from each other. Some tubules appear encroached and degenerated. Several tubules still contain "germinal epithelium" embedded in the Sertoli syncytium.

Fig. 62. (Lower) Ovary of a 12 yr. old mongoloid girl. Note 5 enlarged graafian follicles which apparently failed to involute. The follicles are lined by the theca interna (T) and a perfectly preserved membrana granulosa (G). The latter is lifted from the theca at some points and is floating, but not degenerated. No ova seen in the follicles. The remaining graafian follicles are degenerated.

tory glands which participate in developing sex characteristics (ovaries, adrenals).

TABLE 16.—*Relationship between Female Gonads and Pituitary*

Case No.	Age	Height of Patient, Cm.	Ovary	Pituitary
36/60	2 days	40	Fetal	Inactive chromophobes, necrosis
35/94	6 weeks	49.5	Normal	Inactive chromophobes, necrosis
37/1	7 mos.	65	Normal	Alpha cell shift
33/80	18 mos.	72	Normal	Alpha cell shift
40/57	4½ yrs.	87	No follicular activity. One large follicle, few scars	Alpha, beta, and castration cells
40/47	$8\frac{7}{12}$	98	Slight follicular activity. Few lutein scars. Two large cysts	Chromophobes predominant. Beta and castration cells, colloid
44/134	$9\frac{7}{12}$	113	(1) Small, undeveloped, infantile. (2) Several cysts	Infantile, chromophobic. No chromophils
M. 1	10	108	Cystic follicle atresia	Alpha cells predominant
37/10	12	126	Cystic follicle atresia	Alpha cells predominant. Delta and beta cells
43/100	$15\frac{8}{12}$	140	Fibrotic ovary without activity	Chromophobes predominant
43/126	17½	125	Little follicular activity. Scars and follicle cysts. Numerous atretic scars with fibrous organization. No lutein cells preserved	Castration cells. Few alpha cells. Chromophobes predominant
41/71	28	136	No follicular activity. Atretic scars with degenerated lutein cells	Colloid in cleft. Chromophobes predominant. Small beta cells. No alpha cells
44/129	40	134	No primordial activity. Numerous corpora lutea atretica, not completely involuted. One recently ruptured graafian follicle	Chromophobes predominant. Colloid in cleft. (Chromophobic regression)

It is not surprising, therefore, that the ovaries of mongoloid patients were found abnormal in all instances, with the exception of some babies, whose ovaries were within normal range. This indicates, again, that the primary development is not necessarily abnormal, and the pathology which

is found in older mongoloids is due to lack of stimulation and maturation, which is supported by action from other glands. Hypoplasia of the ovaries was present in all cases, and no mongoloid female was found with ovaries of normal size. The pathology falls into three groups: (1) General hypoplasia without activity of the germinal epithelium; (2) hypoplasia with tendency to persistence of follicular cysts and lack of involution; (3) hypoplasia with little follicular activity, but tendency to persistence of atretic corpora lutea.

The hypoplastic, "resting" ovaries are small bodies with a limited number of primordial graafian follicles, many of them degenerated. No mature stages are found. The fibrous stroma is increased.

The ovary of the second group is characterized by the presence of numerous large follicle cysts. In an ovary of a 12 year old girl, five of those enlarged follicles were easily recognizable by the naked eye. The cortex was small and contained few primordial follicles. The enlarged follicles were lined by the interna and a well-preserved membrana granulosa. The latter was lifted from the theca on some points and floating, but not degenerated. No ova were found in these follicles. The picture indicates that follicle stimulation had taken place, but the agents which bring about degeneration of the follicles must have been missing and involution did not take place.

In the third group another phenomenon was conspicuous. There were no cysts. The whole stroma was filled with atretic corpora lutea, in which the lutein cells were still recognizable, although they had no nuclei and were without lutein. While normally the atretic corpora lutea become connective tissue scars which take little space within the stroma, in these ovaries numerous large atretic bodies were found, which had failed to undergo complete involution.

It is quite obvious that the two patterns of pathology seen in the second and third groups represent two separate types of gonadotropic deficiency. It is suggested that in the second group follicle stimulation is present, but no luteination takes place. In the third group no follicle stimulation is seen, but the LH is operating and preventing complete disappearance of the atretic corpora lutea.

A comparison with the pituitaries of the various cases establishes the fact that the instances of increased follicle stimulation are associated with an eosinophilic shift in the pituitary, while the other type showed prevalence of basophilic cells and deficiency of the eosinophilic cell system. The relationship between the two gonadotropic fractions and the two chromophilic granules of the pituitary which was seen in the males is also recognizable in the females. Absence of chromophilic elements and prevalence of chromophobes is associated with complete hypoplasia of the ovaries. The observations suggest, again, that chromophilic elements in the pituitary are necessary to establish gonadal activity.

The Suprarenal Glands

Anatomy and Postnatal Development

Although the general anatomy of the adult suprarenals is well established and the patterns of pathology which are seen in Addison's disease are known, the adrenals in childhood have been the subject of only a few investigations, and the role of the adrenals in growth disorders is practically unknown. It seems, therefore, worth while to give first a brief outline of the anatomy and a short review of the problems under discussion.

The adrenals consist of cortex and medulla. The cortex surrounds the medulla as a fruit does its kernel. Beneath the capsule a narrow cortical zone is found, which is called the zona glomerulosa. This layer consists of small columnar cells closely packed in ovoid groups or in nests which rest upon the next zone like caps. The nuclei stain deeply, and the cytoplasm is rather scanty. Beneath the zona glomerulosa are found columns of epithelial cells which form the zona fasciculata. This zone constitutes the widest portion of the cortex and consists of polyhedral cells which are larger than those of the first zone. The cytoplasm appears vacuolated and reduced to narrow threads between the numerous lipoid droplets which are scattered throughout the cells. The innermost layer of the cortex is formed by an anastomosing network of cells called the zona reticularis. These cells are about the same size as those of the second layer, but they contain little lipoid and show less vacuolation. Near the medullary border a number of cells contain abundant pigment in their cytoplasm and have, therefore, a brownish green color. These cells are called chromatophores.

The center of the adrenals is formed by a glandular core called the medulla. The cells of the medulla are not found throughout the whole space between the cortical envelope. In the periphery of the medullary core the cortical layers are separated by strands of connective tissue which contain rather large blood vessels. In the center the medulla has its greatest width and separates the cortical layers for a distance of several millimeters. In this "hilus" the medulla is composed of rounded groups or short cords of "basophilic" cells, which surround the large blood vessels and sinusoidal venules. These are the true medullary cells, derivatives of the ectoderm. If the cells are fixed in dichromate, fine brown granules may be found in them, which show the "chromaffin" reaction. In addition, sympathetic ganglion cells are also present.

One peculiarity should be mentioned. The permanent cortex appears sometimes invaginated from the outside around the central vein. It is, therefore, common to find true cortex immediately around the central vessel within the medulla, an observation which is not pathological, but can easily lead to misinterpretation. On the other hand, remnants of fetal cortex are also most likely found in the hilus area.

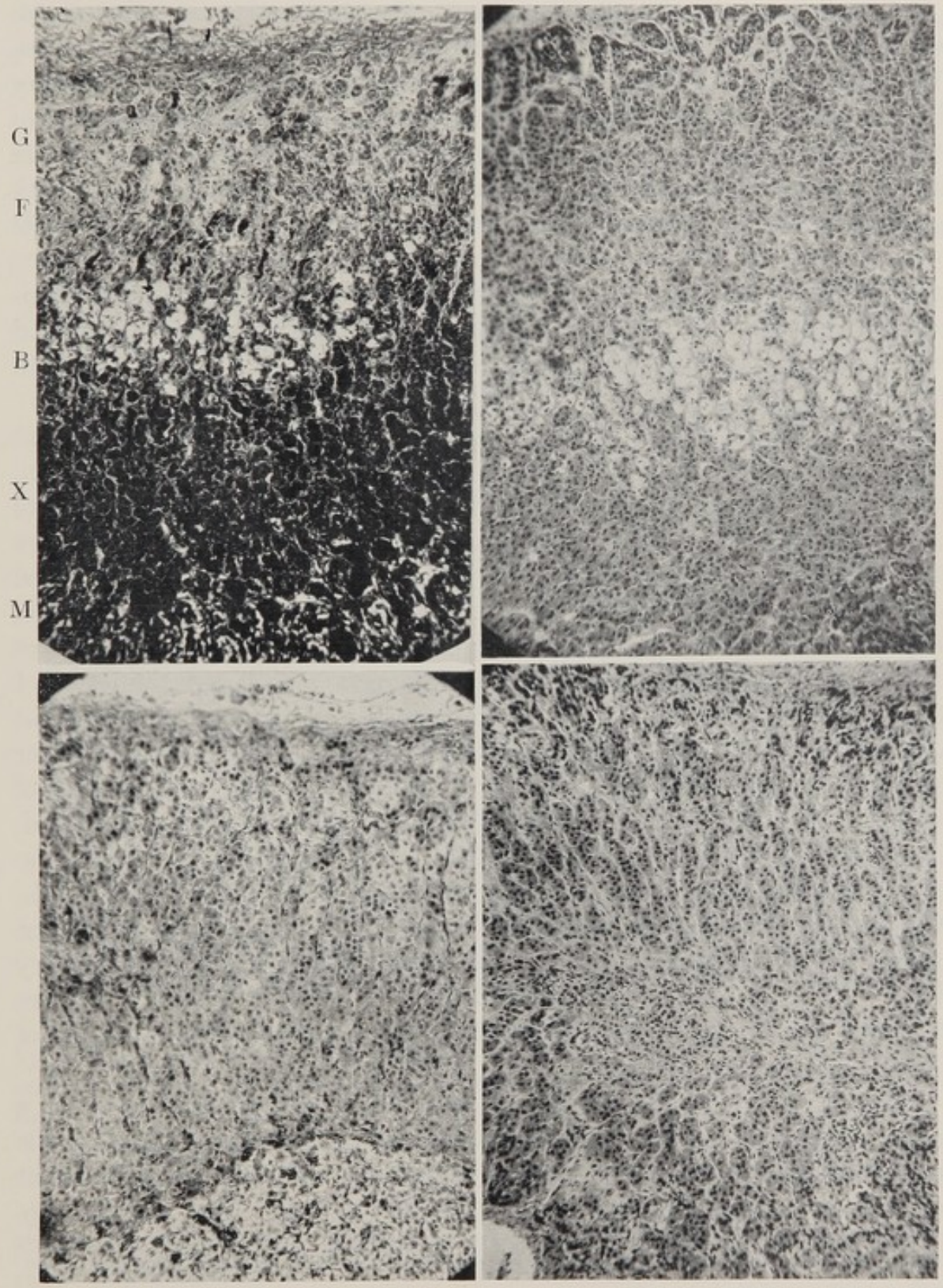

Fig. 63. (Upper left) Adrenal cortex, Masson stain; 17 yr. old mongoloid male. The upper edge represents the capsule (C), beneath the glomerulosa (G) of which some cell nests are recognizable. The fasciculata (F) is almost completely degenerated. The boundary zone (B) is in a condition of involution usually seen in babies shortly after birth. Between boundary zone and medulla (M) a broad zone of eosinophilic cells, the juxtamedullary zone or X zone.

Fig. 64. (Upper right) Adrenal cortex, H & E stain; 17 yr. old mongoloid male. The glomerularis is fairly large. The fasciculata shows no formation of cell columns

It is well known that medulla and cortex are derived from different embryological tissues, and both glandular tissues have a different function. The medulla is concerned with the production of adrenalin or a precursor of that substance. The endocrine function of the cortex has been discovered only in the last few decades. It is now known that the cortex plays an important role in glycogen and salt metabolism, and its activity is closely related to pituitary and gonadal function. Destruction of the cortex as seen in Addison's disease leads to a severe metabolic disorder; tumors of the cortex may have a striking virilizing effect in females. Pituitectomy leads to atrophy of the cortex, especially of the fasciculata and glomerulosa. Complete destruction of the cortex is not compatible with life.

Without going into details of the prenatal development, one point must be remembered. The sympathicogenic tissue, which forms the medulla, immigrates from the outside into a pile of mesodermal cells, the central body (Cramer) or fetal cortex of other authors. The penetration takes place from the medial and caudal surface in groups and strands, until the future medullary cells are piled near the central vessels inside of the fetal cortex. Differentiation of sympathicogenic cells into chromaffin cells takes place mainly after birth, but the immigration is closed long before that time. At birth we find, therefore, three different layers, which enclose each other, fruitlike: (1) the permanent cortex, (2) the fetal cortex or "central body," and (3) the medulla. We shall see that penetration of medullary cells through the cortex and central body is sometimes arrested, and funnel-shaped bundles of medullary cells may be found within the cortex or even outside, resting upon the capsule. These medullary cells, which apparently came too late and found immigration closed, may form the center of isolated settlements around the capsule and form accessory bodies, which are extremely numerous in mongolism. In other instances the cortex alone is separated in smaller nodules, which contain all types of cortical cells, but no medulla.

Development of the human adrenal in postnatal life is associated with a unique involution of the fetal tissue. This has attracted considerable interest in recent years, but it is not yet fully understood. The adrenals at birth are large organs with a smooth, regular surface. Beneath the cap-

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and has an infantile appearance; very narrow. Boundary zone in involution; beneath a well preserved X zone.

Fig. 65. (Lower left) Adrenal cortex, 28 yr. old mongoloid female. At the bottom of picture encapsulated medulla; permanent cortex narrow, infantile, without differentiation of fasciculata; no lipoid.

Fig. 66. (Lower right) Adrenal cortex, 4 yr. old mongoloid male. At the upper margin: capsule and glomerulosa; beneath a narrow fasciculata without lipoid. Note the connective tissue strands which separate the permanent cortex above from a juxtamedullary zone with eosinophilic cell nests. Incomplete involution.

sule a layer of cortical epithelium cells, the so-called permanent cortex, is present in which the zona glomerulosa and z. fasciculata can be distinguished. Inside, toward the medulla, the permanent cortex is lined by a mass of slightly larger eosinophilic cells, which fill the whole center of the gland and include in their midst a pile of neurogenic tissue. At birth the dissolution of the fetal cortex or central body takes place in such a way that, at the border of the permanent cortex in the boundary zone, large

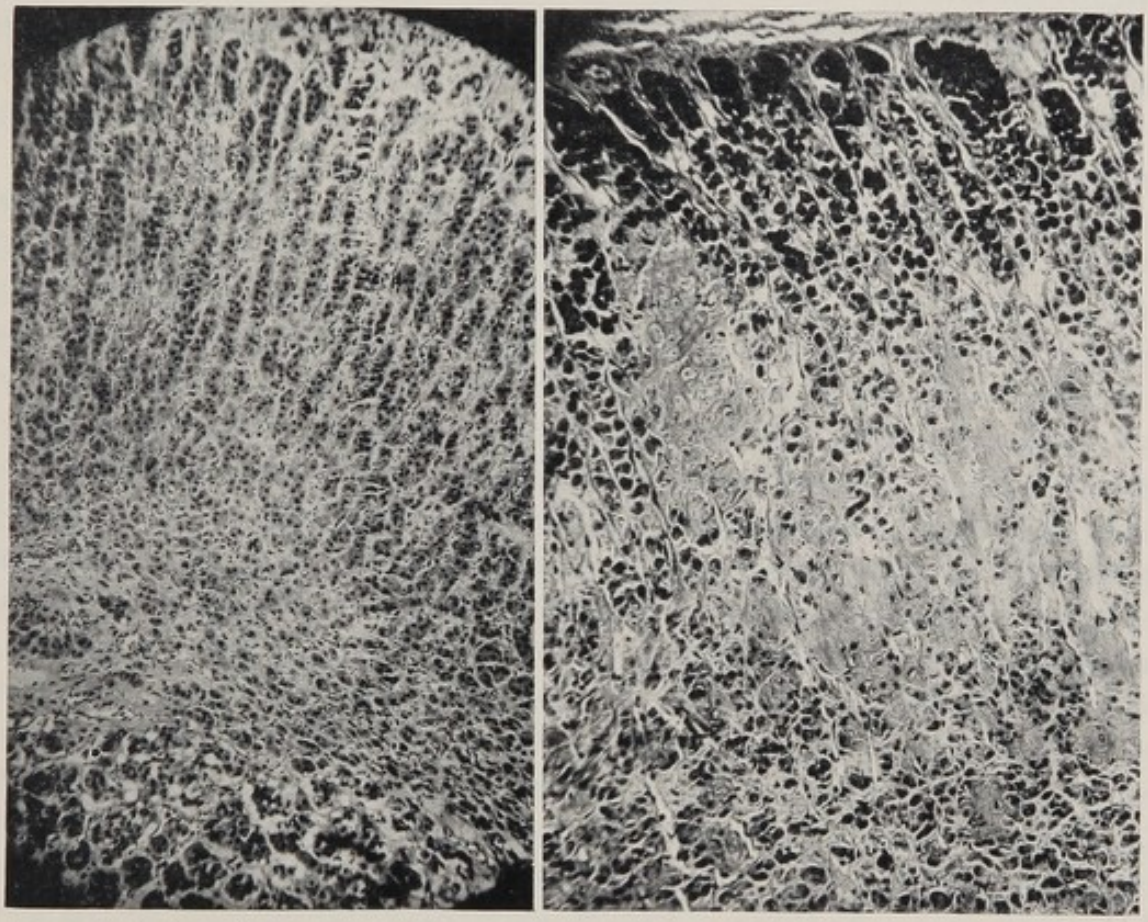


FIG. 67. Adrenal cortex of a 9 yr. old mongoloid male. The fasciculata separated by enlarged capillaries. Cells contain no lipoid. Reticularis shows increased stroma with some islands of persistent fetal cells. Incomplete involution. At bottom: part of medulla.

FIG. 68. Adrenal cortex, 18 yr. old mongoloid male. At upper edge: capsule and glomerulosa. Hyaline degeneration of fasciculata. Fibrosis of reticularis.

sinuses filled with blood are formed and the cells of the fetal cortex undergo rapid degeneration.

In 1927, M. F. Lucas Keene and E. E. Hewer wrote:

> The possible function of those cells constituting the main mass of the human gland during development, the so-called fetal cortex or boundary zone, which disappear during the first year of life offers a most interesting problem, but the very fact that these cells are present mainly during fetal life puts great and very obvious difficulty in the way of any investigation of their physiological significance.

Keene and Hewer point out that during the first year of life the whole gland shrinks, owing to the rapid disappearance of the fetal cortex, the cells of which become first swollen and then lose their nuclei and are later replaced to a certain extent by temporary fibrous tissue, which forms a well-marked zone central to the rapidly developing zona fasciculata. Up to one year the central fibrous tissue is a marked feature, but it can no longer be discerned at 3 years of age. Although the border between permanent cortex and medulla is distinct, owing to the difference of tissue, the two components, cortex and medulla, are not separated by connective tissue strands. The normal medulla is not encapsulated. The permanent cortex increases in size, apparently from the periphery. The greatest amount of mitosis is found in the glomerulosa and in the outer fasciculata.

Although Keene and Hewer do not hold the view of Cramer that the "central body" participates in the formation of the medulla, these authors think that the true cortex, which persists postnatally, and the fetal cortex, which atrophies after birth, are not of common origin. This observation is based on different staining reactions. The cells of the fetal cortex are eosinophilic throughout their existence, whereas the cells of the true cortex are small basophil cells which never give an eosinophilic reaction. The study emphasizes the importance of the "central body" and its possible significance for pathology, but the authors do not offer any definite solution.

Keene and Hewer's view is confirmed by Unto U. Uotila, who has collected ample evidence that the permanent cortex is formed not from the fetal cortex, but from entirely new mesothelial elements proliferating from the celomic wall. The permanent cortex differentiates gradually on the free surface of the fetal cortex and beneath the capsule. The later fate of the fetal cortex is thought to be complete degeneration, which starts during the last ten weeks of intra-uterine life and is completed by the end of the first year. Nothing is known concerning the function of the fetal cortex. It is formed before the permanent cortex and forms the bulk of the fetal adrenal. It persists as a well-developed organ throughout intra-uterine life, but it degenerates soon after birth. This suggests, according to Uotila, "that it serves some important function in the physiology of the embryo and fetus and is not a mere phylogenetic relic. The fetal cortex would seem to belong to that group of pre-natal structures which Streeter would regard as 'temporary devices,' with which some particular needs are met."

Details for the process of the postnatal degeneration of the fetal cortex have recently been provided by Benner and Swinyard. The degeneration is in full swing at the end of the first postnatal week and is completed six to nine months after birth. These authors hold the view that the connective tissue fibers do not separate the boundary zone from the permanent

cortex, but are the original stroma which becomes "increasingly evident" as the cells disappear. They do not think that there is new formation of connective tissue, and the compact band of connective tissue, which encapsulates the medulla at the end of the first year, remains "as a vestige of the stroma of the fetal cortex." During the second year the band obliterates and disappears. The permanent cortex increases in size, while the fetal cortex disappears, and it is now generally held that growth of the permanent cortex takes place from the glomerulosa. The vertical alignment of cells which represent the zona fasciculata appears during the second postnatal week, and the zona reticularis appears in the third postnatal month.

It is held that "the morphological types found in the adrenal cortex are different stages in the life history of the same cells" (Zwemer and co-workers). According to this view, which is now widely accepted, the cortical cells proliferate from the glomerulosa beneath the capsule, form the fasciculata, and finally the reticularis, in which the greatest amount of cell degeneration can be found.

If one summarizes the results of various studies made on animals and on the human adrenal, one may conclude: (1) that the fetal cortex disappears entirely after birth without leaving any trace, except under pathological conditions, as a possible source of tumors (Grollman); (2) that the medulla is formed from neurogenic tissue entirely independent of the permanent cortex and the fetal cortex; and (3) that the permanent cortex is formed from mesothelium, independently from the fetal cortex. The permanent cortex grows from the outside toward the medulla, increasing rapidly after birth and continuing to grow up to an age of 17 to 20 years. The permanent cortex is the main and only source of the adrenocortical hormones.

This view seems fairly satisfactory and compatible with a number of observations which were made in children and in various animal species. It leaves, however, a gap in our knowledge, which is important enough to be emphasized, because a number of observations are not compatible with the view reported above. It may be mentioned that Cramer developed a slightly different opinion about the disappearance of the fetal cortex, or the "central body," as he termed it. In his opinion masses of connective tissue grow in tangential direction through the boundary zone, separating the tissue inside of the connective tissue from that on the outside. The cells between the connective tissue strands and the permanent cortex form a part of the reticularis, which would, therefore, be a different tissue from the other two layers of the permanent cortex. Most of the cells of the central body inside the boundary zone undergo degeneration and are completely destroyed, but a few of the large cells escape destruction and remain

within the medulla as islands or single cells and can be seen even in the adult gland. Cramer thinks that many of the cells of the central body undergo division and participate in the development of the medulla, which is formed "at the expense of the central body." He thinks that one has to look at the central body as the origin of or, at any rate, part of the medulla, and that the final medulla as a source of adrenalin is formed from the two tissues, the neurogenic and the fetal central body. According to Cramer, the medulla would reveal an arrangement similar to that seen in the pituitary, where neurogenic and glandular tissues have united to form one endocrine system. Cramer reports a cretin in whom the formation of the medulla was inhibited, although the connective tissue reaction had commenced. Absence of the central body in hemicephaly has been reported by Elliott and Armour.

Although Cramer's view has not been accepted generally, there are some facts which are unexplainable by the theory that the reticularis is a part of the permanent cortex and develops from the outside layers. Several investigators have associated the presence of the "adrenogenital syndrome" with a proliferation of the reticularis, which is considered by some as "androgenic tissue." Grollman, especially, has emphasized that this androgenic tissue is the source of virilizing influence in girls and may be the cause of abnormal sex differentiation in males and females. The discovery of a special zone, the juxtamedullary zone or x-zone, in certain animals, and its relationship to sex development supports the view that the tissue between permanent cortex and medulla should be considered as a separate tissue with particular functions.

The Adrenals in Mongolism

The observations which were made on 38 cases of mongolism are not only of interest with regard to the pathology of this condition, but they throw, at the same time, some light on the problems which are discussed above. The material can be divided into findings in infants and in children and adults. In infants the adrenals revealed a normal or fairly normal permanent cortex, confirming Hirning and Farber's observations made on 15 infants. The fetal cortex in my material appeared in full degeneration in all cases of that group. What was left was a strong connective tissue stroma, filled with blood and debris. The medulla appeared less developed than one might expect from the study of control material.

In the second group, that of children above 4 years and adults, pathology was consistent and striking in all cases.

The permanent cortex remained at a level present after birth, and very little postnatal growth could be noticed. The fasciculata was narrow, the lipoid was sparse, and the cells and their arrangement were of infantile

patterns. In addition, considerable degeneration was present in a large number of cases. In one case the cortex was destroyed, but no symptoms of Addison's disease had been observed.

The medulla varied greatly in size. True medullary cells were sparse in many cases, but a few showed hypertrophy. A considerable amount of fibrosis was present with the hypertrophy. The observations on the adrenal medulla permit the conclusion that medullary function is inadequate on account of insufficient development of the chromaffin cells.

The most startling observations were made with regard to the "boundary zone," or juxtamedullary zone. While the permanent cortex was hypoplastic and narrow, the zone between fasciculata and medulla was broad and outstanding. The width of this zone was frequently equal to that of the combined two outer layers. The cells of the boundary zone stained bright eosinophilic in the majority of observations. There was a strong fibrous stroma, with bands of connective tissue, which encapsulated the medulla. This "capsule" should normally disappear in the second year.

Interpretation of Observations

The interpretation of the observations is difficult, but the findings suggest a few possibilities which are worth discussing.

The hypertrophic boundary zone seen in almost all cases is either a remnant of the fetal cortex, which has failed to involute, or a hypertrophic juxtamedullary or x-zone. In the former case, the observations are well in line with Cramer's description, who points out that the connective tissue strands penetrate the boundary zone and separate the inner from the outer layer, and that remnants of the central body may persist within the stroma. The pictures which are seen in mongolism lend themselves readily to such an interpretation. It is, however, noteworthy that the infants who died shortly after birth had no signs of persistent fetal tissue. Does this mean that the zone which was seen in older mongoloids developed as a compensatory hypertrophy after infancy, independently from the fetal cortex, or does it indicate that those mongoloids died because their adrenal systems collapsed so completely and rapidly that life was not compatible with so much degeneration? The second possibility, that the tissue is juxtamedullary tissue, is of considerable interest. It appears certain that the tissue is not a hypertrophic "reticularis," because it is impossible to believe that the degenerated outer layers are able to produce this tissue.

If this x-zone is neither persistent fetal cortex nor a part of the normal reticularis, then we have to assume that it developed from the boundary zone independently from the growth of the permanent cortex. Hypertrophy of this zone is considered to give rise to the "adrenogenital" syndrome. In mongolism there is no true mascularization of females or pre-

TABLE 17.—*The Adrenals in Mongolism*

Number	Age	Cortex	Medulla	Remarks
CH 35/94	6 wks.	Left adrenal. Permanent cortex narrow. Some small nodules	Broad medullary core consists entirely of fibrous tissue with large blood sinuses filled with red blood cells. In center a few bundles of medullary tissue	Involution in full development. Conspicuous absence of fetal cortex. Medullary tissue scanty
		Right adrenal. Permanent cortex normal, consisting of glomerulosa and fasciculata	Wide core of fiber tissue filled with blood and single cells of central body in degeneration. Few loose medullary bundles	Normal permanent cortex. Fetal cortex completely destroyed. Medulla scanty
37/6	5 mo. 22 days	Permanent cortex narrow, divided into many small nodules. Glomerulosa and fasciculata distinct	Large fibrous meshwork. Vascularized and congested. Small islands of cortical cells around hilus. Little medullary tissue	Involution of fetal cortex completed. Medullary tissue scanty
44/120	6 mo. 24 days	Permanent cortex, irregular nodulation. Fasciculata rich in lipoid, vacuolated	Broad hilus. One nodule of immigrating neurogenic cells outside of permanent cortex. Involution of fetal cortex in full progress. Scanty, immature sympathicogenic cells	Involution in full swing. Chromaffin tissue scanty
37/1	7 mo. 7 days	Cortex nodulated. Fasciculata vacuolated	Scanty medullary cells. Large meshwork of loose fiber tissue. Congested	Involution of fetal cortex completed
38/15	7 mo. 10 days	Nodulation and disorganization. Fasciculata vacuolated	Broad fibrous meshwork. Congested. Few islands of medullary cells degenerated	Involution completed, no medulla developed
44/152	8 mo. M	Tendency to nodule formation. Fasciculata little vacuolated	Broad strands of fibrous tissue, highly congested. Medulla well developed. Cortical cells within medulla	Involution not completed. Juxtamedullary zone distinct on both sides of connective tissue band

44/154	$1\frac{6}{12}$ M	Fasciculata little vacuolated. Permanent cortex normal. Reticularis present	Broad fibrous meshwork vascularized. Medullary cells almost absent	Complete disappearance of fetal cortex, no chromaffin development. Loose central connective tissue meshwork
44/140	$1\frac{8}{12}$ M	Fasciculata little vacuolated. Permanent cortex not well differentiated. Reticularis present	Fibrous meshwork, congested. Central vein greatly enlarged. Medullary cells present. Hilus contains islands of cortical cells around central vessel separated from permanent cortex by fibrous strands	Involution of fetal cortex completed. Meshwork of fibrous tissue present
43/102	$1\frac{10}{12}$ M	Permanent cortex: glomerulosa and fasciculata normal. Boundary zone congested, fibrotic. Juxtamedullary cells distinct	Broad, fibrous meshwork. Large groups of cortical cells separated from permanent cortex by fiber tissue. Medullary cells present in large numbers, immature	Involution not completed. Condition corresponds to age of few months
42/99	$4\frac{5}{12}$ M	Left adrenal: vessels between fasciculata columns dilated. Some degeneration of cortical cells. Marked lobulation	Medulla separated from permanent cortex by fibrous capsule. Medulla broad, of same width as cortex. Hilus contains large groups of cortical cells	Involution not completed. Fibrotic capsule around medulla. Partial persistence of central body inside fibrotic boundary zone. Broad juxtamedullary zone, but narrow permanent cortex
42/99	$4\frac{5}{12}$ M	Right adrenal: tendency to nodulation. Reticularis fibrous, highly congested	Medulla broad; central body almost completely preserved in some places	
40/57	$4\frac{5}{12}$ F	Extremely congested. Narrow fasciculata, broad boundary zone. Nodulation	Core congested, fibrous tissue. Hilus around central vein contains medullary cells and cortical cells	Involution not completed. Extreme congestion. Broad juxtamedullary zone

TABLE 17.—*The Adrenals in Mongolism—Continued*

Number	Age	Cortex	Medulla	Remarks
43/103	$6\frac{7}{12}$ M	Permanent cortex narrow. Nodulation. Fasciculata partly degenerated with dilation of capillaries. Boundary zone fibrotic	Hilus contains cells of central body and medullary cells	Cortex aplastic. Large medulla, partially fibrotic. Boundary zone distinct, with persistent fibrous stroma
43/124	7 yrs. 17 days M	Permanent cortex narrow. Nodulation. Fasciculata cells separated by dilated capillaries. Boundary zone congested as in active involution	Medulla broad. Contains large islands of cells of central body. Fibrosis and congestion of medulla	State of involution corresponds to weeks after birth. Narrow permanent cortex, huge boundary zone
40/47	$8\frac{7}{12}$	Cortex extremely congested. Fasciculata columns separated by congested capillaries, degenerated. Boundary zone outstanding, congested, fibrotic strands	Congested, fibrotic, with little development of medullary cells. Blood sinuses enlarged, congested, filled with colloid-like fluid. Cells of central body eosinophilic, partially preserved	Cortex aplastic. Medulla fibrotic. Involution not completed. Conspicuous eosinophilic juxtamedullary zone
38/25	$8\frac{8}{12}$ F	Narrow cortex. Capillaries between fasciculata distended and congested. Little lipoid. Boundary zone still fibrotic, with large sinuses. Tendency to nodulation	Unusually broad, hyperplastic medulla, encapsulated, fibrotic. Residuals of central body	Incomplete involution. Aplastic cortex, hypertrophic, fibrotic medulla. Juxtamedullary zone distinct
43/125	$8\frac{9}{12}$ M	Almost no lipoid. Boundary zone with distinct fibrous stroma	Fibrous capsule separates medulla from cortex. Fibrosis of medulla	Cortical aplasia. Medullary fibrosis. Boundary zone distinct
44/134	$9\frac{7}{12}$ F	Capillaries between fasciculata distended. Atrophy of fasciculata in some areas. Small amount of lipoid. Narrow permanent cortex	Broad boundary zone, fibrotic. Medulla encapsulated, numerous cortical cells	Partial persistence of central body. Cortical aplasia. Postnatal involution not completed

38/17	$9\frac{8}{12}$ F	Narrow cortex. Congested. Little lipoid. Atrophy. Congestion and vascularization of boundary zone, with distinct fibrous stroma. Increased nodulation	Persistent groups of fetal cortex. Eosinophily of cells outstanding. Increased nodulation. Medulla encapsulated and fibrotic	Involution not completed. Fibrosis of medulla. Aplasia of cortex. Boundary zone distinct
44/141	$10\frac{9}{12}$ M	Narrow permanent cortex. Glomerulosa conspicuous, in some areas enlarged. Increased nodulation. Fasciculata aplastic	Hypertrophic medulla separated from cortex by fibrous tissue; boundary zone vascularized. Medulla contains many cortical cells, single and in nodules. Marked fibrosis	Partial persistence of central body. Hypertrophic fibrotic medullary body, hypoplastic, irregular permanent cortex
44/139	$11\frac{1}{12}$	Glomerulosa conspicuous. Fasciculata congested and atrophic. Little lipoid. Reticularis congested and fibrotic, distinctly eosinophilic cells	Broad, encapsulated. Contains large islands of cortical cells	Hypertrophic encapsulated medulla. Hypoplastic cortex. Broad, congested boundary zone
37/10	12 F	Adrenals enlarged. Permanent cortex narrow. Broad boundary zone	Persistent central body. Boundary zone only partly developed, with fibrous strands separating medulla from permanent cortex. Medulla consists of fiber tissue and poorly developed medullary cells	Persistent central body. Fibrotic medulla, narrow hypoplastic permanent cortex
44/133	12 F	Fasciculata columns separated by enlarged, congested capillaries. Little lipoid. Boundary zone conspicuous, with increased fibrous strands. (Two necrotic abscesses)	Medulla separated from cortex by fibrous capsule	Encapsulated medulla. Degeneration of cortex

TABLE 17.—*The Adrenals in Mongolism—Continued*

Number	Age	Cortex	Medulla	Remarks
45/155	$14\frac{4}{12}$ M	Fasciculata congested and columns compressed. Little lipoid. Boundary zone broad, congested, with small fibrotic islands, eosinophilic cells. Increased nodulation about capsule	Medulla separated from cortex by fibrous capsule; in some areas fetal cortex continuous with permanent cortex	Aplastic permanent cortex. Persistence of central body. Encapsulated medulla
38/32	$14\frac{11}{12}$ M	Right adrenal: straight, rodlike body. Narrow permanent cortex. Boundary zone congested, fibrous. Active state of involution	Medulla narrow	Incomplete involution. Hypoplastic permanent cortex. Broad boundary zone with fibrotic stroma
		Left adrenal: cortex irregular. Fasciculata partly fibrotic with narrow columns. Boundary zone in state of involution	Medullary cells almost absent	Hypoplastic permanent cortex. Incomplete involution of boundary zone
43/116	$15\frac{4}{12}$ F	Fasciculata congested, columns compressed, lipoid scarce. Reticularis broad, eosinophilic. Stroma distinct	Medulla fairly large, contains many groups of cortical cells	Hypoplastic permanent cortex. Incomplete involution of boundary zone
43/100	$15\frac{8}{12}$ M	Permanent cortex, narrow. Fasciculata reduced to narrow strips. Boundary zone congested. Formation of large blood sinuses	Medullary cells fairly well developed, increased fibrosis	Hypoplastic permanent cortex. Extreme congestion. Incomplete involution of boundary zone, with persistent central body
44/148	$15\frac{10}{12}$ M	Capillaries enlarged, congested. Fasciculata columns compressed and reduced to narrow strands. Boundary zone vascularized and fibrotic. Nodulation	Encapsulated. Contains large groups of eosinophilic cells	Incomplete involution. Hypoplastic permanent cortex. Broad boundary zone with fibrous stroma

42/85	16 M	Compressed fasciculata columns without lipoid, with the exception of one area. Glomerulosa conspicuous. Broad boundary zone. Fibrotic	Encapsulated. Contains large islands of cortical cells	Incomplete involution. Aplastic permanent cortex
41/58	$16\frac{3}{12}$ M	Cortex narrow. Little lipoid. Fasciculata is reduced to thin columns separated by enlarged capillaries. Boundary zone congested	Medulla hyperplastic, filling whole length of the adrenal. Islands of cortical cells	Cortical atrophy, hypertrophy of medulla. Incomplete involution of boundary zone, with fibrotic capsule around medulla
42/90	17 M	Cortex narrow. Fasciculata with little lipoid. Blood spaces enlarged. Boundary zone fibrotic	Encapsulated. Eosinophily of fetal cortex cells	Incomplete involution. Central body partially persistent
42/81	17 M	Narrow cortex with small fasciculata. Boundary zone outstanding, fibrotic strands separating the reticularis cells. Involution of reticularis in full swing	Inside boundary zone persistent central body with very little involution. Medullary cells, nerves, and ganglion cells	Hypoplastic permanent cortex. Involution of boundary zone not completed. Broad eosinophilic juxtamedullary zone
43/126	$17\frac{1}{12}$ F	Irregular partial atrophy of fasciculata. Boundary zone outstanding, fibrous strands separating reticularis cells. Congestion	Medulla hyperplastic, encapsulated. Inside boundary zone cortical cells, some of them strikingly eosinophilic	Partial persistence of central body. Hypertrophic medulla, aplastic permanent cortex
42/83	$17\frac{9}{12}$ M	Cortex narrow and congested. Boundary zone outstanding, congested	Encapsulated. Broad hilus contains islands of cortical cells. Some lymphatic tissue	Atrophy of cortex. Incomplete involution of boundary zone
41/65	$18\frac{1}{12}$ M	Fasciculata narrow, little vacuolated. Boundary zone outstanding. Cells separated by fibrous strands with enlarged blood sinuses	Inside boundary zone persistent central body in several areas. Hilus contains medullary cells separated by fibrous capsule from permanent cortex	Hypoplastic permanent cortex. Encapsulated medulla. Broad boundary zone

TABLE 17.—*The Adrenals in Mongolism—Continued*

Number	Age	Cortex	Medulla	Remarks
44/146	$18\frac{4}{12}$ M	Reduced to small bands of glomerulosa and outer layer of fasciculata. Central part of fasciculata completely degenerated and fibrotic	Contains islands of eosinophilic cells. Otherwise atrophic and fibrotic. No medullary cells	Severe atrophy of cortex. Atrophy of medulla. Persistent islands of central body
M 3	20	Cortex narrow, congested. Atrophy of glomerulosa and fasciculata. Boundary zone outstanding, fibrotic, congested	Medulla encapsulated. In some areas boundary zone still in involution	Hypoplastic permanent cortex. Large boundary zone. Congested, fibrotic medulla
41/7	$28\frac{5}{12}$ F	Cortex narrow. Outstanding boundary zone, vascularized, with fibrotic strands. Large blood sinuses. Tendency to nodulation	Persistence of boundary zone. Small hilus with medullary cells	Hypoplastic permanent cortex. Outstanding boundary zone
44/129	40 F	Cortex, caplike, attached to kidney, consists of one half only. Thin columns of fasciculata. Boundary zone congested, outstanding	No medulla present	Adrenal is attached to kidney without separating capsule. Lower half of adrenal is absent

cocious sex development of males, but this may be due to the fact that the gonads are unable to respond to such a stimulus. Of great interest is the observation that the x-zone disappears at puberty in mice, but persists following castration (Howard). Gersh and Grollman have seen an experimental hypertrophy after administration of thyroid. Whatever the final interpretation will be, the observations in mongolism support the view that the juxtamedullary zone, which may become outstanding under pathological conditions and which may be hypertrophic while the permanent cortex is aplastic, is a functionally and ontogenetically separate tissue, which is not identical with the reticularis of the permanent cortex.

Although the significance of those observations is still unknown, the fact that the adrenals reveal such a particular and consistent pathology is worth recording. The aplasia of the permanent cortex can be attributed to the lack of pituitary activity. In this respect, the observations on the adrenals are well in line with those on the thyroid and gonads. We can now say that the observations add further evidence to the statement that the mongoloid inner secretory system acts like that of experimental hypophysectomy. The permanent cortex fails to grow and is apt to undergo final degeneration. We see in mongolism a functional activity of the adrenal cortex lower than the normal, but the loss is not complete, which is also true for the hypophysectomized animal. The carbohydrate metabolism is most severely lowered.

The relationship of the fetal cortex to the pituitary is not yet known. Could it be possible that a persistent fetal cortex prevents the pituitary from going into action? We know that the fetal cortex degenerates after birth, independently from all other endocrine glands. This disappearance is apparently not controlled by the pituitary. One has to keep in mind that a persistent fetal cortex or a hypertrophic x-zone may possibly hold the pituitary in lock, preventing it from exercising the influence which it seems otherwise suited to activate.

The Adrenals in Cretinism

There are no studies on the adrenals in cretinism available which were done with the purpose of studying the development of the juxtamedullary tissue and the fate of the central body. Cramer, however, mentioned one case of cretinism in which he found retardation of the involution of the central body.

The adrenals of one case of myxedema and congenital aplasia of the thyroid were at my disposal. The permanent cortex appeared normal, especially in comparison with mongoloid adrenals. There was no abnormality of the zona reticularis. The medulla was small and showed lymphatic infiltration, but the cells as such and the arrangement were negative.

Synopsis of the Endocrine Pathology in Cretinism and Mongolism

Mongolism and cretinism are the two great endocrine disorders of childhood, which outrange every other disease by their medical and social importance.

In cretinism (congenital thyroid aplasia) we see an example of an experiment by nature to produce a human being with one important gland, the thyroid, missing. The result is a dwarf with myxedema and mental deficiency, but life is compatible with such a congenital defect. The effects upon bones, skin, metabolism, are well known. Without thyroid, the gonads do not attain maturity. The alterations in the pituitary have been considered by some as a compensatory enlargement. With more knowledge at hand, this interpretation seems hardly appropriate. The enlargement seems due to congestion and secretory stasis and, frequently, cyst formation. The spaces are filled with a colloid-like, mucinous fluid, and the cells undergo regressive changes. The adrenals seem less affected, but our present knowledge is limited. Cramer's observation of delayed involution of the fetal cortex is not yet confirmed by other observations.

It has been thought that cretinism (congenital thyroid aplasia) cannot be recognized at birth and does not become manifest before several months have elapsed. This idea has given rise to the theory that the endocrines of the mother supply the embryo completely and the thyroid of the fetus is not necessary for its full development to term. This view has changed, since it has become evident that thyroid aplasia manifests itself in the newborn in retardation of growth and bone development and in an increase in weight, which are recognizable at the time of birth. This demonstrates clearly that fetal developments depend, to a certain degree, on the participation of the embryo's endocrine system in the metabolism of gestation.

In mongolism the incretion of another even more important gland, the pituitary, is removed from the economy of the body. Mongolism is not associated with pituitary aplasia. Such anomaly seems incompatible with life. Mongolism is a congenital hypopituitarism. Although there is a pituitary body, there is evidence that function is lacking. The mongoloid is a "pituitary cretin."

Some investigators have compared the role of the pituitary with that of a conductor; others have called it the master gland. I have pointed out that the interaction of the glands is not a one-sided relationship, in which one part could act without the others. If we accept the simile that the pituitary is the conductor, we may point out that in mongolism, at the time of birth, the orchestra (thyroid, gonads, adrenals) is ready to play, but the conductor is not present on the stage, to take over. For a number of reasons, which are suggested in Chapter X, he is delayed. After several months of waiting, the conductor seems ready to take over, but the orches-

tra has disintegrated from lack of practice and discipline. The interaction between the glands is out of control. It is a fascinating observation how, in the body, each gland is tuned into the rhythm of development and is requested to participate at a certain point. Without this "falling into line" the organism cannot achieve the complicated assignments which are requested.

The thyroid is the first of all endocrines, the function of which is evident and whose lack of function manifests itself as early as the time of birth. In mongolism 12 per cent of the cases have a thyroid which is so definitely abnormal that the pathology borders on a "cretinoid" condition. In the remaining 88 per cent the gland seems fit for action, but inactivity and stagnation lead rapidly to hypothyroidism. The material at hand does not indicate that the thymus takes part in the chain of pathological events. The adrenal permanent cortex, which seems to participate in the endocrine economy not later than three months after birth, fails to do so for the same reasons as the thyroid. Whether the fate of the fetal cortex is significant is still a matter of speculation. The gonads are the last in exercising any active influence. In mongolism they never do. The result is a complicated endocrine disorder, in which any attempt to put the blame on any particular gland seems hopeless. This, however, is true for any growth disorder, and Harvey Cushing has expressed the situation, with regard to acromegaly, more clearly than anybody else:

> A persistent thymus, a large colloid goitre, enlarged parathyroids, hypertrophy of the pancreas and greatly hypertrophied adrenals due to an adenomatosis of the cortical substance. To any one of these markedly changed glands, an observer might in the 1880's have ascribed the malady with greater seeming probability than to the normal-sized hypophysis.

The collected material on the endocrine pathology of mongolism demonstrates, as did the clinical observations, that the key to this disorder is a chronic insufficiency of pituitary function, which makes mongolism a congenital acromicria.

BIBLIOGRAPHY

Thyroid, Pituitary, and Gonads

Allara, V.: Sulla causa del cretinismo. Milano, 1892.

Aschoff: Sektion eines 6 monatigen Kindes mit Aplasie der Schilddrüse. Deutsche med. Wchnschr., 1899, 5, S.203.

Benda, Carl: Pathologische Anatomie der Hypophyse. Handbuch der pathologischen Anatomie des Nervensystems **2:** 1431, 1904.

Benda, Clemens E.: Studies in Mongolism. II. The Thyroid Gland. Arch. Neurol. & Psychiat. **41:** 243–59, 1939.

——: Studies in Mongolism. III. The Pituitary Body. Arch. Neurol. & Psychiat. **42:** 1–20, 1939.

——: Endocrine Aspects of Mongolism. J. Clinic. Endocrinol. **2:** 737, 1942.
Berblinger, W.: Pathologie u. path. Morphologie der Hypophyse des Menschen. Handb. inn. Secretion. **1:** 910, 1932 (Bibliography).
Bircher, Eugen: Zur Pathologie der Kretinistischen Degeneration. Berlin, 1908.
——: Beiträge zur Kenntnis der Schilddrüse bei Kretinoiden. Frankfurt. Ztschr. f. Path. **11:** 262, 1912.
Bourneville: L'idiotie Mongolienne. Progrès méd. **3:** 117, 1903.
Brauchli, H.: Beiträge zur Pathologischen Anatomie der Hypophyse. Frankfurt. Ztschr. f. Path. **31:** 459, 1925.
Cerise: Quoted by Allara.
Clark, R. M.: The Mongol: A New Explanation. J. Ment. Sc. **74:** 265–69, 739–47, 1928; **75:** 261–62, 1929; **79:** 328–35, 1933.
Collin, R.: L'Hypophyse. Nancy, 1933.
Cushing, H.: The Pituitary Body and Its Disorders. Philadelphia, Lippincott, 1912.
DeCoulon: Über Thyreoidea und Hypophysis der Cretinen. Virch. Arch. **147:** 53, 1897.
DeQuervain, F.: Beiträge zur Pathologie der Schilddrüse. Fischer, Jena, 1926.
——: Cretinisme. Schweiz. Arch. f. Neurol. **14:** 3, 1924.
Eggenberger, Hans: Kropf u. Kretinismus. Handb. inn. Secretion. **3:** 684, 1928.
Erdheim, J. I.: Über Schilddrüsenaplasie. Zieglers Beitr. **35:** 367, 1904.
—— and Stumme: Über Schwangerschaftsveränderungen der Hypophyse. Zieglers Beitr. **46:** 1, 1909.
——: Biologie der Schwangerschafftszellen und ihre Beziehung zum Skelett. Frankfurt. Ztschr. f. Path. **49:** 452, 1936.
Fevold, Harry: The Follicle Stimulating and Luteinizing Hormones of the Anterior Pituitary, in E. Allan: Sex and Internal Secretions. Williams & Wilkins, 1939.
Getzowa: Über die Thyreoidea von Kretins und Idioten. Virch. Arch. **180:** 117, 1905.
Gordon, M. B.: Morphological Changes in the Endocrine Glands in Mongolian Idiocy with Report of Two Cases. Endocrinology **14:** 1, 1930.
Herrmann and Verdun: Persistance des corps postbranchaux chez l'homme. Compt. Rend. Soc. Biol., 1899.
Hertzler, Arthur E.: Diseases of the Thyroid Gland. Hoeber, New York and London.
Isenschmid, R.: Zur Kenntnis der menschl. Schilddrüse im Kindesalter. Frankfurt. Ztschr. f. Path. **5:** 205, 1910.
Kingsbury, B. F.: The Question of a Lateral Thyroid in Mammals, With Special Reference to Man. Am. J. Anat. **65:** 333–59, 1939.
Klose, H., and Buttner, G.: Kachexia Strumipriva. Handb. inn. Secretion. **3:** 591, 1928.
Klose, H.: Über Bau u. Funktion der kindl. Schilddrüse. Arch. Klin. Chir. **124:** 346, 1923.
Kraus, J. E.: Die Beziehungen der Zellen des Vorderlappens der menschl. Hypophyse miteinander unter normalen Verhältnissen u. in Tumoren. Zieglers Beitr. **58:** 159, 1914.
——: Hyperplastic Disease of the Adenohypophysis. J. Clin. Endocrinol. **5:** 42, 1945.
MacCallum and Fabian: On the Anatomy of a Myxedematous Idiot. John Hopkins Hosp. Bull. **18:** 198, 1907.
Marine, D.: Pathological Anatomy and Histology of the Thyroid. Endocrinology and Metabolism **1:** 269, 1922. Appleton.
Myers, C. Roger: An Application of the Control Group Method to the Problem of the

Etiology of Mongolism. Proc. Am. A. Ment. Deficiency, 62nd Ann. Session, Richmond, Va., April 20–23, 1938.
Norris, E. H.: The Parathyroid Glands and the Lateral Thyroid in Man: Their Morphogenesis, Histogenesis, Topographic Anatomy and Pre-natal Growth. Carnegie Inst. publication 479. Contributions to Embryology 159, 249–94.
Pennacchietti, M.: Contributo Anatomo-Pathologico allo Studio della Idiozia Mongoloide. Endocrinol. e pat. Constit. **10:** 148, 1935.
Pineles, F.: Über Thyreoaplasia. Wien. klin. Wchnschr. **43:** 1902.
Ponfick, E.: Myxoedema und Hypophyse. Dtsch. Ztsch. klin. Med. **38,** 1899.
Roesch, C.: Untersuchungen über den Cretinismus in Württemberg. Erlangen, 1844, p. 132.
Rogowitsch, N.: Die Veränderungen der Hypophyse nach Entfernung der Schilddrüse. Zieglers Beitr. **4:** 453, 1888.
Romeis, Benno: Über die Veränderungen d. Hypophysis bei Erkrankungen d. Schilddrüse. Virch. Arch. **251:** 235, 1924.
Rössle: Das Verhalten der menschlichen Hypophyse nach Kastration. Virch. Arch. 216, 1914.
Sawyer, Grace, M.: Reproduction in a Mongoloid. Am. J. Ment. Def., 1949–50, in press.
Schiff, A.: Hypophysis und Thyreoidea in ihrer Einwirkung auf den menschlichen Organismus. Wien. klin. Wchnschr. 1897, no. 12.
Schilder, Paul: Über Missbildungen der Schilddrüse. Virch. Arch. **203:** 246, 1911.
Schultz: Über einen Fall von Athyreosis congenita. Virch. Arch. **232,** 1921.
Severinghaus, A. E.: Anterior Hypophyseal Cytology in Relation to the Reproductive Hormones, in E. Allan: Sex and Internal Secretions. Williams & Wilkins, 1939.
——: The Cytology of the Pituitary Gland. Proc. Assoc. Research Nerv. & Ment. Dis. **17:** 69, 1936.
Stahnke: Zur Histologie u. Klinik jugendlicher Strumen. A. klin. Chir. **125:** 193, 1923.
Tatum: Morphological Studies in Exper. Cretinism. J. Exper. Med. **17,** 1913.
Trautmann, A.: Hypophyse und Thyroidectomie. Frankfurt. Ztschr. f. Path. **18:** 173, 1916.
Van Dyke, John Howard: Behavior of Ultimobranchial Tissue in the Post-natal Thyroid Gland: The Origin of the Thyroid Cystadenomata in the Rat. Six text figures and three plates (twenty figures), Anat. Rec. **68:** 369, 1944.
Wagner, Jauregg V.: Über die Folgen der Exstirpation der Schilddrüse nach Versuchen an Tieren. Wien. med. Bl. **25** and **30,** 1884.
Wegelin, C.: Zur Kenntnis der Cachexia Thyreopriva. Virch. Arch. **254,** 1924.
——, in Henke, F., and Lubarsch, O.: Handbuch der Speziellen Pathologischen Anatomie und Histologie. Berlin, Julius Springer, 1926.
Wetzel, G.: Handbuch der Anatomie des Kindes. Munich, J. F. Bergmann, 1936.
Wydler, A.: Die Histologie der Kretinenstruma, in De Quervain, F.: Beiträge zur Pathologie der Schilddrüse. Jena, G. Fischer, 1926.
Zuckermann: Hypophysenbefund bei Schilddrüsenaplasie. Frankfurt. Ztschr. f. Path. **14,** 1913.

Adrenal Glands

Benner, Miriam: Studies of the Involution of the Fetal Cortex of the Adrenal Glands. Am. J. Path. **16:** 787, 1940.

Cramer, W.: Fever, Heat Regulation, Climate and the Thyroid-Adrenal Apparatus. Longmans, Green, London, 1928.

Elliott, T. R., and Armour, G.: Development of the Adrenal Cortex and Its Condition in Hemicephaly. J. Path. Bact. **15:** 481, 1911.

Grollman, Arthur: The Adrenals. Williams & Wilkins, Baltimore, 1936.

Hirning, L. C., and Farber, S.: Histologic Study of the Adrenal Cortex in Mongolism. Am. J. Path. **10:** 435, 1934.

Keene, M. F. Lucas, and Hewer, E. E.: Observations on the Development of the Human Suprarenal Gland. J. Anat. **61:** 302–24, 1927.

Swinyard, C. A.: Growth of the Human Suprarenal Gland. Anat. Rec. **87:** 141, 1943.

Uotila, Unto U.: Early Embryological Development of the Fetal and Permanent Adrenal Cortex in Man. Anat. Rec. **76:** 183, 1940.

Zwemer, R. L., Wotton, R. M., and Norkus, M. G.: A Study of Cortico-adrenal Cells. Anat. Rec. **72:** 249, 1938.

CHAPTER VI

GENERAL PATHOLOGY

Mongolism

Liver

The liver of the mongoloid has not been described before. Brousseau did not mention any liver pathology in his monograph on mongolism (1928).

The microscopic findings in 43 livers of mongoloids are condensed in Table 18. Four features are found with some regularity: fatty vacuolization, fibrosis, degeneration of the parenchyma, and congestion. A fifth feature, tuberculosis, was added in order to show that there is no correlation between the liver pathology of mongolism and tuberculosis of the liver, although a very high percentage of mongoloids die of this disease. The enumeration of the causes of death adds further evidence that the fatty changes in the liver are not correlated with chronic infections, such as tuberculosis.

Fatty Vacuolization: This descriptive term was used rather than the term "fatty infiltration" or "fatty degeneration" because it has, at the present time, not been demonstrated whether the fat in the livers is "storage fat" or not. In many cases there is no indication that the cells that carry the fat are otherwise injured. On the other hand, the cells often show obvious degeneration, but neither of these findings is conclusive proof of the nature of the fat droplets, and only physiological and histochemical methods can definitely settle the point. Therefore, the noncommittal term "fatty vacuolization" was used. In 12 mongoloids from 9 days to 1 year 10 months old, an abnormal amount of fat (++) occurred in 2 cases, or about 17 per cent. Of 31 cases above 2 years 4 months old, 25 (about 80 per cent) carried a definitely abnormal amount of fat (++ to ++++). Other pathologic characteristics are probably secondary to the fatty changes, except for the cases of severe congestion in infancy.

The initial stages of fatty vacuolization sometimes show a distribution along the central veins, but this is not at all a general rule and the fat is actually more often and to greater extent found around the portal vessels. Two cases were seen in which the fat was accumulated along the central as well as the portal vessels, leaving only the intermediary zones of the lobules relatively free from fat. In the most advanced stages (4 out of 31, or about 13 per cent), all liver cells contained at least one big droplet of fat which filled almost the whole cell and compressed the nucleus. These livers actually simulate fat tissue (see Fig. 70). The fat droplets reach

TABLE 18.—*Condensed Chart of the Findings in the Livers of Mongoloids*

Case No.	Sex	Age	Weight, Gm.	Fat	Fibrosis	Congestion	Cell Degen.	Liver Tb.	Cause of Death
C 76	F	9 days	90	−	−	++	−	−	?
C 94	F	6 wks.	76	−	−	++++	++	−	?
C 162	M	2 mos.	?	−	−	+	−	−	?
C 181	M	2½ "	75	−	−	+++	−	−	?
C 95	M	4½ "	?	+	+	−	−	−	?
C 62	F	6 "	260	++	++	++	−	−	?
120	M	7 "	240	+	+	++	+	−	Lobar pneumonia
15	M	7½ "	160	−	−	+++	−	−	Multiple abscesses
152	M	8 "	190	+	−	++	−	−	Scarlet fever
154	M	1 6/12	295	+	+	−	−	−	Meningitis
140	M	1 8/12	?	++	++	++	++	−	Bronchopneumonia
102	M	1 10/12	390	−	−	−	−	+	Tb., Meningitis
C 102	F	2 4/12	?	+++	++	+	++	−	?
99	M	4 5/12	570	++++	+	−	−	−	Brain edema
57	F	4 5/12	450	+++	++	−	++	−	Septic sinus thrombosis
103	M	6 7/12	680	++	++	+++	+++	−	Lung abscess
124	M	7	640	+++	+++	−	−	−	Lung embolism
118	M	7 13/12	605	++	−	++	++	+	Tb. of lungs
47	F	8 7/12	800	+	++	+	+	−	Diphtheria, pneumonia
25	M	8 8/12	?	++	+	−	−	−	Bronchopneumonia
125	M	8 9/12	670	−	++	+++	++++	+	Tb. of lungs
134	F	9 7/12	710	+	+	+	−	−	Intussusception
17	F	9 8/12	460	+++	++	+++	+++	−	Bronchopneumonia
141	M	10 4/12	740	++++	+	−	−	+	Tb. of lungs
139	M	11 1/12	690	+++	++	+	−	−	Bronchopneumonia
133	F	12	?	++	++	++	−	−	Volvulus
82	F	13 10/12	890	+++	−	−	−	+	Tb. of lungs

155	M	$14\frac{4}{12}$	?	++	−	−	++	+	Tb. of lungs
32	M	$14\frac{11}{12}$	830	+++	+	−	−	−	Bronchopneumonia
116	F	$15\frac{4}{12}$	1100	+	−	−	++	−	Tb., miliary
100	F	$15\frac{8}{12}$	1135	+++	++	++	++	+	Tb. of lungs
148	M	$15\frac{10}{12}$	1650	++++	+	−	−	+	Tb. of lungs
85	M	16	1400	+++	+++	++	++	−	Status epilepticus
58	M	$16\frac{3}{12}$	880	+++	++	++	−	+	Tb. of lungs
81	M	17	1140	++++	++	−	−	+	Tb. of lungs
90	M	17	1590	−	−	−	−	−	Gangrene of lung
126	F	$17\frac{1}{12}$	1050	+++	+++	−	+	−	Tb. of lungs
83	M	$17\frac{9}{12}$	880	+++	+	++++	−	+	Tb. of lungs
65	M	$18\frac{1}{12}$	2100	++	++++	+	++	−	Tb of lungs
146	M	$18\frac{4}{12}$	1510	++	++	−	+++	−	Tb. of lungs
M 3	F	20	?	+	+++	+++	+++	+	Tb.
22	M	$20\frac{6}{12}$	?	+++	++	++	++	−	Bronchopneumonia
71	F	$28\frac{5}{12}$	820	++	++	++	−	+	Tb. of lungs

+: slight degree, pathology questionable.
++: certainly pathological in amount, but not very pronounced.
+++: marked degree.
++++: extreme degree throughout organ.
The presence of tubercular foci is marked with a cross regardless of the degree of involvement.

the size of 50 micra, yet in all these cases of most severe fatty vacuolization it is possible to trace the original pattern of the lobule, the liver cords being only slightly and mechanically displaced. Furthermore, there is a considerable amount of cytoplasm in the spaces between the droplets which appears essentially normal.

Macroscopically, the livers are rarely of the extreme fatty type, even when 50 per cent and more of the cells are seen microscopically to contain large fat droplets. On sections, only one liver was found to be actually oozing fat, and this liver was also the only one that floated on water (Case 148). The great majority of the livers show a yellowish tinge. In those cases in which the fat is diagnosed at autopsy, one is surprised at microscopic examination to see the great amount which is actually present in the cells.

Fibrosis: Fibrosis is not as constant a finding as is the fatty deposit. It occurs, however, in more than 50 per cent of the older age group. Typically, it does not present the picture of a liver cirrhosis. True nodular cirrhosis was not found at all in the 43 cases of this study. The great majority of those cases which show a conspicuous increase in fibrous tissue have a pronounced periportal proliferation and also a thickened capsule, but the intertrabecular spaces show little or no increase in connective tissue. The liver cords, therefore, are not compressed or replaced. Macroscopically, there are sometimes the increased lobular markings characteristic of early liver cirrhosis, but never is the surface of the liver uneven or nodular, and in many cases the slight increase in fibrosis found under the microscope is not diagnosed at autopsy.

Case 125 and Case 65 show fully developed liver cirrhosis, but even here the great amount of fibers is not present in solid masses and does not lead to a conspicuous hardening of the liver or to the formation of nodules. In the foreground is a severe necrosis of the parenchyma with no signs of regenerative foci. Case 65 clearly shows a considerable amount of fatty vacuoles, but none were found in Case 125. This case is that of the only Negro mongoloid in the series. The liver is atypical of mongolism. (Further doubt is thrown on the diagnosis through the fact that the thyroid and pituitary glands were also not typical. The diagnosis was based on the presence of many external stigmata, such as the formation of the skull, hypotonia, and rudimental epicanthal folds.)

In addition to these two cases of liver cirrhosis, one of which is not definitely established as a mongoloid, there are two other cases which might be called "cirrhosis in its initial stages." The majority of cases show a limited but definite periportal fibrosis, which appears to have little tendency to proliferate further at the expense of liver tissue.

Congestion: Two thirds of the cases below 2 years of age showed con-

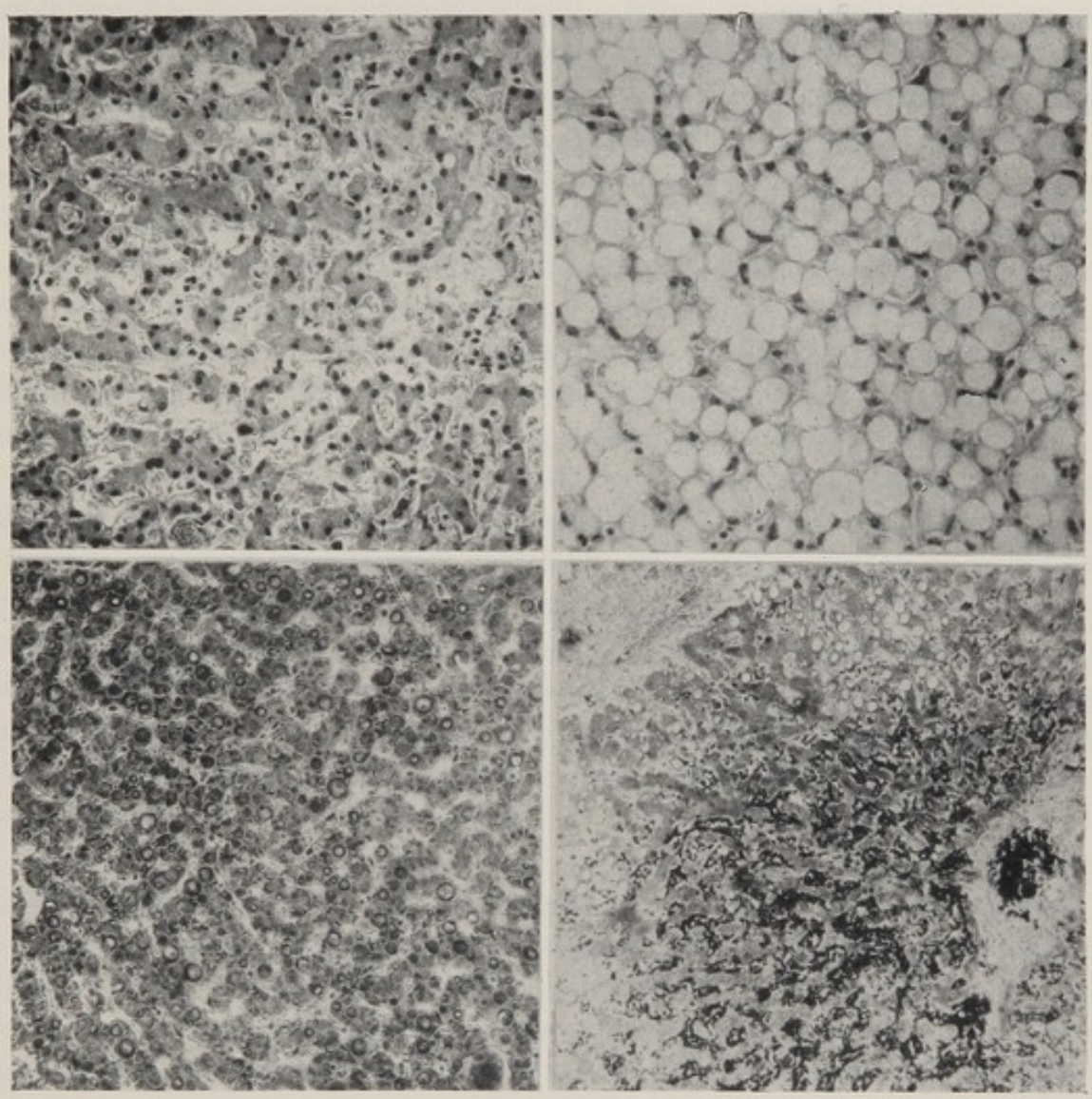


Fig. 69. (Upper left) Liver congestion in a 2½ months old mongoloid baby (C-181). Liver shows a high degree of congestion with severe compression of the liver cords. Fat is rare, but a few fatty vacuoles are visible in the picture. H & E stain, magnification 270 times.

Fig. 70. (Lower left) Fatty vacuolation in the liver of a 16 yr. old mongoloid girl (44/148). The cytoplasm is much compressed by the big fat vacuoles. The center of the lobule is at the right, and liver cords are still traceable. H & E stain, magnification 460 times.

Fig. 71. (Upper right) Fatty infiltration of liver in a 4 yr. old mongoloid (42/99). All liver cells are filled with fat droplets. Sudan IV fat stain, magnification 180 times.

Fig. 72. (Lower right) Congestion and fatty infiltration in a 16 yr. old mongoloid (40/58). Congestion (black in picture) is severe around the lobular centers; fat is accumulated near the portal vessels. Masson stain, magnification 180 times.

gestion, and in a few below 1 year of age this feature dominated the whole picture (Fig. 69). In the extreme cases (C 94, C 181, 15) there was not only a uniform engorgement of all the sinusoids, but there were hemorrhagic

necroses around the central veins. The trabeculae were thinned and compressed and the liver appeared severely injured, as a whole. This high degree of congestion was rarely found in the older cases. It is hardly remarkable that about 45 per cent of these should show congestion of varying degrees, as the terminal diseases and the circulatory failure at death might easily produce this picture. In almost all the cases, the congestion is confined to those areas which do not show extreme fatty vacuolization (Fig. 72). However, the opposite distribution was observed in two cases.

Degeneration: It appears of some significance that severe cell degeneration is so rarely found in mongoloid livers. Necrotic foci and limited areas in which the liver cells appear damaged are frequent, and this is not surprising in view of the fact that so many of the livers show tuberculosis and signs of terminal infections. Severe generalized degeneration and necrosis were found in only four livers, two of which were tubercular.

As a supplement to the account given above, it is interesting to mention the case of a 17 year old mongoloid boy (Case 90) who was clinically regarded as a borderline case. He was of normal body length, 159 cm. His brain weight was the only normal one in the whole series. His gonads were developed better than usual in a mongoloid. His liver turned out to be the only completely normal one seen in thirty-one livers of mongoloids of over 2 years of age.

The liver of the mongoloid of 2 years or older is a fairly well defined pathological entity, with its large amounts of fat accompanied, in many cases, by a definite but limited periportal fibrosis. The question arises how the fatty deposits can be explained. Tuberculosis is supposed to cause fatty infiltration of the liver and half of the mongoloid patients above two years of age die of tuberculosis. However, the incidence of fatty livers is as high in the nontuberculous cases as in the tuberculous cases ($76\frac{1}{2}\%$). A comparison with a group of 50 feebleminded, nonmongoloid patients of the same age group showed that fatty infiltration of the liver occurred half as frequently as in mongoloids, and again the incidence was about the same in nontuberculous and in tuberculous patients. Tuberculosis, therefore, can only play an unimportant role in the etiology of the fatty livers.

When dogs are deprived of both the pituitary and thyroid glands, the liver shows a picture very similar to that found in the mongoloid patient (Chaikoff, Entenmann, etc.). In these dogs it was seen that the fatty deposits always preceded the fibrosis. When only the thyroid was extirpated, the fatty vacuoles were far less pronounced. On the other hand, hypophysectomy alone produced a picture of hepatic cirrhosis which was accompanied in many cases by fatty deposits (Graef, Negrin, and Page). These authors believe that it is not so much the pituitary as the stalk and

the infundibulum which exert an influence on the fatty metabolism of the liver. However, a connection has been supposed to exist between chronic brain pressure and liver fat. It is theoretically possible that chronic brain pressure acting over the infundibulum or the pituitary itself influences the fatty metabolism (Kraus, 1937). Morgan (1937) has demonstrated defects of the hypothalamus of mongoloids, and increased intracranial pressure—not spinal fluid pressure—probably exists at some time during the life of the mongoloid. In addition, it was found that of 8 very fatty livers of non-mongoloid, mentally deficient patients 4 occurred in patients with brain pressure caused by hydro- and microcephaly and in 2 of these cases the infundibulum was severely damaged (Roosen-Runge, 1946).

The fibrosis may well be due primarily to the fat deposits, as it has been observed that cirrhosis can be produced in the liver of a dog by prolonged feeding of a high fat diet (Chaikoff, Eichhorn, etc.), the accumulation of fat always preceding the increase in fibrous tissue. In these dogs, the picture of a typical cirrhosis develops gradually from that of fatty infiltration with initial fibrosis. For some reason, in the mongoloid, this does not take place. However, the mongoloid liver is apparently susceptible to further injury, and the severe degeneration seen in a few cases is probably due to this sensitivity.

One of the outstanding factors in the pathology of the liver of mongoloids is the complete change in the picture at the age of $1\frac{1}{2}$ years to 2 years. Fig. 73 adds significance to this observation by comparing the ponderal index of the mongoloid with that of the normal. The ponderal index—that is, the relative weight—is below normal up to the age of about $1\frac{1}{2}$ years. It is very nearly normal from $1\frac{1}{2}$ to 3 years, and from then on for the rest of the mongoloid's life it remains at a high level above normal. It is hardly a coincidence that the liver fat begins to appear with great regularity at the same time when the mongoloid becomes generally obese. The reason for this obesity is, in all probability, the deficiency in thyroid and pituitary secretions. The endocrinological section of this book presents ample confirmation of this view.

The mongoloid baby is usually underweight and its endocrine balance is obviously different, the difference being reflected in the liver. Many of the livers at this age are normal, but an extraordinary amount of congestion is found often enough to regard it as a typical feature. It has been demonstrated that the abnormalities and deficiencies of the adrenals in the mongoloid infant bring about many of the characteristic features in its development (p. 154). It has also been shown (Conwin) that dogs which are deprived of their adrenals show great vascular congestion and hemorrhages around the central veins in the livers. It appears justified, therefore, to speculate on the possibility that the pathology of the liver of the mongoloid

infant is correlated with a suprarenal insufficiency. The fact is remarkable that all the severely congested livers below 2 years of age are very much underweight. About one third of the livers below 2 years of age were found to be normal.

The weights of the livers are shown in Table 18. Of 34 cases, 20 were underweight, 8 within normal range and 6 overweight (see normal values of

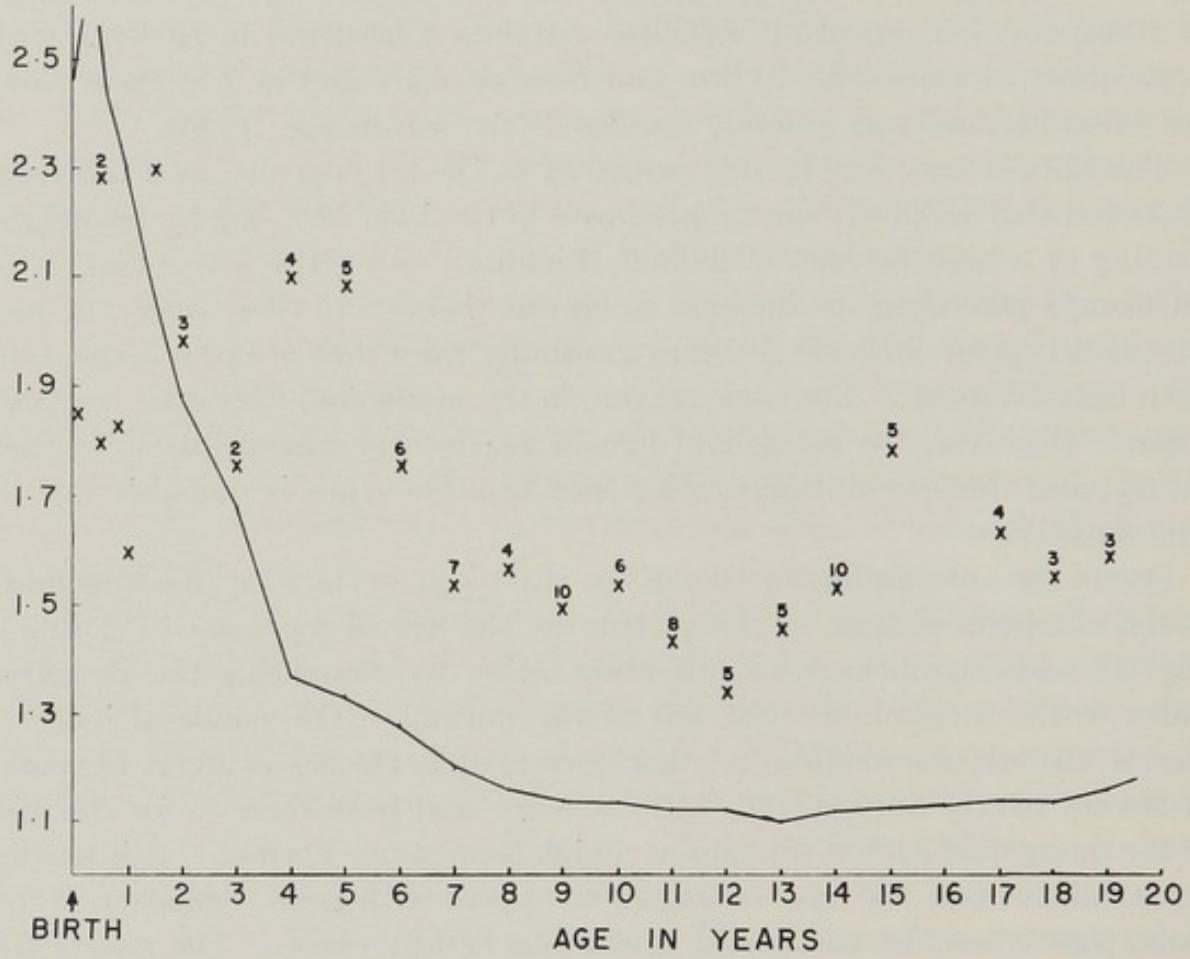


FIG. 73. Ponderal index (weight divided by 100 times the cube of body length) The unbroken line represents the normal values designed for citizens of the United States (Engelbach, 1932). The crosses represent values found in mongoloid patients. The numbers indicate the number of cases of which the value represents an average. Crosses without numbers represent individual cases. The picture indicates clearly that in the first two years of life the ponderal index of mongoloid babies is far below normal while after two years all values are far above.

Coppoletta and Wolbach, 1933). When it is considered that mongoloids are also below normal in height, the low values appear less remarkable. A few livers, such as C 94, C 181, 139, 58, etc., are very much underweight. Case 139, for instance, has a very fatty liver without signs of degeneration of the liver cells, yet the weight of the liver is only about 75 per cent of the normal. Little explanation can be found for this, but the suggestion is

made that the small livers are part of the picture of splanchnomicria described elsewhere.

The liver function of the mongoloid child is not greatly impaired clinically. However, there is a definitely increased glucose tolerance, and the insulin tolerance curves indicate a tendency to a decreased ability to raise the blood sugar level (Bixby and Benda). The material fixed for glycogen preservation, although not conclusive at present, tends to confirm the view that the mongoloid liver is deficient in glycogen. Several possibilities suggest themselves, which together or singly may bring about this deficiency. In the first place, while fatty deposits do not preclude the storage of glycogen, extreme fat accumulation appears to suppress it markedly. Second, the adrenal cortex governs the glycogen storage in the liver and cortical insufficiency decreases the storage. There are reasons to suppose that such an insufficiency may play a direct part in the deficient glycogen storage of the liver in mongolism.

Heart and Vascular System

From the viewpoint of general organ pathology, the mongoloid patient frequently shows an accumulation of developmental anomalies. All point toward the fact that the fetal development has proceeded in an unfavorable milieu. The genesis of some malformations suggests that the most critical time had been the end of the second and the third month, in which period a number of important developments should have taken place.

It has been pointed out in Chapter II that the heart frequently shows congenital defects. Their number is so great that the heart is found abnormal in 75 per cent of the infants who die in the first 2 years of life. In those who survive, about 35 per cent show congenital heart malformations. The intra-auricular septum shows an open foramen ovale in the majority of cases. If the defect is restricted to a small hole which admits the passage of a probe only, it is of no clinical significance. The presence of a real defect in the septum, however, is not rare. Such a defect may be even more conspicuous in the intraventricular septum, where some openings measured as much as 1 inch in diameter. Abnormalities of the arteries, Fallot's tetralogy, patent ductus Botalli, and dextrocardia may be found. Little attention has been paid to the anomalies of the cusps of the mitral and tricuspid valves. The cusps are uneven, short, and the edge nodular. Fetal endocarditis seems suggested, but there is little evidence otherwise, and it appears more likely that these nodules are the nodules of Albini, which are embryonic remnants. This is another confirmation of the general fetalism of the mongoloid child.

The vascular system as such is hypoplastic. All arteries remain narrow, thin, and the vascular tree shows fewer branches than in normal controls.

This is conspicuous in the brain. The capillaries appear congested and enlarged. Hemangiomata in the kidneys, liver, and other organs are not rare. Two children had periarteritis nodosa; one died with the symptoms of intestinal intussusception with generalized periarteritis. The other child had periarteritis in the testes and in a few other organs. In mongoloids beyond 25 years of age, atheromatosis of the arteries is common.

Lungs

It is difficult to say whether or not the lungs in mongolism show certain peculiarities which are characteristic of this condition. Radiologists who have to deal with mongoloid patients consider a diagnosis particularly difficult. It is certain that the respiratory mucosa is extremely vulnerable and susceptible to infections. Tuberculosis is extremely frequent, even in infants, and 75 per cent of the mongoloids above 10 years of age died of tuberculosis. The foci are frequently in the lower lobes, and tuberculosis of the apex is uncommon. Besides tuberculosis, pneumonitis is commonly found. It is almost certain that the lungs are different, but it is not yet possible to specify the particular characteristics.

The Thymus

This organ was found hypoplastic without exception. Hassall bodies are unusually large and the large category may be the only one present. If it is true that in a normal thymus, all stages of development of Hassall's bodies should be present, the observations suggest that the regenerative capacity of the thymus is poor. This is further suggested by hypoplasia of the lymphatic medulla.

Intestinal Organs

Of the abdominal organs, the liver has been discussed in detail. In the intestines microcolon was found three times among forty autopsies, in which this anomaly was looked for.

Kidneys

The kidneys show certain characteristic features which have so far escaped recognition. They are small and underweight. This becomes more conspicuous in the second half of the first decade, when renal infantilism seems at its height. Development of the glomeruli is slow and they remain near the capsule in a distribution characteristic of fetal and early postnatal life. Interstitial fibrosis, however, seems rare, and one may state that the organs of mongoloid patients seem generally weak in interstitial response on the part of the connective tissue. Loose hemangiomata were found in several cases.

General Organ Development

With regard to the size of the organs, some peculiarities deserve special attention. In the study of the liver it was observed that this organ was sometimes surprisingly small for the age of the person and the size of the

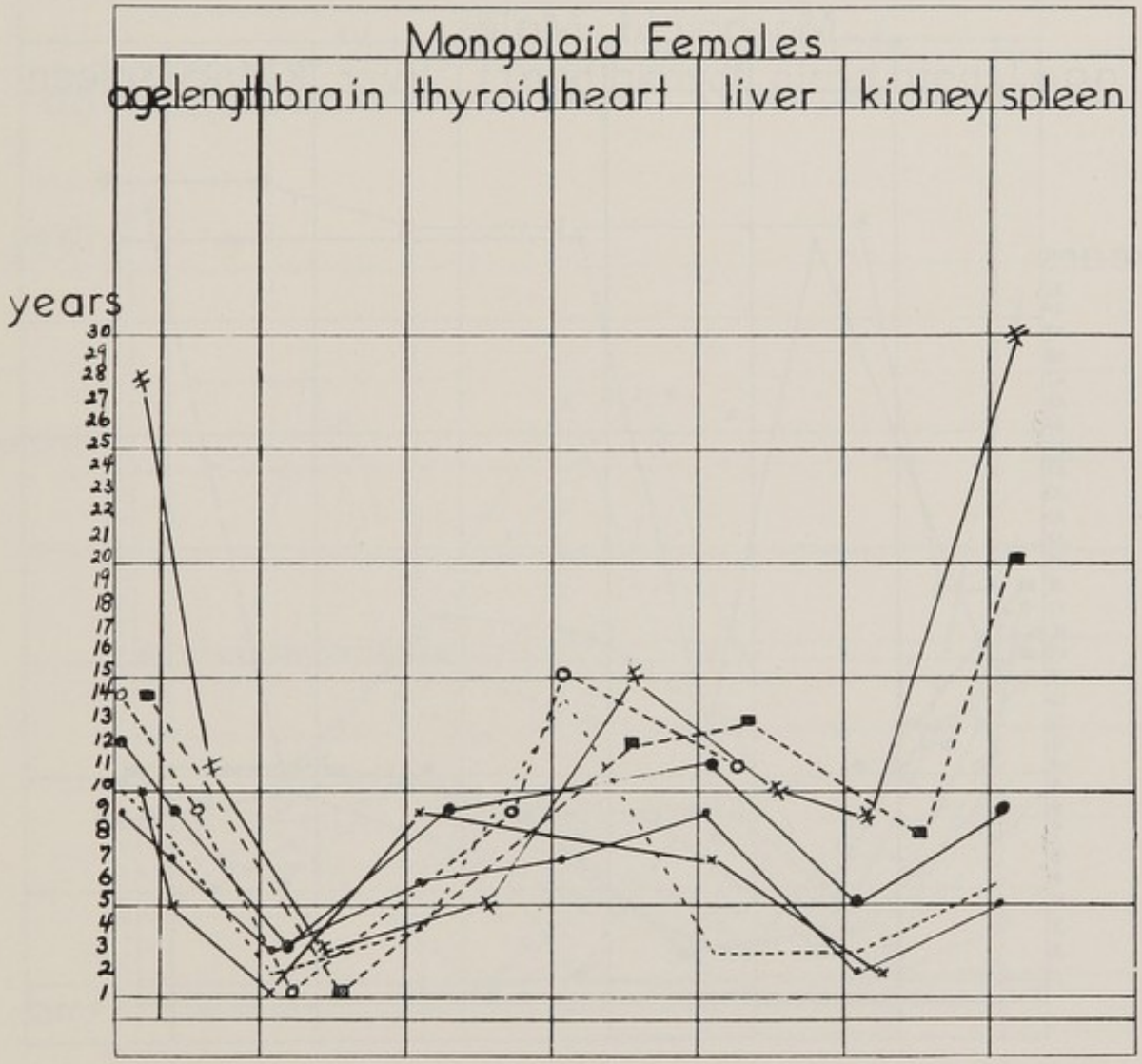


Fig. 74. Correlation chart between chronological age, body length, and developmental age of organs calculated according to weight. Mongoloid girls. The body length is far behind normal standards and remains between 9 and 11 years. Brain weights are all below standards for $3\frac{1}{2}$ years. Thyroid weights are far below normal but in line with physical development. The values for heart correspond to the chronological age. The liver weights are moderately below normal. Striking is the splanchnomicria of the kidneys. Values for the spleen are high and tend to be far above normal.

body. Similar observations could be made on the kidneys. The study of both organs suggested general splanchnomicria. The spleen, however, appeared heavy in many instances. In order to investigate this problem further, a new method was introduced. Adopting the use of "bone age"

and "mental age," which are generally accepted terms for designation of the developmental state of mentality and bones, measurements of the body size and the organs' weight were charted according to their "developmental age." In this way, correlation charts were made for infants and children

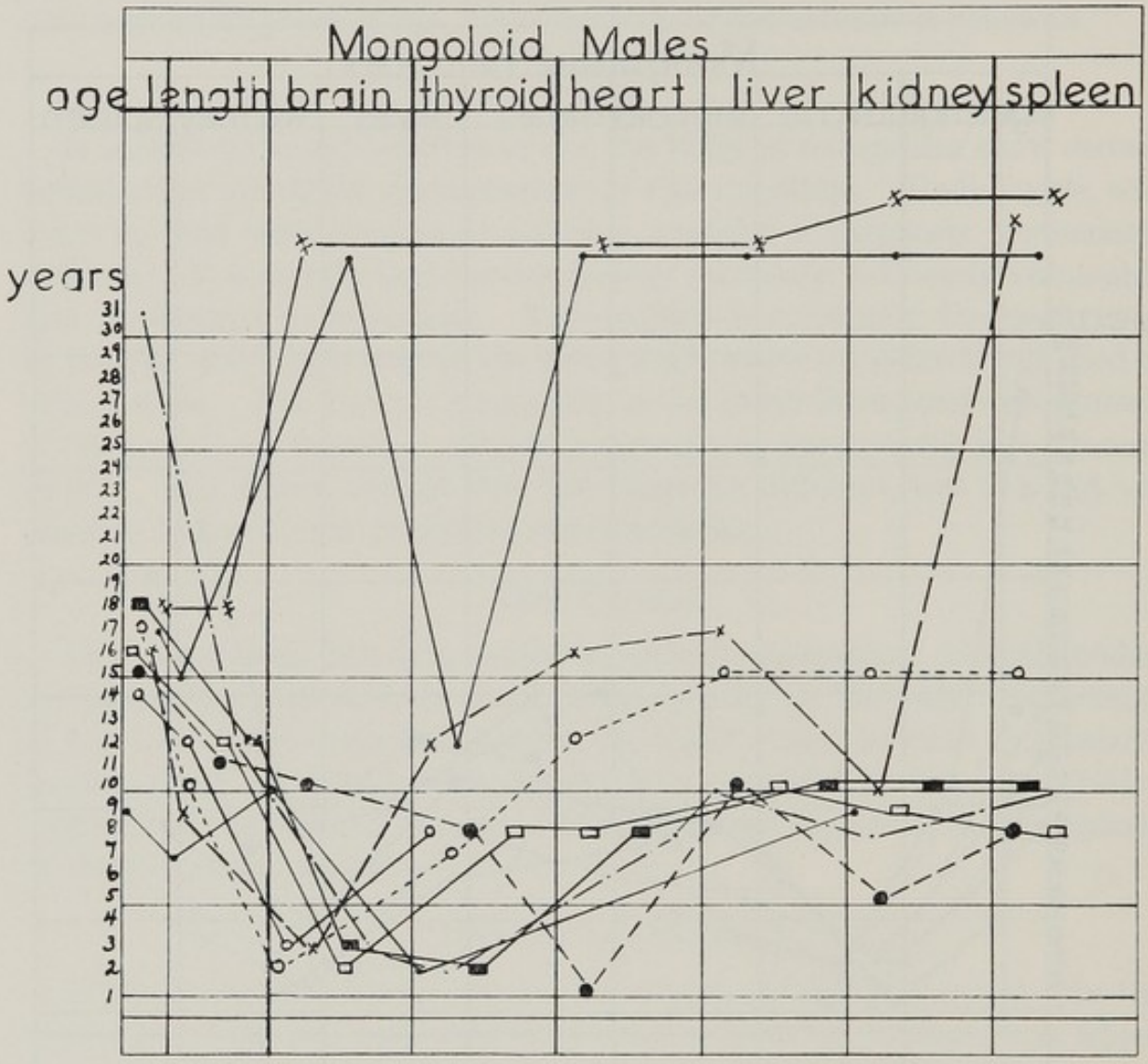


FIG. 75. Correlation chart between chronological age, body length and developmental age of organs calculated according to weight. Mongoloid males. Body length lags far behind chronological age, but less conspicuously than in females. Brain values are below 4 years in the majority but two brains are exceptionally heavy. Thyroid values are all low. The liver weights are slightly below normal for body length and kidney values are still lower. Note that two cases show tendency to splanchnomegaly.

according to age and sex. The four charts which follow give a clear idea of the correlations which were found in mongolism. A quick glance at the charts shows that all mongoloids indicate a great retardation in body development. The largest height reached by any mongoloid female was the size of an 11 year child, while most adult mongoloids remained on a 9 year

level. Maximum size of the males was that of 12 year old boys, with two exceptions. Most striking is the retardation in brain development in female adults. This does not manifest itself in infants. The mongoloid male shows generally the same trend, but two cases showed a paradoxical increase in weight. Thyroid hypoplasia is more striking in the males than

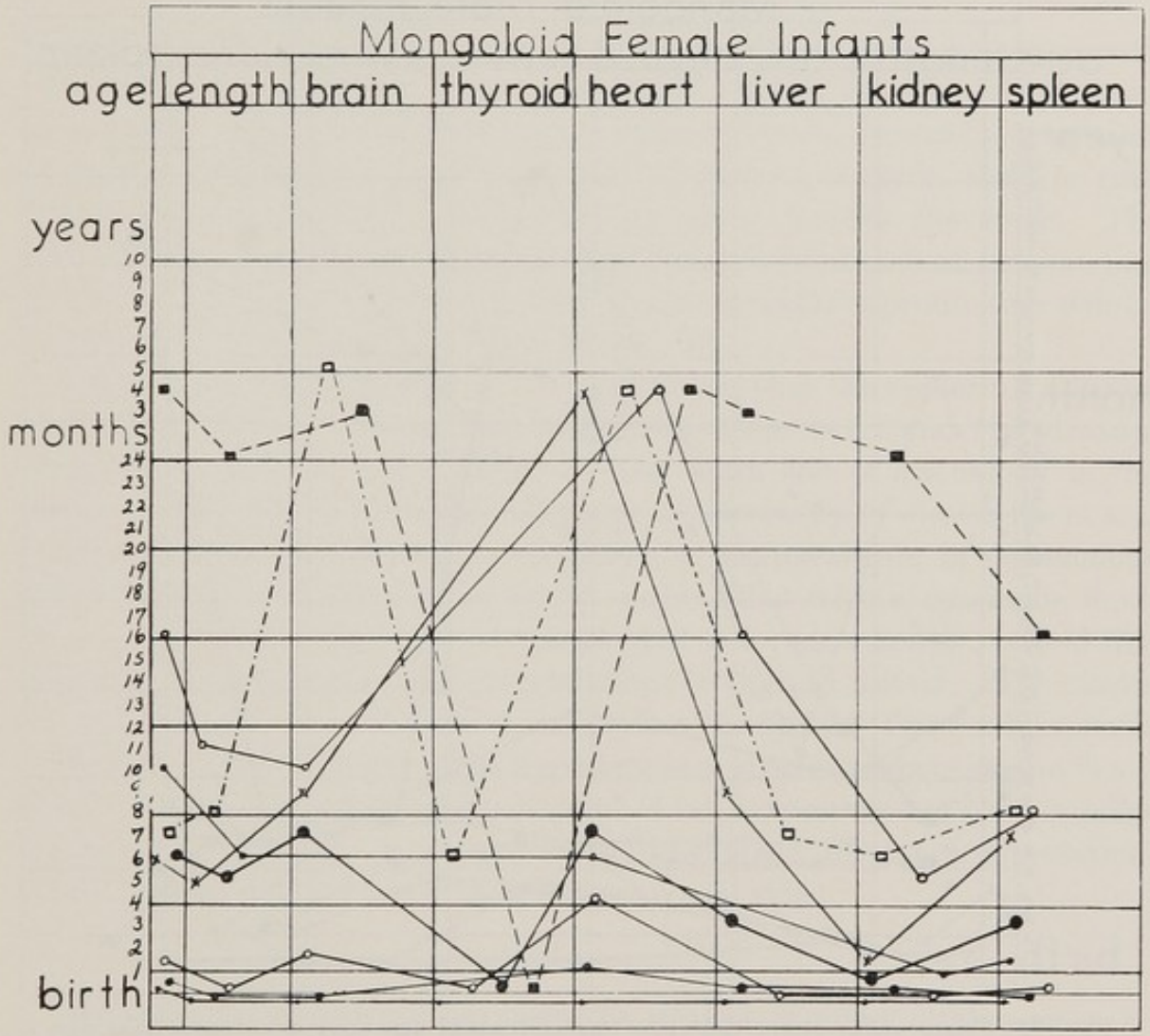


FIG. 76. Correlation chart between chronological age and developmental age of organs of mongoloid female infants. Body length lags behind chronological age. The brain values are fairly normal in that age group. Thyroid is definitely underweight while the heart keeps within the chronological age. The liver weight is below normal and splanchnomicria of kidneys is present. The spleen shows tendency to splanchnomegaly.

in the females. The heart shows a tendency to hypertrophy in both sexes. The liver is small, even compared with the developmental age of the body, indicating that the growth of the liver depends on certain factors which are suspected of being of endocrine origin. Hypoplasia of the kidneys is also a general trend. The two males who had a paradoxical brain weight showed the same increase in weight of heart, liver, kidney, and spleen. In

contrast to the splanchnomicria of other cases, a splanchnomegaly was noted in these two. The spleen showed increase in weight in all cases, clearly indicating that the weight of the spleen as a lymphatic organ depends upon other factors. It may be mentioned that in two mongoloid

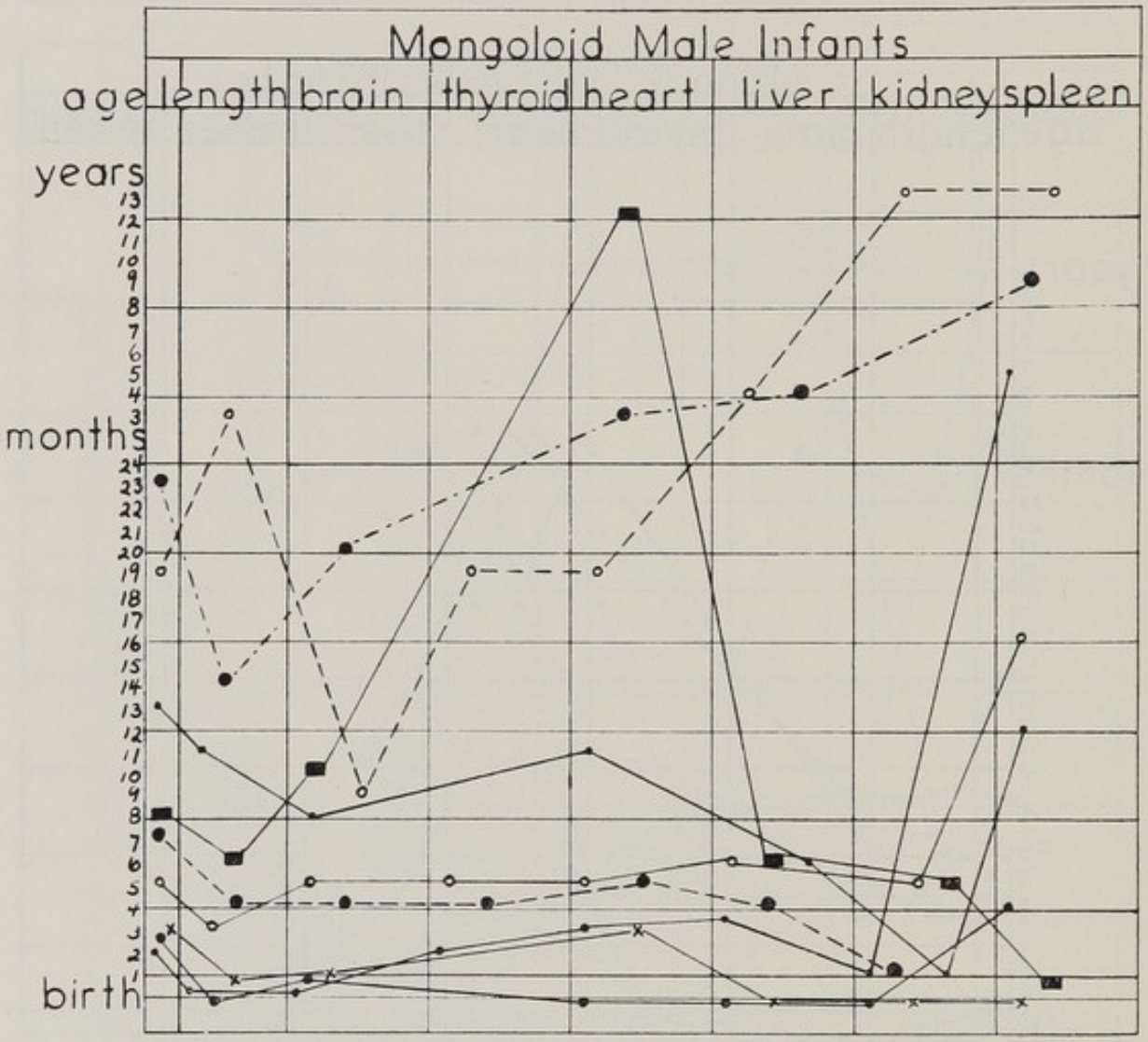


FIG. 77. Correlation chart between chronological age and developmental age of organs of mongoloid male infants. Body length lags behind chronological age with the exception of one case with far advanced body length. Brain weight and thyroid weight are not strikingly abnormal. Note the tendency to splanchnomegaly in two cases and the general tendency to increased weight of spleen.

infants the diagnosis of splenomegaly and hepatomegaly was made at autopsy, and lymphatic leukemia was found in blood studies.

Cretinism

The general pathology of cretinism reveals certain characteristics which are consistently found in untreated cases. The number of autopsies,

however, is so small that no investigator is able to present a complete description without referring mainly to observations scattered throughout the literature. Such a literary review is not within the scope of this book. A few principal observations may be reported.

Skin

Since the first description of the myxedematous skin, which is filled with "mucinous" material, there have been quite a number of arguments about myxedema. Several well-known writers have denied the existence of such a mucinous condition. In 1931, Reuter presented a study in which he confirmed the observations described in the early English literature. The case with the pituitary described on page 138 presented such an outstanding picture of myxedema of the skin that a photographic reproduction will be welcomed by many readers (Figs. 78 and 79).

A section through the skin of the chest shows that the epidermis appears negative. The two layers, the stratum corneum (s.c.) and the stratum malpighii (s.m.), are well outlined. The main site of pathology is the corium. This layer, normally composed of a network of elastic fibers and collagenous bundles, shows, in cretinism, a disappearance of collagenous tissue which is transformed in cystic spaces filled with a mucinous fluid. In some cysts this fluid is so stagnant that it forms a brittle, colloid-like substance, which could easily be mistaken for thyroid colloid. The elastic fibers in the corium are distended and enclose the cysts. There is lymphatic infiltration in the cavities. The hypodermis or stratum subcutaneum (s.s.), which usually contains a certain amount of fat, is composed of fiber bundles which are coarse and dense and leave little space for fat accumulation. There is really less fat tissue than in the normal skin.

Heart

The heart in myxedema has been the subject of many studies since H. Zondek's introduction of the term "myxedema heart." Size and weight of the heart are increased. The ventricles are dilated, and the heart muscle is flabby. In microscopic sections the fibers are separated by edema, the cells swollen, and "cloudy swelling" is conspicuous. There is some moderate lymphatic infiltration. The larger vessels participate in the dilation and relaxation.

Other Organs

The mucosa of the lungs may be thickened.

The liver seems to be smaller than might be expected from the size of the body. A correlation chart of the developmental age of liver and kidneys indicated a retardation in growth similar to that seen in mongolism.

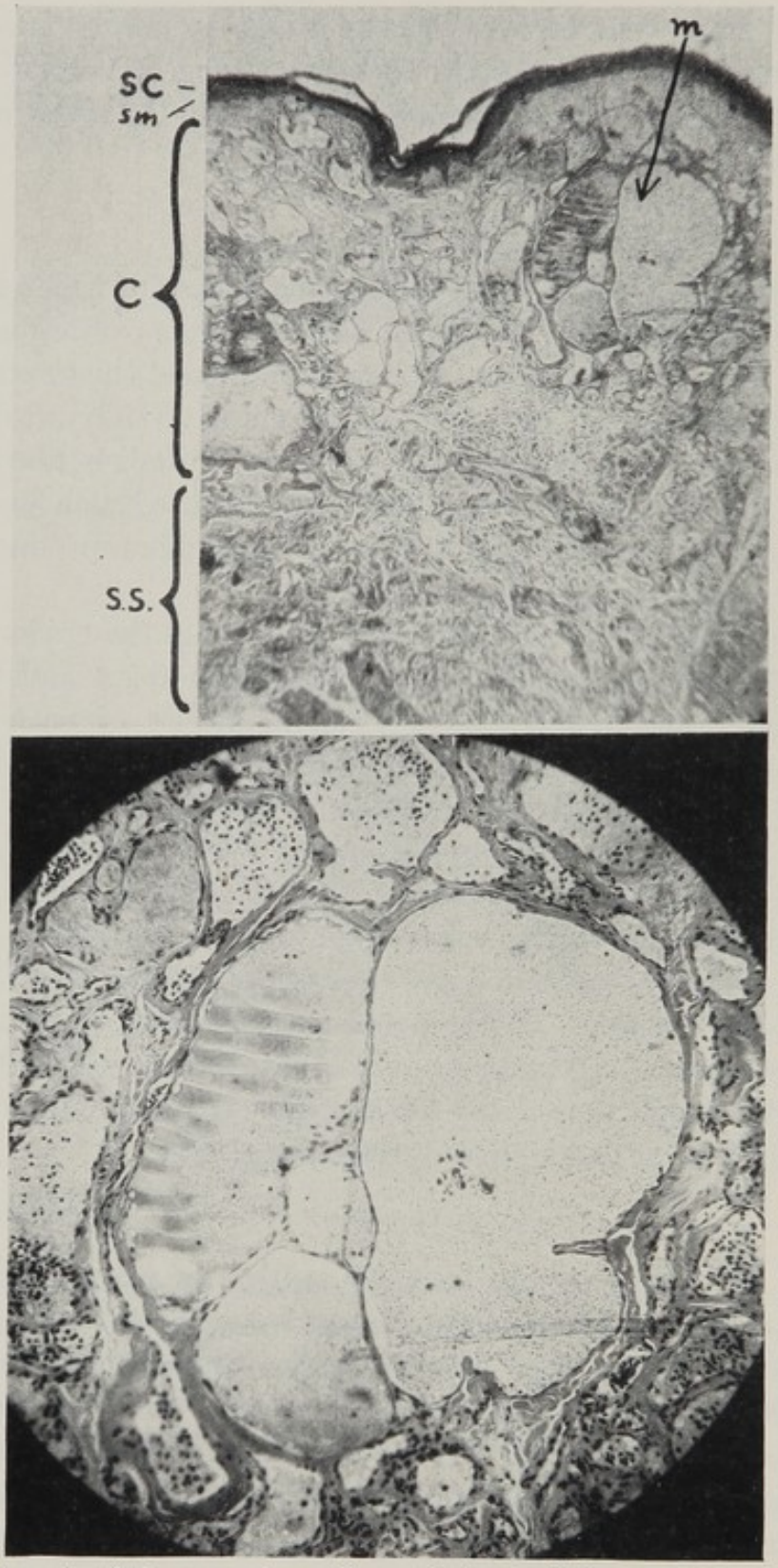


FIG. 78. (Upper) Skin myxedema in cretinism. S.C., stratum corneum, S.M., stratum malpighii, C., corium, S. S., stratum subcutaneum. Note large cysts in corium filled with stagnant albuminous fluid.

FIG. 79. (Lower) High magnification of cyst in Fig. 78. Note stagnant "colloid"-like fluid in cyst, lymphatic infiltration in smaller cavities. Cysts separated by thin connective tissue strands. The "colloid" cyst could easily be mistaken for part of the thyroid.

Experimental studies in the influence of the thyroid upon the growth of the liver suggest definitely that such a splanchnomicria is due to endocrine factors. Whether the result is produced by damage of the pituitary, which is frequently found in cretinism, is not possible to decide. Experimental thyroidectomy produces moderate increase in liver fat.

The kidneys are also usually smaller in cretinism than in controls of corresponding developmental age.

The intestines are atonic and dilated.

BIBLIOGRAPHY

Banting, F. G., and Gairns, S.: Suprarenal Insufficiency. Am. J. Physiol. **77:** 100, 1926.

Bixby, E. M., and Benda, C. E.: Glucose Tolerance and Insulin Tolerance in Mongolism. Am. J. Ment. Def. **47:** 158, 1942.

Chaikoff, I. L., Eichhorn, K. B., Connor, C. L., and Entenmann, C.: The Production of Cirrhosis in the Liver of the Normal Dog by Prolonged Feeding of a High-fat Diet. Am. J. Path. **19:** 9–21, 1943.

Chaikoff, I. L., Entenmann, C., Rinehart, J. F., and Reichert, F. L.: Development of Cirrhosis in the Liver of Dogs Deprived of Both Pituitary and Thyroid Glands. Proc. Soc. Biol. Med. **54:** 170–71, 1943.

Conwin, Warren C.: The Relationship of the Endocrine Glands to Changes in the Fat Content of the Liver. Am. J. Path. **16:** 675–76, 1940.

Graef, L., Negrin, T. Soc., and Page, L. H.: The Development of Hepatic Cirrhosis in Dogs after Hypophysectomy. Am. J. Path. **20:** 823–55, 1944,

Kraus, E. J.: Chronischer Hirndruck und Leberverfettung. Virchows Arch. f. path. Anat. **300:** 617–40, 1937.

Morgan, L. O.: Alterations in the Hypothalamus in Mental Deficiency. Psychosomatic Med. **1:** 496, 1934.

Reuter, M. J.: Histopathology of the Skin in Myxedema. Arch. Dermat. & Syph. **24:** 55, 1931.

Roosen-Runge, E. C.: Fatty Infiltration of the Liver in Patients with Mongolism and in Some Children with Hydro- and Microcephaly. Am. J. Path., 1946.

Wieland, Emil: Die Hypothyreosen im Kindesalter. Handbuch Innere Secretion **3:** 103. Leipzig, 1928.

Zondek, Hermann: Das Myxoedemherz. München. med. Wchnschr. **43,** 1918, and **25,** 1919.

——: Die Krankheiten der Endokrinen Drüsen. Berlin, 1926 (2d ed.).

CHAPTER VII

GROWTH AND DEVELOPMENT OF SKULL AND BONES

Skull in Mongolism

Ever since human curiosity has made conjectures from the shape of the skull as to the function and activity of the brain hidden beneath its bony envelope, the relation between the brain and the skull has been a subject of great interest. Phrenology and physiognomy, which flourished at the beginning of the last century, did not leave the uncertain ground of speculation until 1858, when Rudolf Virchow made the first attempt to study the development of the skull by histological means. His famous work on cretinism, in which he explained the peculiar appearance of cretins as being due to an early ossification of the base of the skull, proved to be mistaken as far as cretinism is concerned; but his principal ideas about the importance of the synchondrosis spheno-occipitalis and other sutures are generally accepted, and numerous reports have followed his work dealing with the development of the skull.

Fig. 80 tabulates measurements of the normal circumference of the skull and the circumference of 125 mongoloid children. Three points shall be stressed in considering the normal growth of the skull. First, there is a remarkable increase during the first year of life, during which time the head gains more than 10 cm. in circumference. Second, there is a steady, but slower increase in size during the next 5 years of life; and third, there is a new impulse of growth after about the twelfth year of life. The growth of the normal skull continues up to about the twentieth year.

Anatomists are of the opinion that the last period of growth of the skull does not greatly increase the brain cavity but does increase the size of the skull through development of the sinus system, especially of the frontal sinus, through the development of the diploe of the skull and through periosteal proliferation.

In regard to the mongoloid skull, there is a marked difference from the normal development. At birth the circumference is for the most part within normal limits. Only a few mongoloids show measurements which are definitely below the normal. After birth, in the first few months of life, the mongoloid skull shows a remarkable retardation in growth. At the age of 1 year the skull does not even reach the size of that of a normal 6 months old child, and at the age of 2 years the mongoloid skull corresponds to that of a 9 months old baby. The most impressive fact is that mongoloid chil-

dren need almost 9 years to reach the level of a normal 1 year old baby. The mongoloid skull stops growth at an age of about 14 years, reaching a circumference corresponding to that of normal children between 3 and 4 years old.

Fig. 81 gives more details in regard to the growth disorder of the skull. It is obvious that the failure in development is due to a marked lack of growth in length. After two years the mongoloid skull does not even

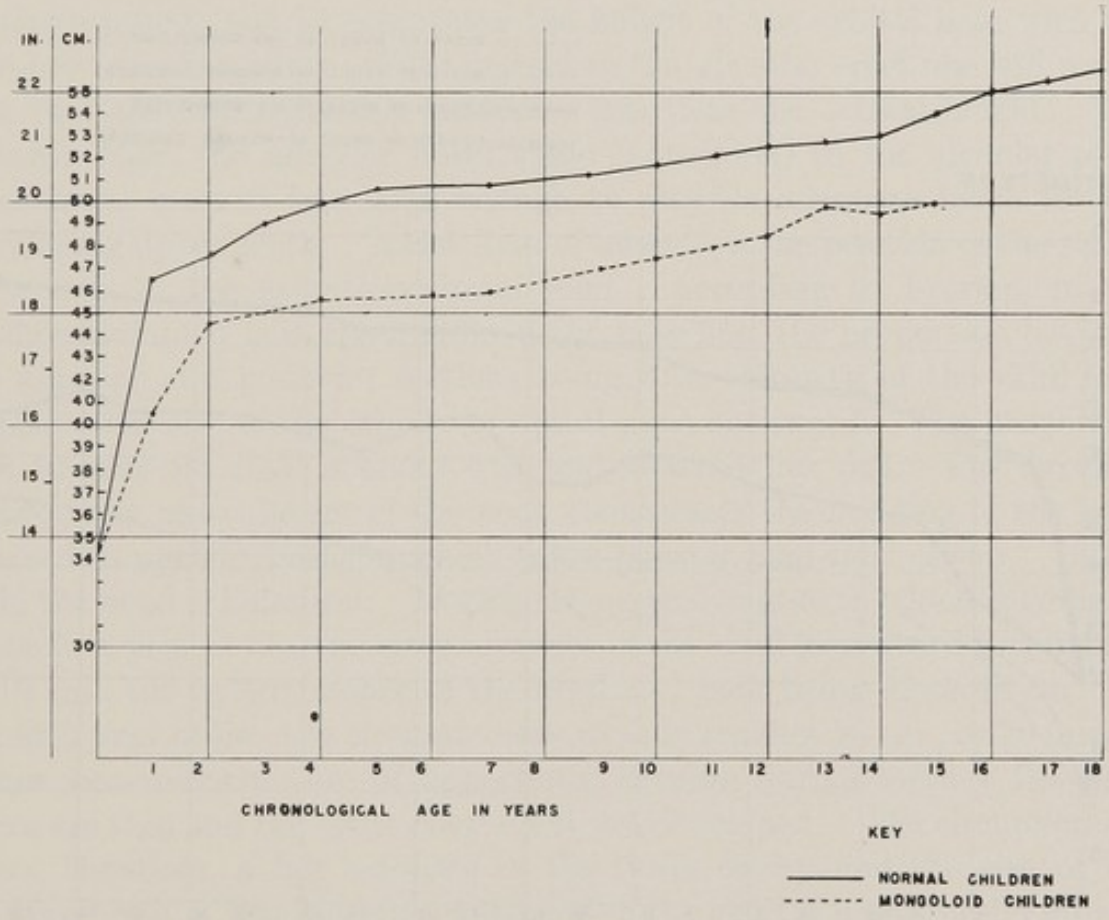


Fig. 80. Circumference of skull, normal development and in mongolism. The straight line represents standard values; the dotted line observations on 125 cases of mongolism. Note the great delay of skull expansion in the first year; at 1 year the skull circumference of the mongoloid baby hardly equals that of a 6 months old child and at 2 years the skull circumference corresponds to a 9 months old baby. After that time the skull expands slowly and lags about 2 inches behind the normal.

correspond to that of a normal child of 6 months, and at an age of 4 years it reaches the length of a 9 months old child. It takes almost eight years for the skull of a mongoloid child to reach the average length of the skull of a 1 year old baby, and the skull of mongoloids in our material never exceeded the length of that of a 3 year old child.

The width of the skull is slightly below the normal. The high cephalic index is therefore due not to a real broadening of the skull, but entirely

to the failure of growth in length. One may conclude from these observations that in mongolism certain factors are at work which especially involve the growth in length.

A better understanding of the growth disorder will be reached by comparing it with the normal development from birth to adult life. To a great extent, anatomists have dwelled upon the changes of the normal skull which occur during the period of development and which are persistent in spite

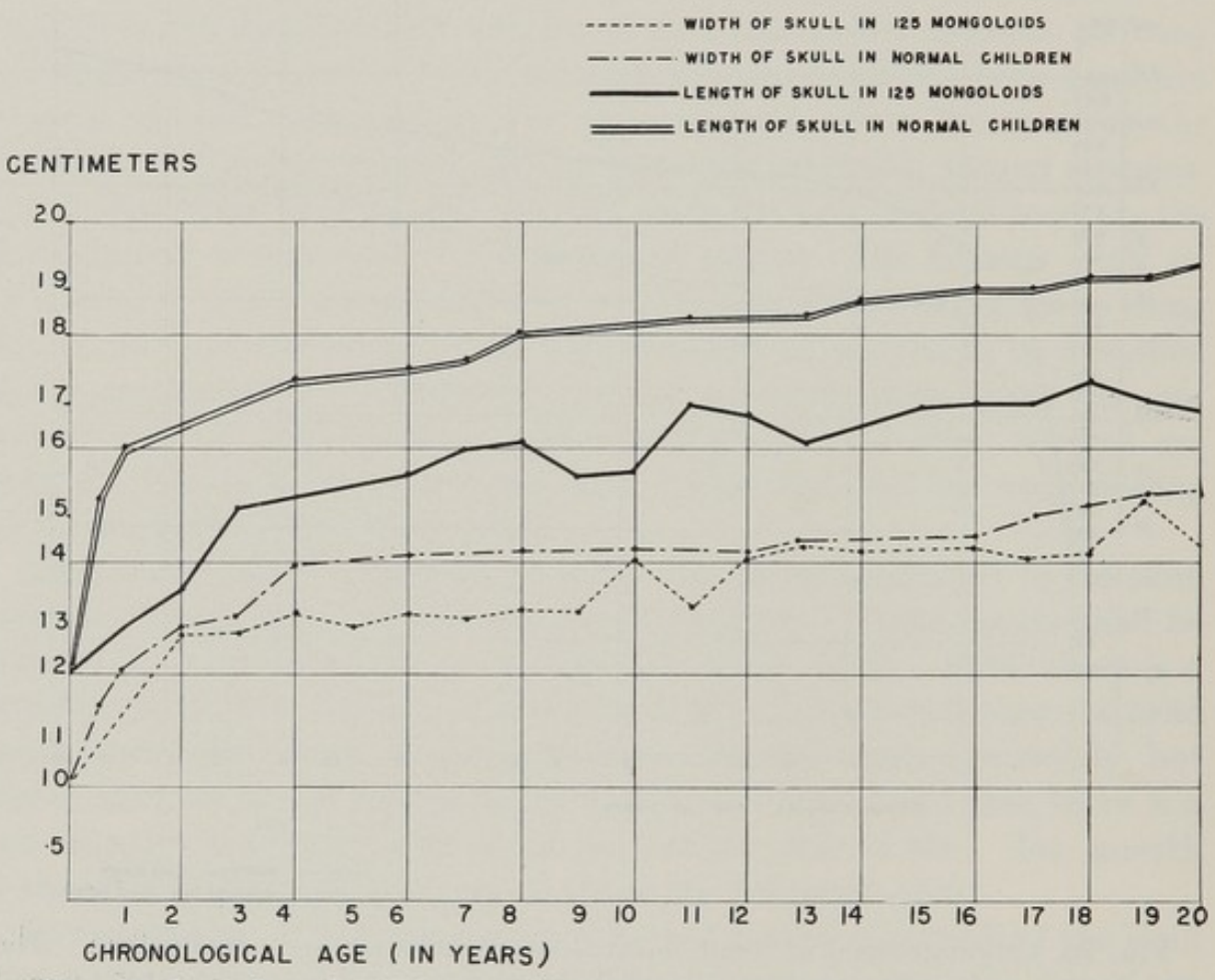


FIG. 81. Length and width of skull, normal standards and in mongolism. The two lines represent normal standards. In mongolism growth of the skull in length is exceptionally deficient resulting in extreme brachycephaly. The width of the skull is relatively better developed but remains below normal.

of the encountered variations of familial and racial appearance. In studying skulls, one places the specimen in such a position that the so-called "base line" or Frankfurter horizontal (a line which runs through the inferior margin of the orbit hole and the superior margin of the external auditory meatus) is in a horizontal position. A perpendicular line is drawn through the alveolar process in front of the face. The skull of the newborn infant differs from that of the adult in several points, and it may be useful to mention a few measurements and proportions which are of importance

for the understanding of normal development as well as of the mongoloid growth disorder. Most outstanding in the newborn skull are the large brain cavity and the small face. Average length, measured from the glabella to the occipital point, is 11.5 to 12 cm.; average parietal width (bip.), 9.5 cm. The circumference of the skull is 34 cm., or 13.5 inches. In studying the proportions of the face, it is noteworthy that the vertical distance from the vertex to the nasion is twice as large as that from the latter to the alveolar point. The orbital holes appear disproportionately large in the newborn infant, and in comparing the height of the orbital hole with the distance from the lower orbital margin to the alveolar crest one will recognize that the latter distance measures less than the orbital height. The distance from the anterior nasal spine (acanthion) to the alveolar point (prosthion) is short but large enough to provide adequate berth for the developing upper teeth. A last item of interest is the position of the transverse axis of the atlanto-occipital joint. According to Froriep, in the newborn infant it is in the middle of the base line, the proportion between the anterior and posterior sections being 3:3. Growth of the skull base displaces the site of the atlanto-occipital joint backward. The proportion in a 10 year old child is about 4:3, and in adult life, 5:3. The development of the musculature of the neck counteracts the nodding of the head forward in upright position which takes place if man falls asleep. In the child the head is balanced. During the extensive growth which is going on in the first year of life, the circumference of the skull increases 3 to 4 inches, or 10 cm., the circumference of the head at 1 year being 42 to 44 cm. In the fifth year of life, the circumference usually reaches 50 cm., or 20 inches. These measurements are of importance because during infancy the skull bones are thin and the sinus system not yet developed. The circumference offers, therefore, a fair estimate of the brain cavity and the size of the growing brain. The increase of the size of the skull is produced by growth of the skull base in the lines of the cartilaginous and membranous synchondroses and by osseous proliferation about the margins of the flat skull bones, the sutures acting like the epiphyseal lines of the long bones. Even more impressive than the increase of the brain cavity is the growth of the facial bones in postnatal life. The distance from the nasal spine to the alveolar crest increases rapidly; the lower orbit margin moves farther and farther apart from the alveolar crest, while the orbit holes gain very little in size. In the adult skull, the distance from the nasion to the alveolar point is equal to the height of the forehead. The mandible increases in size and the mandibular angulation becomes more marked.

Comparison of the mongoloid skull with the normal development demonstrates impressively the failure of an adequate growth of the former. To speak of "the" mongoloid skull is justified by considering the striking re-

semblance in all of them. Greig points out: "How closely alike these skulls are to each other, superimposition of their outlines conclusively demonstrates whether the orientation be lateral or facial. Nor is there any reason to believe that increased age would have altered their main characteristic." This is well demonstrated by Greig, who superimposed the outlines of three mongoloid skulls. In Fig. 82 I have outlined one mongoloid skull which demonstrates well the whole pathology. The transverse axis of the atlanto-occipital joint is still in the middle of the base line in spite of the notorious

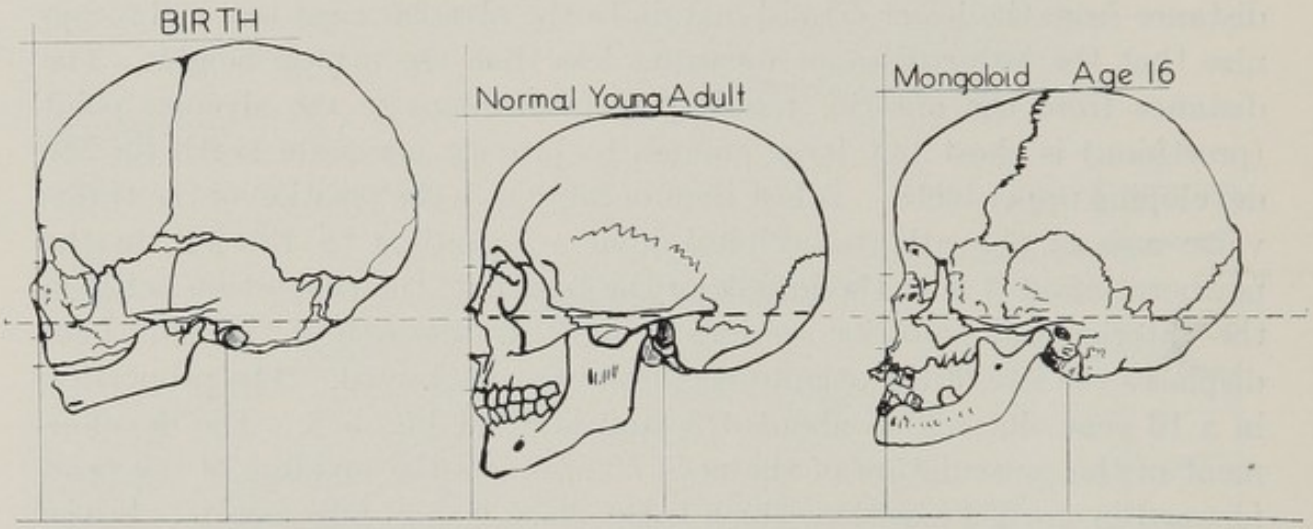


FIG. 82. Comparison between normal skull and mongoloid skull. The configuration of the skull (A) at birth, (B) in a young adult, and (C) in a mongoloid. Note the large brain cavity and the small face at birth. The distance from the bregma to the nasal root measures twice the length from the nasal root to the alveolar crest. Note the short distance from the nasal spine and the inferior orbit margin to the alveolar crest. Note shape of infantile mandible. The transverse axis of the atlanto-occipital joint is in the middle of the base line.

The outstanding feature in the young adult is the increase in size of the facial bones. The lower margin of the orbit hole is far apart from the alveolar crest. The mandible shows angulation.

The mongoloid skull preserves the fetal proportions although there is some increase in size noticeable. The face remains small. The nasion and maxilla are underdeveloped and the mandible shows fetal shape. The transverse axis of the atlanto-occipital joint is still in the middle of the base line, or sometimes even nearer to the front line.

brachycephaly of the mongoloid skull. This is due to the extreme shortness of the skull basis in mongolism. A second factor is the failure of growth of the maxilla and the nasal portion. The proportion between forehead and face is still fetal. The deficiency of development of the maxilla places the lower margin of the orbit near the alveolar crest and the distance from the nasal spine to the alveolar point is as short as in a normal newborn baby. The incisor teeth have no space for their roots and protrude. The angulation of the mandible is flat and definitely fetal in shape, but its out-

line is somewhat confused by the fact that the mental process is protruding and the anterior branch is bent. This feature appears to me to be due to the fact that on account of the underdevelopment of the maxilla and the teeth, the mandible does not find the normal counteraction. The strong muscle pull bends the anterior rami of the mandible upward.

In summarizing the abnormality of the facial development of the mongoloid skull, it appears striking that the mongoloid skull is deficient in growth of all those structures which show the most marked development after birth, the nasal bone, ethmoid, and maxilla, resulting in a persistence of fetal proportions of the face. The outline of the mandible is sometimes confused in later life through protrusion, and prognathism occurs owing to muscle traction of the masticatory apparatus, but these secondary changes do not influence the essential feature of mongolism, which consists in the failure of development of the protruding structures, the summits of the face. The micrognathic deficiency is only a part of the picture. The skull basis remains short on account of the insufficient growth of the synchondroses spheno-occipitalis and spheno-ethmoidalis. Another factor which contributes to the shortness of the skull base is the absence of development of the frontal and sphenoid sinuses. A brief glance over the picture of a transverse section through the normal skull reveals how definitely the sinus expansion influences the skull shape. By eliminating the sinus system from the skull, one obtains the true outline of a sagittal section through the mongoloid skull (Fig. 83). Another factor is the failure of the flat skull bones to produce sufficient growth at the bone margins. This failure is indicated clinically by the slow closure of the fontanelles, which remain patent for several years. It is also indicated by the remainder of sutures which disappear normally shortly after birth (frontal suture and sagittal suture) and the creviced sutures at the skull basis which were found by Greig. A last item, worth mentioning, is the thinness of the flat skull bones owing to failure of diploe development. In my autopsy material, the skull bones measured 3 to 4 mm. only instead of 6 to 10 mm. except in a few cases in which marked brain atrophy had increased internal bone proliferation. The mongoloid skull is extremely light, and the skull bones are sometimes paper thin with irregular foramina where ossification is wanting. Table 19 shows a comparison of four mongoloid skulls with those of four mentally deficient children who corresponded in age and in skull circumference to the mongoloids.

It is obvious that the mongoloid calvarium is definitely lighter than that of the control cases. Most outstanding is a weight of 66 Gm. of the calvarium of a mongoloid girl, aged 12 years. But even ignoring such an extreme value, the tendency of the skull weight is obvious.

Greig offers a few measurements which also impressively demonstrate the facts presented above.

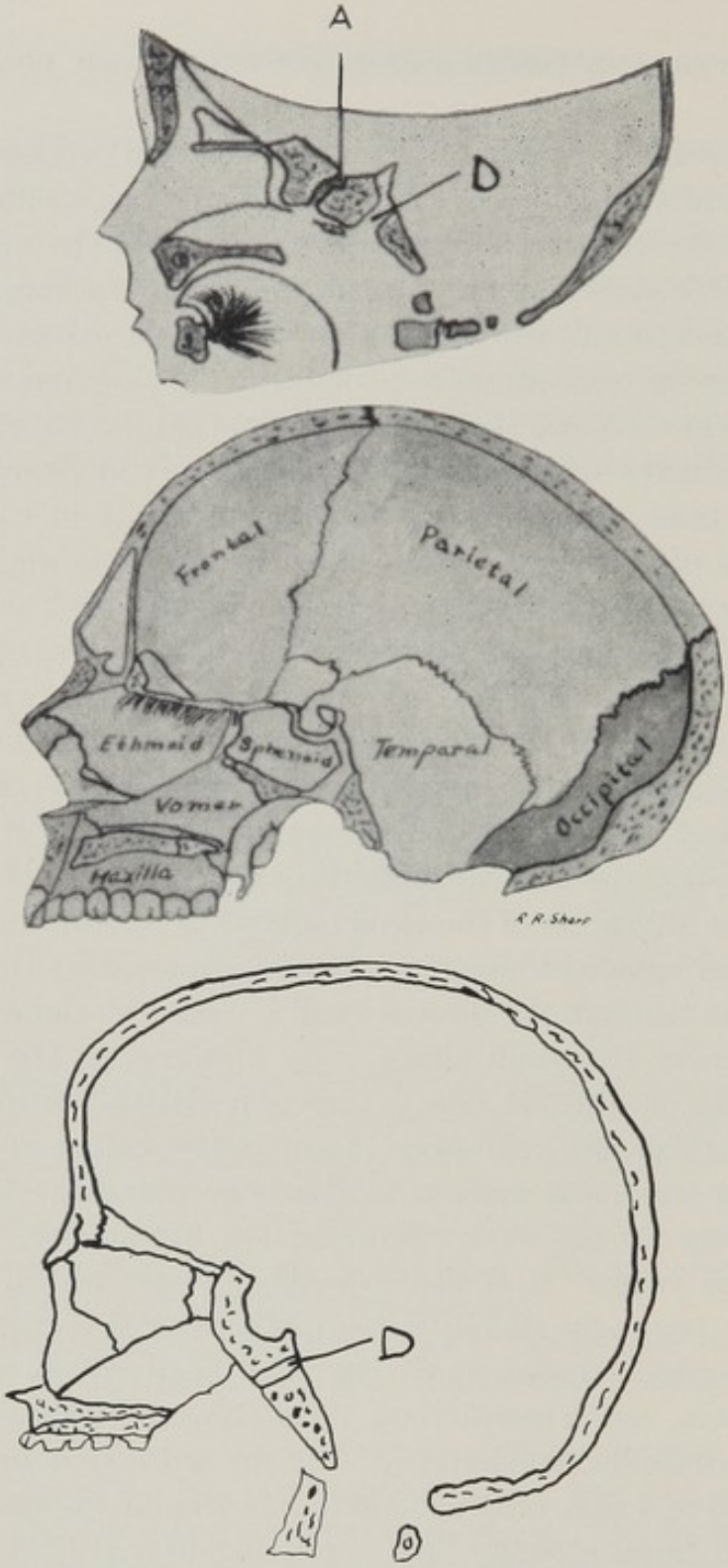


Fig. 83. Skull diagrams, normal and in mongolism. 1. Diagram of a skull of a year old child after Virchow. Note cartilaginous disk between clivus and sphenoid body (D) and cartilage separating the sphenoid body (A). During development the anterior part of the sphenoid body moves downward and resumes a more horizontal position. Note site of future sphenoid sinus and frontal sinus.

2. Diagram of a normal adult skull. Note large size of sphenoid sinus and frontal sinus, and note influence of these sinuses upon configuration of skull and face.

3. Diagram of a mongoloid skull. The sphenoid sinus is missing and the sphenoid body hypoplastic. This body appears upright and normal angulation between clivus and sphenoid is missing. Note absence of frontal sinus which results in a straight infantile forehead. The whole anterior cavity is shorter, steeper, and on a higher plane than normal. Note retraction of nasion, hypoplasia of maxilla, and absence of diploe formation of the flat skull bones.

If three averaged mongoloid skulls are compared with three averaged microcephalic skulls of approximately the same age, the difference is outstanding.

Although the circumference of the three mongoloid skulls averaged 44.4 against the 37.5 cm. of the microcephalic patients, and the cranial capacity was 982 against 543, the three mongoloid skulls had almost exactly the same weight (316.57 to 311.85 Gm.). Measuring of the ophryo-alveolar length (distance from point between eyebrows to alveolar point) and of the superior facial index $\left(\frac{\text{ophryo-alveolar length} \times 100}{\text{bizygomatic width}}\right)$ illustrates the failure

TABLE 19

Mongoloids			Undetermined Idiots		
Age	Head Circum., Cm.	Calvarium Weight, Gm.	Age	Head Circum., Cm.	Calvarium Weight, Gm.
8 yrs. 7 mo.	47.0	184	8 yrs. 9 mo.	51.0	290
12 yrs.	48.0	66	12 yrs.	48.5	280
15 yrs.	49.5	250	16 yrs.	43.0	330
20 yrs. 6 mo.	50.8	230	17 yrs.	52.0	320

TABLE 20

	Mongoloid	Microcephalic
Circumference (cm.)	44.40	37.50
Ophryo-mental length (mm.)	96.00	117.00
Ophryo-alveolar length (mm.)	68.00	85.00
Superior facial index	69.92	86.42
Cranial capacity (cc.)	982.00	543.00
Weight of skull (Gm.)	316.57	311.85

of facial growth of mongoloids in contrast to the facial development of microcephalic patients.

These observations prove definitely that the peculiar shape of the mongoloid skull is due to a deficiency of growth and confirm the assumption that the absence of proliferative growth of cartilaginous and fibrous tissue is an essential factor in this disorder.

Besides Greig's description of several skulls and my own autopsy observations, there are five detailed accounts of the skull formation in mongolism. The first one, given by Fraser, has been mentioned before. Two skulls were described by Nieuwenhuyse, one by van der Scheer, and one by H. C. Jelgersma. Regardless of minor variations, the descriptions are well in line with each other. The sutures were found either open or, when

ossified, still movable. The frontal suture was open in Jelgersma's skull. The nasion was present or absent but always hypoplastic. Jelgersma also observed the absence of the sinus system which I have described in detail and the steep angle between clivus and the alae parvae.

Ossification in Cretinism and Mongolism

There are two conditions known associated with a marked shortening of the base of the skull—chondrodysplasia and cretinism. My studies have proved that mongolism is also associated with a failure of the development of the skull in length.

If we compare histologically the three disorders, chondrodysplasia, cretinism, and mongolism, we may say that in chondrodysplasia growth of the base of the skull is arrested because of lack of development of the cartilage, which is absorbed early and replaced by ossified tissue. In cretinism, growth of the bones of the skull is delayed because of lack of transformation of cartilage into bony tissue. The cartilaginous spaces in cretinism are open much longer than is normal.

In mongolism, another aspect of ossification manifests itself. The synchondrosis spheno-ethmoidalis, in contrast to the synchondrosis spheno-occipitalis, consists of fibrous tissue. It undergoes ossification according to the process which unites the sutures of the skull and ossifies the membranous bones. In a mongoloid boy of 9 years and 8 months, the anterior clinoid process was found far apart from the dorsum sellae and no ossification was taking place. Only the edges of the synchondrosis and of the anterior clinoid process were heavily ossified. It is of interest that this synchondrosis formed a fibrous tongue protruding into the sphenoid body. In another specimen from a 15 year old mongoloid child the synchondrosis spheno-ethmoidalis was also wide apart, without signs of ossification. This fact is of interest because Timme described the shape of the sella turcica in mongolism and noticed a peculiar appearance of the anterior part of the sella by x-ray examination. The same observation was later recorded by Tumpeer. Timme interpreted this change to be the result of enlargement of the pituitary gland. Microscopic examination, however, shows that the radiographical appearance is due to the wide open synchondrosis and that the shape of the sella is independent of the size of the pituitary gland in mongolism. Moreover, the appearance of the sella turcica in mongolism corresponds to the x-ray appearance of a full term embryo in which the sella turcica also is separated into two sections.

In 1916, Stoccada published a paper on the synchondrosis spheno-occipitalis, its normal development, and the alterations occurring in cretinism. In this paper he described the synchondrosis at the time of birth, during

the first decade, the second decade, and after further growth had ceased. My observations on control cases are in accordance with those of Stoccada. It may, therefore, be worth while to record a few points of interest concerning the development of the synchondrosis. The cartilage which lies between the occiput and the sphenoid bone does not form a simple disk at the time of birth but continues to develop toward the posterior clinoid process as a cartilage slide of the same size as the disk, forming the rostral dorsum of the clivus blumenbachii and the posterior clinoid process. The cartilage disk of the synchondrosis averages from 3 to 3.5 mm. in thickness. The cartilage cells form vertical columns in the center and are arranged in horizontal columns toward the occipital bone and the sphenoid body. Growth occurs in two directions. The cartilage disk grows in a vertical direction and the height of the disk increases steadily from about 7 mm. at birth to between 13 and 15 mm. at the age of 17 years. The horizontal cartilage columns proliferate in the same manner as the epiphyseal lines of the long bones. The thickness of the cartilage disk is about 3 mm. and remains this size for almost the first 20 years of life. At about the age of 20 years the cartilage becomes gradually absorbed and disappears. According to Stoccada the area of proliferation measures between 200 and 300μ and the area of ossification about 150μ. The appearance is identical with that seen in the ribs and the epiphyseal lines of the long bones. It may be mentioned that the cartilage proliferation appears slightly more active toward the occiput than toward the sphenoid. After the first year the cartilage frequently shows a tongue-like protrusion into the sphenoid body. Therefore, the synchondrosis appears F-shaped. This cartilage tongue was found regularly in my material.

Although the histological appearance of the cartilage in cretinism and mongolism appears to be somewhat similar at first sight, there are marked differences if observed in more detail. In cretinism the cartilaginous border of bone forms a straight line with few or no primary medullary cavities. The ridge of ossification is rather thin. The preparatory columns show a normal appearance; the cartilage, however, degenerates when lack of thyroid is not corrected by therapy or experimentally produced by complete thyroidectomy. According to Stoccada, this is easily recognizable; the marrow cavities are rare, irregular in shape, and separated from the cartilage by a ridge of bone. The disorder of ossification causes a persistence of cartilage. Siegert and Stoccada interpreted the lack of ossification as being due to a deficiency of the bone marrow which is not able to absorb the cartilage and to stimulate sufficient growth. In mongolism the histological appearance is usually different, although at times the condition may be confused by a secondary thyroid deficiency. The ossification is active and calcification of the spongiosa is not delayed. There are a num-

ber of medullary cavities. The border of the bone is arcade-shaped. Lack of proliferation of cartilage is easily recognizable. The cartilage disks are extremely small, and proliferation and formation of preparatory columns are arrested.

These observations are in accord with Lauche's studies of metatarsal bones. His Cases 1 and 4, mongoloid children aged 4 and 18 months respectively, showed a complete lack of cartilaginous proliferation. The cartilage was found to be covered with a more or less thick ridge of bony tissue which separated the cartilage from enlarged marrow cavities. In Cases 2 and 3, children 10 and 12 months old respectively, slight traces of cartilaginous proliferation were still recognizable. The bony tissue formed transverse ridges parallel to the cartilage border, which caused the formation of small secondary marrow spaces. Lauche pointed out that in normal children growth goes on during the ossification period, except in the ribs, as long as cartilage is available for ossification. In mongolism this growth is arrested, although enough cartilaginous tissue is still available. In 1902, Kassowitz reported that the marrow spaces were not finger-like processes, but occurred in the form of rounded, knob-like projections into the zone of cell columns, and that consequently the spongy bone did not consist of long tracts of bone but rather of rounded cavities.

The few studies of the growth of bone in mongolism are well in accord when the same bone structure is concerned. It is the distal and not the proximal epiphyseal lines that are noteworthy. Moreover, one has to bear in mind that growth in mongolism is somewhat irregular and periods of retardation may be followed by periods of more active growth.

The facts presented above—especially the more regular appearance of the centers of ossification, but delay of further growth, the small size of the cartilage disks, and the general growth disorder involving not only the cartilaginous epiphyseal lines but the membranous bones of the skull—indicate that the growth disorder is definitely different from that of cretinism. If the arrest of growth were restricted to the skull, the simplest explanation would be that the lack of development of the brain is the cause of the lack of further development of the skull. Such an explanation is correct for many forms of microcephaly in which the growth of the brain is arrested while the growth of the body continues undisturbed. Although it is true that many microcephalic patients remain dwarfs and that general endocrine deficiency is frequently associated with microcephaly, the arrest of growth of the brain and of the skull precedes the arrest of the growth of the body for many years. Microcephalic patients show a striking disproportion between circumference of the skull and the rest of the body, and observations prove that these patients grow at a normal rate during the first years of life while the skull remains undersized. Not until several years of life

have passed does the growth disorder of the body become apparent. The fact, however, that in later life microcephaly is frequently associated with a general endocrine disorder indicates an influence of the brain on the endocrine glands. In mongolism measurements and studies of the brain development indicate that during the first half year of life the weight of the brain corresponds to normal, while at the same time a general growth disorder of the skull and the long bones is recognizable. The arrest of differentiation and the absence of growth stimulation apparently parallel the arrest of further development of the brain but do not depend on it. Moreover, the alterations of the vertebrae and of the long bones are independent of the brain and develop at the same time arrest of growth of the skull occurs.

Evaluation of all factors at hand indicates strongly that the growth disorder in mongolism is due to the absence of agents which induce differentiation and growth. It is generally assumed that these factors are related to the pituitary gland.

Erdheim, who studied the growth disorder of the cartilage in acromegaly, emphasized that in this condition proliferation of cartilage is renewed if cartilage remnants are available (ribs and long bones of young adults). If the cartilage in the epiphyseal lines has disappeared further proliferation is impossible, but the cartilage of the joints shows activity which eventually leads to degeneration. Erdheim is of the opinion that a renewal of cartilage activity is one of the main factors in the acromegalic disorder. On the other hand, hypofunction of the pituitary gland inhibits enchondral ossification and the epiphyseal lines remain open. Erdheim earlier had stressed the fact that the Paltauf dwarf is astonishingly small because the proliferation of cartilage in the epiphyseal lines is completely arrested or markedly diminished through hypofunction of the pituitary. The epiphyseal lines remain open and enchondral ossification is completely or almost completely arrested. The assumption expressed by earlier writers that the cause of dwarfism is a premature ossification of the epiphyseal lines is therefore incorrect, according to Erdheim.

Recent experiments, however, may modify the conclusions drawn by Erdheim. We have to bear in mind that in animals, in whom the epiphyseal cartilage usually disappears, this cartilage will persist if the animals are castrated. It is possible, therefore, that the persistence of cartilage in dwarfs and mongoloids is due not to a direct dysfunction but to a hypoplasia of the gonads which is almost always associated with pituitary dysfunction.

Of even more importance in regard to the relation between growth disorders of bone, especially of the skull, and pituitary dysfunction is the work of Mortimer. He studied the effect of hypophysectomy on young rats, and his results may be quoted briefly as follows:

Comparing the measurements of the hypophysectomized and the control, it appears that the greatest disturbance of growth in the hypophysectomized animal's cranium is in the anteroposterior direction, both cranial height and width showing no failure in growth. Occipito-nasal length is 16.1 per cent less and fronto-occipital length is 11.4 per cent less than the control, but the chief defect is in the nasal bones, which are almost a quarter less long than normal. . . . Even more marked is the resultant defect on the lower incisor and mandible, as shown by 34 per cent retardation in the lower incisor and a 43 per cent in the body of the jaw. . . . Absence of the anterior lobe of the pituitary imposes a handicap on growing bone in general which tends, peculiarly and particularly, to affect the growing snout, owing to the cancellous type of bone of which it is largely composed, the brain-case being structurally of more compact bone, which, while undoubtedly affected by hypophysectomy, is so to a less degree.

The frontal bone is similarly affected in the areas between the vascular expansions, which suffer to a marked degree. This is particularly true in the anterior expansion which occupies the site more closely homologous to the human frontal sinus. It is not only much shorter anteroposteriorly (two-thirds the length), but is also much less in its vertical measurement, while its outer table, instead of forming the convexity of the fronto-nasal angle is depressed and somewhat concave, and its contained marrow aplastic. A similar condition is present in the basal bones of the skull which are considerably less "expanded" than normal, and in length are 20 per cent shorter than in the control. The ethmoid and its cribriform plate, as well as the zygoma, are considerably smaller.

It is obvious that the postnatal growth disorder in mongolism is similar to the effect of hypophysectomy in rats. The mongoloid deficiency is marked by delay in growth in length of the base of the skull, lack of development of the masticatory apparatus, lack of sinus development and pneumatization of the skull, shortness of the nose with depressed bridge, and fetal proportion between brain case and face.

Skull in Cretinism

In previous paragraphs, the histological appearance of the cartilage in cretinism and the peculiarity of the growth disorder have been compared with mongolism. From a historical point of view it is of interest that Virchow, in 1858, recorded three cases of "cretinism" in which he attempted to prove that premature ossification of the base, the "os tribasilaris," was present. He concluded that this gave rise to the peculiar appearance of cretins. Virchow demonstrated that the possibility of growth of the skull in different directions is dependent on long persistence of the sutures and cartilaginous spaces. If there is lack of cartilage through premature synostosis, there is no possibility for the bones to grow, and a deep-set nose, protruding forehead, and malformation of the orbit appear.

Bayon refuted Virchow's statement with great emphasis, demonstrating that premature ossification cannot play an important role in cretinism. By that time the cause of cretinism was better understood. Cretinism was

proved to depend on athyroidism or hypothyroidism. Retarded ossification and persistence of cartilaginous spaces could be demonstrated in all classes of cretinism. Bayon was undoubtedly right when he refuted Virchow's statements about cretinism, but at the time of Virchow's investigations the difference between cretinism, achondroplasia, and mongolism was not yet known. Remarks in his paper suggest that he was conscious of dealing with different forms of "cretinism"; he distinguished at least two, and probably three, types.

Weygandt re-examined one of Virchow's specimens and concluded that Virchow was dealing with a case of achondroplasia.

While growth is impossible because of the heavy osseous deposits at the cartilage border, the same process leads to short, broad, and heavy bones. In young cretins the skull appears heavier than the normal skull, and later in life the weight of the skull is 50 per cent increased. The skulls of cretins are almost the heaviest which one may find at autopsy. The structure is dense and solid, and there is no porosity.

The observation that the skull is richer in minerals, especially calcium, in cretinism has been put on a solid scientific basis by Aub, Bauer, Ropes, and Heath, who studied the calcium metabolism in hypothyroidism and demonstrated that calcium and phosphorus are deposited in greater concentration. It is evident that such a special process leads to characteristic structural changes, which lend themselves readily to x-ray studies. These will be discussed in the next chapter.

BIBLIOGRAPHY

Aub, J. C., Bauer, W., Ropes, M., and Heath, C.: The Relation of the Thyroid Gland to Calcium Metabolism. Tr. A. Am. Physicians **42:** 344, 1927.

Bayon, P. G.: Ueber angebliche verfrühte Synostose bei Kretinen und die hypothetischen Beziehungen der chondrodystrophia foetalis zur Athyreosis. Beitr. z. path. Anat. u. z. allg. Path. **36:** 119, 1904.

Benda, Clemens E.: Growth Disorder of the Skull in Mongolism. Am. J. Path. **16:** 71, 1940.

——: Studies in Mongolism. I. Growth and Physical Development. Arch. Neurol. & Psychiat. **41:** 83–97, 1939.

——: Further Clinical and Anatomical Studies in Mongolism. Proc. Am. A. Ment. Deficiency, 63rd Ann. Session, Chicago, May 3–6, 1939.

Erdheim, J.: Der Gehirnschädel in seiner Beziehung zum Gehirn unter normalen und pathologischen Umständen. Virchows Arch. f. path. Anat. **301:** 763–818, 1938.

——: Die Lebensvorgänge im normalen Knorpel und seine Wucherung bei Akromegalie. Pathologie und Klinik in Einzeldarstellungen, Aschoff, L., Elias, H., Eppinger, H., Sternberg, C., and Wenckebach, K. F., eds. Julius Springer, Berlin **3:** 1931.

Froriep, August: Anatomie für Künstler. Breitkopf and Härtel, Leipzig, 1899.

Greig, David M.: The Skull of the Mongolian Imbecile. Edinburgh M. J. **34:** 253, 1927.

Jelgersma, H. C.: Beschreibung des Schädels einer Mongoloiden Idiotin. Ztschr. f. d. ges. Neurol. **150:** 446–50, 1934.

Lauche, A.: Zur Histologie der Knochenwachstumsstörungen bei Mongolismus. Virchows Arch. f. path. Anat. **249:** 315–34, 1924.

Mortimer, Hector: Pituitary and Associated Hormone Factors in Cranial Growth and Differentiation in the White Rat: A Roentgenological Study. Radiology **28:** 5–39, 1937.

Nieuwenhuyse: Psychiat. en Neurol. Bl., Feestb. Winkler, 1918.

Stoccada, Fabio: Untersuchungen über die Synchondrosis sphenooccipitalis und den Ossifikationsprozess bei Kretinismus und Athyreosis. Beitr. z. path. Anat. u. z. allg. Path. **61:** 450–513, 1916.

Timme, Walter: The Mongolian Idiot. Arch. Neurol. & Psychiat. **5:** 568–71, 1921.

Tumpeer, I. Harrison: Mongolian Idiocy in a Chinese Boy. J. A. M. A. **79:** 14–16, 1922.

Virchow, R.: Knochenwachsthum und Schädelform, mit besonderer Rücksicht auf Cretinismus. Virchows Arch. f. path. Anat. **13:** 323, 1858.

Weygandt, W.: Ueber Virchow's Kretinentheorie. Neurol. Centralbl. **23:** 290, 1904.

CHAPTER VIII

X-RAY STUDIES IN MONGOLISM AND CRETINISM

X-Ray Characteristics of Mongoloid and Cretin Skull

The usefulness of roentgenographic studies of the bones in cretinism is well recognized, but almost no use has been made of x-rays for the study of mongolism. Even the most modern textbooks of roentgenology hardly mention mongolism, and cretinism is not too thoroughly treated either. Schüller and Clift have dealt with the skull in mongolism, and the metacarpal bones and fingers have been studied by Hefke in recent years.

The value of x-ray studies for the recognition of hypothyroidism rests upon the fact that the centers of ossification appear successively over a period of about fourteen years. The union of epiphyseal lines of the various bones is spread over a period of more than twenty-five years. Since the calendar of ossification from birth to adulthood is well established, x-rays offer an unparalleled opportunity to check on the progress of osseous development throughout life. The determination of the "bone age" is a standard method for the recognition of thyroid diseases.

Many physicians who have seen only a few sporadic cases of mongolism have seen only those in which there was no doubt about the diagnosis. Those physicians apparently felt that there was nothing to do about it. They did not realize that there are many cases in which the diagnosis is quite difficult in the first six months of life and that x-ray examination offers a valuable help in establishing the diagnosis. Moreover, x-ray studies enable the physician to determine the degree of retardation and the presence of malformations, which is helpful in establishing what can be expected from any therapy. Last but not least, periodical follow-ups make it possible to check on the effect of therapy in the same way as in cretinism.

The anatomical data which were reported in the last chapter provide evidence that mongolism and cretinism are each characterized by a specific structure of the skull.

Earlier investigators placed emphasis upon an x-ray study of the sella turcica. The outline of the sella is, however, not abnormal in mongolism (Gordon, Bell, Benda). But in turning attention to the proportions and the angulation of the skull base and face, x-ray pictures of the mongoloid skull

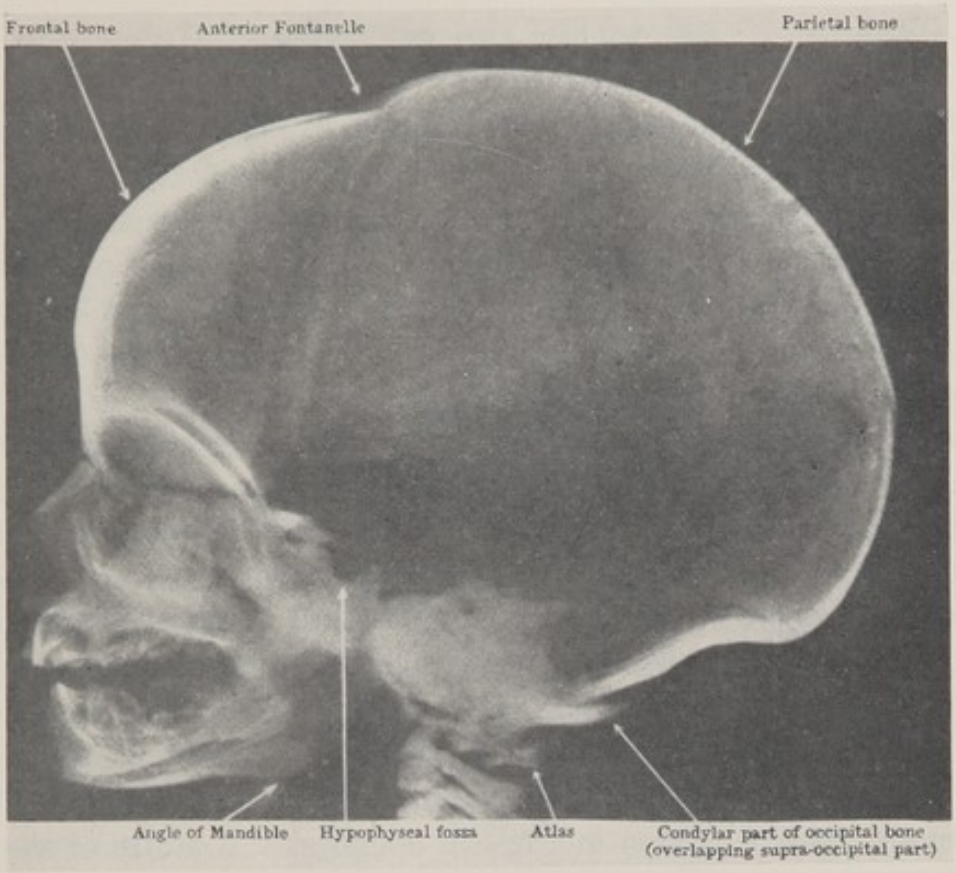
are of indispensable value for an understanding of the anatomy. One x-ray picture will demonstrate the essential items better than the description of many skulls (Fig. 84). It is obvious that the sphenoid body is smaller than normal and, most important, its position is more upright. The distance from the anterior clinoid process to the acanthion is shorter than normal, and the plane of the cribriform plate is displaced to a higher level. The smallness of the maxilla is remarkable. The nasal spine is close to the alveolar ridge, and the ridge appears on the same level as the sella instead of being on the same plane with the skull base. The axis of the atlanto-occipital joint is nearer to the face line than to the occiput, indicating the smallness of the bones forming the skull basis and the facial scaffolding.

Another item is the condition of the skull sutures. All sutures may be separated, and one may find that the sagittal suture is not in approximation and the parietal bones are separated $\frac{1}{2}$ cm. or more. The frontal suture, which normally disappears within a few days after birth, may be found open even several months to years after birth. The same delay is recognizable about the lateral fontanelle and those sutures which cross the sides of the skull.

It is noteworthy that the lateral view does not always reveal brachycephaly in infants. Later in life, brachycephaly is a persistent feature. The abnormal position of the sphenoid body remains throughout life. Sinus formation is absent, and the sphenoid body remains small.

The confusing features of the anterior cavity are better understood when compared with anatomical observations made at autopsy.

The anterior cavity in cases of mongolism is characterized by the extreme protrusion of the roofs of the orbits. Slight projection of the roofs is normally observed, but in patients with mongolism they form a marked protuberance. The cribriform bone is short and retracted and forms a small, deep valley between the arches of the orbits. Another peculiarity of the roofs of the orbits is that they ascend laterally toward the frontal bone without leaving any deepening between the top and the facies temporalis of the frontal squama. This gives the anterior cavity as a whole a curved shape, the floor sloping upward anteriorly and laterally toward the frontal bone. The sphenoid bone is small and the body of the bone underdeveloped. It is noteworthy that neither the frontal nor a sphenoid sinus is to be seen in cases of mongolism. Although these sinuses are not fully developed before the seventh year of life, slight pneumatization is noticeable several years before that age, and comparison of the normal body of the sphenoid bone and that in cases of mongolism reveals that the latter is underdeveloped.



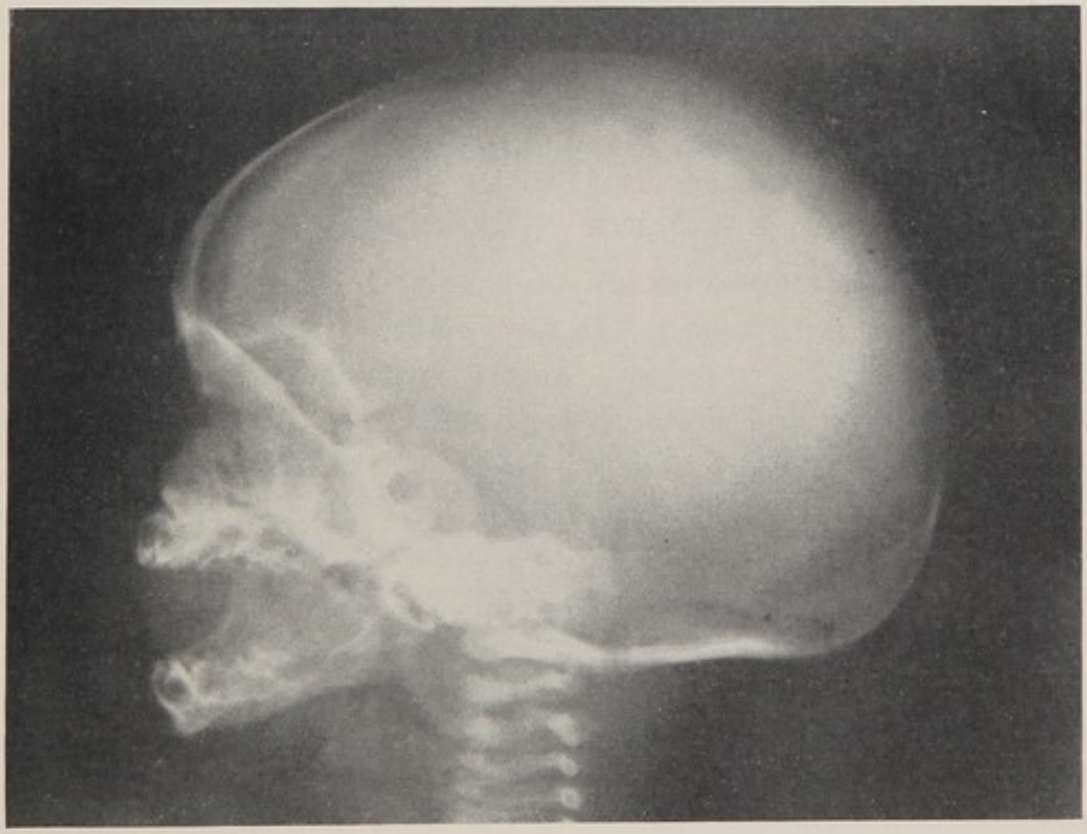


FIG. 84. X-rays of normal skull and mongoloid shortly after birth. A. (Upper) Lateral view of full term fetus after Cunningham's *Textbook of Anatomy*. Note size and angulation of sphenoid body and plane of cribriform plate. Note development of nasion and maxilla.

B. (Lower) X-ray of a 5 week old mongoloid baby representing about a dozen cases of same age group. Note abnormal backward displacement of sphenoid body, small size of that body; abnormal plane of cribriform plate; retraction of nasion and absence of bone; hypoplasia of maxilla. The alveolar crest is at the same plane as the posterior clinoid process instead of the skull basis. Note thinness of flat skull bones.

The middle cavity appears deep and is overshadowed by the projecting major wings of the sphenoid bone. The posterior cavity shows typical signs. The occipital squama is steep and upright, instead of lying in a rather horizontal position behind the foramen magnum. Sometimes the occiput slopes in a way that continues the line of the spine. The foramen magnum in several cases was observed to be small and transversely ellipsoid, showing so-called frontal stenosis.

A postero-anterior view adds an important fact to the previous observation. In a normal skull the supra-orbital notch indicates the highest point of the supra-orbital margin. Laterally, the margin curves downward and articulates at its external end with the frontal process of the zygomatic bone. In the mongoloid skull the supra-orbital border follows an upward curve toward the external end, forming at this point a rather sharp angle with the zygomatic process. Therefore, in cases of mongolism, the supra-orbital notch does not represent the highest elevation of the upper orbital margin. As a matter of fact, the slanting eyes of patients with mongolism are caused by slanting orbital openings. A study of the upper orbital margin in cases of mongolism indicates the deformity of the skull and is suggestive of the diagnosis of mongolism. The Mongolian race does not show such an upward curvature of the orbital margin. Lack of formation of the frontal sinus is easily recognizable in the postero-anterior view of the skull of a mongoloid child after the seventh year.

The Skull in Cretinism

The orbit holes in mongolism are egg-shaped, in striking contrast to the normal orbit shape in cretinism. In this condition, the flat skull bones become heavily calcified. In infancy, however, the width of the flat bones is small. The skull basis is short and shows clearly the cartilaginous disk between the clivus and the sphenoid body. This disk is recognizable as a bright band separating the two bones. The position of the sphenoid body is normal and not upright as in mongolism. The anterior cavity has a normal shape. The membranous bones are delayed in ossification but become heavily ossified and appear rather thick later in life. The sutures, however, and the fontanelles remain open for a long time. The basis of the skull remains short. As the cretin becomes older, ossification is heavy. The disk is still recognizable at a time when it has disappeared in normal children. It is a significant aspect of the skull of the adult cretin that the calvarium is thick and heavily ossified while, at the same time, the suture lines are still distinct and the site of the anterior fontanelle may be paper thin. In any other condition which is associated with heavy calcification of the skull, the suture lines disappear completely.

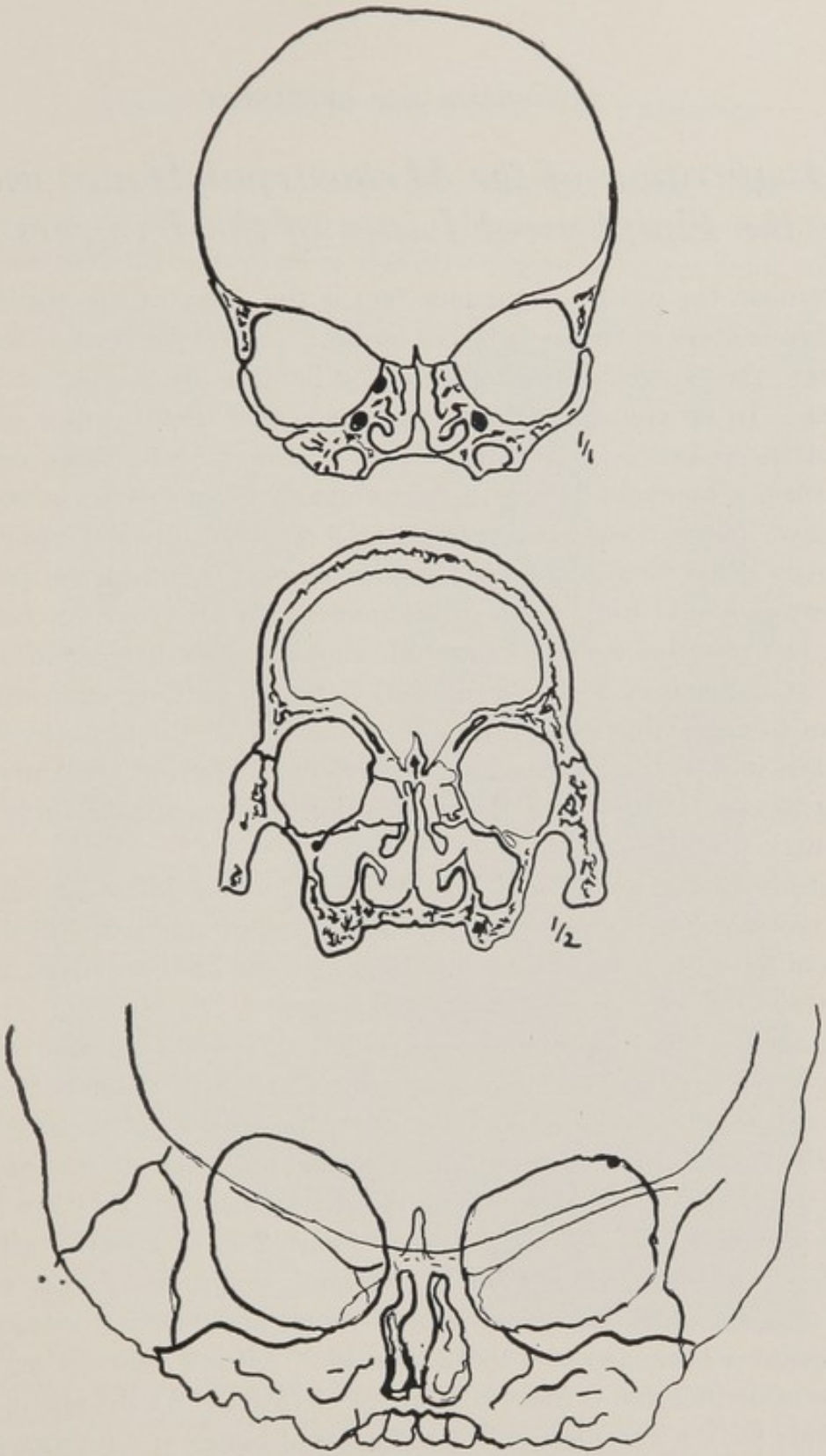


FIG. 85. Frontal diagram of skull, normal and in mongolism. A. Diagram of frontal section through skull of normal newborn. Note large brain cavity; the distance between bregma and nasal root is more than twice the length between nasal root and crest of upper jaw. Note smallness of malar bones.

B. Diagram of frontal section through adult skull: note the different shape of orbit holes and the great development of maxilla. The distance between bregma and nasion is now equal to that between nasion and maxillary crest. Note extension of malar bones. The upper roof of the orbital holes slants downward laterally and the supraorbital foramen forms the highest point.

C. Diagrammatic tracing of postero-anterior x-ray of a 7 mos. old mongoloid baby. Note egg-shaped orbit holes which are slanting upward laterally and preserve the fetal shape. The supraorbital foramen is lower than the lateral angle. Note the underdevelopment of the malar bones and of the whole maxilla.

Ossification of the Metacarpal Bones and the Epiphyseal Lines of the Fingers

In cretinism the most conspicuous fact is the delay of the appearance of ossification centers in the metacarpal bones. In 100 per cent of the normal population, the centers of the capitate and hamate are present at an age of 6 months. In 90 per cent of the population, the distal center of the epiphysis of the radius is present at 1 year of age. These three ossification centers form a basic landmark for x-ray examinations of an infant's hand. In cretinism the two centers expected at 6 months may not appear before many years after birth. I have already pointed out that the presence of these centers would not exclude the diagnosis of athyroidism, acquired in infancy, but their presence does exclude the diagnosis of congenital thyroid aplasia. Comparison with the normal hand at various ages enables the physician to determine the bone age of the cretin or the hypothyrotic child and makes it possible to check on the effect of thyroid treatment. It is startling to observe how fast the ossification centers appear under thyroid treatment.

The study of the epiphyseal lines renders further information. In untreated cretinism the epiphyseal lines remain open and are still distinct in patients of 30 or 40 years of age. As long as these lines are open, treatment is indicated and some growth may be expected.

In mongolism the features are somewhat different, but it may be said at the very beginning that the appearance of ossification centers is frequently retarded and resembles, therefore, the picture of cretinism. As a whole, the appearance is irregular. In the majority of mongoloids the capitate and hamate are present at 6 months of age, but they are tiny. In some of my observations they were present 2 or 3 months after birth. After the first three centers have appeared, eruption of new centers is usually delayed until the age of 4 or 5 years, and many a mongoloid has at that point a bone age of 6 to 12 months. After 4 years of age, the appearance of ossification centers is more accelerated. At the age of 15, most mongoloids have a complete set of metacarpal bones and further growth is arrested.

By x-ray examination the mongoloid hands show some more peculiarities which are not present in cretinism. The bones are delicate, slender, and short, and calcification is poor. In a large percentage, the first metacarpal bone of the thumb, which normally has a proximal epiphysis, will show in addition a distal epiphysis. The first metacarpal bone of the index finger, which normally has a distal epiphysis but not a proximal epiphysis, will show a proximal epiphysis in addition to the distal one. Much more attention has been attached to the middle phalanx of the little finger. This is

short and hypoplastic in a large percentage of cases. The well-known curvature of the little finger is due to the anomaly of the middle phalanx. Hefke has found a curvature of the little finger in 62 per cent, while in my

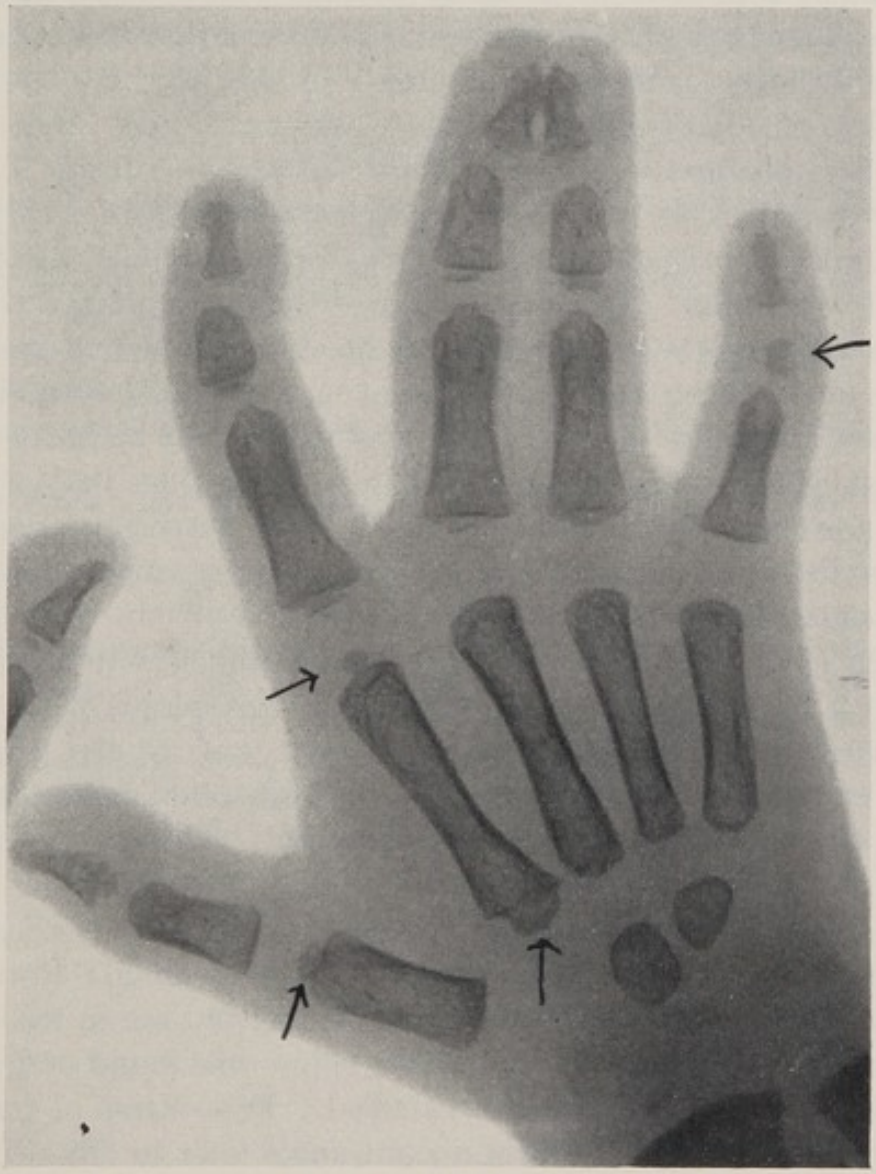


FIG. 86. X-ray of hand of a mongoloid child 3 yrs. of age. Most outstanding is the syndactyly, which is, however, not too frequent in mongolism. The x-ray shows several peculiarities which are frequently found in mongolism. Note the distal epiphysis on the first phalanx of the thumb and a proximal epiphysis on the first phalanx of the index finger. Note the rudimentary middle phalanx of the little finger and general shortness and delicacy of bones. Note the deficiency of calcification. Only two metacarpal bones are present and the epiphysis of radius is missing. Bone age 6 months.

own material I have seen such a curvature in 36.2 per cent only. It is, however, true that, even if the curvature is not outstanding, a slight anomaly is present in almost 90 per cent. X-ray studies of the hand reveal that the index finger also shows shortness of the second phalanx in a con-

siderable number of cases. The end phalanges of all fingers are short and hypoplastic.

With regard to the postnatal growth of the hands, Hefke noticed that the mongoloid hand is from 10 to 30 per cent shorter than normal hands. I measured the length of the end phalanx and the length of the first phalanx of the fourth finger in 28 x-ray pictures. In this way, it became obvious that the first phalanx is relatively shorter than expected. The proportion length of first phalanx to length of third phalanx was below 2 in 7 cases, with an average of 1.64; it was between 2 and 3 in 18 cases, with an average of 2.43. In 2 cases the proportion of 3 was found, and in 1 case the proportion of 4.1 was found. In normal x-rays the proportion is 2.5 to 3. We may conclude that those structures which are expected to increase most in size are impaired to the greatest extent, and since the metacarpal bones and the first phalanges have to grow more extensively than the third phalanx, the shortness of those bones is more striking than that of the latter. There is, however, an absolute shortening of all three phalanges, and the thinness of the distal phalanx is an important item which does not appear in the measurement of the length.

Although x-ray examination of the hands is sufficient in a large number of cases, it is frequently advisable to include x-ray plates of the pelvis and femur. These structures offer the advantage that, at the time of birth, the lower end of the femur should show an ossification center, which is expected in the ninth month of intra-uterine life. The center for the head of the femur should be present at 6 months. It is important to confirm the diagnosis of congenital thyroid aplasia by x-rays of the legs, because in this condition the ossification centers will be missing. Retardation of ossification is frequently more marked in the pelvis than in the hands. In my material of cretinism the neck of the femur was found underdeveloped in all cases, and the head was little calcified. Dislocation of the hip is not rare. Neck and shafts may form a right angle later in life. The crest of the pelvic bone was irregular and the cartilaginous structure was still present in a cretin of over 15 years of age. A further peculiarity of the long bones of cretins is the presence of rings in the femur and humerus shaft. Wieland has compared these lines with the annual growth rings of trees. Goetzky, Weihe, and Wieland describe them as areas of increased density or shadows, while in my material I found the lines which cross the shaft at a certain distance from each other near the distal end brighter than the rest of the bone. The above authors consider these lines as manifestations of "periodic athyrotic inhibition of endochondral ossification." The relationship of these lines to rickets is a matter of argument.

It has been little recognized that in mongolism the ossification of the

pelvis and femur shows also greater irregularities than that of the hands. In some cases the picture resembles strikingly that of athyroidism.

These few remarks may suffice to show that x-ray examinations in mongolism and cretinism are a most helpful aid in the diagnosis and treatment and deserve more attention in the textbooks of roentgenology in future editions.

BIBLIOGRAPHY

Benda, Clemens E.: Studies in Mongolism. I. Growth and Physical Development. Arch. Neurol. & Psychiat. **41:** 83–97, 1939.

——: Further Clinical and Anatomical Studies in Mongolism. Proc. Am. A. Ment. Deficiency, 63rd Ann. Session, Chicago, May 3–6, 1939.

——: Observations on the Malformation of the Head in Mongoloid Deficiency. J. Pediat. **19:** 800, 1941.

Clift, W.: Roentgenological Findings in Mongolism. Am. J. Roentgenol. **9:** 420, 1922.

Goetzky and Weihe: Über die Bedeutung der Epiphysenschatten beim Myxoedem. Ztschr. f. Kinderh., 1914.

Gordon, Murray B., and Bell, A. L. L.: Further Roentgenographic Studies of the Sella Turcica in Abnormal Children. J. Pediat. **9:** 781–93, 1936.

Hefke, H. W.: Roentgenologic Study of Anomalies of the Hands in One Hundred Cases of Mongolism. Am. J. Dis. Child. **60:** 1319–23, 1940.

Pollock, Henry M., and Levene, George: Hypophyseal Influence on Cranial Structure with Relational Mental Development. Am. J. Ment. Def. **43,** 90–99, 1938.

Schüller, Arthur: Infantilismus. Wien. med. Wchnschr. **57:** 629, 1907.

CHAPTER IX

HEMATOLOGY AND BIOCHEMISTRY

Hematology

Blood Groups

Penrose was the first to show that English mongoloids had the same distribution of the four blood groups as had 226 other English persons with mental deficiency and 500 English soldiers. There is no tendency toward the distribution found in people of the Mongolian race. A study of American mongoloids shows the same percentage distribution as has been reported for a total of 10,536 Americans.

The frequencies of the agglutinogens A and B for our American mongoloid defectives found by Bernstein's formula, based on his triple allelomorph theory, agree closely with those calculated for average Americans and also with the results found by Penrose for his English mongoloid patients. Table 21 includes combined totals for the English and American mongoloids as well as figures for Japanese and Chinese calculated from Strandskov's data for comparison.

Since the frequency of agglutinogen B is relatively high in the Mongolian race and low in American and European populations, the data support those of Penrose in opposing the hypothesis of Down and Crookshank that mongoloid deficiency is due to racial regression.

Blood Counts

The following data are based on a blood study of 100 mongoloid children ranging in age from the first year of life to 15 years. The patients were carefully selected with view to excluding all infections. One has, however, to keep in mind that with the inherent inclination to infectious diseases characteristic of these patients, a few of the values may indicate a latent infection.

1. *Number of Erythrocytes, Including Reticulocytes.* The general trend is low, but the majority of cases are within the normal range of 4,000,000 to 5,000,000 red cells. About a quarter of the patients have counts below 4,000,000, but only a few had counts near the 3,000,000 line. In the age groups from 1 to 4 years, about 20 per cent had counts below 4,000,000; in the age group between 4 and 15, the percentage of low counts was about the same. For the latter group the average counts range between 4,270,000 and 4,450,000.

The reticulocyte count shows a range between 0.3 per cent and 1.9 per

cent, with an average of 0.84 per cent. This average is definitely far below what is generally considered average (1.5 per cent), but only three counts fell below 0.5 per cent, which is considered the lower edge of normal.

2. *Hemoglobin.* The hemoglobin values are spread over a large range. The distribution of the values is the same in the 1 to 3 year group and in the 4 to 15 year group, with no tendency to higher or lower counts in either group, although the former is entitled to lower values. Although some values are fairly low, it may be noted that a considerable number is unusually high.

3. *Cell Volume.* The cell volume values fall within the normal range of 31 to 41 cc. The average for 1 to 4 years, with 36.2, is slightly below the

TABLE 21.—*Distribution of Blood Groups*

Subjects	Total	Number in Blood Group*				Percentage in Blood Group*				Frequencies of Agglutinogens	
		I AB	II A	III B	IV O	I AB	II A	III B	IV O	A	B
Americans (Strandskov)	10,536	477	4,121	1,208	4,730	4.5	39.1	11.5	44.9	24.9	8.3
Persons with mongolism, American	125	5	48	12	60	4.0	38.4	9.6	48.0	24.1	7.1
Persons with mongolism, English (Penrose)	166	3	83	14	66	1.8	50.0	8.4	39.8	30.6	5.2
Persons with mongolism, American and English	291	8	131	26	126	2.8	45.0	8.9	43.3	27.8	6.0
Japanese (Strandskov)	12,327	1,120	4,655	2,599	3,953	9.1	37.8	21.1	32.0	16.5	27.1
Chinese (Strandskov)	2,500	249	823	652	776	10.0	32.9	26.1	31.0	24.4	20.1

* Roman numerals indicate Moss groups and letters Landsteiner groups.

normal average of 38.86, as is the 36.9 average for the 4 to 15 years below the 38.52 cc. normal average.

4. *Sedimentation Rate.* The sedimentation rate is within normal range for the majority of cases. Of 17 cases in which the rate was determined, 2 fell below the normal rate, both cases being in the age group of 1 to 3 years. Five cases were above the average, with one in the 1 to 3 year age group.

5. *Fragility Test.* The values for fragility test represent 19 cases. Although there is a slight difference of opinion as to the normal, it was evident that all values coincided with Osgood's range and only 6 were outside by one tube. All complete hemolysis values lie in the normal range.

6. *Total Leukocytic Counts.* In the age group of 1 to 3 years, 27 cases were studied. The majority of these cases are equally distributed over the range of 6,000 to 11,000. Six cases fall below the 6,000 line, with 3

between 5,000 and 6,000 and 3 between 4,000 and 5,000. Of the 37 cases studied in the age group of 4 to 7 years, 26 were within the 5,500 to 11,000 range. One case fell below the 5,000 line, and 9 were found above the

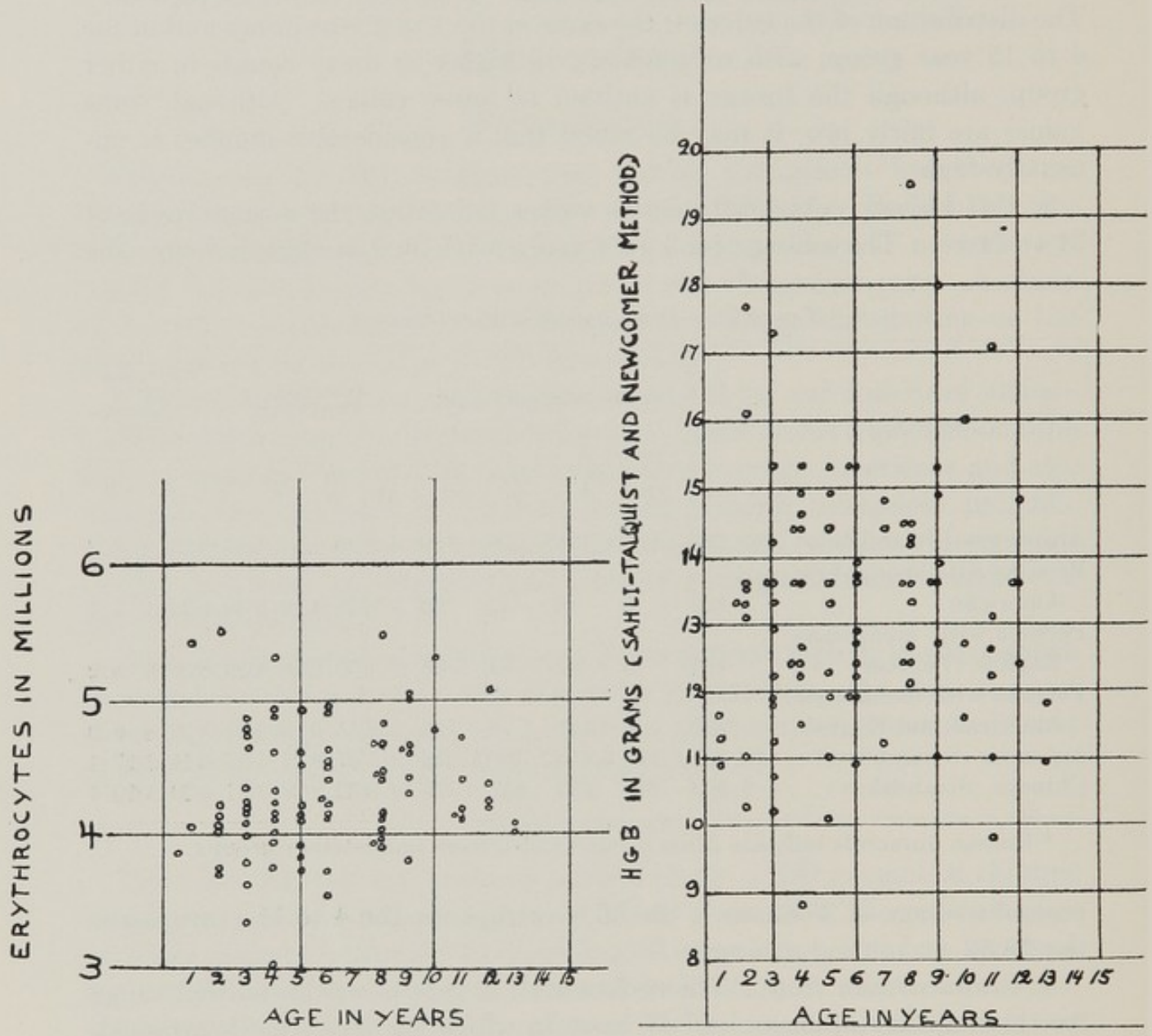


FIG. 87. A. Erythrocyte counts in mongolism. The majority of cases have counts between 4 and 5 million with several counts between 5 and 6 million. Several cases of moderate anemia with counts below 4 million.

B. Hemoglobin values in gram per 100 cc. blood according to Talquist and Newcomber methods. Note that few cases have low values and the majority have high average and even above average.

11,000 border. The other cases are again rather evenly distributed over the normal range, with as many or slightly more below the 9,000 line than above. Of the 36 cases in the age group of 8 to 14 years, only 2 cases were

above the 11,000 line. Four cases were below the 5,500 mark. Of the cases within the normal range, 11 are below the 7,500 line and 17 between 7,500 and 11,000.

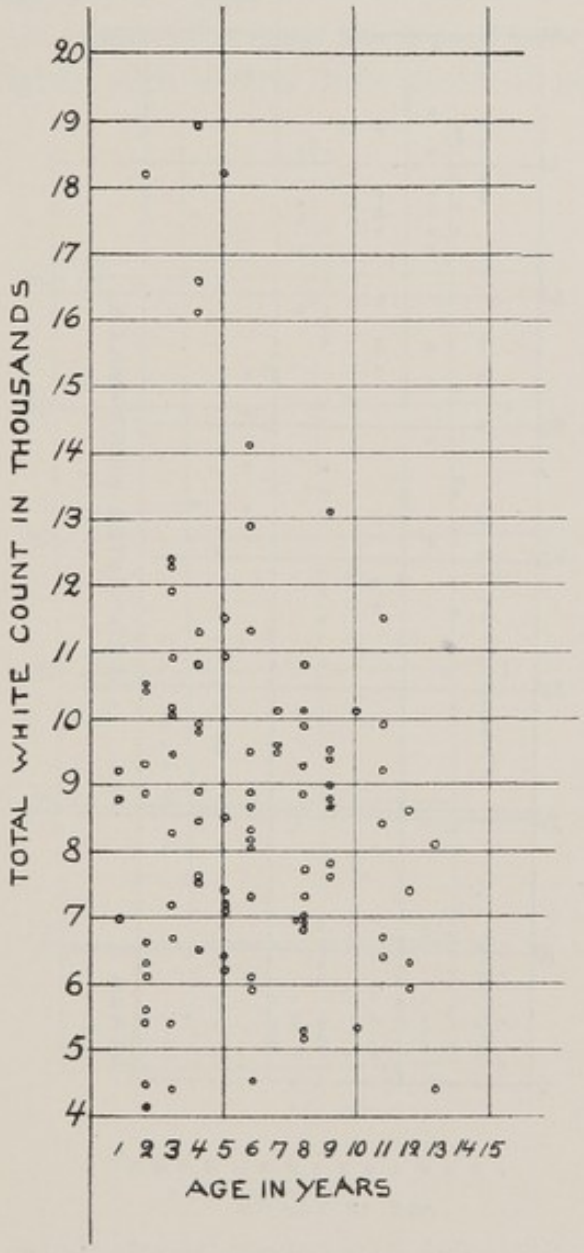


FIG. 88. Total white counts in thousands

7. *The Percentage Differential.* Differential counts of the polymorphonuclear cells show the same percentage distribution from the first year to 10 years of age, while in the group between 10 and 15 the majority of cases show a lower average than in the former group. Of 25 patients below 4 years of age, 10 had percentages of less than 50, ranging between 30 and 50. Seventeen cases had a percentage above 50, with half of them close to 70

per cent below or above. In the age group between 4 and 10 years, 31 cases fell below the 60 per cent line while 27 were above, ranging up to 80 per cent. In the age group above 10, all but 2 stayed below the 60 per cent line—most of them even below 50 per cent.

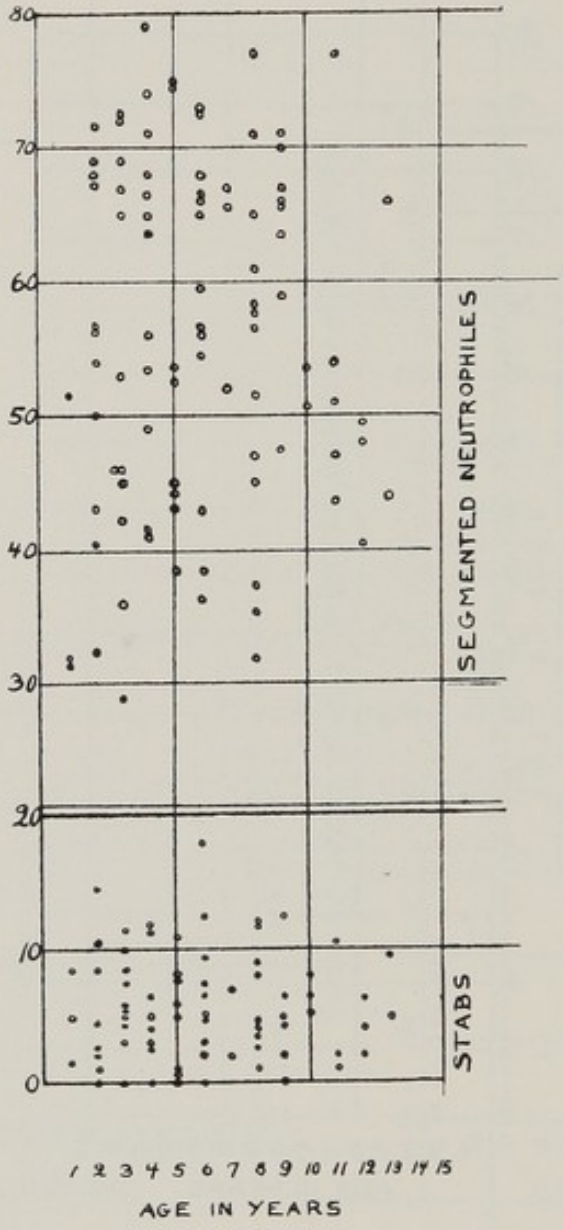


Fig. 89. Differential white counts: stabs and segmented neutrophiles

Percentage counts of the stab cells showed a definite tendency to increase, with more than half of the cases above the 5 per cent line, numerous cases ranging between 10 and 14 per cent.

The lymphocytic counts ran below average, with 18 per cent below the 20 per cent limit. The majority of cases run in the lower twenties, and only a few cases trespass beyond a 40 per cent line.

In the eosinophils, the percentages run low, with two thirds of all cases

below 3 per cent, many without eosinophils at all. Only occasionally higher percentages were observed, the highest seen being one case with 8 per cent.

The monocytes average low in the 1 to 3 year group, with all cases but 2 below 8 per cent and only 2 falling above 10 per cent. In the 4 to 14 year group, the majority of cases fall within the 4 to 8 per cent range, but the average is slightly higher, with several cases above 10 per cent. The baso-

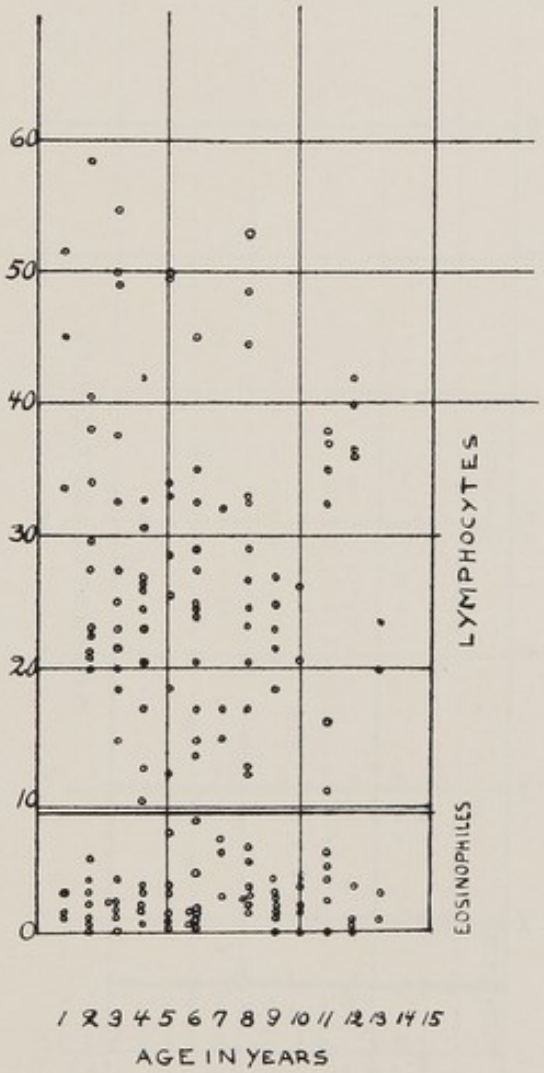


FIG. 90. Differential white counts: eosinophiles and lymphocytes in percentage

phils are normal. There seems to be a slight increase in disintegrating cells, although most of them are within range.

8. *Absolute Differential.* Although absolute counts of each type of leukocyte are seldom presented, it appeared important to determine whether there was overactivity of certain hematopoietic systems present or rather a general trend to underactivity. The absolute differential shows that there is a wide range of numbers, but, as a whole, the absolute count keeps below 7,000 with a few exceptions. It is impressive how many counts of

segmented polys are below the 3,000 line. The same is true for the lymphocyte counts, where the vast majority are below 3,000, and almost half of the cases are below a 2,000 line. The majority of the monocyte counts

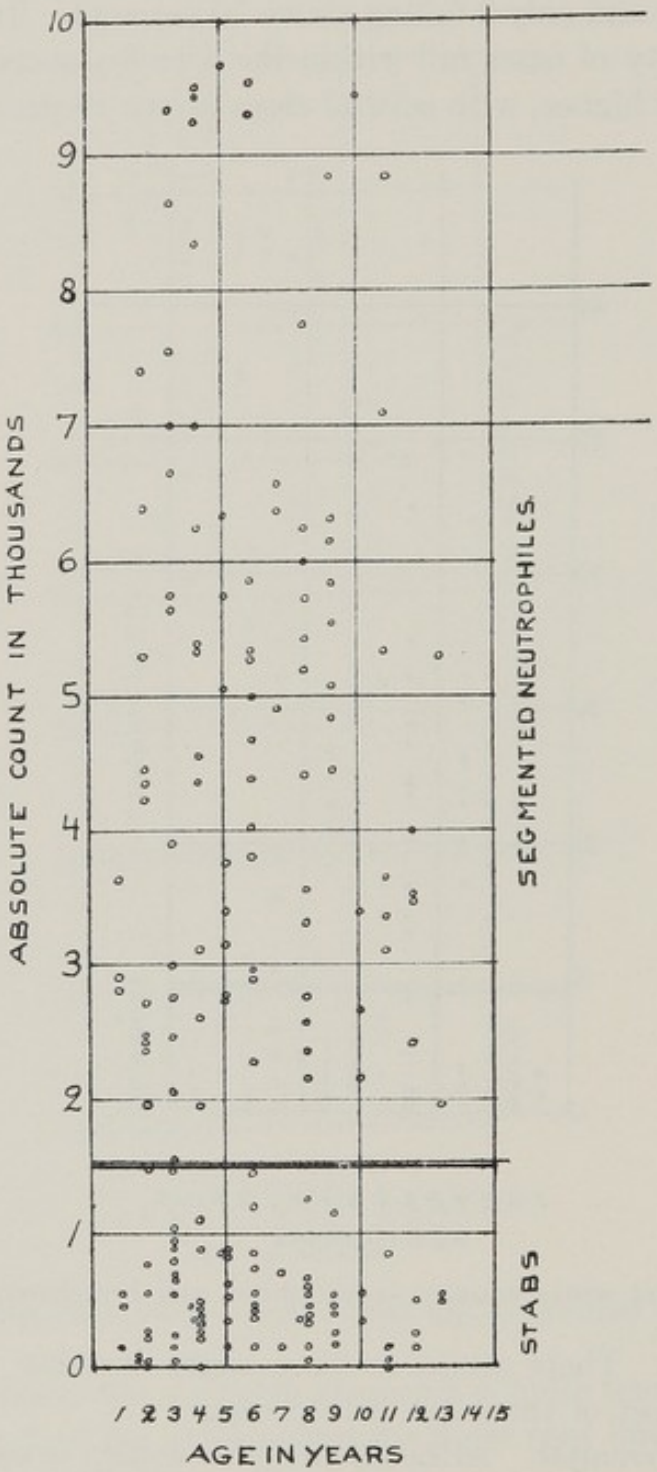


FIG. 91. Absolute white counts in mongolism: stabs and segmented neutrophiles

range between 100 and 750, with very little tendency to trespass on this line.

It may be of interest to consider a few studies which have been reported

in the literature. A brief report on the *Humoral Syndrome* of mongolism was given by H. Manitz, in 1932. The number of erythrocytes was normal in the majority of cases, but the counts were slightly higher than those reported from our laboratory. Values below 4,000,000 were present in only 10.3 per cent, and values above 5,000,000 were found in 34 per cent. Manitz believes that when anemia is found, it is a temporary phenomenon.

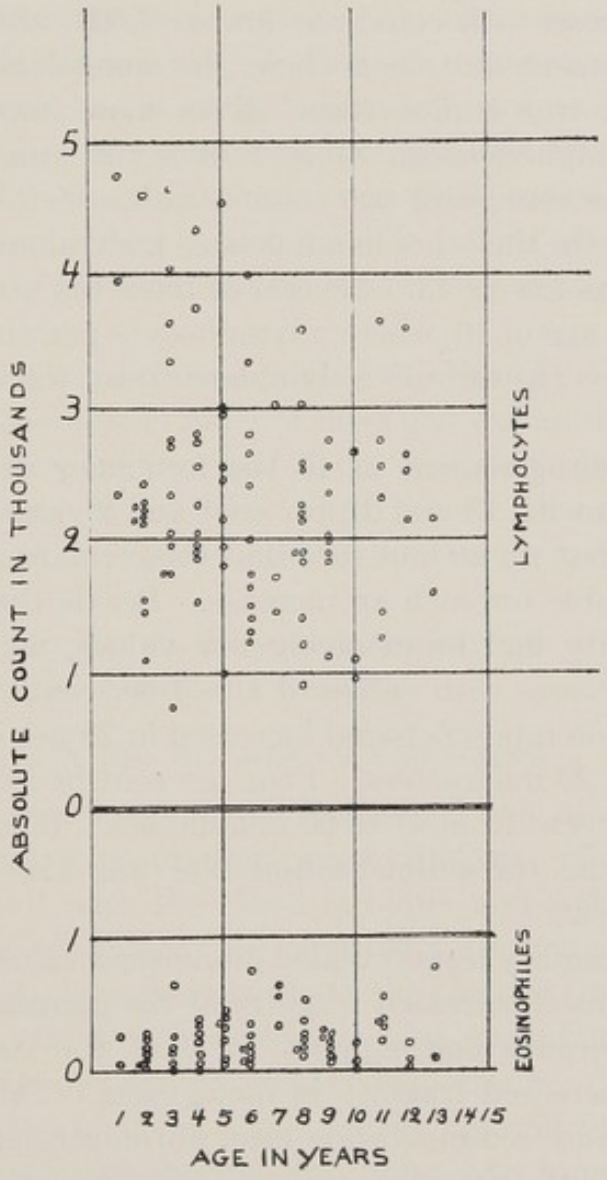


FIG. 92. Absolute white counts in mongolism: eosinophiles and lymphocytes

Herrmann reported anemia in mongoloids and cretins, and he thinks that the anemia reacts well to thyroid therapy. The hemoglobin values were in most cases above 70 in Manitz' material, and only 13.8 per cent showed values below 70. His observations on the white blood cells were similar to those reported above. If one reads his conclusions only, one gets the impression that leukocytosis and lymphocytosis are frequent in mongolism

—a notion which is repeated time and again in the literature. A study of the actual values reveals, however, that this conclusion is wrong. Manitz considers every count above 8,000 as pathological. Of his cases, 53.6 per cent had counts above 8,000, but most of these counts are around 10,000, with only a few between 12,000 and 15,000. There is no indication that all cases with possible infections were excluded. The blood picture does not reveal a real tendency to an increase in the number of white cells. There are many cases with counts as low as 4,500, and Manitz' material bears out the statement that, as a whole, the mongoloid blood is incapable of reacting with a true leukocytosis. Even more impressive is the misstatement of a lymphocytosis. Only 7 of his 27 cases had lymphocyte counts above 30 per cent, with two counts of 38, which is the highest value reported by him. On the other hand, 9 cases had values below 20 per cent, with some values as low as 13. Several of these low values were found in children below the age of 10, where a lymphocyte percentage of 40 per cent would be normal. Instead of a lymphocytosis, the material indicates lymphopenia.

There is some disagreement as to the frequency of eosinophilic cells. There were 2 cases with 13 and 21 per cent and 2 cases with 8 per cent in Manitz' material, but we are not sure that these children had no particular conditions responsible for such an increase. Beside these cases with high values, the majority had impressively low values, with 2 cases without eosinophils and 15 cases with values of 1 to 3 per cent.

The sedimentation rate was found increased in 28 per cent of tests, which had an increase to 20 millimeters. Four per cent had from 21 to 40 millimeters, and 24 per cent from 41 to 60 millimeters. It may be remembered that in our material the sedimentation rate was also slightly increased, though to less extent.

In 80 per cent, fragility tests revealed diminished values, and only 3 cases, or 12 per cent, showed increased fragility of the plasma. Our own values fall within normal range and support, at least, the statement of Manitz that there is no increased fragility in mongolism. This observation is of some interest, because sedimentation rate, fibrinogen, and fragility usually run parallel, and with increased sedimentation rate the fragility may be increased also. This is the "normal" reaction in infectious diseases. If, however, sedimentation rate and fibrinogen are increased and the fragility is low, some other factors have to be considered, and Georgi has expressed the idea that endocrine factors are possibly responsible for such outcome. Manitz reported also on the viscosity of the blood. He found decrease in 36 per cent and normal values in 56 per cent. There was an increase in 8 per cent. In his opinion, a decrease is frequently found in hyperthyroidism, while elevated values indicate hypothyroidism.

The blood groups had similar distribution as other European races, and the few data of Manitz corroborate those reported by Penrose and me. The Abderhalden reaction indicated Abbau of testes, ovaries, thyroid, and pituitary. Although a few investigators consider this reaction reliable, the majority feel that no conclusions can be drawn.

Summary of Observations in Mongolism

A study of the blood picture reveals only one consistent abnormality. The lymphocyte counts are low, in absolute number as well as in percentage. This observation is of much interest, because lymphatic tissue is increased. In spite of the numerous lymph nodes which may be found in the sternal notch, the mediastinum, and the mesocolon, the number of lymphocytes in the circulating blood is low. This observation confirms earlier observations of the same nature, which were made in chronic adrenal insufficiency.

Hemoglobin values were normal in the majority of cases, but it is worth noticing that a considerable number of cases had extraordinarily high values —13 per cent above normal limit and 26 per cent above average. The same is true for the number of red cells, which were high normal. Anemia is rare in mongolism; if it is present, it is temporary and responds well to therapy.

There is a slight increase in the sedimentation rate and, as we shall see, in the fibrinogen, but no increase in fragility.

Blood Studies in Cretinism

It was Kocher, especially, who emphasized the importance of blood studies in cretinism and postoperative athyroidism. Since then many investigators have dealt with the blood in hypo- and a-thyroidism, but the results were not as satisfactory as expected. De Quervain, in 1926, followed Kocher's line and emphasized that "the blood is the carrier of thyroid function, although the lymph system is also geared in and the central nervous system is a transformer of second importance. It is expected that the constitution of the blood is influenced by thyroid function." The alterations, however, are not specific, and hypo- and hyper-thyroidism may affect the blood in the same way. In both conditions, there can be a relative increase in lymphocytes.

On the basis of the reports in the literature and of our own observations, it may be safe to summarize that hypothyroidism and athyroidism are associated with a lowering of the hemoglobin values, which usually are between 60 and 80 per cent of the normal. The number of erythrocytes is decreased, and the majority of cases have a count of 3,000,000 to 4,000,000, with a number of patients having normal counts between 4,000,000 and

5,000,000. In a few instances, a severe anemia develops with counts below 3,000,000. The white count is considered not remarkable by Means, but most investigators feel that the total white count is relatively low and that leukopenia is more frequent than leukocytosis. Only Waechli reported true leukocytosis, and Wieland makes a difference between athyroidism and hypothyroidism. He found in the former condition a leukopenia, while hypothyroidism may be associated with an increase in leukocytes.

It must be said that the reports are confusing, because some authors use the terms "leukocytosis" and "lymphocytosis" to indicate a relative increase in the differential percentage, without regard to the absolute numbers, while others do not consider mere shifts in percentage as justification for the use of such terms. Moreover, the standards which were used were by no means uniform, and no consideration was given to the physiological shifts according to age. Newest publications, for instance, consider 36 per cent polys and 47.8 per cent lymphs as normal for the age group of 4 to 5 years, while at 20 years of age 53.9 per cent polys and 38.1 per cent lymphs are considered average.

From observations collected in our laboratory, it seems to me that the situation in cretinism and mongolism is the same. The total white count is relatively low; there is no real leukocytosis, which is mentioned by several investigators. The percentage of lymphocytes remains in the neighborhood of 50, which is within normal range for infants. The results of some of the investigators are given in the following table.

TABLE 22.—*Blood Picture in Myxedema*

Name	Hgb.	Red Count	Leukocytes	Lymphocytes	Eosinophils
Zondeck	60%	Decreased	Decreased	Increased	—
Falta	—	—	—	Increased	Increased
Wieland	Anemia	Decreased	Decreased	Relatively increased	—
Kocher	—	—	Decreased	Relatively increased	—
Waechli	—	—	Increased	Increased	—
Curschmann	50–80%	3–4 mil.	4200–5800	33–58%	—
Siegert	Decreased	Decreased	47%	50%	Increased
Means	60–80%	3.5–4 mil.	Not remarkable	—	—

Biochemistry

It is seen that the serum calciums of these patients are essentially within the normal limits (8 to 11.5 mg. per 100 cc.) established for this method by Schoenthal and Lurie in a study of 250 healthy children. The values for

TABLE 23

Sex	Age*	Calcium Mg. %	Inorganic Phosphorus Mg. %	Phosphatase Bodansky Units
F	4.11	9.1	5.3	9.8
F	5.6	9.5	4.8	13.4
F	5.8	10.1	4.9	6.1
F	6.5	9.4	5.9	10.1
F	6.5	10.1	4.5	9.2
M	6.8	10.7	5.3	7.4
M	7.6	9.6	5.3	8.3
F	7.10	9.2	5.6	9.0
M	8.3	10.3	4.9	8.1
M	8.6	9.4	5.4	7.6
M	8.11	9.7	5.2	8.7
M	10.4	9.5	4.9	8.2
F	10.4	9.4	5.3	9.7
M	11.0	10.0	4.9	7.8
F	11.7	10.4	4.9	12.2
M	11.10	9.1	5.4	7.6
F	11.11	9.7	4.5	8.9
M	12.9	9.8	5.2	7.0
M	13.1	10.0	4.2	5.8
F	13.9	9.6	4.1	6.1
F	13.9	9.6	4.6	5.7
M	15.6	10.0	5.1	7.7
F	17.0	11.8	3.9	4.3
M	29.6	9.9	3.7	3.5
F	30.2	9.7	3.5	2.9

* Age in this and the following tables is given in years before the decimal point and number of months after.

TABLE 24.—*Blood Chlorides, Mongoloid Defectives*

Age	Sex	NaCl Mg. %	Age	Sex	NaCl Mg. %
6.0	F	519	20.3	M	519
8.11	M	500	20.4	M	482
9.2	M	523	22.4	F	506
11.1	F	535	22.9	M	496
12.6	M	495	24.0	F	502
12.8	M	542	24.5	M	501
13.6	M	509	25.9	M	480
14.5	F	498	27.2	F	530
14.5	F	522			
14.7	M	491			
15.11	F	530			
16.7	M	489			
17.4	F	480			
17.6	F	535			
17.8	F	510			
18.3	F	498			
19.7	F	530			

inorganic phosphorus are also within normal range, which is 3 to 4 mg. per 100 cc. for adults and 4 to 6 mg. per 100 cc. for children. Likewise, the results for the serum phosphatase activity expressed in Bodansky units are within established normal limits (1.5 to 4.0 units per 100 cc. for adults and 5.0 to 14.0 units per 100 cc. for children).

Table 24 shows the blood chlorides of 25 mongoloid patients from 6 to 27 years of age. The values fall within the normal range, given by Mattice as from 450 to 500 mg. per cent, or 350 to 550 mg. per cent according to Osgood, or 444 to 549 mg. per cent according to Karlson and Norberg (76 to 94 m.eq./l.).

Table 25 represents the sodium values of 17 cases, ranging from 3 to 31 years of age. The normal average is given in the textbook of Gradwohl as 330 mg. per cent sodium, or 143 m.eq./l. The balance of sodium is kept

TABLE 25.—*Serum Sodiums*

Age	Sex	Sodium		Age	Sex	Sodium	
		Mg. %	M.eq./1.			Mg. %	M.eq./1.
3.3	M	325	141	12.8	F	318	138
4.9	F	319	139	14.2	M	324	141
4.11	M	320	139	14.10	F	328	143
5.2	M	321	140	14.10	F	322	140
6.1	F	325	141	16.7	M	332	144
7.9	M	315	137	18.1	F	321	140
8.11	F	319	139	24.0	F	334	145
9.4	M	318	138	31.3	F	315	137
11.6	F	319	139				

Range: 315 to 334 mg. per cent, or 137 to 145 m.eq./1.

rather constant in any blood serum, and the variations from the normal are slightly smaller than those of most substances in the blood. From Table 25 it appears that 8 of these 17 values fall between 315 and 320 or are 4.5 per cent below average. Six values fall between 321 and 325, being still at the lower edge of normal range. Only 3 of all values fall between 328 and 334, or exactly within the normal range. These facts are worth noticing, because they seem to indicate a moderate loss of sodium in contrast to the chlorides which were within normal range.

M. and O. Bodansky consider 315 mg. per cent as normal average and a decrease as significant only when below 315. From this point of view, all reported values in mongolism are normal.

The serum total proteins shown in Table 26 for 12 mongoloid patients from 8 to 26 years of age are within normal limits, being 6.4 to 7.3 grams per cent. (Normal: 6 to 8 per cent.)

Although the total proteins fall grossly between the normal average range of 6 to 8 mg. per cent, it is noteworthy that in this series all but 3 values were below 7, and only 3 fall between 7 and 7.3 g. per cent. None of the values counteracted the low tendency seen in this series. It was, however, felt that the values may not be representative for a larger group and more information was needed.

On Table 27, 38 more total protein values are recorded. About half of them were done by the Kj. method, the others by the K-B method. Kj. values range between 6.67 and 7.90, the average being 7.35. The values seem slightly lower than average. One may possibly conclude that there is a trend toward low values, but the result is still well within normal range and the significance is, therefore, not statistical.

TABLE 26.—*Mongoloid Serum Total Nitrogen, Nonprotein Nitrogen, and Total Protein*

Age	Sex	T.N. Mg. %	N.P.N. Mg. %	T.P. G. %
8.3	M	1106	*	6.75
8.8	M	1145	22	7.02
9.1	M	1061	23	6.49
9.4	M	1099	*	6.72
11.6	M	1045	25	6.38
12.0	F	1122	21	6.88
12.1	F	1064	22	6.51
12.3	M	1114	*	6.81
12.5	M	1196	24	7.32
12.8	F	1135	22	6.96
19.5	F	1188	24	7.28
26.10	F	1110	27	6.77

* N.P.N. assumed to be 25 mg. per cent.

In the same series of tests, using the Kingsley-Kjeldahl method, the albumin averaged this time 4.93 Gm. per cent, with values ranging from 4.65 to 5.48. In the same test series done by the K-Kj method, the globulins range from 1.93 to 2.89, with an average of 2.44. Considering 2.5 Gm. per cent as a fair average, it is obvious that very few values are above this line, but many values are below. The albumin-globulin ratio is debatable. A number of cases fall below the 2 line, and practically all values remain below 2.5 but all seem to be within normal range.

The fibrinogen is high with both the Andersch-Gibson method and the Kjeldahl method. In a series of 15 tests done with the former method, 4 cases were above 0.50 per cent, which appears pathological, while 10 further values were above 0.35. Only a single test fell on the 0.30 line. The method is unreliable. The tendency to high values of fibrinogen

TABLE 27.—*Serum Proteins of Mongoloid Defectives*

No.	Sex	Age		Total Prot. G. %		Albumin G. %		Globulin G. %		Fibrin G. %	Alb./Glob. by Diff.		Remarks
		Yrs.	Mos.	Kj	K-B	K-Kj	K-B	K-Kj	K-B	Kj	K-Kj	K-B	
2	F	2	6	—	6.25	—	4.89	—	1.36	0.25	—	3.60	Serum unless otherwise indicated
		2	7	6.67	—	4.65	4.50	2.02	—	0.29	2.30	—	
3	F	3	1	—	6.53	—	4.85	—	1.68	—	—	2.89	Fibrins on oxalated plasma
		3	2	7.58	—	5.11	5.05	2.47	—	0.50	2.07	—	Total proteins are without fibrin
		3	2	7.76	7.73	5.28	5.08	2.48	2.65	0.49	2.13	1.92	
4	M	3	1	—	6.76	—	5.13	—	1.63	0.29	—	3.15	Globulins by difference, without fibrin
		3	2	6.86	6.91	—	5.07	—	1.84	0.30	—	2.76	
5	M	3	10	—	5.85	—	4.72	—	1.13	0.25	—	4.18	K—Kingsley separation
		3	10	6.85	—	4.92	4.65	1.93	—	0.35	2.55	—	Kj—Kjeldahl analysis
6	M	5	0	7.42	7.48	4.77	4.85	2.65	2.63	0.29	1.80	1.84	B—Kingsley biuret analysis
7	M	5	9	7.54	7.65	4.75	4.68	2.79	2.97	0.31	1.70	1.58	*—0.1 cc. serum used instead of 0.08 cc.
9	F	9	8	7.04	6.86	4.92	4.85	2.12	2.01	0.27	2.32	2.41	
10	M	13	8	7.48	7.17	—	4.95	—	2.22	0.39	—	2.23	h—Heparinized plasma
		13	9	7.50	7.46	5.05	4.99	2.45	2.47	0.35	2.06	2.02	H—Howe separation
11	M	13	11	7.35	—	4.93	—	2.42	—	0.27	2.04	—	x—oxalated plasma
12	F	15	9	7.26	6.90*	4.76	4.85	2.50	2.05	0.28	1.90	2.37	
13	M	16	3	7.01	6.78	4.78	4.72	2.23	2.06	0.27	2.14	2.29	
14	F	16	7	7.58	7.60*	4.96	4.92	2.62	2.68	0.20	1.89	1.84	
16	M	18	8	7.53	7.62*	4.84	4.78	2.69	2.84	0.34	1.80	1.68	
17	F	21	0	7.90	7.72*	5.48	5.41	2.42	2.31	0.28	2.26	2.34	
18	M	27	0	6.72h	—	4.40h	—	2.32h	—	0.24	1.90h	—	
				6.14x		4.03Hh							
19	F	28	7	7.70	7.37*	4.81	—	2.89	—	0.28	1.66	—	
20	F	32	1	7.24h	—	4.60h	—	2.64h	—	0.35	1.74h	—	
				6.90x		4.44Hh							
Low				6.67		4.65		1.93			1.66		Excluding Nos. 18 and 20
High				7.90		5.48		2.89			2.55		" " " " "
Average				7.35		4.93		2.44		0.30	2.04		" " " " "

is less demonstrated in the second series with the more reliable method of Kjeldahl. In this series Case 3 had a constantly elevated value of 0.50 and 0.49 respectively, and 5 more values were 0.35 or more. On the other hand,

TABLE 28.—*Values of Total Cholesterol of Serum during Fasting*

Male		Female	
Age	Cholesterol Mg./100 cc.	Age	Cholesterol Mg./100 cc.
2.9	218	3.8	269
2.10	227	3.10	308
3.3	205	4.9	195
3.3	192	4.3	76
3.10	278		80
4.11	219		77
5.2	204	4.6	320
7.1	140	5.0	200
7.6	180	6.1	245
7.9	188	6.7	219
8.0	247	7.1	179
8.2	163	7.5	215
9.8	189	8.6	220
10.4	198	9.2	234
10.4	312	10.0	170
10.7	291	11.3	248
10.9	244	11.4	152
10.10	144	11.5	170
11.2	205	11.6	178
12.2	223	11.6	168
12.3	170	13.2	228
12.3	202	14.0	197
13.5	191	14.1	224
13.9	173	15.8	248
14.6	206	16.5	236
14.7	149	17.7	163
15.8	151	17.11	135
16.11	150	18.1	140
17.3	181	20.3	217
17.7	201	25.3	268
18.5	192	26.0	254
19.5	196	27.8	248
22.6	155	28.5	254
23.3	207	29.0	234
23.10	140		
27.9	194		

some of the values in the series are low, like that of Case 14, with a value of 0.20.

In Table 28 serum cholesterol values are registered for 34 males and 27

females ranging from 2 years 9 months to 29 years. Fourteen of the 34 males and 17 of the 27 females show values above 200 mg./100 cc., with a few values above 300. Several patients had repeated tests, and all were of the same height. In addition, 10 males had values between 180 and 200, and two more females are also above 180 mg. per cent. This gives a total of 43 patients out of 61 who had cholesterol values above 180. On the other

TABLE 29.—*Total and Esterified Cholesterol Values of Serum and of Whole Blood*

Subject	Sex	Age		Cells %	Total Serum Cholesterol Mg.	Total Blood Cholesterol Mg.	Serum Ester		Blood Ester Mg.
		Yr.	Mo.				Mg.	%	
PERSONS WITH MONGOLISM									
1	M	2	10	—	227	—	144	62	—
					227	—	137	—	—
2	M	7	9	41	188	171	124	68	69
					188	170	129	—	68
					186	—	128	—	—
3	M	10	7	46	291	233	206	70	84
					283	234	194	—	81
		10	9	46	244	200	196	80	114
						201	—	—	107
4	M	12	2	—	218	193	—	—	—
					227	191	—	—	—
5	M	13	5	45	189	165	116	61	56
					191	165	116	—	59
					191	—	109	—	—
6	F	17	11	40	130	145	88	66	53
					133	148	88	—	55
						149	—	—	—
		18	1	41	140	141	103	74	56
					140	140	103	—	—
7	M	18	5	—	195	164	—	—	—
					189	169	—	—	—
8	M	23	10	—	140	140	—	—	—
					140	140	—	—	—
9	F	29	—	—	233	191	—	—	—
					234	199	—	—	—

hand, one female mongoloid baby with almost cretinoid features had values of 76, 77, and 80 mg. per cent, respectively, on three occasions.

Results of tests, which are presented in Table 29, show the same relation as the values for the controls between the total cholesterol and the cholesterol esters of whole blood and of serum. It is seen that the values for total cholesterol in the whole blood and in the serum are not nearly as equal and interchangeable as might be inferred from the literature. The total

cholesterol in the blood tends to be nearer or equal to the total in the serum when it is low. The percentages of ester in mongoloid serum, varying from 61 to 80, were about the same as those in controls, 57 to 71. These results correspond with published data for normal plasma or serum.

Reports in the literature on cholesterol in general are conflicting, and those on infants are meager and questionable. It is said that normally at birth the cholesterol of the child is much lower than that of the mother. According to Palacios-Costa and Falsia, the average total cholesterol of umbilical cord blood is 108 mg. per cent and independent of the maternal level. It is difficult to learn at just what age the value may reach a fairly constant level for the individual. Offenkrantz and Karshan give the tota serum cholesterols of 19 boys and 11 girls of from 2 months to 3 years o age as 174.1 ± 45.3 mg. per cent (128.8 to 219.4 mg. per cent) and for 51 boys and 40 girls of from 4 to 6 years as 177.5 ± 30.4 mg. per cent (147.1 to 207.9 mg. per cent). These authors used the Schoenheimer-Sperry method (modified), which is said to be 5 to 15 per cent lower than the Sackett procedure (Mattice), which in turn has been found to check very closely with the modified Bloor method, used in our laboratory.

There is only one publication dealing with cholesterol values in mongolism, that by Mader and Bingenheimer. The results of these authors differ so considerably from our observations that it is worth mentioning. They come to the conclusion that in mongolism, cholesterol averages as low as 80 mg. per cent up to 10 years, and they conclude that in this condition "the cholesterol curve follows the normal curve in a distance of 40 to 50 mg. per cent without ever approaching the normal values." Values between 120 and 180 were considered normal—the same range which is given by Gradwohl, Bodansky, Mason, and others.

Mader's and Bingenheimer's values are in striking contrast to all other observations and have not been confirmed by other investigators. They are mentioned here because the results are sometimes quoted in the literature.

Since Epstein and Lande, in 1922, first noted the elevation of blood cholesterol in hypothyroidism, several investigators have studied this matter. Mason, Hunt, and Hurxthal have attempted to correlate blood cholesterol values and metabolic rate. Their correlation chart indicates clearly that persons with a metabolic rate above 10 have cholesterol values below 180, ranging from 60 to 180 mg. per cent. On the other hand, persons with metabolic rates below 10 have cholesterol values above 200. It is true there is no definite correlation between single cholesterol values and the metabolic rate, in so far as a patient with hyperthyroidism may have a metabolic rate of +30 and a cholesterol of 180, while the next patient with the same metabolic rate may have a cholesterol as low as 60, the

same as another patient with a metabolic rate as high as +100. On the other hand, a cretin may have a metabolic rate of −20 and a cholesterol of over 360, while the next cretin may have a rate of −35, but a cholesterol of 210. But if the general trend of the values is observed, a correlation between cholesterol value and metabolic rate is obvious. It seems that each individual has his personal cholesterol level, which is fairly constant. Benda and Bixby have followed up patients over many years and found almost identical values in each test. In hypothyroidism the cholesterol values are elevated in reciprocal relation to the falling metabolic rate. Thus Gilligan, Volk, Davis, and Blumgart established such a reciprocal relationship between cholesterol and metabolic rate in experimental thyroidectomy. A week after removal of the thyroid, the metabolic rate was down 15 per cent, while the cholesterol was elevated 50 mg. per cent. Three months after operation, the metabolic rate was minus 30, while the cholesterol was increased 120 mg. per cent above the original level. This relationship is of value in following up the effect of thyroid therapy. Withdrawal of thyroid in cretinism automatically raises the cholesterol level, which can be decreased again by administration of thyroid.

There is one point, briefly mentioned before, which needs further attention. Some cretins and mongoloids have unusually low cholesterol values (below 100). The mongoloid with the lowest values in our material (76, 80, 77 mg. per cent on three different determinations) had been diagnosed a cretin before, and another true cretin (thyroid aplasia) had also persistent low values. It seems not yet established at what age the cholesterol climbs to the high values and under what conditions it remains below the normal limit.

Basal Metabolism

The cholesterol values in mongolism, as demonstrated in Fig. 93, show definitely a trend toward elevation, but they remain below the level of cretinism. The same is true for the metabolic rates. They are definitely on the minus side, but between the normal and the level of athyroidism. Means, in discussing the metabolic rates, introduces a diagram of three levels of living: the level of normal living, the level of pituitaryless living, and the level of thyroidless living. It is quite obvious that the values in mongolism place the patient on Means' "pituitaryless" level.

The importance of basal metabolism in hypothyroidism and cretinism is so well established that there is no need to discuss the matter in detail. In cretinism the values range usually between −20 and −50 per cent. It is noteworthy that the lowering of the metabolic rate seems frequently less pronounced in thyroid aplastic congenital cretins, while the most outstanding values are seen in postoperative or spontaneous myxedema of

adults. A few values, which corroborate those published by others, are reported in Table 30 and in Fig. 93. Results in mongolism are also reported in Table 30 and additional ones in Fig. 93. The metabolic rate is definitely lowered in mongolism and falls between the level of normal living and cretinism.

Results: When based on the Mayo Foundation standards, the basal metabolic rates of 25 persons with mongolism are on the minus side (Table

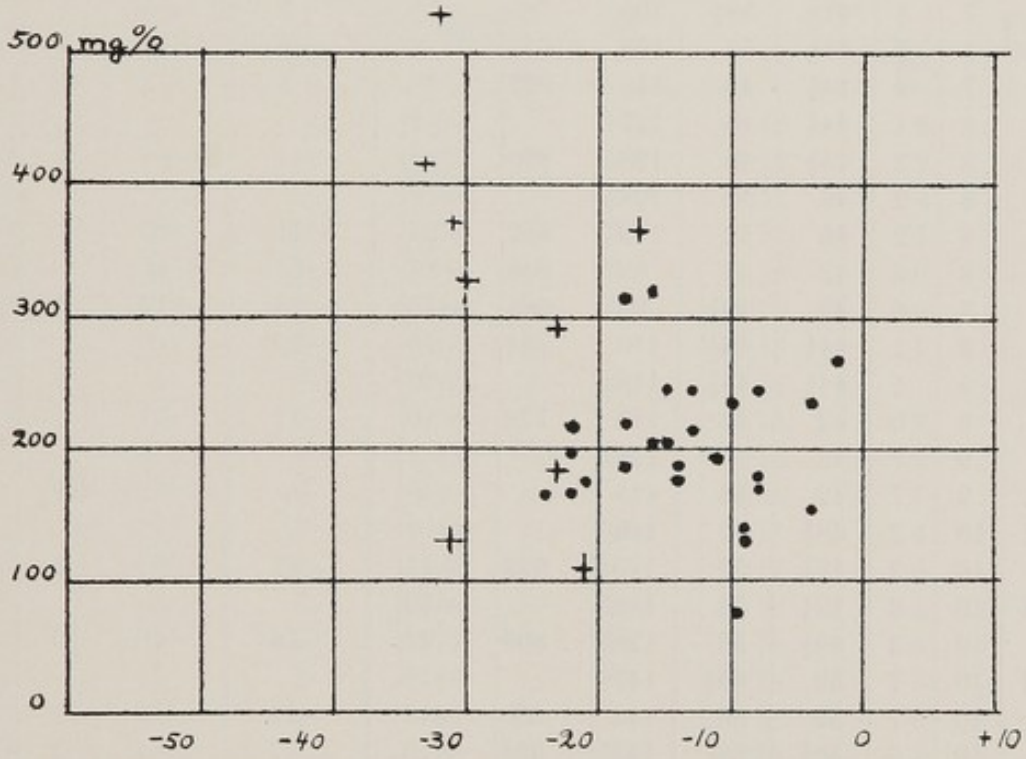


FIG. 93. Blood serum cholesterol in mongolism (black dots) and cretinism (crosses) and their relation to basal metabolic rates. The average serum cholesterol level in mongolism is between 180 and 280 with some values between 140 and 180 and a few values above 300. The metabolic rate is on the minus side, the majority of cases between minus 10 and minus 20 with several values between 0 and minus 10 and a few values below minus 20. The cholesterol values in cretinism are usually above 300 but the figure shows that three values in cretin babies were between 100 and 200. The metabolic rate in cretinism is below minus 20, with the majority of cases below minus 30, but there is a definite overlapping in the cholesterol values and the metabolic rates between mongolism and cretinism.

30). None are plus, 8 are between 0 and −10 per cent, 8 range from −11 per cent through −15 per cent, and 9 are below −15 per cent. The calculations based on the Talbot standards for children give different results. With use of the weight standards, 4 of the rates are on the plus side, and only 4 are below −15 per cent (excluding subject 24, an adult). When the Talbot height standards are used, all rates except 1 (−17 per cent) come into normal range. In contrast, all calculations for 3 typical cretins, interpolated because of the patients' small stature, were below normal limits,

TABLE 30.—*Basal Metabolic Rates of Persons with Mongolism and Cretinism*

Subject	Sex	Age		Height In.	Weight Lb.	O_2 Cc. per Min.	Cal. per 24 Hr.	Metabolic Rate, %			No. of Tests	Cholesterol Mg. per 100 Cc. Serum
								Mayo	Talbot			
		Yr.	Mo.						Wt.	Ht.		
PERSONS WITH MONGOLISM*												
1	F	6	1	40½	39	98	681	−22	−14	−10	2	219
2	F	6	1	40	33	107	744	−8	+4	0	2	245
3	M	6	8	42	38½	122	—	−9				
		6	11	42¼	38	121	841	−9	+7	+3	4	140
4	F	7	0	43½	47	121	—	−12				
		7	0	43½	47	120	834	−13	−5	+3	2	215
5	F	7	1	41¼	38½	105	730	−14	−7	−5	4	179
6	M	7	6	47½	55	155	1,077	−8	+5	+14	5	180
7	M	7	9	44¼	43	119	827	−18	−3	−2	2	188
8	M	8	1	44½	46	127	—	−13				
		8	2	44½	46	128	890	−14	−1	+4	3	247
9	M	8	2	46	52	128	—	−18				
		8	2	46	52	119	827	−24	−11	−5	2	163
10	F	8	6	42	41	93	646	−24	−21	−17		
		8	6	42	40½	99	688	−18	−15	−12	2	220
11	F	9	1	44¼	43½	110	764	−13	−10	−8		
		9	1	44¼	43½	113	—	−10	—	—	2	234
12	F	9	0	42	46	112	778	−10	−11	−1		
		9	7	42	46	116	—	−7				
		9	7	42	46	115	—	−8	—	—	4	170
13	M	10	2	48½	60	149	—	−9				
		10	2	48½	60	140	973	−14	−11	+1	2	189
14	M	10	3	49¼	58	134	—	−20				
		10	3	49¼	59	128	899	−22	−18	−10	2	198
15	M	10	7	52	65½	147	—	−16				
		10	7	52	66	144	1,000	−18	−12	−6	2	312
16	F	10	9	50¼	58	133	924	−15	−7	−4	2	248
17	F	10	11	50¾	61	155	—	−4				
		10	11	50¾	62	156	—	−4				
		11	2	51¾	66	161	1,119	−4	+5	+11	4	152
18	F	11	0	52½	79	154	—	−15				
		11	0	52½	80	143	994	−22	−16	−3	2	168
19	M	11	1	48½	58	135	938	−15	−13	−3	3	205
20	F	11	6	49	56	119	827	−21	−15	−12	2	178
21	M	12	3	51	71	147	1,022	−16	−14	−2	5	202
22	M	13	5	52¼	63	155	—	−8				
		13	6	51¼	64	151	1,049	−11	−6	−3	3	191
23	F	18	0	54	104	151	—	−9				
		18	3	54	102	150	1,042	−9	−22	−4	3	140
24	F	26	2	54½	101½	157	1,091	−2	(−18)	(−1)	3	268; 254
25	F	29	5	59½	100½	164	1,139	−4	(−14)	(−13)	4	234
CRETINS												
26	F	16	7	46½	58	95	660	−23	−33	−25	2	294
27	F	33	1	51	88½	119	827	−17 (Harris-Benedict, −26)	(−33)	(−16)	2	362
28	F	42	8	55	150½	134	931	−30 (Harris-Benedict, −31)	(−44)	(−18)	2	335

* Parentheses are used around the Talbot figures when the patients were adults, because the Talbot standards are for children.

whether based on Mayo Foundation standards, on Talbot weight and Talbot height standards (although 2 subjects were adults), or on Harris-Benedict standards.

Pennacchietti, who advanced the theory of a hyperthyroidism in mongolism, has reported a few metabolic rates which do not support his view.

TABLE 31.—*Blood Sugar Values of Persons with Mongolism during Fasting*

Sex	Age		Blood Sugar Mg./100 Cc.	Sex	Age		Blood Sugar Mg./100 Cc.
	Yr.	Mo.			Yr.	Mo.	
F	5	3	92	F	13	6	95
M	5	4	69	F	14	2	83
M	6	5	93	F	14	8	94
M	6	10	75	F	14	11	109
M	6	11	85	F	15	0	97
M	7	2	111	F	15	0	84
M	7	5	98		15	1	94
M	7	6	85	F	15	1	104
M	7	7	88		15	2	96
F	7	8	78	M	15	6	83
	7	9	82		15	7	82
M	7	10	94	M	17	4	101
M	7	11	105	F	17	6	94
M	8	5	108	M	18	5	86
M	8	6	77	F	18	5	94
M	9	3	88	F	18	5	91
F	9	8	91		18	6	77
M	10	1	79	F	19	4	87
F	10	5	94	M	19	5	97
F	10	5	92	F	21	9	101
M	10	7	93	F	21	9	102
M	10	10	93	F	22	5	103
M	11	9	80		22	6	99
F	11	9	99	F	23	0	90
M	12	0	99	F	23	5	103
F	12	7	93	M	23	11	100
M	12	9	78	F	24	8	95
	12	10	84	F	28	5	95
M	13	4	77	F	29	0	113

Although his results are on the plus side, all are within acceptable normal limits, especially if one considers the difficulty of attaining a so-called basal condition in young children. Calculations from his data give a percentage of +10, +10, +14, +10, +8, and +17, respectively. In contrast to Pennacchietti's values, our values were all on the minus side.

Blood Sugar and Glucose Tolerance

Results: The fasting blood sugar values of 51 persons with mongolism aged from 5 to 29 years were normal, ranging from 69 to 113 mg. per hundred cubic centimeters of capillary blood (Table 31). However, dextrose tolerance tests on 10 mongoloid children (Figure 94) indicated a delayed

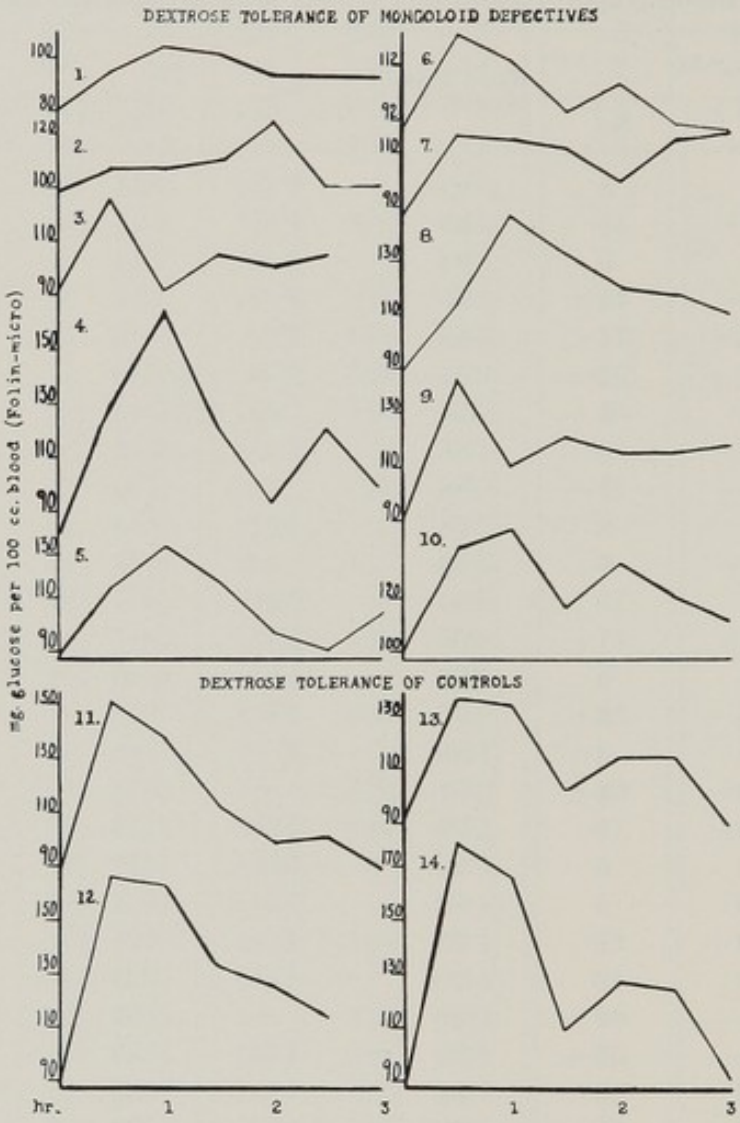


Fig. 94. Dextrose tolerance curves, mongolism and controls. The figure indicates delayed glycemic response. There is a tendency for late peak, for a low curve, and for slow return to the fasting level. Only curve 9 shows a fairly high peak at the half-hour interval but it shows also a slow return to the fasting level after 3 hours.

glycemic response. There seems to be a tendency for a late peak, for a low curve, for a slow return to the fasting level, or for a combination of these. The single curve (9) with a fairly high peak at the half-hour interval was still 28 mg. above the fasting level after three hours. In none of these cases was sugar found in the urine. In a case (4) in which there was a high

late peak no urine was voided. For comparison, tolerance curves of 4 controls are presented.

Inasmuch as it is only by an accumulation of data from many cases that one can come to any definite conclusion, five more glucose tolerance tests of mongoloid children are added herewith (Table 32) to the 10 cases above. Again one observes evidence of delayed glycemic response, such as a low or late peak or a relatively slow return to the fasting level, confirming Brousseau's statement that there is a high sugar tolerance in mongolism. However, these evidences do not seem so marked for 2 of the 3 year olds.

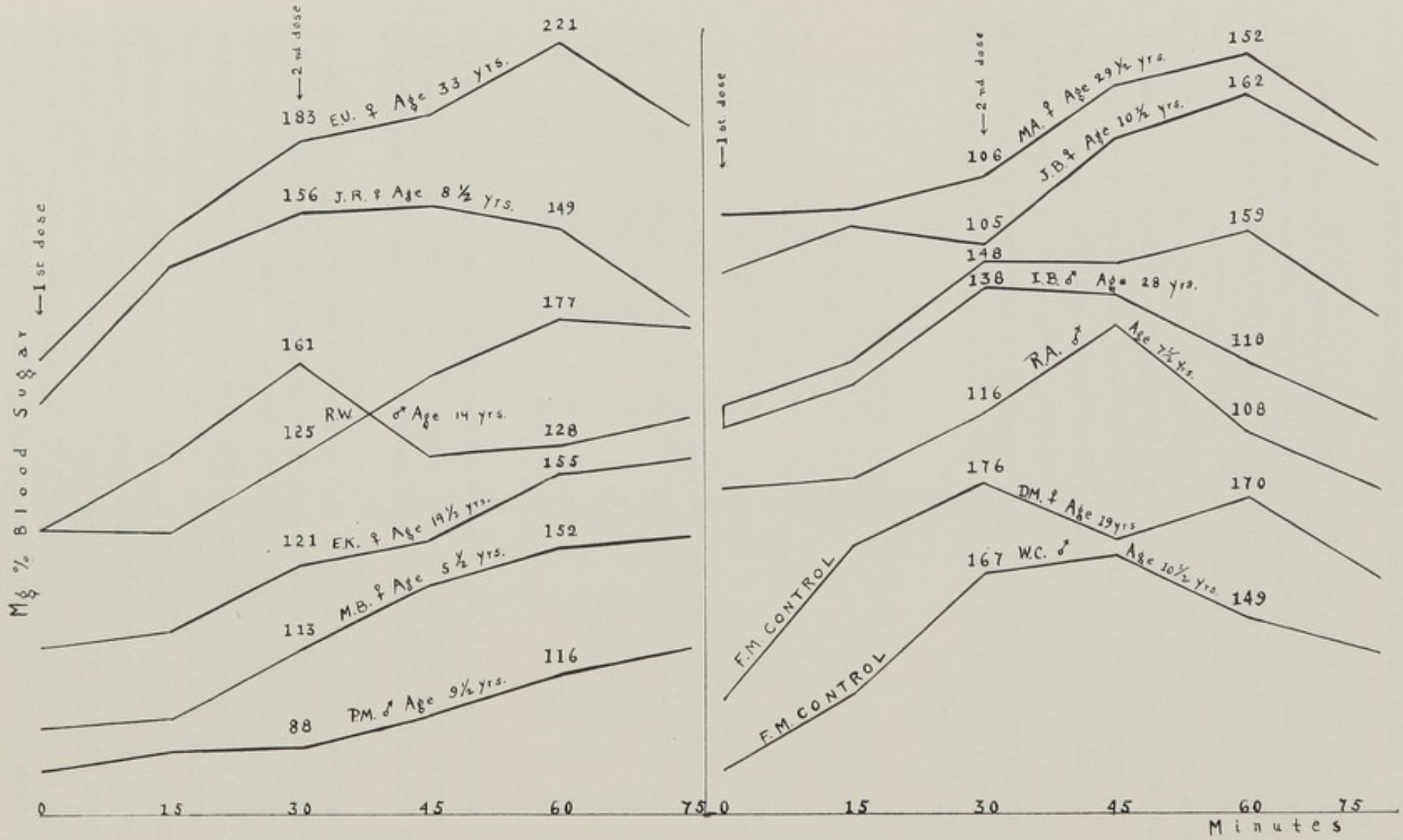
It was considered that the Exton-Rose (divided-dose, one-hour) test might throw more light on the mechanism responsible for these results. We have performed such tests on 10 mongoloid patients, aged 5 to 33 years, using capillary blood, the micro method of Folin, and the modification of Gould et al. (Fig. 95).

TABLE 32.—*Glucose Tolerance*

Age		Sex	Min. after Glucose						
			0	30	60	90	120	150	180
Yrs.	Mos.		Mg. % Blood Sugar						
MONGOLOID DEFECTIVES									
3	4	M	90	103	124	113	101	104	75
3	10	F	98	165	175	140	125	129	103
3	10	F	80	135	84	109	88	106	86
10	5	M	94	144	134	130	120	122	80
12	0	M	85	145	145	132	90	109	89

In most instances the blood glucose of the mongoloids continued to rise after the second half-dose instead of falling normally, thus confirming the suggestion that the carbohydrate metabolism of the mongoloid is probably abnormal.

The insulin tolerance curves of the mongoloid patients and controls all show fasting levels within normal range, although three of the control values are higher than all others (Figs. 96, 97, 98). After insulin, with one exception, the blood sugars responded normally, falling in 20 to 30 minutes to about one half the fasting levels. At this point both mongoloid and control curves promptly rose again. However, two hours after insulin, when (according to Fraser, Albright, and Smith) the blood sugars should have returned at least to the fasting level, the control values were slightly (0 to 12 and 15 mg.) below fasting while the mongoloid values were, with few exceptions, further (13 to 29 mg.) below the fasting levels. The absolute values of the mongoloid levels at the end of the two hours were 63 to



I EXTON-ROSE GLUCOSE TOLERANCES OF MONGOLOIDS.

FIG. 95. Exton-Rose divided dose, one hour test in mongolism. In most instances the blood glucose continued to rise after the second half dose instead of falling.

83 and 89 mg. per cent, while those of the controls were 80 to 94 mg. per cent.

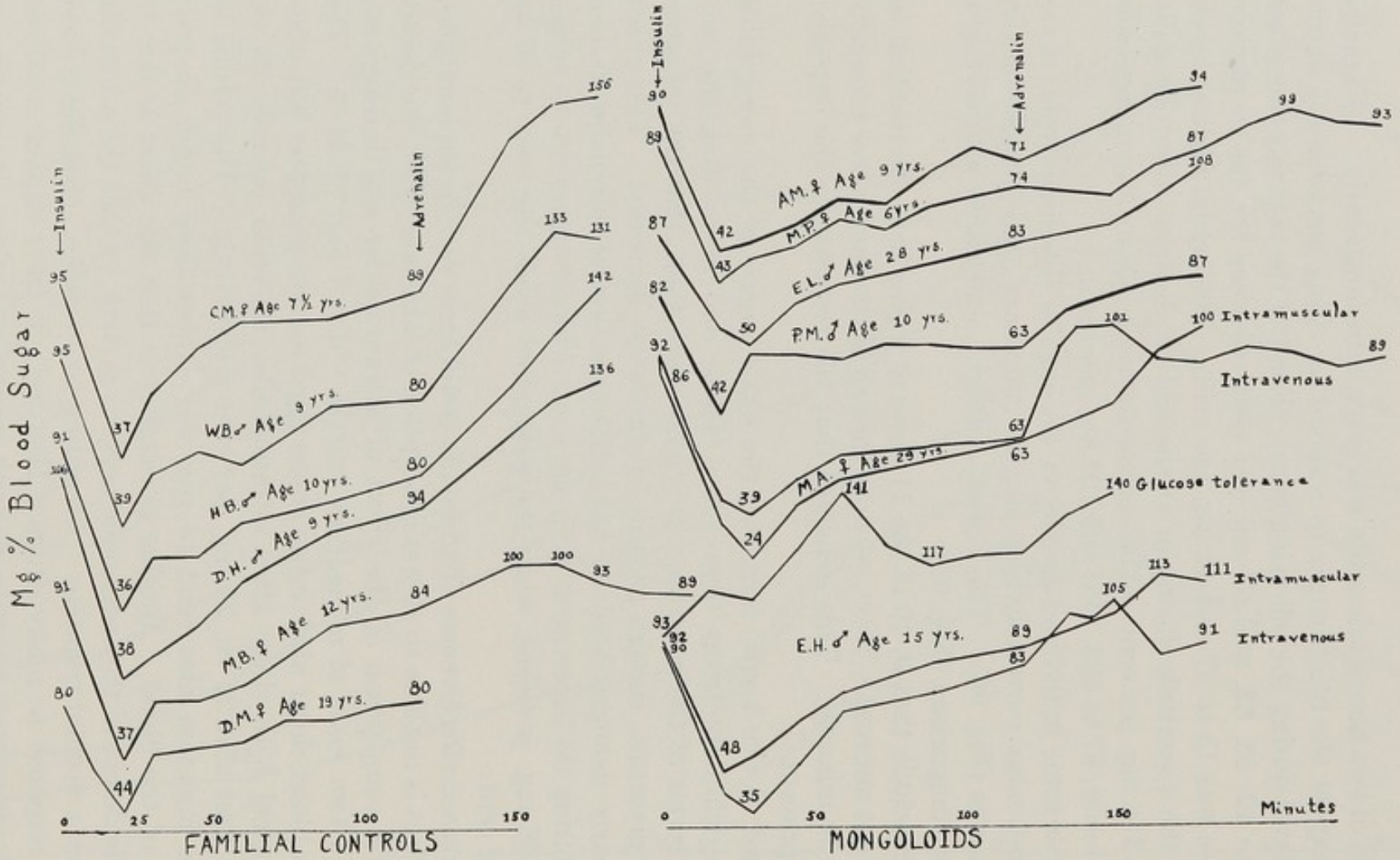
At the end of two hours, adrenalin was given intramuscularly. Normally one would expect the blood sugar to respond by rising considerably above the fasting level during the following hour. For 4 of the controls this effect amounted to 42, 53, 62, and 67 mg. per cent, whereas for the mongoloid cases the rise was 13 to 37 and 42 mg. per cent. The actual highest levels reached by the 4 controls during or at the end of one hour after adrenalin were 133 to 156 mg. per cent, while corresponding levels for the mongoloids were much lower, 87 to 108, 113, and 123 mg. per cent.

Along with some individual graphs of the insulin tolerance tests, there are presented also corresponding glucose tolerance and glucose-insulin tolerance curves (Fig. 96). The Fraser, Albright, and Smith normal curve is shown for comparison (Fig. 97).

We can conclude that in 10 of the 11 cases of mongolism the reaction to insulin was not unusual. Next, we note that all of the curves rose promptly after 20 to 30 minutes. This indicates that the response to the hypoglycemia was prompt.

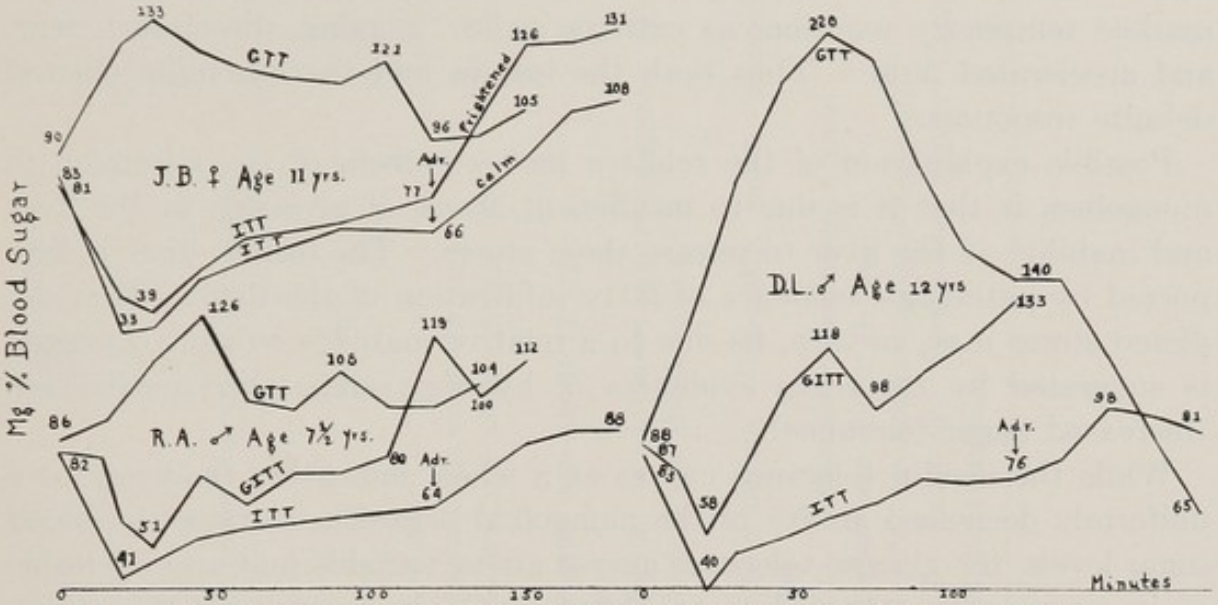
At the end of two hours, however, the blood sugars of the mongoloids tend to be definitely lower than when fasting and lower than the corresponding levels of the controls. It would seem, then, that the response to the hypoglycemia, though prompt, is somewhat decreased. This effect is more clearly demonstrated by the administration of adrenalin at two hours, for during the subsequent hour the control blood sugars rise to values of 133 to 156 mg. per cent, while the mongoloid levels rise only to 87 to 123 mg. per cent.

This decreased effectiveness of adrenalin could have various explanations. That the effect is not due to slower absorption of adrenalin from the tissues is proved by comparison of the effect of intramuscular and intravenous injections in two cases of mongolism (curves "M.A." and "E.H."). The increases in blood sugar after intravenous injection are prompter but practically identical with those after intramuscular injection, namely 38 vs. 37 mg. per cent and 22 vs. 23 mg. per cent respectively. The results of intravenous injection also tend to rule out explanations based on poor circulation of the blood. Another possibility is that the effect is due to some specific defect of the autonomic nervous system, so that the adrenalin fails to elicit a normal response. According to Joedicke, mongoloids have a lessened response to many drugs. However, in their clinical reactions the mongoloids seemed sensitive to both insulin and adrenalin, reacting to the insulin even more and for a somewhat longer time than the controls, exhibiting a more prolonged degree of sleepiness and sweating, an increased temperature, a desire to urinate, and in some cases, tremor. After in-



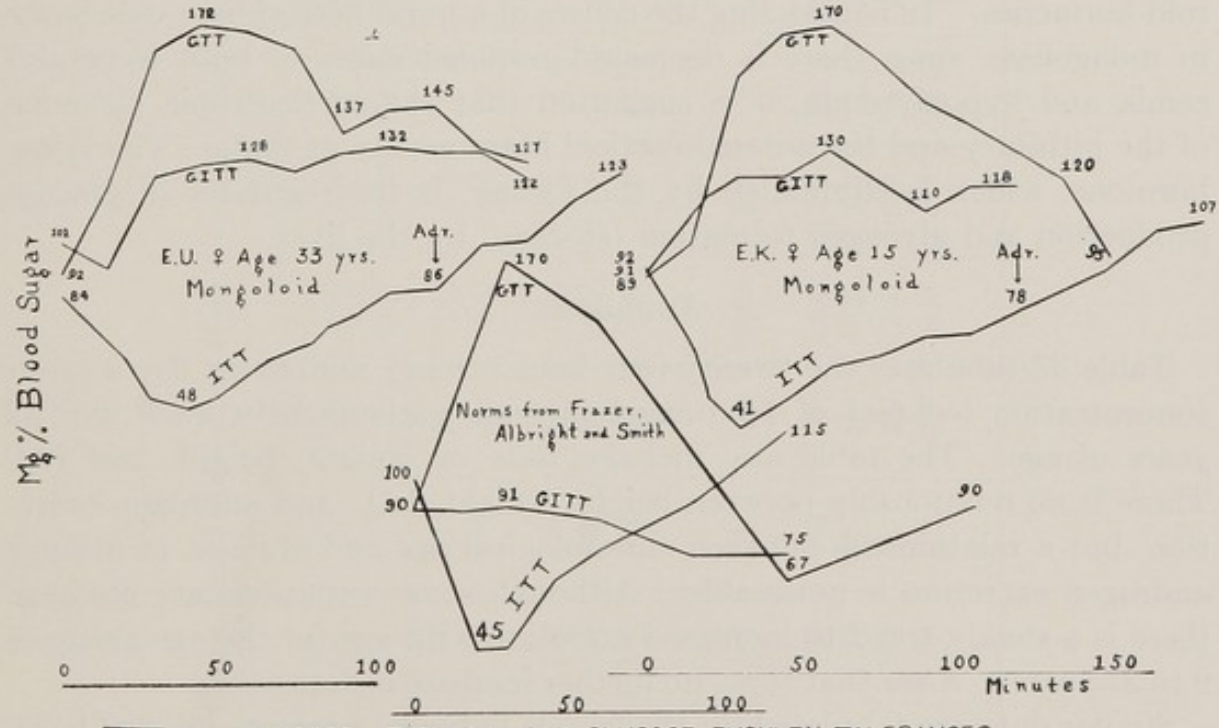
II INSULIN TOLERANCES

FIG. 96. Insulin tolerance in mongolism. After insulin the blood sugars responded normally, falling to about half the fasting level in 20 to 30 minutes. At the end of the 2 hour period the blood level was still below fasting levels. Adrenalin injections at the end of 2 hours produced much less effect than in normal controls.



III GLUCOSE, INSULIN, AND GLUCOSE-INSULIN TOLERANCES IN MONGOLISM.

FIG. 97. Combined glucose, insulin, and glucose insulin tolerance tests in mongolism. Compared with the normal curve given in Figure 98, it is seen that the effect of the insulin upon the glucose curve is stronger than normal, depressing the sugar level to a considerable degree. After one hour the effect of insulin is less manifest and the curve rises above the normal level.



IV GLUCOSE, INSULIN, AND GLUCOSE-INSULIN TOLERANCES.

FIG. 98. Glucose insulin and combined glucose insulin tolerance tests in mongolism compared with the normal. In these two cases of mongolism the effect of the sugar was stronger than that of the insulin and the combined curves run above normal.

travenous injection of the adrenalin two mongoloids showed immediate marked temporary reactions as extreme pallor, gagging, discomfort, fear, and accelerated pulse. Thus both the insulin and the adrenalin elicited definite responses.

Possible explanation of the relative ineffectiveness of the adrenalin in mongolism is that it is due to insufficient stores of glycogen in the liver and inability of the liver to release these stores. The former view is supported by pathologic evidence of fatty infiltration of the liver. That depleted stores may, in turn, be due to a relative inability to store glycogen is suggested by the many evidences of hyperglycemia unresponsiveness (increased sugar tolerance).

While the insulin tolerance curves as a whole indicate a tendency to a uniformly decreased ability of the mongoloid organism to raise the blood sugar levels, the glucose tolerance curves are as variable and unpredictable as in acromegaly. According to Fraser et al., in acromegaly this variability is due in part to the combined effects of increased growth hormone of the pituitary lowering the blood sugar, and sometimes a compensatedly increased glycotropic hormone, resisting the insulin action. I question whether the high glucose tolerance curves in acromegaly may not be due in part to a decreased ability of the liver to store glycogen, this function having suffered from the originally low blood sugars, owing to excess thyroid hormones. In considering the causes of a hypothetical liver deficiency in mongolism, since there is decreased responsiveness to both hyperglycemia and hypoglycemia, it is suggested that the corticotropic hormone of the pituitary and the adrenal cortical hormone are at fault. The latter hormone, which is stimulated by the former, is the regulator of glucose production and glycogen formation (storage) by the liver.

Androgens

Table 33 tabulates the twenty-four hour urinary androgens (by a semiconcentration technic) of 14 mongoloid male patients between 9 and 32 years of age. The table also includes data on weight, height, and I.Q. There is no relationship between height, weight, I.Q., and androgen excretion, but a relationship between chronological age and amount of urinary androgen excretion is noticeable. Although some variations are obvious, there is a steady trend to increased excretion with age for the age group of 9 to 21 years. After that time, no further increase is noticeable.

Similar data are tabulated for the female patients, presented in Table 34. They are all of adult age, chronologically. From a biological point of view, however, most of them are still in a prepuberty state of development, and their biological age has not progressed beyond 12 to 16 years.

TABLE 34.—*Twenty-Four Hour Urinary Androgens (as Androsterone) of Female Mongoloid Defectives*

Case	Age Yrs.	Wt. Lbs.	Ht. In.	I.Q. %	Semiconc. Technic			Dilute Reaction		Remarks
					Urine Vol. Ml/24′	Androgens		Urine Vol. Ml/24′	Androgens Mg./24′	
						Mg./24′	Mg./L.			
F. F.	19	96	57	26	1185	4.5	3.8	948	7.9	Physiological age about 15 yrs.
V. R.	21	99	56½	22	610	1.3	2.1	720	—	Physiological age about 15 yrs.
L. R.	21							1665	8.5	.....
L. B.	22	102	55½	23	868	4.3	4.9			Physiological age about 12 yrs.
M. C.	22½	108	56½	22	1528	19.8	13.0	2593	13.1	Hirsutism
A. B.	23	106	61½	22	820	4.6	5.6	1510	9.3	Physiological development relatively good
A. F.	23							3150	5.4	Physiological age about 16 yrs.
								4365	4.8	
R. C.	24	107	54	26	1385	6.9	5.0	573	6.8	Complete alopecia. Generally much underdeveloped
E. H.	30	95	51½	15	1402	16.9	12.1	2170	31.2	Hirsutism. Abnormal external sex organs
M. A.	32	96	54	34	1525	3.9	2.5	2338	10.0	Physiological age about 14 yrs.
J. T.	34½	107	56	29	1750	9.4	5.4	2030	10.2	Physiological development relatively good
E. U.	35	93	59½	27	940	2.4	2.5	1573	2.9	Physically infantile. Premature aging. Cessation of menstruation

TABLE 33.—*Twenty-Four Hour Urinary Androgens (as Androsterone) of Male Mongoloid Defectives*

Case	Age Yrs.	Wt. Lbs.	Ht. In.	I.Q. %	Semiconc. Technic			Dilute Reaction		Remarks
					Urine Vol. Ml/24′	Androgens Mg./24′	Androgens Mg./L.	Urine Vol. Ml/24′	Androgens Mg./24′	
G. Be	9	50	44	30	1073	2.4	2.2			Physiological age about 6 yrs.
J. M.	11	57½	49	24	1077	5.5	5.1			Hypoplastic genitalia
G. Bu	11	75	53½	33	1009	6.1	6.0			Physiological age about 8 yrs.
R. G.	14	88½	57½	22	870	3.1	3.5			Physiological age about 13 yrs.
D. L.	14	107	59½	21	1503	4.2	2.8	1993	2.9	Physiological age about 13 yrs.
R. D.	15	80½	57	27	1410	6.5	4.6			Physiological age about 13 yrs.
F. S.	15	92	55½	22	1310	7.3	5.5	900	3.8	No beard. Much underdeveloped. Infantile penis
								1279	—	
E. H.	17	100	58½	40	925	6.1	6.6	1805	16.3	Physiological age about 14 yrs. Soft beard
C. M.	21	161	62	16	1795	10.0	5.5			Mulatto. Coarse black beard. Fat
J. L.	21							1850	7.5	.....
W. E.	25	109	61	25	3855	8.9	2.3			Physiological age about 17 yrs.
B. B.	26	189	58	20	1860	6.7	3.6	2240	10.6	Soft beard. Malformed sex organs. No penis
E. L.	30	154	64	43	2870	9.4	3.3			Physiological age about 17 yrs.
E. B.	32	105	58	15	2275	8.5	3.8	1950	4.8	Physiological age about 15 yrs. Light beard

Also presented in the tables are the twenty-four hour urine volumes, which seem to be high in some instances, especially for older patients.

Supporting data of additional twenty-four hour urine volumes and of the corresponding androgen content determined by the Neustadt dilute procedure are also listed.

Both tables show that the majority of the results seem to fall within what is given as "normal range" by various authors, with a few rather

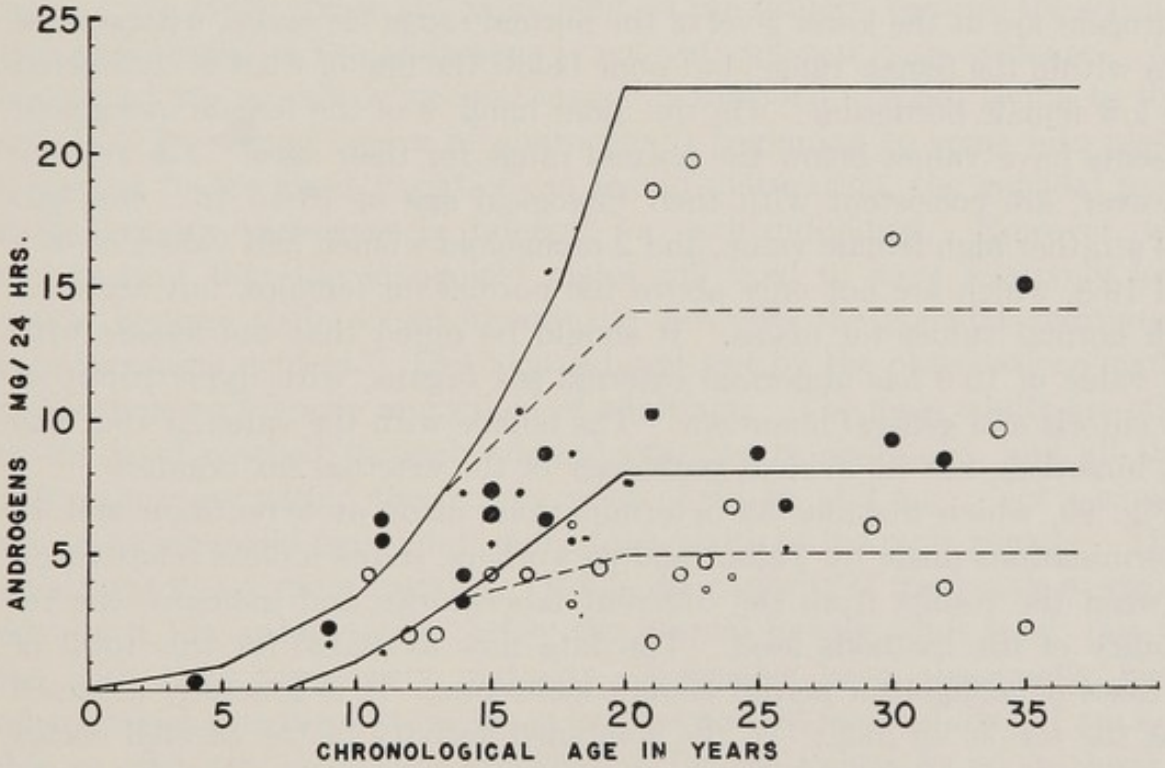


FIG. 99. Thirty-two determinations of 17-ketosteroid and 13 determinations collected by Talbot et al. The straight line indicates the bracket of normal range for males, the dotted line indicates the normal female range. Note that up to an age of 17 the values for males and females are within normal range. After 17 the values for females tend to be low with the majority of the determinations definitely below normal range. There are, however, three determinations far above the normal female range within high normal male range. The values for mongoloid males are within the female range with one exception but are also within normal male range although definitely low. One male determination was average. Black dots: males.

high and a few rather low tests. The situation becomes clearer if we consider, not whether the results are "within normal range," but whether they reveal some special trends which give insight into the complicated endocrine dysfunction associated with mongolism. Fig. 99 shows 32 androgen values in mongolism according to chronological age superimposed on areas representing the ranges for published normal male and female values. The data have been further increased by including 13 results published by N. Talbot and co-workers. In comparing the findings for mongoloid chil-

dren with the normal range, it is obvious that mongoloid children at an age level between 8 and 12 years have a normal androgen excretion. As a matter of fact, 3 of the tests are at the upper level of the normal range, and only 3 results (by Talbot) fall on the lower line of average. In each group between 14 and 18 years, practically every person with mongolism has a value which is to be considered well within normal range. Only one boy of 18 shows a result which is low normal.

Observations on male patients above 18 years of age show that their androgens are at the lower level of the normal range for males, with several data within the female range, but none below the line of what is considered the low female borderline. On the other hand, 9 of the female mongoloid patients have values below the normal range for their ages. The results, however, are consistent with their biological age of 10 to 16. One girl had a rather high female value, and 2 mongoloid women had values of 16.9 and 19.8, which are not only above the normal for females, but are even high normal values for males. It should be noted that the female with the value of 16.9 has abnormal external sex organs, with hypertrophy of the clitoris and general hirsutism. The female with the value of 19.8 also has hirsutism, but no evident pathology of the external sex organs.

Fig. 99, which includes 32 determinations made at Wrentham and 13 determinations made by Talbot and co-workers, shows a close relationship between the results from the different laboratories and indicates the reliability of the methods used. The data now available for this total of 45 cases of mongolism permit some conclusions. It is generally assumed that the test is an index "of the combined activity of the adrenal cortex and the male gonads, and that in the male, therefore, it is an index of the activity of the adrenal cortex and the male gonads, and that in the female, it is an index of activity of the adrenal cortex alone." Fraser and co-workers suggest that "all the urinary 17-ketosteroids are derived from the male gonads and the adrenal cortex, about 9 mg. in round numbers coming from the adrenal cortex and about 5 mg. from the male gonads." Thus the normal female would average about 9 mg./24 hrs., while the average of the normal male is 14 mg., with a range for the adult female of from 5.1 to 14.2 mg./24 hrs., and a range for the male of from 8.1 to 22.6 mg./24 hrs. Reports on the 17-ketosteroid output of normal children have shown that the values rise slowly from zero to the adult level which is finally reached between the ages of 18 and 20 years. The chief source of the androgens in childhood seems to be the adrenal, which is equally active in both sexes. At the time of puberty, the male values tend to become slightly higher than the female values, owing to the gradually increasing activity of the male gonads. If we accept the hypothesis offered by Fraser and co-workers, the results in mongolism allow the following interpretation. As

far as the amount produced by the adrenal cortex is concerned, the values are within normal range. It may be noticed, that some values are really at a rather high level, especially if the general immaturity of the mongoloid patient is taken into consideration. Thus one may be tempted to suspect a rather high adrenal cortical activity in early childhood. The males between 14 and 18 years of age all have values "within normal range," indicating that adrenal function is still maintained at a normal level at this age. We do not expect that further tests on patients between 14 and 18 years of age would throw any more light on the subject, because the second (gonadal) source of the androgens is not yet sufficiently in evidence. At this period the so-called "normal range" is unusually broad, owing to the fact that the second source of androgens is beginning to come into play. According to the great variations in sexual maturation, the gonadal part of the urinary androgens is different for each individual. However, we may suspect that the mongoloid males will tend to have relatively low values, because their sexual immaturity prevents the gonadal androgens from becoming evident. This idea is borne out by the observations made on the male and female mongoloid of adult age. The male adults are still on the level reached through adrenal function in childhood, and all the male values are within the female range of 5.1 to 14.2 mg. Not a single test on a mongoloid male adult indicates activity of the male gonads. The female results are more variable. While the majority of the female mongoloids have low values—even below the normal female adult level, but in line with their prepuberty maturity—2 females have abnormally high values, which put them at the same level as normal male adults. I am not able to offer any pathologic explanation for the values found in these 2 patients, except that they showed hirsutism. From observations made on other mongoloids, it may be suspected that a number of mongoloid females suffer from severe degrees of abnormal sex differentiation.

Brain Metabolism

Results of studies on brain metabolism in mongolism have been reported by H. E. Himwich, J. F. Fazekas, and Sarah Nesin. A constant supply of energy must be available for any organ to function properly. This energy is obtained from the oxidation of various foodstuffs. In contrast to some body tissues like muscle, which can oxidize fat when carbohydrate is not available, cerebral metabolism is entirely depending on carbohydrates as its foodstuff. When deprived of this single source of energy, the brain can no longer carry on, and coma may finally develop. The brain removes large amounts of carbohydrates from each circulation. For human subjects, this is estimated to be about 14.6 mg. per cent. Since the brain has but little reserve carbohydrates as its disposal, it depends directly on the blood stream for its constant food supply. The oxygen consumption of

the adult human brain is 7.43 vol. per cent. Experiments with insulin shock therapy emphasize the fact that anoxia and hypoglycemia exercise the same effect in depressing brain metabolism. Low blood sugar acts, therefore, like anoxia on the central nervous system.

Himwich and co-workers studied the cerebral metabolism in 65 mongoloid individuals. Their results disclose that the cerebral oxygen consumption is reduced in mongoloid infants, children, and adults:

> The oxygen uptake of the brain of normal infants as determined by comparison of the oxygen content of the arterial and fontanel blood is 8.59 vol.%. The average value of 3.63 vol.% though obtained only in 4 mongoloid infants is significantly below the normal by a difference of 4.76 vol.%, a reduction of 57.7%. A similar low value, 3.72 vol.%, is observed by comparison of the oxygen contents of the arterial blood and that from the internal jugular vein in 6 instances. The brain of 14 mongoloid children exhibits a larger oxygen uptake of 4.98 vol.% and the cerebral oxygen utilization of 45 so-called adult mongoloids is further increased to 5.62 vol.%. Nevertheless this value, too, is significantly less than the average of normal individuals of 7.43 vol.%. The difference of 1.81 vol.% reveals a reduction of 24.4%. This value is especially important because of the large number of the adult controls as well as of the mongoloid persons. The use of sugar is also diminished. The uptake is 7 mgm.% for the mongoloid in contrast with 14.6 mgm.% for the control. It must be emphasized that the lessened utilization of sugar is in accordance with what was to be expected from the diminished oxygen uptake and therefore confirms the latter observation to reinforce the conclusion of an impairment of cerebral metabolism in mongolian idiocy. The utilization of blood sugar affords evidence that in the mongoloid individual, as in the normal, carbohydrate is the chief source of cerebral energy. Mongolian idiocy is not caused by a shift of the brain to an unusual foodstuff. The same food is used, but at a slower rate.

Comparison between Biochemistry of Mongolism and of Cretinism

Biochemical and hematological data on the mongoloid patient are presented in detail because they are not available in any book, and they form the basic facts on the metabolism of mongolism. As can be expected in any chronic deficiency disease, the deviations from the normal are far less conspicuous than in any acute condition resulting from diseases like tuberculosis and vascular incidences or produced by experimental removal. Many data are within normal range if considered alone, but if the collected biochemical observations are analyzed as a whole there are several items of significance. Most definite is the pathology of carbohydrate metabolism. The fasting blood sugar values are low, within normal range, but sugar tolerance is increased, the tolerance curves are flat, and no glycosuria can be produced. Adrenalin is not able to raise the blood sugar significantly.

The lipid metabolism shows a definite elevation of the cholesterol level in the majority of cases, the values being between the normal level and the level of athyroidism. Basal metabolism is low.

The values of sodium and total protein are slightly below average, but

within normal range, while values for fibrinogen may show a tendency to elevation.

Compared with the biochemistry of cretinism, it may be said that both conditions show similar trends of deviation. If there should be a doubt with regard to the diagnosis of mongolism or cretinism in a certain case, biochemical tests would be of no avail, because the test results of both conditions overlap each other.

The sugar metabolism in cretinism shows the same trends, and the curves in cretinism are identical with those published on pages 232 for mongoloids. The same is true for absence of glucosuria.

The lipid metabolism in cretinism shows higher cholesterol values on the average, but single tests may easily be found among the values seen in mongolism (p. 239). Moreover, young cretins may have exceedingly low cholesterol values and their cholesterol may increase with thyroid treatment. (See case records, p. 48). The basal metabolism is low in myxedema, but it ranges actually between −20 and −40 in thyroid aplasia, the congenital type, comparable with mongolism.

Of the biochemical observations in myxedema, a fairly important one is the elevation of the total protein in the spinal fluid. Neuropsychiatrists are usually not aware of this fact.

The blood plasma volume in hypothyroidism is lower than normal. Thompson reported an average of 35.4 cc. per Kg., compared with a normal average value of 43 cc. It is interesting to note that the plasma volume was also found decreased in mongolism, with most values ranging between 33 and 37.5 cc. and only a few values above 40, which increased the reported average to 38.6.

The decreased calcium metabolism with decreased urinary excretion of calcium, observed by Aub, Bauer, and co-workers, has been mentioned in Chapter VII.

Although the tests may not be necessary for the diagnosis, they are of extreme value in studying the effect of therapy, in both conditions. The effect of thyroid therapy in cretinism can be checked by cholesterol determinations, basal metabolism, blood studies, and several other tests. It is expected that, when therapy of mongolism is carried out on a larger scale, the presented data will be of value for comparison.

BIBLIOGRAPHY

The biochemical data presented in this chapter are based on studies which have been published in part in the following papers of Dr. E. M. Bixby. In these publications, the methods which were used are discussed and pertinent references given.

Bixby, E. M.: Biochemical Studies in Mongolism. Am. J. Ment. Deficiency **44**: 59, 1939.

Bixby, E. M.: Further Biochemical Studies in Mongolism. Am. J. Ment. Deficiency **45:** 201, 1940.

——: Biochemical Studies in Mongolism. III. Am. J. Ment. Deficiency **46:** 183, 1941.

——, and Benda, C. E.: Glucose Tolerance and Insulin Tolerance in Mongolism. Am. J. Ment. Deficiency **47:** 158, 1942.

——, ——: Androgens in Mongoloid Deficiency. Am. J. Ment. Deficiency **49:** No. 2, 138–48, 1944.

——, ——: Function of the Thyroid and the Pituitary in Mongolism. Am. J. Dis. Child. **58:** 1240, 1939.

Further Bibliography

Bingenheimer, E.: Ztschr. f. d. ges. exper. Med. **87:** 816, 1933.

Bodansky, Meyer, and Bodansky, Oscar: Biochemistry of Disease. Macmillan, New York, 1940.

Consolazio, W. V., and Talbott, J. H.: Extraction and Determination of 17-Ketosteroids in Urine. Endocrinology **27:** 355, 1940.

Epstein, A. A., and Lande, H.: Studies on Blood Lipoids: Relation of Cholesterol and Protein Deficiency to Basal Metabolism. Arch. Int. Med. **30:** 563, 1922.

Fraser, R. W., Albright, F., and Smith, P. H.: The Value of the Glucose Tolerance Test, the Insulin Tolerance Test, and the Glucose-Insulin Tolerance Test in the Diagnosis of Endocrinologic Disorders of Glucose Metabolism. J. Clin. Endocrinology **1:** 297, 1941.

——, Forbes, A. P., Albright, F., Sulkowitch, H., and Reifenstein, E. C., Jr.: Colorimetric Assay of 17-Ketosteroids in Urine. J. Clin. Endocrinology **1:** 234, 1941.

Gilligan, D. R., Volk, M. C., Davis, D., and Blumgart, H. L.: Relationship Between Serum Cholesterol Values, Basal Metabolic Rate and Clinical Aspects of Hypothyroidism. Arch. Int. Med. **54,** 746, 1934.

Gradwohl, R. B. H.: Clinical Laboratory Methods and Diagnosis. C. B. Mosby Co., 1938.

Grollman, A.: The Adrenals. Williams & Wilkins, Baltimore, 1936.

Himwich, H. E., Fazekas, J. F., and Nesin, S.: Brain Metabolism in Mongolian Idiocy and Phenyl Pyruvic Oligophrenia. Am. J. Ment. Deficiency **45:** 37, 1940.

——, ——: Cerebral Metabolism in Mongolian Idiocy and Phenylpyruvic Oligophrenia. Arch. Neurol. **44:** 1213, 1940.

Hurxthal, L. M.: Blood Cholesterol and Thyroid Disease. III. Myxedema and Hypercholesteremia. Arch. Int. Med. **53:** 762, 1934.

——: Blood Cholesterol and Hypometabolism, Suprarenal and Pituitary Deficiency. Arch. Int. Med. **53:** 825, 1934.

Joedicke, P.: Über innersecretorische Stoffwechselstörungen bei Athyreosis, mongoloider Idiotie und Akromegalie. Ztschr. f. d. Erforschung u. Behandlung d. Jugendl. Schwachsinns **6:** 286, 1913.

Kocher, A.: Die histologische und chemische Veränderung der Schilddrüse bei Morbus Basedowii und ihre Beziehung zur Funktion der Drüse. Virchows Arch. f. path. Anat. **208:** 86, 1912.

Mader, A., and Bingenheimer, E.: Die Roentgenbestrahlung des Mongolismus und ihr Einfluss auf den Blut-Cholesterinspiegel. J. f. Kinderkr. **138:** 9, 1933.

Manitz, Hans: Das humorale Syndrom der Mongoloiden. Deutsche Ztschr. f. Nervenh. **126:** 80, 1932.

Mason, R. L., Hunt, H. M., and Hurxthal, L. M.: Blood Cholesterol Values in Hyperthyroidism and Hypothyroidism—Their Significance. New England J. Med. **203:** 1273, 1930.

Nathanson, I. T., Towne, L. E., and Aub, J. C.: The Daily Excretion of Urinary Androgens in Normal Children. Endocrinology **24:** 335, 1939.

Neustadt, R.: Photo-Colorimetric Method for the Determination of Androsterones in Urine. Endocrinology **23:** 711, 1938.

Oesting, R. B., and Webster, B.: The Sex Hormone Excretion of Children. Endocrinology **22:** 307, 1938.

Offenkrantz, F. M., and Karshan, M.: Serum Cholesterol Values for Children. Am. J. Dis. Child. **52:** 784, 1936.

Osgood, E. E.: A Textbook of Laboratory Diagnosis. Blakiston's, Philadelphia, 1935.

Pennacchietti, M.: Contributo anatomo-pathologico allo studio della idiozia mongoloide. Endocrinol. e pat. costit. **10:** 148, 1935.

Penrose, L. S.: Blood Grouping of Mongolian Imbeciles. Lancet **1:** 394, 1932.

Svensgaard, E.: Blood Sugar in Normal and Sick Children. Acta Pædiat. **12:** 10, 1931.

Sweeney, J. S., Muirhead, J. J., and Allday, L. E.: Observations on the One-Hour Two-Dose Dextrose Tolerance Test. Am. J. Clin. Path. **7:** 482, 1937.

Talbot, F. B.: Basal Metabolism Standards for Children. Am. J. Dis. Child. **55:** 455, 1938.

Talbot, N., Butler, A. M., Berman, R. A., Rodriguez, P. M., and MacLachlan, E. A.: Excretion of 17-Keto Steroids by Normal and by Abnormal Children. Am. J. Dis. Child. **65,** 364, 1943.

Thompson, W. O., Thompson, P. K., Silvens, E., and Dailey, M. E.: The Cerebro Spinal Fluid in Myxedema. Arch. Int. Med. **44:** 368, 1929.

CHAPTER X

RELATIONSHIP OF MONGOLISM TO THE MATERNAL CONDITION

The mongoloid baby shows at birth the principal stigmata of his condition. The deficiency must have developed, therefore, in the prenatal period during intra-uterine life. Three main theories have been advanced to account for the cause of mongolism. These are concerned with (1) hereditary factors, (2) damage to the germ plasm (either paternal or maternal), and (3) a noxious factor originating in the mother during gestation.

Heredity

A small group of investigators (Macklin, Penrose, Doxiades, and Portius and Schröder) have felt that hereditary factors are responsible for mongolism. Their conclusion is based either upon theoretical arguments or on the study of relatives of mongoloid patients. These authors are under the impression that an increased number of mental defectives or persons with congenital malformations can be found in the kinship of a mongoloid child. These observations are, however, not confirmed by many other investigators. My own material of more than 500 families accumulates evidence that hereditary factors are of no importance.

Mongolism is found in all social strata; it is spread over the population and has no correlation with the intellectual status of other members of the family. Of course, feeblemindedness in a family is no protection against a mongoloid child. A few authors have succeeded, therefore, in finding mental deficiency in other family members.

In my material I have seen a few cases of familial feeblemindedness, where older siblings of the mongoloid patient were of a moron level. The point is that genetic factors may explain the feeblemindedness of the offspring, but the typical growth disorder of mongolism cannot be explained by a genetic deficiency.

A factor which, strangely enough, has not been sufficiently emphasized, greatly supports the idea that genetic factors are unimportant: the number of children affected with any genetic disorder can be expected to increase if the family size is increased. When a sibship consists of five or less in a random group of families, the majority will show only one affected offspring. Not until the sibship's size increases to six or more may one expect more instances in which two or more children are affected. Among the families of 255 cases studied in the first investigation, there were 75

instances in which the affected child was born in a family of 6 or more children; among Lahdensuu's material, 50 instances of this type were found. 125 out of 429, or 29.1 per cent, of the mongoloids came from sibships of six or more. Only once, in a family of 13 children, were 2 mongoloids observed. It is obvious that these observations do not suggest inheritance.

The rate of consanguinity among parents, whose offspring is affected by a rare hereditary unit recessive trait, is higher than among the general population. Consanguinity has not been more frequently observed among parents who had a mongoloid child.

Twins

With regard to the question of whether hereditary factors are significant, research on pairs of twins is of special interest. The importance that twin research has attracted in recent years justifies a brief discussion of such observations.

Twins, in the human species, are considered to come from two sources. The first group occurs as the result of the complete cleavage of one fertilized ovum and the development of two separate individuals. This type of twinning is called "enzygotic" or "monozygotic," because the twins have developed from one zygote or fertilized ovum. Other terms that are used are "uni-ovular," "similar," and "identical." These twins are always of the same sex and show identical color of hair and of eyes, the same blood groups, the same patterns of the hand lines, and many other minor details. In the vast majority of cases they develop from one placenta and have the same fetal membranes. The second type of twins is produced through fertilization of two ova at the same time, both ova coming either from the same ovary or from separate ovaries. These twins are called "dizygotic," arising from two zygotes. They are also called "binovular," "dissimilar," and "fraternal." These twins, who happen to be born at the same time, resemble each other as much or as little as any pair of siblings do. They may be of the same or of the opposite sex. They will differ in many ways and may have no more in common with each other than any two children of the same parents.

In a group of 90 pairs of twins, 60 may be expected to be of one sex and 30 of opposite sex. The twin pairs of opposite sex are undoubtedly dizygotic. The remaining 60 pairs of twins of one sex have to be divided into monozygotic and dizygotic. According to statistics, one-half of these 60 pairs are likely to be dizygotic and one-half monozygotic.

If a pathological condition is found in both twins the condition is called "concordant." If the condition is present in only one it is called "discordant."

Although more than 80 twins with mongolism have been reported in the literature, only about 63 reports are reliable and can be used in a discussion of the facts. Both twins were mongoloids in 14 instances. A study of the fetal membranes and exact comparison of the twins made it likely that 7 of these twins were monozygotic or identical. The other 7 cases of concordant twins were not studied well enough to assure identity. One has to keep in mind that mongoloid babies look very much alike in any case and there will be similarities in color of hair, color of eyes, skin ridges of the hand and in other patterns, if the children are not identical twins or are not even related to each other at all.

There are 27 pairs of dissimilar twins known who were discordant and of unlike sex. In 21 cases the children were of similar sex, but only one was affected with mongolism. From the observations so far at hand, it has been concluded that monozygotic twins are always concordant, and that concordance always indicates that the twins were monozygotic. In dizygotic twinning, discordance will always be present.

In recent years, however, four instances of concordance in dizygotic twins have been reported. This observation is of considerable importance, as it makes the acceptance of a genetic hypothesis still more difficult. George A. Jervis, who reported the fourth instance of concordant dizygotic mongoloid twinning, points out, a genetic theory "is consistent with the finding of concordance in monozygotic twins and non-concordance in dizygotic twins; it is also consistent with the finding of a certain number of dizygotic, concordant twins. However, if exclusively chromosomal factors are operating, the proportion of concordant dizygotic twins to discordant dizygotic twins should be reasonably close to the proportion of sibships with two members affected to sibships with only one member affected. Although reliable data concerning the incidence of familial mongolism are scanty, one may reasonably assume that no more, and probably less, than 1 per cent of affected sibships show more than 1 mongoloid. The proportion of concordant dizygotic twins to discordant dizygotic twins is 6.8 per cent of 7 times, and probably more, the incidence of familial mongolism. This discrepancy appears significant. It would suggest that other than genetic factors are present."

Plasmatic Theory

The second theory postulates that mongolism is caused by some damage to the germ plasm. This theory considers either the possibility of a gametic mutation or the fertilization of an abnormal ovum which was not suited to produce a normal offspring. In view of the four instances of concordant dizygotic twins and the possibility that some of such cases have been missed, the mutation theory appears unlikely. A spontaneous mutation is a rare occurrence which is highly improbable.

This leaves as the most adequate explanation of mongolism two possibilities: the fertilization of an over-aged ovum, and the operation of abnormal noxious factors during gestation.

Pathologists have observed in biopsy and autopsy material that the condition of the ovaries usually reflects fairly accurately the age of a woman. In some instances, however, younger women show a premature aging of their gonads and have ovaries usually not found before menopause.

Recent animal experiments on frogs' eggs suggested that, if eggs are overaged, a large number of these ova develop malformed specimens. If ova are still more overaged most of the developing embryos die before maturity is reached. Several investigators in recent years have felt that this offers an explanation for mongolism in the human race. It is true that a number of graafian follicles in the human ovary mature at the same time, but only one is supposed to rupture in the middle of each menstrual cycle. Theoretically, it is perfectly possible that ova which have been dormant for a long time may become fertilized and develop in an abnormal way. This theory might well apply to cases of older women in menopause, or the cases where impregnation takes place immediately after the birth of a child before the menstrual cycle has been re-established. While it is not possible to exclude the possibility of fertilization of an abnormal ovum as a cause of mongolism, many data point towards the fact that an abnormal condition of the mother during the early months of pregnancy is responsible for the abnormal development of the fetus which results in mongolism. Such a theory is even compatible with the observations reported above on mongoloid twins.

There is evidence that the environmental ("peristatic") factors in non-identical twins differ to a great extent, owing to differences in placental circulation and other dynamic factors. An unfavorable position is frequently the cause of a malformation or a disease in one of twins. Infantile cerebral paralysis, hydrocephalus, microcephalus, cretinism, and even congenital syphilis have been reported in one of twins.

One may assume that, if the deficiency which leads to mongolism in the offspring is very severe, both babies may be affected, while in a deficiency of moderate degree one twin may be spared while the other becomes abnormal. It may be remembered that twinning as such is an abnormal condition in man in spite of its frequency, and that twinning may favor a deficiency disease in one of the twins. Some authors feel that mongolism in twins is slightly more frequent than may be expected.

There is still another possibility which ought to be considered. Non-identical twins are usually considered to be the result of simultaneous fertilization of two ova. If the observations which will be reported later are correct, the possibility of a superimposed pregnancy has to be taken into consideration. In man and those animals who carry one embryo only,

some defense mechanism comes into play immediately after fertilization of one ovum to prevent the fertilization of a second ovum. It is possible, however, that not all twins are derived from ova fertilized at the same time. If the defense mechanism against a second fertilization is lacking, fertilization of a second ovum may take place a few days to weeks after the first impregnation. The great difference in size between twins of whom one was a mongoloid suggests that such an event has to be seriously considered.

The occurrence of superfecundation in the human has been recently scientifically proven through an interesting case. Examination of a twin sister pair revealed that the alleged father was the father of one of the twins, but he could be excluded as the father of the other twin by an examination of the blood grouping and blood factors. The children had both the blood group B but one had an antigen M and the other MN. The father's blood showed the group AB and factor N. Experiments and testings, carried out independently by three experts, provided scientific proof that the alleged father could not be the father of one of the twins and that, therefore, superfecundation, or impregnation of a second ovum matured in the same ovulation cycle, can exist in humans. (Heberer)

Multiple Incidence of Mongolism in a Family

The problem of mongoloid twins is closely related to the problem of multiple instances of mongolism in one family. Almost every mother who has had a mongoloid child and who wants more children will consult her physician as to whether there is any possibility that she may have another mongoloid baby. It can be stated that according to the experience of all writers the occurrence of more than one mongoloid in a family is extremely rare. A mother can, therefore, be encouraged to have more children without risk. It is, however, advisable for the physician to make a careful medical examination and a study of the family background, because it is known that such a misfortune has occurred twice or thrice.

When van der Scheer prepared his monograph on mongolism, he was very much interested in the multiple incidence of this condition. In his original material of 79 cases, he found 2 instances. Later on, when he collected material from all over Holland, a large number of physicians collaborated, and he was able to spot 7 families out of 338 in which more than one child was a mongoloid. In spite of these numbers, van der Scheer did not doubt that mongolism is not a hereditary condition, but the result of a pathological pregnancy. Orel, in 1931, collected 21 families from the literature in which more than one mongoloid was found. Reports on single cases have been made by several authors.

In spite of the fact that I had access to 500 case histories, only 5 families were found with more than one mongoloid child, besides the cases of concordant mongoloid twins mentioned above. In one family, 2 out of 13

living children were mongoloids; in one family, all 3 children were mongoloids; in one, 2 of 4; and in two, 2 of 3.

These observations as well as the study of cases reported in the literature indicate that multiple mongolism is due to the coincidence of several factors. In the majority of these cases hereditary factors indicating a germinal inferiority are evident. The mongoloid characteristics are superimposed and due to certain factors within the mother which are similar to those seen in mothers who had one mongoloid child only. One may, therefore, conclude that in the average healthy family a second mongoloid child may not be expected. It is, however, noticeable that there is an increased tendency to miscarriages. One may wonder if some of these miscarriages are not abortions of mongoloid babies. As a matter of fact, recent examination of a stillborn younger sibling of a mongoloid proved that this child was a mongoloid also.

Prenatal Maternal Factors

The third possibility for the occurrence of mongolism is a pathologic condition of the mother in the beginning of pregnancy. The question is whether we can collect indubitable evidence that the factors leading to mongolism are present in the organism of the mother.

A series of investigations culminated in 1928 in a study by Adrien Bleyer. The analysis was based on the material of 2,822 cases and rendered evidence that the age of the mother plays a role in mongolism. The average age of the mother at the time of the birth of a mongoloid child was found more than ten years higher than the average maternal age at the time of birth of two million children who were born in the United States in 1934. More than 50 per cent of mothers were beyond the age of 35 when their mongoloid child was born. Fig. 100 shows the age of 255 mothers of mongoloid children of the Wrentham material. This chart confirms earlier observations that many mongoloid children are born to mothers beyond the age of 35. Instead of comparing the material with normal children, a comparison with the ages of mothers at birth of mentally defective children of another type was made. These cases had been diagnosed as familial, or germ plasm defect. The differences between the two groups are striking. Most of the mothers of familial mentally defective children were below the age of 30 and only 3 per cent were over 40 years. In the mongoloid group 27 per cent of mothers are over 40 years.

Age, however, cannot be the only factor in producing mongolism, because 107 of the 255 mothers in this group were under 35 years of age. Thus, about 41 per cent of mothers are in an age group (under 35) which is favorable for childbearing. Although a maternal age of over 35 years

may favor the occurrence of a mongoloid child, it is clear that the factors which produce mongolism are not invariably linked with age.

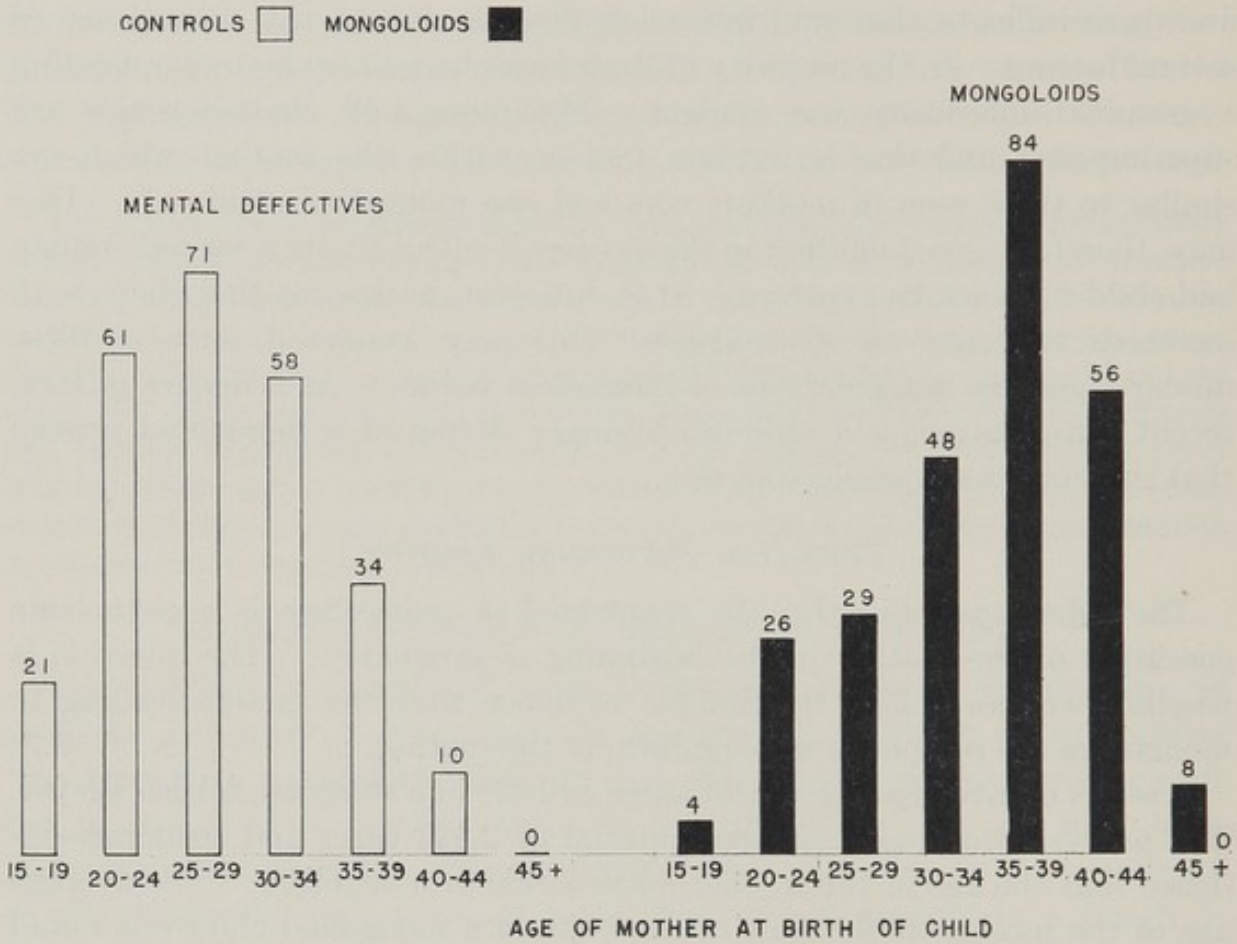


FIG. 100. Age of mothers at birth of mongoloid child. In a control series of 255 cases, the age distribution of the mothers corresponds to the normal distribution with the largest number of children born between the ages of 25 and 29 years. The largest number of mongoloids are born to mothers between 35 and 39 years of age. The age difference between the two groups is almost 10 years.

BIRTH ORDER

Whether the condition of the mother or a gametic factor is responsible for mongolism may be answered by a study of the birth order of the mongoloid child.

The birth of a mentally defective child in which the defect is due to germinal deficiency may be expected to occur at any place in the line of siblings. It is well known that defectives of the familial type occur as first children, in the middle of the family, or as last children. Apparently the birth of the mental defective has no influence upon the ability of the mother to have more children. Here we are dealing with a problem of genetics and expect no disturbance of the birth order. On the other hand, if a pathologic condition of the mother were the cause of a defect, we would

expect a difference between the number of siblings born before and the number born after the affected child.

From the statistical point of view, it is obvious that a study of an unbiased sample of families in which all children are analyzed might be expected to show that as many children will be born before the individual with a given characteristic as will be born after the affected individual. In some families, the affected sibling may be born first, in other families last. However, these differences will cancel each other in the long run, and the findings will show a balance of siblings born before and after the affected child.

TABLE 35.—*Order of Birth in 4,316 Mentally Defective Public School Children*
Analysis Confined to Families with One to Nine Children ever Born
(Dayton)

Order of Birth of Ment. Def. Child	Size of Family									Total
	1	2	3	4	5	6	7	8	9	
1	209	193	190	156	149	119	77	40	16	1,149
2	—	175	146	141	154	123	85	56	38	918
3	—	—	133	144	137	107	88	72	44	725
4	—	—	—	117	109	93	91	76	61	547
5	—	—	—	—	98	80	84	67	52	381
6	—	—	—	—	—	96	82	68	43	289
7	—	—	—	—	—	—	70	56	44	170
8	—	—	—	—	—	—	—	58	37	95
9	—	—	—	—	—	—	—	—	42	42
Total	209	368	469	558	647	618	577	493	377	4,316

As Dayton has shown previously in a study of birth order in 4,316 mentally defective children of all types, there is no evidence that the mentally defective child tends to be born in the first or in the last position of the family. Taken as a whole, the trait of a mental deficiency occurs with almost equal frequency at any place in the birth order. The material confined to the birth order of the first 9 children is presented in Table 35.

Table 36 shows the number of siblings born before and after the mentally deficient child by size of family. We note that 8,999 children, or 39.2 per cent, were born before the mentally defective child and 9,588, or 41.8 per cent, afterwards. This is very close to the expectation. Mental defect as a characteristic does not appear to be associated with any particular disturbance of the birth order.

In order to provide further material for direct comparison, we studied the order of birth of 255 feebleminded children in the Wrentham State

School. All had been diagnosed as familial mental defect. Counting the whole number of siblings of the defective child, 54 per cent were born previously and 46 per cent were born subsequently to the patient. This represents a variation which is well within the expected variation and offers, again, proof of the theoretical assumption.

Fig. 102 represents the situation in mongoloid families by age of mother. Since the number of cases is identical in Fig. 101 and Fig. 102 immediate comparison is possible. The first column shows the mongoloid as the first child of young mothers, aged 15 to 19 years. The striking item in this age group is the small number of siblings who were born afterwards. Only

TABLE 36.—*Siblings Born Before and Subsequent to Birth of Mentally Defective Child, by Size of Family*

Size of Family	Total Siblings Born	Siblings Born before Patient	Patient Affected	Siblings Born after Patient
1	209	0	209	0
2	736	175	368	193
3	1,407	412	469	526
4	2,232	780	558	894
5	3,235	1,147	647	1,441
6	3,708	1,416	618	1,674
7	4,039	1,700	577	1,762
8	3,944	1,778	493	1,673
9	3,393	1,591	377	1,425
Total	22,903	8,999	4,316	9,588
Per cent	100	39.2	18.8	41.8

9 children were born after the mongoloid as compared with 50 siblings born after the mental defective (control material). In the age group 20–24 years, the number of children born afterwards is larger than that of siblings born before, but only a total of 32 children is born from 26 mothers in that age group. In the age group 25–29 years the reversal of the birth order is already present, while the control group shows the theoretical balance between those born before and afterwards. In the mongoloid group, the 29 mothers aged 25–29 years had only 25 children afterwards, or less than half of the number born before (52). Most striking is the unexpected drop of children born afterwards in mothers aged 30–34 years, where only 29 children appear as compared with 117 born afterwards in the control group.

One point is worth noticing. In families with a mongoloid child, the number of normal previously born siblings from mothers between the ages of 30 and 34 is very small, while in the age groups of 35 to 39 and 40 to 44, the number of normal siblings is much larger than in the controls. This

seems to indicate that in families with a mongoloid child at the end of the childbearing period, the age of the mother at the time when their normal children were born was higher than in other families. In other words, these mothers have started childbearing at a higher age than the control group.

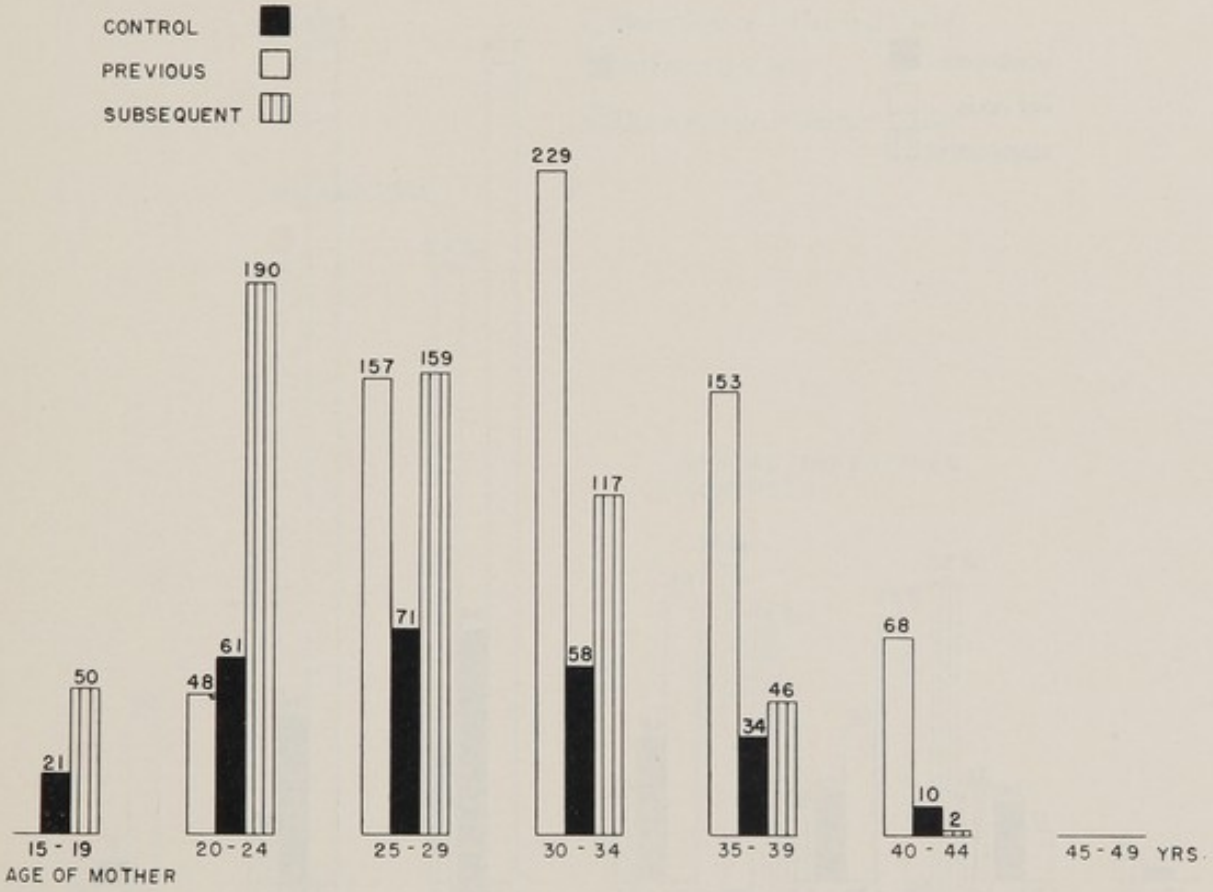


FIG. 101. Number of siblings born previous and subsequent to control birth. In the age group between 25 and 29 years almost exactly as many siblings are born after the defective child as before. In the age group 20 to 24 years the number of siblings born after a defective child is four times that of siblings born before, indicating that the birth of an hereditary defective child has no influence upon the birth rate afterwards. In the age group 30 to 34 years about half as many children are born after a defective as before.

In comparing the number of siblings born before and after a mongoloid child, the striking result is found that 84 per cent of the total number of brothers and sisters (100 per cent) is born before the mongoloid child and only 16 per cent is born afterwards. If the number of siblings born before and afterwards is calculated according to expectancy, the result is the following: There was a total number of 1,179 children. Two hundred fifty-five of them were mongoloids. Therefore, we might expect to have one half of the difference between 1,179 and 255, or 462, as the figure representing the children born *before* the mongoloids and the other half, or 462

children, born afterwards. Instead, we find that 776 children were born before the mongoloid and 148 afterwards. The figures are outlined in Table 37 and Fig. 103. We have 12.5 per cent of siblings born after the mongoloid when we might expect 39.2 per cent. Thus, more than three times as many children are expected after a mongoloid as actually are born.

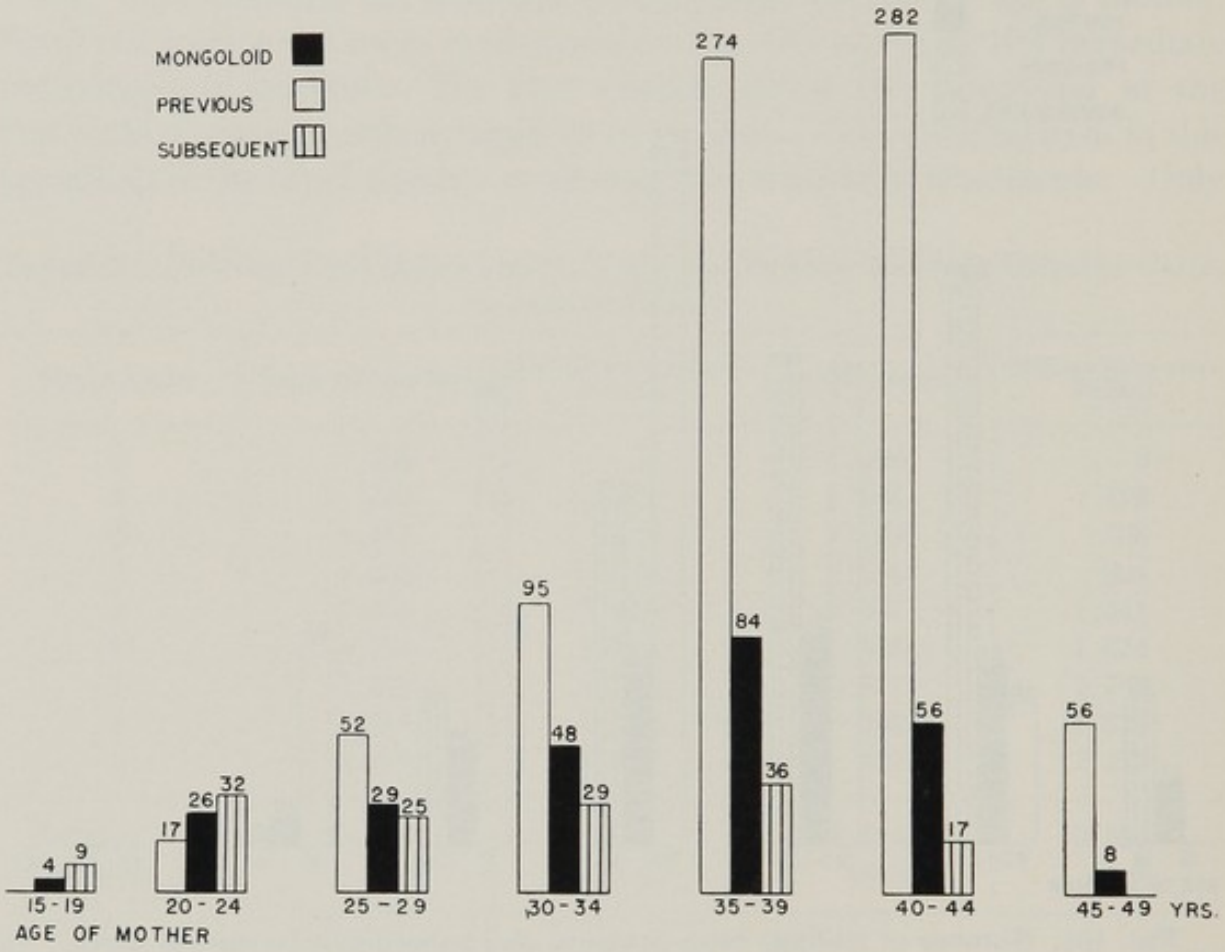


FIG. 102. Number of siblings born previous and subsequent to mongoloid birth. In the age group 25 to 29 years only half as many children are born after the mongoloid as before, instead of the same number, and in the age group 20 to 24 years less than twice as many children are born after a mongoloid as before, instead of four times as many.

The total number of siblings born in 255 families with mongoloid children is 924, which is only slightly less than the control group with 1,219. In the mongoloid group, the total number of children born before the defective child is 776, while in the control group 655 children were born before. In other words, mothers who later gave birth to a mongoloid child had a period in their lives when they had children at, or even above, the average rate for all mothers. Then something happened: as a result a mongoloid was born, and from that point on these mothers produced at a rate which was much below the average. The imbalance between the number of children born before and afterwards suggests that the birth of a mongoloid

child indicates the development of a pathologic condition of the mother which bears a definite relationship to her ability to have children. The decrease in fecundity of the mother after a mongoloid child is not complete, as a small number of children are born afterwards. The condition of the mother is not irreversible; and yet, the material shows that the birth of a

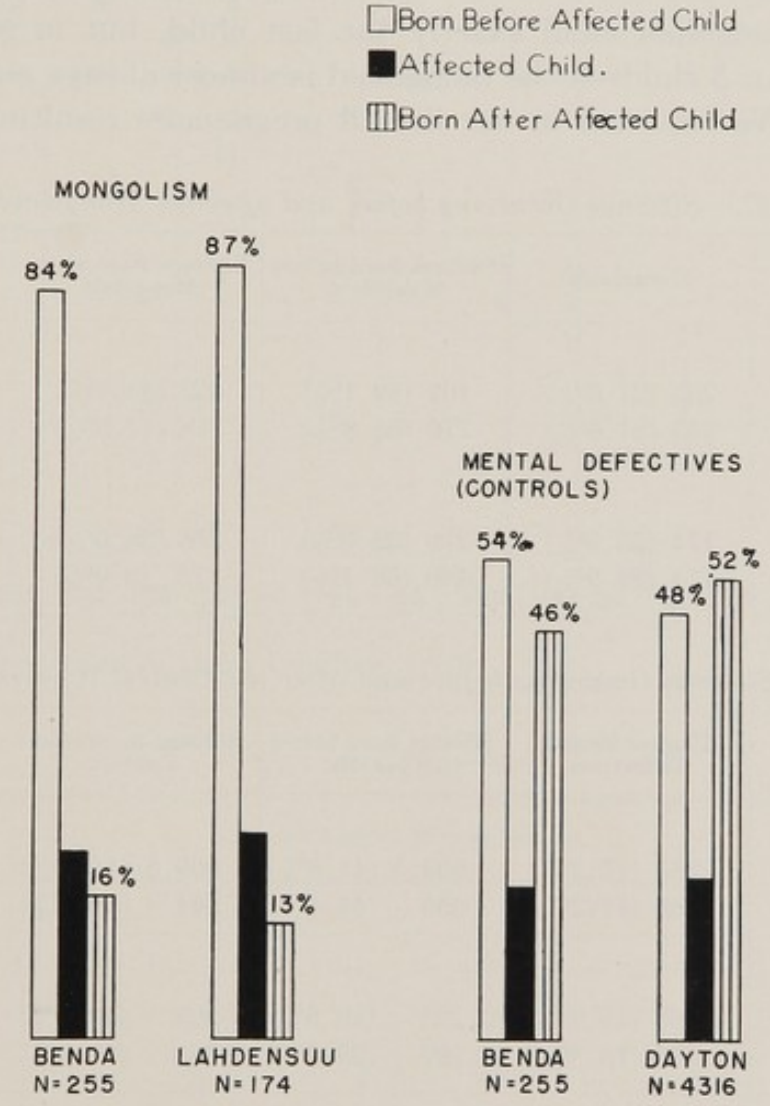


FIG. 103. Percentages of siblings born before and after hereditary defectives and mongoloids. If the total number of siblings born before and after a defective child is compared, the number is about equal in the control group while in the mongoloid group 84 to 87 per cent of all siblings are born before the mongoloid and only 13 to 16 per cent after the mongoloid.

mongoloid child marks a turning point which is followed by a decided diminution in the number of children born subsequently.

In Table 39 the birth order of mongoloid children is presented. In order to show that the peculiarities of the birth order are not confined to the Wrentham material, material from a recent publication of Sakari Lahdensuu is added. Both charts show identical trends. There is a definite

difference between those families where the mongoloid is among the first 5 children and where the mongoloid is born in a family of more than 6. In contrast to Table 35, in which mentally deficient children appear on any place of birth order, the mongoloid child never occurred among the first children in those families who had 6 to 15 siblings. The larger the family, the more definite the trend toward the end of the birth line. Not in every case is the mongoloid child exactly the last child, but in those families with more than 5 children the mongoloid is almost always among the last 3 children. We recorded in our list all pregnancies resulting in a living

TABLE 37.—*Siblings Occurring before and after the Mongoloid Birth*

	Mongoloids	Siblings Born before Mongoloid	Siblings Born after Mongoloid	Total	
Benda					
Expected	255 (21.6%)	462 (39.1%)	462 (39.1%)	1,179	100%
Observed	255 (21.6%)	776 (65.8%)	148 (12.5%)	1,179	100%
Lahdensuu					
Expected	174 (23.9%)	276 (38.0%)	276 (38.0%)	726	100%
Observed	174 (23.9%)	480 (66.1%)	72 (9.9%)	726	100%

TABLE 38.—*Siblings Occurring before and after the Control (Control Defectives)*

	Control Mental Defectives	Siblings Born before Control	Siblings Born after Control	Total	
Benda					
Expected	255 (17.2%)	609.5 (41.3%)	609.5 (41.3%)	1,474	100%
Observed	255 (17.2%)	655 (44.4%)	564 (38.2%)	1,474	100%
Dayton					
Expected	4,316 (18.8%)	9,293 (40.5%)	9,293 (40.5%)	22,903	100%
Observed	4,316 (18.8%)	8,999 (39.2%)	9,588 (41.8%)	22,903	100%

child. It may be mentioned that a study of the siblings revealed that in a rather large number of cases, the siblings born after a mongoloid have died shortly after birth. Many more mongoloids are, therefore, the last living child than appear in that position on our table. In these families, the siblings born before the mongoloid appear normal. The mothers of these families have revealed no pathology in their younger years and have offered evidence of their ability to give birth to a rather large number of normal children. In each case, the pathology in the offspring occurred only as the mother was approaching the end of her childbearing period or had reached the condition in which menstruation had become irregular.

TABLE 39.—*Order of Birth in 255 Mongoloids at the Wrentham State School Compared with Data of Lahdensuu (174 Cases)*

Order of Birth of Mongoloid	No. of Children Born in Family															Total No. of Mongoloids
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	
1	20	12	8	1	3	—	—	—	—	—	—	—	—	—	—	44
2	—	40	9	4	1	—	—	1	—	—	—	—	—	—	—	55
3	—	—	33	9	4	2	1	—	—	—	—	—	—	—	—	49
4	—	—	—	20	5	1	—	—	—	—	—	—	—	—	—	26
5	—	—	—	—	11	4	—	—	—	—	—	—	—	—	—	15
6	—	—	—	—	—	7	5	1	—	—	—	—	—	—	—	13
7	—	—	—	—	—	—	7	5	—	1	—	—	—	—	—	13
8	—	—	—	—	—	—	—	5	6	1	1	—	—	1	—	14
9	—	—	—	—	—	—	—	—	6	3	—	—	—	—	—	9
10	—	—	—	—	—	—	—	—	—	5	—	1	—	—	—	6
11	—	—	—	—	—	—	—	—	—	—	5	1	1	—	—	7
12	—	—	—	—	—	—	—	—	—	—	—	1	1	—	—	2
13	—	—	—	—	—	—	—	—	—	—	—	—	1	—	—	1
14	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
15	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1	1
	20	104	150	136	120	84	91	96	108	100	66	36	39	14	15	255

Total children born in these families, 1,179.

SAKARI LAHDENSUU

Order of Birth of Mongoloid	No. of Children Born in Family													Total No. of Mongoloids
	1	2	3	4	5	6	7	8	9	10	11	12	13	
1	36	11	2	1	1	—	—	—	—	—	—	—	—	51
2	—	18	4	1	2	1	—	—	—	—	—	—	—	26
3	—	—	14	3	2	—	—	1	—	—	—	—	—	20
4	—	—	—	20	—	2	—	—	—	—	—	—	—	22
5	—	—	—	—	9	—	—	1	—	—	—	—	—	10
6	—	—	—	—	—	8	1	1	1	—	—	—	—	11
7	—	—	—	—	—	—	12	2	1	1	—	—	—	16
8	—	—	—	—	—	—	—	5	—	—	—	—	—	5
9	—	—	—	—	—	—	—	—	4	—	—	—	—	4
10	—	—	—	—	—	—	—	—	—	2	1	—	—	3
11	—	—	—	—	—	—	—	—	—	—	3	1	—	4
12	—	—	—	—	—	—	—	—	—	—	—	1	—	1
13	—	—	—	—	—	—	—	—	—	—	—	—	1	1
	36	58	60	100	70	66	91	80	54	30	44	24	13	174

Total children born, 726.

I mentioned that it seems of importance at what age the normal pregnancies occurred. From the tables one learns that many of the normal siblings were born after the mother was 30 years of age; the 6 to 15 pregnancies which some of these mothers had are not spread over a period of ten to twenty years but are sometimes found crowded into a rather short period after the maternal age of 30. Obviously childbearing after 30 represents a heavier strain on the organism of the mother than would the same number of children in a young mother. The observation on this group of

TABLE 40.—*Correlation between Age of Mother and Number of Pregnancies*

Age Group of Mother	No. of Mothers	No Child	One Child	Two Children	Three or More Children	Total Children
BEFORE MONGOLOID BIRTHS						
15–19	4	4	0	0	0 (0 children)	0
20–24	26	14	10	0	2 (7 ")	17
25–29	29	4	9	10	6 (23 ")	52
30–34	48	8	14	18	9 (45 ")	95
35–39	84	9	18	14	43 (228 ")	274
40–44	56	5	4	7	40 (264 ")	282
45–49	8	0	0	0	8 (56 ")	56
Total.....	255	44	55	49	108 (623 ")	776
AFTER MONGOLOID BIRTHS						
15–19	4	1	1	0	2 (8 children)	9
20–24	26	8	9	7	2 (9 ")	32
25–29	29	16	5	5	3 (10 ")	25
30–34	48	31	11	3	3 (12 ")	29
35–39	84	57	21	4	2 (7 ")	36
40–44	56	41	13	2	0 (0 ")	17
45–49	8	8	0	0	0 (0 ")	0
Total.....	255	162	60	21	12 (46 ")	148

families seems to confirm the theory of Shuttleworth, who called the mongoloid child an "exhaustion product," the occurrence of which is "dependent upon conditions adversely affecting the maternal reproductive powers; the advanced age of the mothers and the frequent childbearing being the most noticeable causative factors—exhaustion, illness of whatever kind during the period of gestation may produce imperfection in the evolution of the fœtus and its tissues which we know as mongolism."

Age and exhaustion, however, cannot be the only factors, because we find in our other group that a large number of mongoloids are the first

children in the family and that the total number of children in these families is rather small. If one investigates the correlation between the age of the mother and the number of children one finds that mongoloids occur mainly under two conditions. Of those 8 mothers who were above 45, all had more than 3 children, with a total of 56 children. Among 56 mothers between 40 and 44, 40 had more than 3 children, totaling 264 children, but in 5 instances the mongoloid was the result of the first pregnancy. In the age group between 35 and 39, we find 84 mothers, of whom 43 had more than 3 children, totaling 228 children, while 9 in that group had no child before. One may therefore conclude that the risk of childbearing at an age beyond 35 is increased in any case, regardless of whether many pregnancies or no pregnancy had occurred before. In the latter instance, the maternal organism has apparently lost its adaptability for pregnancy. In the age group of 20 to 24, we find 26 mothers of whom 14 had a mongoloid as their first child, but 2 women had already given birth to a total of 7 children; in the age group of 25 to 29, 4 mothers had no children before the mongoloid but 6 had borne a total of 23 children before.

We see that a rapid sequence of pregnancies may "exhaust" even a young mother and produce a temporary condition of unfitness for gestation. On the other hand, the first fertilization may find an unprepared organism, which is too slow or insufficient to accomplish the necessary adjustments of the endocrine environment. If mongolism occurs in the first pregnancy, the mother may well be able to react normally in a second and a third pregnancy.

Psychosomatic Disorder of Mother

In the following I comment briefly on the psychosomatic factors common in mothers who have given birth to a mongoloid child:

1. High-strung, nervous, easily upset
2. Frequency of abortions
3. Bleedings during pregnancy
4. Inability to keep a full term pregnancy (prematurity of baby)
5. Inability to become pregnant
6. Endocrine imbalance

The Nervous Temperament

1. The description of the mother as "high-strung," or extremely nervous, was found 62 times in the material. This high number refers in the first place to the 107 instances where the mother was below 34 years of age. It may be remembered that the "high-strung" type of woman shows a

psychosomatic reaction which is characterized by psychic lability and by instability of circulatory and autonomic functions.

Abortions

2. The frequency of abortions is one of the most striking features in case histories of mongolism.

This table shows that 80 out of 255 mothers have reported a total of 126 miscarriages. Although we have to remember how often this information is unreliable, our investigation showed that 95 miscarriages preceded the birth of a mongoloid child and 31 followed afterwards. The more material has become available in recent years, the more frequently we have found that the first signal for threatening mongolism was given in a miscarriage.

The incidence of spontaneous abortions in the general population has attracted much interest on the part of obstetricians and pathologists. In a recent article A. T. Hertig and R. G. Livingstone reviewed this subject and found the incidence to be 10.6 per cent. The summarized findings of

Table 41.—*Miscarriages and Stillbirths in 255 Mothers Having a Mongoloid Child*

Age Groups	No.	No. of Mothers Having Miscarriages	No. of Miscarriages before and after Pt.		Total	Percentage
			Before	After		
15–19	4	1	1	0	1	25
20–24	26	5	0	5	5	19.2
25–29	29	7	6	6	12	24
30–34	48	19	21	7	28	39.3
35–39	84	29	42	12	54	29
40–44	56	15	19	1	20	26.9
45–49	8	4	6	0	6	50
Total.....	255	80	95	31	126	31.2

various authors indicate that a percentage of 9.8 pregnancies terminate in spontaneous abortion. In families where a mongoloid child is born, the average for the whole group is 31.2 per cent, with variations from 19.2 per cent to 50 per cent, according to age groups. This indicates a three times higher rate of spontaneous abortions than in the general population. The material of the Lying-in Hospital, Boston, investigated with regard to mongolism by Beidleman, revealed an incidence of 19 per cent abortions, or twice the number of the control group.

The high incidence of abortions has recently led M. Engler to find the "sole cause" of mongolism in a preceding artificial or spontaneous abortion which has caused "a serious alteration of the mucous membrane of the

uterus." The implanted ovum finds pathological conditions which hamper its nourishment. This is a revival of the old nidation theory, with the modification that not chronic but acute changes in the uterine mucosa are the cause. This incidence of previous abortions (in Engler's own material 18.9 per cent), however, is far too low to base a theory of faulty nidation on it. Moreover, the many normal children born after a mongoloid make the uterine nidation theory still less tenable. The frequency of abortions is an important clinical symptom, the interpretation of which will be given later.

Bleedings

3. Probably closely related to the frequent miscarriages is another phenomenon. Many times the mother has observed a continuation of her regular menstruation during the second and third months of her pregnancy which terminated in a mongoloid child. Sometimes bleedings were irregular, or abortion threatened but was prevented through rest. The continuation of menstruation during pregnancy indicates that the endocrine mechanism preventing a uterine bleeding is at fault.

Threatened Abortion. While continuation of menstruation during the first 3 months of pregnancy is otherwise rare, threatened abortion has been carefully studied. The concept of a threatened abortion is not uniform, because some writers consider the occurrence of uterine cramps as a sign of impending abortion. In my study only those cases were recorded where actual bleedings were observed. The percentage was 14.6. Beidleman found an incidence of 23 per cent in the Boston Lying-in Hospital mongoloid material. The figure of threatened abortion is 4 per cent for the same hospital for the general population, according to Rutherford, and 3.8 per cent, according to Paine. Several writers, including Hertig, feel that the percentage is slightly higher in private practice, but even then, a percentage of 14.6 to 23 is again at least three times higher than what one might expect.

Prematurity

4. Table 42 shows the increased incidence of prematurity in mongolism. Of the limited number of cases where I found a definite birth record, prematurity was recorded 44 times in contrast to 12 instances of prematurity in our feebleminded control material. Prematurity is very likely a part of the general disorder which results in a mongoloid child.

Beidleman found in his material a prematurity incidence of 43 per cent in mongoloid babies against 3.2 per cent for all other babies born at the Lying-in Hospital. Twenty-five per cent of the mongoloid babies weighed 5 pounds 11 ounches or less. The incidence of prematurity in mongolism

is, therefore, many times that of the hospital total. In my material, the incidence was 17.2 per cent.

Sterility

5. An item of great interest is the difficulty that the mother has in becoming pregnant. I observed many instances, where the mongoloid was the first or the second child, in which the mother had vainly waited many years for a pregnancy, or an unusually long time had elapsed between her first and her second child. Several times, the waiting period lasted as long as seventeen years. This decreased ability to become pregnant was evi-

Table 42.—*Birth Records of Mongoloid and Control Patients*

	Age Groups							Total
	15–19	20–24	25–29	30–34	35–39	40–44	45–49	
Premature:								
Mongoloid	1	7	3	12	14	6	1	44
Control	1	3	4	2	1	1	0	12
Instrumental:								
Mongoloid	1	5	4	5	7	8	0	30
Control	2	5	5	3	2	5	0	22
Prolonged labor:								
Mongoloid	1	2	1	3	6	6	1	20
Control	1	3	4	1	0	0	0	9
Cesarian:								
Mongoloid	0	0	0	1	1	1	0	3
Control	0	2	1	2	1	0	0	6

dent in several instances before the mongoloid child was born. In many cases fertility was definitely impaired after a mongoloid birth. It is true that quite a number of children are born after a mongoloid and that the loss in fecundity is not absolute, but little attention has yet been paid to how severely the maternal fertility has suffered in cases where a mongoloid child was born in the mother's best years. Of the total of 255 mothers, 162, or 64 per cent, had no children afterwards. Only 1 mother in 3 had a child after a mongoloid. This statement refers to the whole material. The picture is more striking if we consider only those cases where the mongoloid appears near the beginning of the childbearing period. In 17 per cent of our material, the mongoloid was the first child, and in 45 per cent of these cases he remained the only child; in 73 per cent of the cases where the mongoloid was a second child, he remained the last child. (In Lahden-

suu's material 63 per cent of the first-born mongoloids remained only children, and 69 per cent of the second-born mongoloids had no younger siblings.) From the 4 mothers who had a mongoloid child between the age of 15 and 19 years, one had no other child and one had one child only afterwards. Of the 26 mothers of the age between 20 and 24 years, 8, or 30 per cent, remained sterile for the rest of their lives. Of the 29 mothers aged 25 to 29, a total of 16, or more than 50 per cent, remained sterile. These numbers prove beyond doubt that in the majority of cases the birth of a mongoloid child reveals a maternal condition which renders unfit for childbearing afterwards. Since some investigators have tried to explain the drop in the birth rate by assuming that after the birth of a mongoloid child the mother is afraid to have more offspring, I have checked this statement carefully and found it irrelevant for three reasons: 1. In contrast to those striking malformations like hydrocephalus or microcephalus, the mongoloid baby does not appear distasteful and is considered by many as even "cute." 2. In more than half of the material, the mongoloid baby was not recognized as pathologic before several years had elapsed; there was plenty of opportunity for the mother to become pregnant again. 3. Control material of severe malformations (Little's spastic paraplegia, hydrocephalus, microcephalus, and other striking conditions) shows that many of these cases are found in first children and that the majority of parents are not discouraged to have more children afterwards.

New Series of Case Histories

After having collected evidence from that series of 255 families by statistical means that the maternal condition at the time of pregnancy is the decisive factor for the fetal growth disorder, it appeared of interest to find out whether a medical analysis of a new series of cases would yield more evidence as to the specific conditions under which this happens. The last 75 cases which came under observation were investigated by means of a personally conducted special query in which emphasis was placed on those factors which were found of importance in the previous analysis. A brief summary of the data obtained for each case will convey a clear idea of the essential facts. The material can easily be arranged into five main groups.

GROUP I

Women above Forty Years

Case 1. Age 52.* Italian woman, big and stout. Mongoloid is product of eleventh pregnancy. The first 7 children are normal; some are married and have children of their own. Eighth pregnancy ended in a miscarriage; the ninth child died at the

* The age of the mother refers in each case to the age when her mongoloid child was born.

age of 5 months, of pneumonia. The tenth pregnancy ended again in a miscarriage. The eleventh child is the mongoloid. The mother felt different during this pregnancy from the very beginning. She suffered from acidity and vomiting, felt "deathly sick all the time." She did not expect to become pregnant at that age.

Case 2. Age 47. Had 4 children by her first marriage when she was between 23 and 33. She was a widow for five years and married again when 44 years of age. By this second marriage she had 1 child who is intelligent and in good physical health. Menopause occurred at 46, and she had not menstruated for six months when new pregnancy occurred which ended in the birth of a mongoloid. She did not believe she could become pregnant.

Case 3. Age 46. Married in 1923 and did not become pregnant until 1930, when an antiflection of the uterus was straightened out and tubes dilated. She became pregnant after that operation. There was an interval of eight years between the first and second pregnancy, in which time mother did not become pregnant in spite of desire for a second child. Suddenly became pregnant at 46 and gave birth to a mongoloid child. Put on 20 pounds during pregnancy; easily upset.

Case 4. Age 46. Child is product of ninth pregnancy. First 7 pregnancies normal. During the eighth pregnancy mother developed high blood pressure and had to stay in bed for the last seven weeks. After three years became pregnant again, and pregnancy resulted in a mongoloid child. Condition during pregnancy was poor; high blood pressure. Had to stay in bed for four and one half months. Easily upset, anxious, easily fatigued.

Case 5. Age 46. Child the result of thirteenth pregnancy. The oldest daughter is now 32, married and has a child. Two of the siblings died in early infancy, one at 22 months, of acute infection, and one at 9 months, of "teeth trouble." The other children are normal. Last pregnancy before mongoloid ended in a miscarriage in the seventh month. Pregnancy two years later resulted in a mongoloid child.

Case 6. Age 45. Married in 1916. Had 5 children between 1917 and 1927. Five year interval between the last child and pregnancy which resulted in a mongoloid child. Did not want another child. Expected that "family was complete." Plump, rather heavy woman, 170 pounds in weight, and 5 feet 7 inches in height.

Case 7. Age 45. Married in 1926. Six normal children. Two miscarriages. When 45, did not expect a child any more. The last pregnancy resulted in birth of a mongoloid baby. Rather tall woman, 5 feet 10 inches. Weight 165 pounds. Had nervous breakdown at the age of 27 when working hard in school and in stores. Was ill about a year.

Case 8. Age 44. Three children by first husband, ranging from 19 to 15, and 6 children by second husband, all well. Mongoloid child product of tenth pregnancy. Mother sick with renal hypertension and cardiac disease. Nervous, high-strung, easily upset, depressed, and fatigued.

Case 9. Age 43. First child at age of 25. No pregnancy during the last eighteen years. Mongoloid by second husband after that long interval.

Case 10. Age 43. Married in 1919. Three normal children between 1926 and 1930. Mongoloid was born after interval of seven years. Menstruated twice during pregnancy. At second month had a large hemorrhage and loss of blood. It was thought to be a miscarriage.

Case 11. Age 43. Both parents in their forties. Married late, but urgently wanted a child. Mother finally became pregnant, and a boy was born, to the great joy of the whole family. The doctors declared the child "perfect." Not until six months later was it realized that the child was abnormal, although the mother had been suspicious and had consulted several doctors to hear their opinion.

Case 12. Age 42. Married at age of 19. First child at 20. One miscarriage after first child. Was ten years separated from husband, he being in Italy. Had 4 normal children between 1930 and 1935. After seven years, pregnant again, resulting in mongoloid child. Did not expect child, was "careful." Child not wanted. Mother sick all the time during pregnancy. Italian woman, stocky, gallbladder trouble, easily upset, fatigued.

Case 13. Age 42. Married at 29, had 6 normal children between 30 and 39. Three year interval. New pregnancy accepted, but not expected; ended in birth of mongoloid.

Case 14. Age 42. Marriage at 23, 6 normal children between 24 and 39. There were six years between fifth and sixth child, when mother did not become pregnant in spite of opportunity and desire. After three more years new pregnancy occurred which resulted in mongoloid baby. Mother was diagnosed as thyroid deficient with signs of puffiness and low metabolism, two years before her sixth child, when she did not become pregnant. Two grains of thyroid daily since then. Her last child was first diagnosed as cretin; later diagnosis of "cretinism, mongolism" was made in outstanding hospital.

Case 15. Age 41. Married at age of 36. Mongoloid is product of first pregnancy (!) after five years' waiting. There are 3 (!) normal siblings who were born after mongoloid when mother was between 42 and 46.

Case 16. Age 41. Mother married at age of 26. Had 9 normal children between 27 and 38. Two died of internal infections. Mongoloid product of tenth pregnancy. Not expected; accepted, but not wanted. Mother felt tired, depressed, did not feel life of baby. There were two miscarriages between second and third and fifth and sixth pregnancies respectively. Two miscarriages after mongoloid.

Case 17. Age 41. Mother married at 39. Had spontaneous (?) abortion at two months during first pregnancy, when almost 40. Second pregnancy terminated in mongoloid baby. Enlargement of thyroid had been diagnosed two years before marriage, and treated. Had 2 normal children after mongoloid at age of 42 and 43.

Case 18. Age 40. Italian woman, said to be very nervous and excitable. First child at 30. Five normal children between 30 and 38. Mongoloid product of sixth pregnancy. Father out of work, in court for nonsupport. There is 1 normal child after mongoloid. The last 4 pregnancies (8–11) ended in miscarriages.

Case 19. Age 40. First marriage at 18, 1 normal child at 19. Second marriage at age of 31, had 2 normal children in four year interval. Last child, mongoloid, not wanted. Poor health, gallbladder trouble, gallbladder finally removed two months after delivery. Was depressed about three years before birth of mongoloid.

Case 20. Age 40. Married when 29, had 2 normal children at 30 and 32. Had 2 miscarriages, one before and one after her second (normal) child. Did not become pregnant for eight years, no preventive measures taken. Slender woman, considered nervous. Tall, weight 117. Prematurely aged. Lost weight and had metabolism test on account of suspected thyroid disorder.

Case 21. Age 40. Married at age of 20. Had 2 children at 22 and 24 respectively. Interval of eleven years between second and third child. No preventive measures, did not become pregnant. Another interval of four years. Last pregnancy resulted in mongoloid child. Mother stout, heavy, 5 feet 2½ inches in height, weight 170 pounds. Menarche relatively late (17).

Case 22. Age 40. Married at 23, had 8 normal children, ranging from 2 to 18 years. After birth of last child, at 38, 2 miscarriages and no menstruation before pregnant again. Did not expect child at all, which was a mongoloid.

Case 23. Age 40. Married at 31. First child two years after marriage. Child died at 17 months of acidosis (fat intolerance). Had bleedings during the following 2 pregnancies, but children were normal. Next child a mongoloid. Had 1 normal child born two years after mongoloid, when mother was 42. Mother did not expect mongoloid child till she was six months pregnant. Thought to be in menopause. Both parents have to be careful of fat, inclination to acidity. Had liver and gall-bladder trouble. Is high-strung, easily upset, very fatigued, white hair at 50.

Case 24. Age 40. Married at 23. Did not become pregnant for thirteen years in spite of desire. After that period pregnancy terminated in miscarriage. Two normal children at 37 and 38. Last child at 40, mongoloid.

Case 25. Age 40. Married at age of 23. Had 9 normal children ranging now from 24 to 10. During tenth pregnancy, which terminated with birth of mongoloid baby, mother was threatened with abortion at four months. Stayed in bed and hemorrhage stopped. Had 2 more normal children at 42 and 44½.

Case 26. Age 40. Married at 23. Both parents professional people. Mother did not want children as long as professionally busy. After fifteen years of married life, decided to have a child. Pregnancy ended in birth of mongoloid.

GROUP II

Women in Their Thirties

Case 27. Age 38. Married at that time, never before pregnant. No pregnancy afterwards. Stout woman with elephantiatic features, fair intelligence, kind. Father temporarily alcoholic. Mongoloid baby three weeks premature, weight 4 pounds 11 ounces.

Case 28. Age 31. Married in her early twenties. First pregnancy, miscarriage in second month. Second pregnancy, three years after first, miscarriage at six months. Third and fourth pregnancies produced normal children. Fifth child, eleven years afterwards, a mongoloid. One child afterwards. Mother showed tendency to anemia. Prenatal condition poor, high blood pressure, much of time in bed. After mongoloid, operated on for goiter in Lahey Clinic.

Case 29. Age 38. Mother married at about 30. Had 1 child at 31 who is normal and bright. Interval of seven years before pregnant again. Second child mongoloid. Parents superior people. No use of anticonceptional means, but use of "safe times." Pregnancy of mongoloid a few days after menstruation. Mother felt sick all the time, could not eat, felt difference between first and second pregnancy.

Case 30. Age 38. Married at 35. One child at 36, small baby, one month premature. Two years later second pregnancy terminated with mongoloid baby. Next 2 pregnancies ended in miscarriages. Thyroid of mother was noticed to be large. Very high-strung, excitable person, cries easily.

Case 31. Age 30. First pregnancy ended in miscarriage in third month, second in second month. Mongoloid product of third pregnancy. Was threatened with abortion five months before delivery, but child was kept.

Case 32. Age 38½. Married at 28. First pregnancy ended in miscarriage at three months. One normal child at age of 37. One year later severe hemorrhages for several months. Next pregnancy ended in premature birth of mongoloid. Next year again severe hemorrhages. No other child. Thyroid reported enlarged. Was twice operated on for "parathyroid cysts." Easily upset, worries considerably, gets "blue" spells.

Case 33. Age 35. Mother married year before. Mongoloid result of only pregnancy.

Case 34. Age 37. Married at age of 20. Five pregnancies. Two children live and are normal; 3 died, one at 18 of rheumatic fever, and two at 3 months of infections (?). Menarche at 18. Cardiac disease. Ovarial operation. Child not wanted, prenatal condition poor, in bed last three weeks. Mongoloid premature.

Case 35. Age 37. In first marriage 1 child, who died shortly after birth. One miscarriage. Married again at age of 34. Mongoloid is only child, born three years after marriage. No pregnancies afterwards. Mother high-strung, nervous.

Case 36. Age 39. Married at age of 23. First 3 children normal. Two years before mongoloid, miscarriage. Mongoloid came six years after last child. Child wanted previously but mother did not become pregnant.

Case 37. Age 30. Married at 19. First child at 20, normal and well. No pregnancy for four years. Second pregnancy ended with birth of dead baby, "had been dead about 1 month." After eight year interval, new pregnancy which ended with birth of mongoloid. Child "very much desired." Mother 5 feet 1 inch tall, rather attractive, young looking. Weight now 131 pounds. Gained 75 pounds during pregnancy with mongoloid, and weighed more than 180 pounds at that time.

Case 38. Age 30. Married at age of 23. Had 2 normal children. Third pregnancy ended in miscarriage. One year later mongoloid baby. Was threatened with abortion, had menstrual hemorrhages at second and third month. Stayed in bed. After birth of mongoloid again hemorrhages. Two children afterwards, normal. Menstruation irregular, every twenty-one days. Lasts seven days, terrible pains. High-strung, easily upset, very nervous.

Case 39. Age 39. Married at age of 23. Had 3 normal children between 24 and 30. Seven year interval. Last pregnancy ended with birth of mongoloid.

Case 40. Age 34. Married at age of 23. Became pregnant soon after marriage. At six months eclampsia for three weeks. Cesarean section, child died. Did not become pregnant for eight years in spite of desire. Next pregnancy, normal, girl, prematurely born. One year later new pregnancy ended in miscarriage. Profuse menstrual bleedings, treated by x-ray of uterus and ovaries. Two years later new pregnancy terminated in birth of mongoloid. Had continued to menstruate during two periods of the pregnancy.

Case 41. Age 37. Married at 25. Had a normal child at 27. Ten year inteval, which was only partly voluntary. Child desired for quite a time. Second pregnancy ended with birth of mongoloid.

Case 42. Age 31. Married at 22. Six years after marriage, first child. Waiting time partly voluntary. Wanted another child after first, but did not become pregnant for two years. Mongoloid three weeks premature. Menstrual history: menarche at 15, a whole year only twice. Later every second or third month, till shortly before pregnancy with first child. Slender woman, 117 pounds.

Case 43. Age 33. Married at 23. Did not become pregnant till six years after marriage. First child fine. Four year interval. Second child mongoloid. Mother had kidney trouble, hydropelvis. High-strung, easily upset.

Case 44. Age 34. Married at 28. Normal child at 29. Then five year interval. Second child mongoloid. Never became pregnant again in spite of desire. Wanted many children. Menarche at 9. Menopause at 42. Operative removal of uterus and one ovary. Ovarial cyst, uterus fibrosis. Stout, obese woman, prematurely aged.

Case 45. Age 38. Married at 23 in 1926. Had her first child in 1928, a healthy girl. Not pregnant for twelve years in spite of desire to have another child. Second child a mongoloid

Case 46. Age 35. Married at 28 in 1935. First child in 1938, normal boy. Did not become pregnant again until four years later. In third month threatened abortion, in bed for several days. This pregnancy ended in birth of mongoloid.

Case 47. Age 39. Married at 21 in 1921. First child in 1922, second 1928. Did not become pregnant again for eleven years. No contraceptive measures. Child desired. Unexpected pregnancy. Had been in hospital for goiter treatment. Poor condition during pregnancy, lost 30 pounds, vomited all the time. Child was mongoloid.

Case 48. Age 36. Married at 30. First five years without child, first voluntarily, later involuntarily. Was put on thyroid two or three months before first pregnancy. Took thyroid during whole gestation period. First child normal. Had tumor between major and minor labia which was considered malignant and treated with radium. Second pregnancy ended in birth of mongoloid. No thyroid during pregnancy. Third pregnancy a year later ended in miscarriage. A nervous, high-strung woman, frigid. Had hysterical fits before every menstruation.

Case 49. Age 38 Married at age of 30. First baby died at birth. Large baby, birth injury. Three months after birth mother was operated on for tumor of right ovary and tube; appendix removed in same operation. Second child born by cesarean section, when mother started to bleed in seventh month of pregnancy. Last pregnancy ended with birth of mongoloid.

Case 50. Age 35. Married at age of 21 in 1927. Had 2 normal children in 1928 and 1929, respectively. Became blind on account of kidney trouble, edema, eclampsia, with convulsions. Next 2 children, born in 1933 and 1933, were normal. In 1939, mother operated for ovarial cyst. Two years later pregnant with twins. One of twins normal, the other a mongoloid, blind. Three years later mother operated for malignant tumor of ovary.

Case 51. Age 39. Married at age of 23. Had 3 normal children in eight years following her marriage. No pregnancy after third child for four years. Fourth pregnancy ended in miscarriage. Two years later, six years after last living child, new pregnancy, which terminated in birth of mongoloid. Child desired, no contraceptives used between last child and this one.

Case 52. Age 31. Married at age of 21. One normal girl two years later. Next pregnancy eight years later terminated in birth of mongoloid. Child desired for more than five years, but no pregnancy occurred.

Case 53. Age 35. Married at age of 25 in 1928. First pregnancy terminated toxic in 1929. Miscarriage in 1934. The third child, a normal girl, born in 1937. During the last pregnancy, which ended with birth of mongoloid in 1940, mother bled at each menstrual term and stayed in bed. After birth of mongoloid, irregular menstruation.

Case 54. Age 35. First and only pregnancy of 35 year old woman ended in birth of mongoloid. Child "accepted," mother's condition during pregnancy poor. Easily upset, unstable woman, asthma, now divorced.

GROUP III

Women in Their Twenties

Case 55. Age 22. Mother married at age of 19. Soon became pregnant, felt tired, severely depressed. Eight months after first child became pregnant again. Metabolism −20. Took some thyroid. In beginning of fourth pregnancy-month threatened with abortion. Stayed in bed for several days. Mongoloid was born ten days prematurely. Mother allergic to chocolate, dust, weeds and certain foods.

Case 56. Age 28. Married at age of 23. First pregnancy started one month after marriage. Child died five months after birth, of bronchopneumonia. Second pregnancy, six months after this child, ended in miscarriage. Third pregnancy ended in miscarriage one year later. Mongoloid is the result of fourth pregnancy. Had uterine bleedings during this pregnancy. Had 1 normal baby after the mongoloid.

Case 57. Age 20. Married at 18 and had her first child a year after marriage. Next year became pregnant again, child not wanted, but accepted. Vomited every morning. Menstruation had been irregular since birth of first child. At time of pregnancy, when third menstruation was due, had severe hemorrhages, lasting five days. Stayed in bed for two weeks. Pregnancy terminated in birth of mongoloid boy.

Case 58. Age 23. Married in 1931 at age of 18, had her first child, a normal boy, in 1932. Another boy in 1933. Became pregnant again in 1936, used "safe days" in the interval. Her menstruation was irregular and she had severe hemorrhages, lasting seven days, during which time she had to stay in bed. During this pregnancy, which terminated in a mongoloid, she had a threatened abortion in seventh month. Regular pains, beginning of labor. Physician stopped bleedings. Mother's prenatal condition poor, "cried all the time," easily upset, depressed, overworked. At the time of impregnation, had "grippe" and did not expect to become pregnant. Had fourth child in 1939, "fine baby."

Case 59. Age 26. Married in 1937 at age of 22. Menarche at 14, had irregular menstruations between 18 and 24. Became pregnant in 1940, normal child. Very shortly after delivery, before normal menstruation was established, a new pregnancy started. This pregnancy terminated six weeks prematurely in birth of mongoloid.

Case 60. Age 21. Married at 20. Menarche at 11. Had menstrual trouble at 17, severe pains, and ovary cyst was suspected by physician in charge. Had infantile paralysis as child of 6. Child desired. During pregnancy at time of second menstruation slight bleeding. Mother gained 30 pounds during pregnancy, having weighed 125 pounds at the beginning. Mongoloid was born twenty-five days prematurely. Had "flu" in the fifth month of gestation. Her second child, born two years later, is normal.

GROUP IV

Mongolism and Attempted Abortion

Case 61. Age 28. First child at 17, an imbecile of familial type. Second child, two years later, in 1929, said to be normal. After birth of this child, did not want another child. Became pregnant five times between 1930 and 1937. Each pregnancy ended in abortion by curettage. Last pregnancy terminated with birth of mongoloid girl.

Case 62. Age 42. Born in 1898, had goiter in 1926. Tremors, restless, nervous. Married in 1929. Had two normal children in 1930 and 1932, respectively. Eleven months after second child, miscarriage due to shock from being beaten by insane. Next year, miscarriage due to "pills." Six years later, again took pills to interrupt pregnancy, but was not successful. Felt very bad during whole pregnancy, inactive, could not sleep. This pregnancy terminated one week prematurely in birth of mongoloid girl.

Case 63. Age 29. Married at 26. At the age of 22, mother had a "nervous breakdown." When she became pregnant, she did not want to go through with pregnancy. Took ergot pills, but no bleeding resulted. Gave birth to a mongoloid. A year later, became pregnant again and gave birth to a normal child.

Case 64. Age 43. Married at 17 for the first time and gave birth to normal girl at 18. Four years later had artificial abortion. Married at 42 for second time. When pregnant, went to doctor to get rid of baby. Gave some injections, which resulted in short hemorrhage. Pregnancy resulted in birth of a 4 pound mongoloid boy.

Case 65. Age 20. Attractive girl, "crazy for sailors." Previous abortions suspected. Illegitimate child, not wanted, was mongoloid. Attempted abortion suspected.

Case 66. Age 30. Married at 19 in 1922. Had 3 normal children between 1923 and 1932. A few months after birth of third child became pregnant again. Took "pills" unsuccessfully. Child not wanted. Pregnancy terminated in birth of mongoloid boy. Next year again pregnant. Took pills and bled for three or four weeks. Pregnancy ended in miscarriage in third month.

Case 67. Age 28. Married at 20 in 1935. Had 4 normal children between 1936 and 1941. When again pregnant, two years later, took pills for several weeks. Child not wanted. Pregnancy terminated about a week prematurely with birth of mongoloid boy.

GROUP V

Unexplained Cases

In about 10 per cent of the material, information was not satisfactory. These cases remain unexplained. Analysis of the case histories shows either that the history was taken by a person not thoroughly familiar with the problems involved or that the relatives of the child were reluctant to give a full account. There remain other cases where one cannot hope to obtain all data without metabolic and biochemical studies of the mother.

No one who glances through the series of case histories above can escape the conclusion that the cause of mongolism is to be found in the condition of the mother at the beginning of pregnancy.

The Causes of Ill-Finished Children

Many investigators have been interested in the varying causes of mongolism. Brousseau was able to obtain definite data concerning the health of the mother in 376 cases and found in 179, or 47 per cent, that the mother had been in ill health. Goddard goes so far as to state that "the sole and adequate cause of mongolian imbecility is to be sought in the condition of the mother during pregnancy." A rather large number of investigators feel that thyroid deficiency is of importance. Clark, Stoeltzner, Myers, Alt, DeSanctis, Schob, Abderhalden, and Vas express the opinion that either hyperthyroidism or hypothyroidism of the mother may account for the production of mongolism. Myers, in a study of 215 mongoloid cases and 215 controls, states, "Some abnormal condition in the mother during pregnancy was reported in more than twice as many of the mongolians as the control mothers. An analysis of this difference in the health of the mother revealed a greater frequency of recognizable thyroid disorders (9 to 1) and of acute nervous excitement (13 to 1)."

Another explanation for the mongoloid deformity was offered by van der Scheer, in 1927. This author concluded that (1) "a too narrow amnion prevents or inhibits the physiologic stretching of the embryo in the sixth or seventh week of pregnancy, and (2) anomalies in the structure of the uterus are the cause of the abnormal amnion sac." This theory, called the "nidation theory," explains the great variety of deformities on the basis of mechanical factors. It is hardly necessary to repeat the numerous arguments which make it impossible to accept such a mechanical explanation. Knowledge of the physiology of pregnancy has increased so greatly in the last decades that we know that such delicate biochemical reactions take

TABLE 43.—*Summary of All Causes*

	Number of Instances	Incidence Percentage
Actual cessation of menstruation (menopause)	9	12.1
Inability to become pregnant (involuntary long intervals)	22	29.2
Old primiparas	4	5.3
Habitual abortions	7	9.3
Numerous artificial abortions	2	2.6
Attempted abortions	7	9.3
Continuation of menstruation and threatened abortions	11	14.6
Thyroid deficiencies and goiter	10	13.3
Ovarial cysts and operations	6	8.0
X-ray or radium treatment of uterus and ovaries	2	2.6
Gallbladder	3	4.0
Heart diseases	2	2.6
Depressive states	5	6.6
Kidney trouble	3	4.0
One of twins	1	1.3
New pregnancy immediately after another child	1	1.3
Unusual weight gain during pregnancy	1	1.3
No explanation	8	10.6

place in pregnancy that the diversity of malformations seen in mongolism cannot be laid to so simple a common denominator as a narrow amnion sac. Moreover, some of the malformations date back to an earlier time than the sixth or seventh week, and those disorders take place at a time when mechanical pressure of the membranes is of no significance whatsoever.

The 75 case histories offered above make it possible to analyze the conditioning factors much more precisely than was possible before. Table 43 summarizes all causes found in the material regardless of age. In several instances, of course, more than one factor was present.

Nine women, or 12 per cent of all cases, but 33 per cent of the women above 40, showed actual cessation of menstruation before the pregnancy

which resulted in a mongoloid child. The most impressive factor of all is the inability to become pregnant which manifested itself in involuntary long intervals between pregnancies. These intervals, ranging from more than five to eighteen years, occurred in spite of the desire of the parents to have a child. Twenty-nine per cent showed this inability. The factor of next greatest importance is the continuation of menstruation and threatened abortion during pregnancy which resulted in a mongoloid child; 14.6 per cent of the cases showed this phenomenon. The continuation of menstruation and the bleedings during pregnancy are certainly not the cause of mongolism, but they are significant in indicating that the mechanism preventing uterine bleedings was at fault. This factor is further exemplified by the inclination to habitual abortions which was found in 9.3 per cent of the material.

The prenatal maternal factors have been the subject of another investigation by the author during the last two years. The new observations confirm the previous material and provide still more evidence as to specific data. Of the women above 41 years of age, 53.9 per cent were actually in the menopause or showed evidence of approaching menopause by irregularities of menstruation; 92 per cent had an interval of 4 to 16 years between the last 2 pregnancies. In the maternal age group of 31 to 40 years, 47.6 per cent showed menstrual irregularities like those usually seen in the menopause; 81 per cent had an interval of 3 to 12 years between the last 2 pregnancies; 48.8 per cent had bleedings during pregnancy, 38.5 per cent had thyroid trouble and 63.5 per cent had a history of uterine and ovarial dysfunction. In the maternal age group of 21 to 30, a long interval was found in 46 per cent, and 38.5 per cent had bleeding during pregnancy and thyroid disorders. In this group, the incidence of previous abortions was also 38.5 per cent. In a group of women 18 to 20 years of age, more than one-half of them had menstrual irregularities before they became pregnant and had also bleedings during pregnancy. Most outstanding in this new study is the high incidence of thyroid disorders (38.5 per cent) in the younger age groups. This observation is the more important as the advanced age group did not reveal such a high percentage. This suggests a relationship between thyroid disorders and mongolism which has been confirmed by Myers in a study of the geographic distribution of mongolism in the Province of Ontario, Canada.

The material indicates that potentially, under certain conditions, every mother can give birth to a mongoloid child. If the families recorded above had not had a mongoloid among their children the group as a whole would certainly represent a sample above average in intelligence, health, and fertility. No one can, therefore, construct a theory of hereditary inferiority

or constitutional factors as such. The factors which condition the development of a mongoloid child, although varying to some degree, seem to be uniform in the one result that they interfere with the endocrine environment of the fetus. The inadequacy of the hormonal environment of the fetus is borne out by many indications.

The material at hand suggests that the inner secretory response to a pregnancy is at fault. Fertilization puts a heavy tax upon the maternal organism which is met through a number of quick adjustments and changes

TABLE 44.—*Chief Demands of Pregnancy upon Endocrine Environment of Maternal Organism*

Pit.: Pituitary: Development of "pregnancy cells"
Increased production of
1. Growth hormones
2. Adrenocorticotropic hormone
3. Thyrotropic hormone
4. Gonadotropic hormone
5. Luteinizing hormone (L.H.)
6. Glycotropic hormone

Th.: Thyroid: Thyroxin
1. Direct influence upon growth of embryo
2. Indirect: maintenance of maternal metabolism
3. Action upon ovary?
4. Action upon adrenals?

Ad.: Adrenals:
1. Cortical influence upon sex differentiation
2. Gluconeogenesis
3. Metabolic action

O.: Ovary: Estrogenic substances

C.L.: Corpus luteum: Progesterone (pregnanediol)
Influence upon growth

U.: Uterus

P.: Placenta
1. Estrogenic substances
2. Gonadotropic hormone
3. Progestin

in the endocrine environment. In Table 44 the chief demands of pregnancy upon the endocrine environment of the maternal organisms are mentioned. Some of the finer adjustments of the endocrine system are not yet fully understood; it may be pointed out that with every week of pregnancy the balance between the various endocrine organs changes. Immediately after fertilization, before the placenta is fully developed, the corpus luteum is of special importance and its proper function is an essential factor for preventing abortion and guaranteeing a proper development of the fetus.

In the last two thirds of pregnancy, the placenta seems to take over numerous endocrine functions and the importance of the corpus luteum is decreased. It is known that faulty corpus luteum function is one of the main causes of abortion in the first part of pregnancy. This is primarily due either to dysfunction of the ovary or to insufficient production of the L.H. action of the pituitary. The pituitary reacts to a pregnancy through development of the so-called "pregnancy cells," which are thought to produce some of the essential growth hormones (Erdheim). It is probable that in mongolism either the maternal pituitary or the corpus luteum itself is at fault. We have overwhelming evidence that the mongoloid child occurs mainly on the threshold of hormonal sterility, and one may call this "ill-finished child" the unfortunate survivor of a threatened abortion.

The hormone metabolism of pregnancy has become a subject of increasing interest and a great amount of data has been collected. The excretion of estrogenic compounds increases steadily during pregnancy. Measured in the urine, the excretion is about 100 times higher at the end of pregnancy than in a nonpregnant menstruating woman (Zondek). Concentration in the blood rises from a normal level of 25 rat units to 50 units according to Frank, while Zondek reported a rise up to 1000 units at the time of term. The source of estrogenic substances is the placenta, but in addition, several other organs seem to contribute to it. Smith and co-workers came, therefore, to the conclusion that the general cholesterol metabolism was possibly the source of estrogenic compounds. A remarkable increase is also noticed in the production of progestational hormones (pregnanediol), the excretion of which rises from about 5 mg. per 24 hours to about 18 mg. at term. Most impressive is the rise in gonadotropic hormones which are excreted in the urine.

All these hormones are kept in a delicate balance and if one is too powerful or another too weak, the balance is disturbed and bleedings and abortion occur. Weakness of corpus luteum hormone is a frequent cause of abortion, but on the other hand too powerful estrogenic substances have the same effect. The responsiveness of the uterus to these hormones undergoes a permanent change and balance is kept by the presence of vitamin E which introduces another influence of great importance.

Evan Shute has gone a step further in analyzing the biochemical changes leading to miscarriages and found that

> a large percentage of patients who miscarry or are prematurely delivered show an excess of an estrogenic substance in the blood serum. This produces a resistance in that blood serum to its digestion by such a proteolytic enzyme as trypsin. This resistance disappears from the maternal blood stream upon administration of an adequate quantity of fresh vitamin E. There is a reasonable basis for the theory that in the blood serum of women in whom pregnancy is spontaneously interrupted

at any time prior to term, a relative or absolute deficiency of vitamin E has permitted an estrogenic substance to acquire a dominant position.

We have seen that mongolism occurs under the same conditions as abortion, threatened abortion, prematurity and hormonal sterility. We have further seen that there are indications of thyroid and pituitary deficiency. Although the exact mechanism of the deficiency resulting in congenital acromicria of the baby is still a matter of speculation, the facts at hand are sufficient to narrow the possible causes to a small number of factors and to proceed with a constructive program of preventive obstetrics.

BIBLIOGRAPHY

Bauer, A.: Über die Ätiologie des Mongolismus an Hand der bisherigen Ergebnisse der Zwillingsforschung. Arch. f. Kinderh. **90:** 169, 1930.

Beidleman, Barkley: Mongolism: A Selective Review Including an Analysis of Forty-Two Cases from the Records of the Boston Lying-In Hospital. Am. J. Ment. Def. **50,** 35, 1945.

Benda, Clemens E., Dayton, N. A., and Prouty, R.: On the Etiology and Prevention of Mongolism. Am. J. Psychiat. **99:** 822, 1943.

——: Prenatal Maternal Factors in Mongolism. J. A.M. A. **139:** 979, 1949.

Bennholdt-Thomsen: Über den Mongolismus und andere angeborene Abartungen in ihrer Beziehung zum hohen Alter der Mütter. Ztschr. f. Kinderh. **53:** 427, 1932.

Bleyer, Adrien: Rôle of Advanced Maternal Age in Causing Mongolism. Am. J. Dis. Child. **55:** 79, 1938.

Bodansky, M., and Bodansky, O.: Biochemistry of Disease. The Macmillan Co., New York, 1944.

Crookshank, F. G.: The Mongol in Our Midst. Dutton, New York, 1931.

Dayton, Neil: Order of Birth and Size of Family. Am. J. Psychiat. **8,** 1929.

Doxiades, L., and Portius, W.: Aetiologie des Mongolismus. Ztschr. f. menschl. Vererb. u. Konstitutionslehre. **21:** 384, 1938.

Engler, Marcus: The Causation of Mongolism and Its Prognosis. Proc. Roy. Soc. Med. **38:** 211, 1944.

Fanconi, G.: Die Mutationstheorie des Mongolismus. Schweiz. med. Wchnschr. **69:** 82, 1939.

Frank, R. T.: Sex-Endocrine Factors in Blood and Urine in Health and Disease. J. Am. Med. Assoc. **104:** 1991, 1935.

Halbersma: Über Mongoloide Idiotie. Nederl. tijdschr. v. geneesk., 1922.

Heberer, Heinrich: "Die Superfecundatio beim Menschen". Dtsch. Med. Wchnschr. **74:** 417, 1949.

Ingalls, Theodore H., and Davies, J. A. V.: Mongolism following Intercurrent Infectious Disease in Pregnancy. New England J. Med. **236:** 437, 1947.

Jervis, George: Mongolism in Twins. Am. J. Ment. Def. **47:** 364, 1943.

Lahdensuu, Sakari: Über Vorkommen und Ätiologie der Idiotia mongoloidea im Lichte des in Finnland gesammelten Materials. Acta Pædiat. **21:** 256, 1937.

MacKaye, L.: Mongolism in Non-identical Twins. Am. J. Dis. Child. **52:** 141, 1936.

Macklin, M. T.: Mongolian Idiocy. Am. J. Ment. Sc. **178:** 315, 1929.

Penrose, Lionel S.: Relative Effects of Paternal and Maternal Age in Mongolism, J. Genetics **27:** 219, 1933.

Penrose, Lionel S.: Relative Aetiological Importance of Birth Order and Maternal Age in Mongolism. Proc. Roy. Soc., London, **115:** 431, 1934.

Rosanoff, Aaron J., and Handy, L.: Etiology of Mongolism with Special Reference to its Occurrence in Twins. Am. J. Dis. Child. **48:** 764, 1934.

Russell, P. M. G.: Mongolism in Twins. Lancet **1:** 802, 1933.

Schulz, B.: Zur Genealogie des Mongolismus. Ztschr. f. d. ges. Neurol. **134:** 268, 1931.

Shute, Evan: Resistance to Proteolysis Found in the Blood-Serum of Aborting Women. J. Obst. & Gynec. Brit. Emp. **42:** 1071, 1935.

Shute, Evan: Anti-Proteolytic Properties of Human Blood-Serum in Cases of Miscarriage and Premature Labour. J. Obst. & Gynec. Brit. Emp. **44:** 253, 1937.

Smith, G. van S., and Smith, O. W.: Observations Concerning the Metabolism of Estrogens in Women. Am. J. Obst. & Gynec. **36:** 769, 1938.

Smith, G. van S., and Smith, O. W.: The Quantitative Determination of Urinary Oestrin. Am. J. Physiol. **112:** 340, 1935.

Smith, G. van S., and Smith, O. W.: The Urinary Excretion of Estrogenic and Gonadotropic Hormones during Menstrual Cycles, the Period of Conception and Early Pregnancy. New England J. of Med. **215:** 908, 1936.

Smith, G. Van S., Smith, O. W., and Pincus, G.: Total Urinary Estrogen, Estrone and Estriol During a Menstrual Cycle and a Pregnancy. Am. J. Physiol. **121:** 98, 1938.

Van der Scheer, W. M.: Multiple Cases of Mongolian Idiocy in a Family. J. A. M. A. **72:** 1114, 1919.

Zondek, B.: Die Hormone des Ovariums und des Hypophysenvorderlappens. Berlin, 1931.

CHAPTER XI

PREVENTION OF MONGOLISM

Preventive Obstetrics

To those who are not very familiar with mongolism, the idea of preventing this condition seems far beyond reach. If mongolism occurs in two to three births among a thousand, how can it be possible to predict those few instances? Mongolism occurs in the rich and the poor, the old and the young, the intelligent and those of limited mental capacities. It seems to happen without any rule, "out of the blue sky." How can a busy obstetrician predict who of his many patients may be a future mother of a mongoloid?

Mongolism as a congenital deficiency disease is not likely to be entirely ameliorated in postnatal life, even if future pharmacological development brings about new and better endocrine medication. The main goal will, therefore, always remain the prevention of the development of mongolism in the unborn baby.

What means are available to determine a pathological pregnancy? If the facts on mongolism are thoroughly analyzed, it is evident that mongolism is conditioned by a number of circumstantial factors which repeat themselves with surprising monotony. One has only to read the 67 case histories, one after another, to realize that the symptoms which can be observed are alarming enough to draw attention to the possibility of an abnormal pregnancy. In each instance the case history has to be studied by the experienced physician himself. No routine questionnaire will suffice. In the following I shall analyze each factor which ought to be considered.

Age

It is beyond argument that age is an important factor which narrows considerably the number of possible mongoloid pregnancies. We may soon be able to discover pending mongolism in a 46 year old pregnant woman, but it will be a long time before such a case can be spotted in a group of 20 year old primiparas.

The frequency of mongolism in relation to the age of the mother is demonstrated in statistics prepared by Bennholdt-Thomsen. This shows readily how the percentage of mongoloid births increases with age.

Table 45 shows that a physician or a maternity clinic may see 1,000 patients between 20 and 24 years of age before a single case of mongolism is encountered. But among 100 pregnant women of 45 to 47, more than

12 will have a mongoloid child, and if the age approaches 50, the number of pathological pregnancies will reach a percentage of more than 25.

There are many normal and fine children born to mothers beyond 40 years of age, and some are born even after a mongoloid child. Age is, therefore, not the essential factor in itself. It merely helps to condition a pathological pregnancy by the physiological aging of the maternal organism, which will function on a lower level of vitality than it did twenty years before. Investigators who have too much trust in statistics forget that statistics obliterate the individual differences and are likely to obscure certain important facts. The woman who has a mongoloid in her forties is usually a different woman from one who has a mongoloid at 31. The former may be the mother of a whole number of fine, average youngsters; she is the Mrs. Hardy one may meet anywhere, any time. Every woman in her middle forties is a potential mother of a mongoloid. But the woman

TABLE 45

	Maternal Age, Yrs.					
	20–24	25–29	30–34	35–39	40–44	45–47
Percentage of mongoloid births	0.082	0.152	0.236	0.857	4.242	12.5

who has a mongoloid at 31 is usually a different case. She is not likely to have many children afterwards, although she may have one or two. If she had a large number of children before, she is now, in her thirties, already worn out and likely to have many complaints and ailments.

Age is the only factor in those instances where a pregnancy occurred in the initial stages of menopause. Otherwise, the case is "without explanation." In other cases, two, but in the majority of cases three or more, factors could be discovered which had created the conditions for an abnormal pregnancy. The patterns of conditioning are of importance and must be remembered if one is to succeed in discovering impending mongolism.

Order of Birth

Statistically, a first-born mongoloid counts the same, regardless of whether his mother is 42 or 22, but from a biological point of view there is much difference. In the former case it is of significance that a woman more than 40 years of age had no child before and her first pregnancy occurred at that time terminating with the birth of a mongoloid. In a young woman the fact that there were no children before has to be expected and is, therefore, statistically insignificant. If we analyze the case histories according to age groups, with the viewpoint of prevention in mind, what are the out-

standing factors in mothers of mongoloids of that group? We see that a considerable number had many children (five to twelve), which is more than one expects in a society where two or three children are the average. The time and again repeated story in these large sized families is that a woman, having had so many children, has one or two miscarriages and finally enters menopause expecting that her family is "complete." She

TABLE 46.—*Women in Their Forties and Fifties*

Constellation of factors present during pregnancy which terminated in birth of mongoloid child

No.	No. of Pregnancies Before	Previous Abortions	Threatened Abortions	Menopause	Long Interval	Deficient Thyroid	Health during Pregnancy
1	7	+		+			Poor
2	5			+			
3	0			+	+		
4	8				+		High blood pressure
5	12	+					
6	5				+		
7	6	+		+			
8	9						Renal hypertension
9	1				+		
10	3		+		+		
11	0				+		
12	5	+			+		Poor
13	6				+		
14	6				+	+	
15	0				+		
16	9	+					Poor
17	0	+	+			+	
18	5						Poor
19	3		?		+		Gallbladder trouble
20	2	+			+	+	
21	3				+		
22	8	+		+			
23			+	?			Liver, gallbladder trouble
24	2	+			+		
25	9		+				
26	0				+		Poor

suddenly becomes pregnant against expectation, is in poor health, has some bleedings, but pregnancy continues. Poor health may consist in high blood pressure, kidney or heart trouble, or unspecific complaints of being tired and worn out. Obviously, this is the woman who has to be observed with watchful attention and has to be subjected to further studies.

The second type among the women in their forties is the woman who had

no child before, the aged primipara, or the mother who had a few children many years ago (five to eighteen year interval), and who finds herself suddenly confronted with a pregnancy. This patient may have married late in life and now wants a child or had children from a previous marriage many years ago. She is now married for the second time and wants to give her second husband a child of his own. It may be said that most mongoloids are wanted children, but some just occur against every expectation. These cases fall into the category of "women with long intervals." I made these intervals the subject of a special inquiry and found that the intervals were involuntary in most instances. These women do not become pregnant in spite of their desire. Some investigators believe that in the preclimacteric period, a sudden rise in susceptibility occurs, owing to increased estrogen production before the cycle ceases. Some women of my material have waited in vain all their lives until impregnation took place in that critical period.

In Table 46 the factors are presented which were present in addition to advanced age. As will be seen, the first three cases were actually in the menopause and pregnancy took place against expectation. In some of the cases around the age of 45, menstruation was still regular, but the women had had no children for a long time. We find both categories, (1) the woman with many children, the mongoloid being the last in a long line, and (2) the woman without a child, or with one or two, but fifteen to twenty years ago.

If these few items are observed closely, the physician will have a hint as to those cases in which the prenatal care should exceed the dietary and gynecological management and should be extended to a careful endocrine examination.

In summary, the most outstanding factors which were found in the first group (women in advanced age) are habitual abortions, threatened abortion, menopause, and previous inability to become pregnant, which lasted more than three years. This long interval was not necessarily found directly before the last pregnancy, but may have been present during the prime of life.

Women in Their Thirties

It is to be expected that the prospective mongoloid mother in her thirties is a different woman from the one who has a mongoloid child in her forties. In this age group, the most outstanding factor is the inability to become pregnant. Seventeen of 27 mothers, or 63 per cent, gave this history. If we add that most of these women previously had one or more abortions, and that in addition the pregnancy which terminated in the birth of a mongoloid was threatened by abortion, then we see that the mongoloid is

born under conditions which may be recognized in advance. These mothers are known to every obstetrician as the women with habitual abortions and inability to have children.

TABLE 47.—*Women in Their Thirties*

Constellation of factors present during pregnancy which terminated in birth of mongoloid child

No.	First Pregnancy	Habitual Abortions and Miscarriages	Long Involuntary Interval	Thyroid Disorder	Threatened Abortion	Gestation Period	Ovarial Cyst
27	+						
28		+	+			High blood pressure	
29		Conception during menstruation	+			Poor	
30		+		+			
31		+			+		
32		+		+			
33	+						
34						Cardiac disease	+
35		+	+				
36		+	+				
37		+	+				
38		+			+		
39			+				
40		+	+		+		
41			+				
42			+				
43			+			Kidney disease	
44			+				+
45			+				
46			+		+		
47			+	+			
48			+	+		X-ray treatment	
49					+		+
50						Kidney trouble	+
51		+	+				
52			+				
53		+			+		
54	+						

It may not be mere chance that of all further factors which repeated themselves, we find thyroid disorders (hypothyroidism) mentioned four times and ovarial cysts or ovarial "trouble" mentioned another four times. Bad health during pregnancy was no significant item.

Women in Their Twenties

Studying the six case histories of women who gave birth to a mongoloid in their twenties, one item is most striking—the frequency of threatened abortion. It can hardly be a mere coincidence that five pregnancies of six were threatened with termination by spontaneous abortion. It may also be noted that in this group, and only in this group, three women gave a history of having had considerable difficulties with their menstruation before they became pregnant. Most of the mongoloids born in this group were first children. It is suspected that the "threshold of sterility," in this group, is due to physiological immaturity of the mother, whose organism was not yet prepared for pregnancy.*

TABLE 48.—*Women in Their Twenties*

Constellation of factors present during pregnancy which terminated in birth of mongoloid child

No.	Previous Abortions	Threatened Abortions	Thyroid Disorder	Health during Pregnancy	History of Irregular Menstruation
55		+	+		
56	+	+			
57		+			
58		+		Poor	+
59					+
60		+		Poor	+

I mentioned that most of the mongoloids are very much desired children and that, therefore, attempted abortion is not a significant item. I added, however, a group of seven cases in which such a history was given. There can be little doubt that the unsuccessful attempt to interrupt a pregnancy may lead to uterine bleedings and placental thrombi which interfere with the fetal circulation and nutrition.

In a few cases the history indicated that pregnancy occurred immediately after abortion or childbirth, before the regular cycle was restored. These cases add evidence to the theory that insufficient progestational preparation of the uterine mucosa is of some importance as a factor in mongolism, but the cases do not permit us to establish a theory of abnormal nidation as the cause of mongolism.

* In the last half year several more instances of mongolism in first children of mothers in their teens or early twenties were observed. Menarche was sometimes delayed but usually normal. There was, however, always a period of irregular menstruation previous to the pregnancy terminating in mongolism.

The facts presented above and in the preceding chapter offer evidence that the mother of a mongoloid is an "endocrine case" herself. The many aspects of the case histories add up conclusively to a concept of hormonal "threshold of sterility."

The literature on spontaneous abortions and pathological conditions of pregnancy abounds. It is generally agreed that the corpus luteum is responsible for progestational proliferation of the endometrium, necessary for the implantation, nutrition, and development of the embryo, and that persistent corpus luteum activity protects the pregnancy until the function is taken over by the placenta. This change takes place between the end of the second month and the beginning of fourth month of gestation. This period of transition is considered as the most critical of pregnancy. Since the fate of the mongoloid seems to be sealed as early as in that critical period, it is safe to assume that abnormal corpus luteum function is one link in the chain of abnormal events. I am inclined, however, not to think that corpus luteum inefficiency represents the whole story. Corpus luteum activity is due to pituitary-thyroid-adrenal action. Hypothyroidism, for instance, which is so frequently observed in mothers of mongoloids, is another item in the endocrine condition which results in and is caused by "exhaustion."

Van den Berg has expressed the idea that "a cretin inherits a thyroid with a generating capacity so low that the physical and mental development is inhibited to a degree that is very obvious. There are also those who inherit a thyroid with the generating capacity lowered just enough to make the starting of the machinery a bit slow and laborious and to hinder it from zooming along with ease."

There is sufficient evidence that frequent pregnancies are likely to bring about a subclinical hypothyroidism which is latent, but effective enough to slow down the endocrine response to fertilization. Pregnancy will greatly increase potential hypothyroidism.

Since mongolism is a congenital hypopituitarism and the endocrine balance of pregnancy depends upon maternal pituitary regulation, hypopituitarism of the mother may be expected to be the most important factor.

In obstetrical terms (which so readily border on cynicism) the mongoloid is "a salvaged abortion." Modern obstetricians and endocrinologists consider "fetal salvage" a major problem of preventive obstetrics (E. Allen), while the neuropsychiatrist looks with some apprehension at the increasing number of mongoloids reported by different sources. The problem ahead is, therefore, a clearer conception of the fact that mere salvage of a pending abortion is not enough in many cases. If abortion and threatened abortion are due to corpus luteum deficiency alone in an otherwise healthy mother, it seems perfectly safe to save the fetus, but if more factors are present

which aggravate the situation, the maternal condition has to be examined with more care.

The question of a possible increase in abnormal children has been studied by a number of obstetricians. Although the number of observations is still small, they have come to the conclusion that such a danger does not exist. It is obvious that the mothers of a prospective mongoloid are patients who consult their obstetricians for similar difficulties. My material does not indicate that these mothers had been treated for pending abortion, except by bed rest and sedatives. If sufficiently large material is available for statistical calculations, it will be of great interest to see whether treatment with corpus luteum hormones is able not only to save an abortion, but to prevent the development of a mongoloid child. Although the benefits of prevention are less conspicuous than the successful treatment of a disease, such a triumph of preventive medicine should rank among the major achievements of science.

Tests

The material at hand gives clear indication as to who must be studied during the period of prenatal care. Such a study should include all tests which offer opportunities of discovering latent hypothyroidism, hypogonadism, and hypopituitarism.

Not every woman needs to undergo a series of biochemical tests and it can, therefore, be not avoided that some mongoloid children will be born to mothers in their twenties and early thirties. If, however, the history indicates the probability of an abnormal pregnancy, a number of tests may discover the essential disorder and provide means for a rational substitute therapy. Starting with routine tests on the oldest patients it should be possible to collect material within a few years which would permit us to discover pending mongolism in the embryo with accuracy.

Basal Metabolism. The B.M. rate is increased during pregnancy varying from +4 per cent to +35 per cent just before delivery. Several mothers, who have borne mongoloid children, had metabolic tests before they became pregnant and were found to be definitely on the minus side. Since pregnancy puts a heavy tax upon thyroid function which has to be met with greatly increased output, metabolism tests are indicated and should be repeated in monthly intervals.

Cholesterol determination is not only indicated by the relationship between cholesterol level and thyroid function, but the role of cholesterol metabolism as a source of estrogenic compounds emphasizes further the importance of such a test.

Sugar metabolism and mineral metabolism have also to be checked.

Of great scientific interest as well as practical importance is the delicate

balance between estrogenic substances, pregnanediol and vitamin E which should be carefully studied.

E. Shute's test for proteolysis promises to render important information through a rather simple procedure which can be easily adopted by any laboratory. Quantitative determinations of fractions of the various hormones are still limited to a few laboratories prepared for such a task, but the near future may bring sufficient advances to organize such a service on a broad basis. This is already true for the simpler pregnancy tests and determination of gonadotropic hormones. Determination of 17-ketosteroids is a matter of routine in many laboratories.

In one of my patients an x-ray picture of the pelvis happened to be taken two weeks before delivery. Although the outline of the fetus does not permit the diagnosis of mongolism, the hypoplasia and immaturity of the fetus is clearly recognizable by the small head. X-ray may, therefore, become of practical importance during the last month of pregnancy to find out, at least, what may be expected.

Besides all the theoretical interest, such a program of extended prenatal care would bring many women with latent hypothyroidism, hypopituitarism and hypogonadism to medical attention and treatment. The role of vitamin E deficiency is hardly sufficiently recognized. This vitamin has probably a more important role during gestation than some of the others which are routinely provided, sometimes in excess with harmful effects.

Detection of a pending mongoloid pregnancy confronts the physician with a number of difficult decisions. No general rule can be given. I would doubt that it is advisable to save a fetus in an unexpected pregnancy with threatened abortion, in a woman within or near her menopause, although there is no doubt that normal children may be born at that time. A closer co-operation between endocrinologist and obstetrician in the prenatal care will provide exact means for differentiating the various endocrine deficiencies and will help the obstetrician to decide which pregnancy can be safely continued.

BIBLIOGRAPHY

Allen, Edward: A Report on Sequential Abortion. Am. J. Obst. & Gynec. **46:** 70, 1943.

Collins, C. G., Weed, John C., and Collins, Jason H.: The Treatment of Spontaneous, Threatened or Habitual Abortion. Surg., Gynec. & Obst. **70:** 783, 1940.

Falls, F. H.: The Use of Progestin in Obstetrical Complications. Illinois M. J. **76:** 507, 1939.

Hertig, Arthur T., and Livingstone, Robert G.: Spontaneous, Threatened and Habitual Abortion: Its Pathogenesis and Treatment. New England J. Med. **230:** 797, 1944.

Lubin, Samuel, and Waltman, Richard: The Use of Synthetic Vitamin E in the Treatment of Abortion. Am. J. Obst. & Gynec. **41:** 960, 1941.

Mason, Lyman W.: Spontaneous Abortion and its Treatment with Progesterone. Am. J. Obst. & Gynec. **44:** 630, 1942.

Paine, A. K.: Pathology of Embryo and Abortion. Am. J. Obst. & Gynec. **43:** 245, 1942.

Shute, Evan: Resistance to Proteolysis Found in the Blood Serum of Aborting Women. J. Obst. & Gynec. Brit. Emp. **42:** 1071, 1935.

Shute, Evan: Anti-Proteolytic Properties of Human Blood-Serum in Cases of Miscarriage and Premature Labour. J. Obst. & Gynec. Brit. Emp. **44:** 253, 1937.

Van den Berg, Henry J.: Prevalence of Mild Hypothyroidism with a Normal Metabolic Rate. Tr. Am. A. Study Goiter, 1941.

CHAPTER XII

PRINCIPLES OF TREATMENT

Mongolism

Prognosis

The data presented in this book indicate that the mongoloid newborn has suffered from a deceleration of the fetal growth rate, which prevented the unborn child from reaching full physiologic maturity at the time of birth. The newborn shows evidence that he is not ready to lead an independent life outside of the maternal organism. Many mongoloid newborn die, some apparently unrecognized, of heart defects or with the diagnosis of "pre-maturity." The surviving usually progress very slowly after birth and even lose ground. If we study the developmental rate in the mongoloid infant and child, we may see that it is about 30 per cent of the norm. Rarely does the mental and physical growth rate step up to more than 50 per cent of the normal.

Most physicians still consider the mongoloid child as a kind of unique specimen for whom nothing can be done. They do not realize that mongolism is a deficiency disease which needs attention and treatment. Time and again the statement is made that treatment is unsuccessful and that the mongoloid child cannot be improved. Some give thyroid, half-heartedly, for a month or so, one-tenth of a grain, and then give up, stating that they have done everything and thyroid is of no use. Few physicians have ever attempted to treat mongolism from birth on, and to continue treatment over many years in a similar way as the cretin is treated by substitute endocrine therapy. Those physicians who have treated mongoloid children, even of older ages, have often seen unmistakable changes and have been quite satisfied with the results. Parents usually soon recognize the change which takes place in the mongoloid child under treatment. For the last eight years, the author has been treating a number of infants and children as early as possible after birth and the changes which result are encouraging enough to insist on an attitude that the mongoloid infant deserves medical attention as a patient with a specific growth deficiency. The "all or nothing" attitude of some pediatricians toward the treatment of mongoloids is not justified. There are many other conditions where only partial success can be expected, and yet every effort is made to achieve any improvement, no matter how small. Medicine can only progress step by step, and many experiments are needed to reach the final goal.

Before attempts are made to treat a mongoloid child, several factors have to be taken into consideration. The organism of the baby was under the influence of a faulty metabolism for many months. Some of the damage is irreparable, and some of the retardation in development cannot be overcome in postnatal life. There are degrees in the fetal retardation. The presence of severe malformations, such as syndactyly, congenital heart, cataracts of the eyes, make the prognosis still worse. All these factors explain why treatment encounters serious difficulties, even when started immediately after birth.

What can be expected from the treatment of a mongoloid child? The observations at hand indicate that the majority of untreated mongoloids eventually reach an I.Q. between 35 and 45, and only a few go beyond a mental age of between 5 and 8 years.

Although, under present conditions, treatment cannot restore full intelligence, the results of careful treatment carried out over several years lie between the normal and the level usually reached by untreated patients. This should be clearly explained to the parents so that they may make their own decision whether or not they want treatment. If "institutionalization" is the only answer, there is little use to carry out treatment which will prematurely be interrupted and the inadequate results will confirm pessimistic prejudices. The treatment of the mongoloid is not a matter of giving thyroid or other extracts only. Modern child psychiatry has accumulated overwhelming evidence that early institutionalization, lack of emotional mothering, premature separation from the parents, rejection and other psychodynamic factors affect the development of any children in intelligence and personality structure. The mongoloid child who is so much more dependent than other children, needs even more psychologic support, and "treatment" of the mongoloid is a combination of special education, emotional security and care, and medication. Each factor alone is insufficient, but combined, surprising results can be expected.

Thyroid Treatment

At the present time, thyroid substance is the only effective endocrine gland which is available in large amounts and the use of which can be properly controlled. What are the indications for thyroid treatment in mongolism? We know that the thyroid of the mongoloid infant is inadequate and needs to be stimulated. The difficulty is that the administration of thyroid increases the "resting" colloid storage and counteracts the thyrotropic hormones of the pituitary. From this point of view, thyroid is not indicated. At the same time, one must admit that thyroid is the only general metabolic stimulus which is available and that it is, there-

fore, impossible to get along without it. The beneficial influence of thyroid far outweighs its untoward effects. The influence of the thyroid on the vascular system improves the weak circulation and overcomes the stasis. This is especially important for the brain, pituitary, and liver. It prevents the

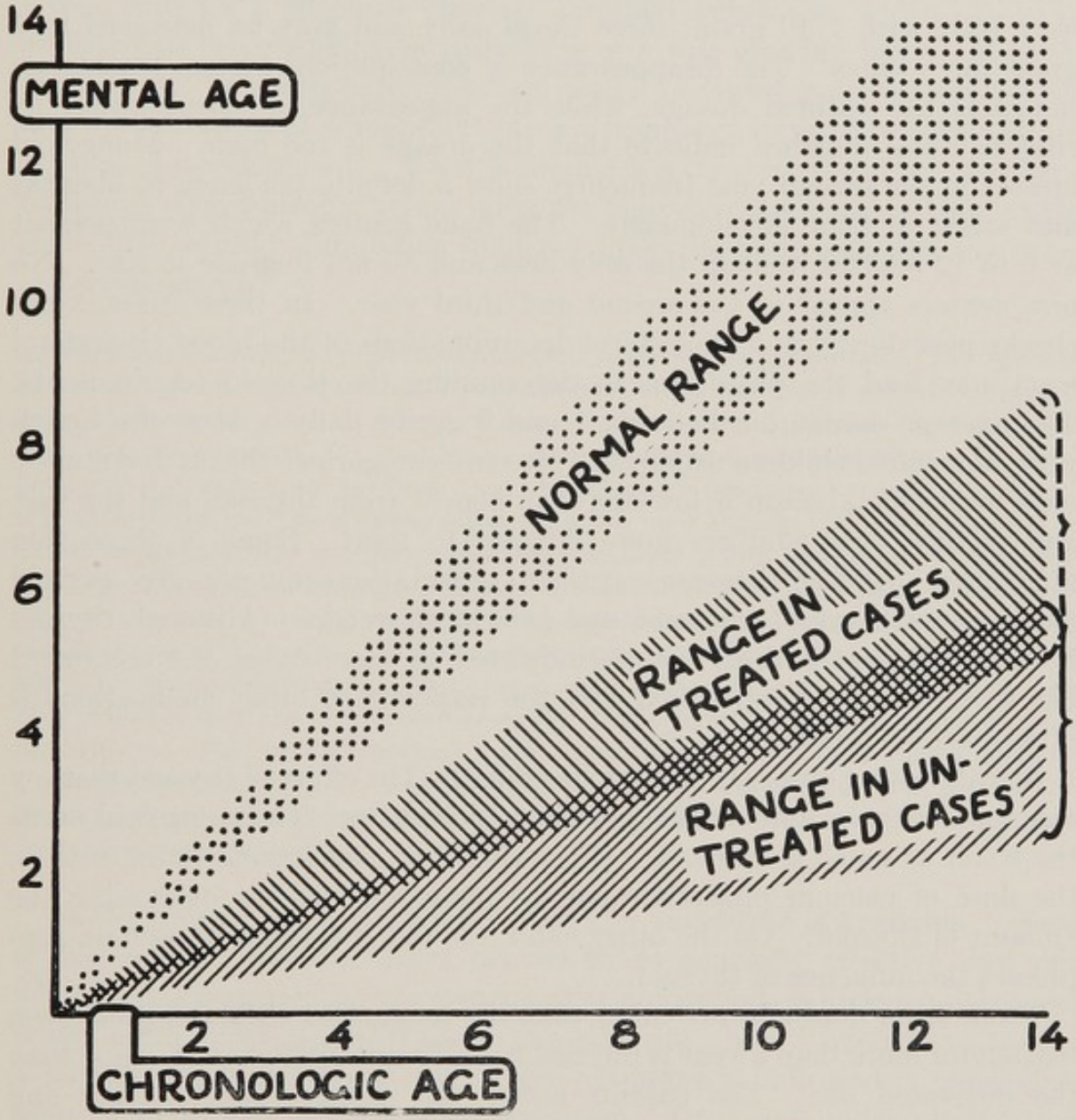


FIG. 104. Expectation of range of mental development in untreated and treated mongoloid children compared with normal development.

bone cartilage from premature degeneration and improves normal ossification. The influence upon absorption of sugar in the intestines, general metabolism, calcium and phosphorus metabolism, and the condition of the skin makes the administration of thyroid not only desirable but necessary. The application of thyroid is, however, different from its use in cretinism.

In this condition, it is much easier to establish the most suitable dosage by gradually increasing the amount until the threshold of hyperthyroidism is reached. Some mongoloids, especially in infancy, are slow, listless, quiet, have a dry skin, dry tongue, constipation and a flabby skin with the tendency to retain fat and fluids. In these cases, thyroid treatment may start with 1/10 grain, three times daily and may be increased to 1 grain three times. The disappearance of constipation, edema, listlessness indicates the optimal dosage, while the appearance of sleeplessness, irritability and diarrhea indicate that the dosage is too high. Mongoloid infants in the second year frequently show a definite tendency to obesitas and arrest of bone development. The bone centers which were present at 6 to 12 months, remain the only ones and do not increase in size. No new centers appear in the second and third year. In these cases, x-ray checks periodically and cholesterol determinations of the blood cholesterol level may lead the physicians in determining the thyroid requirements. The average dosage lies between 1 and 3 grains daily. After the fourth year, mongoloid children usually fall into two categories: the fat and stubby ones whose metabolism is low and who benefit from thyroid, and the thin and restless ones who are more difficult to treat. Some of these thin mongoloid children become—against expectation—quieter by thyroid treatment with small amounts, and gain more weight. Although thyroid is, therefore, not entirely counterindicated in these cases, the treatment has to be carefully supervised and the response to other medications is often more adequate.

An interesting observation may be added. The effect of thyroid therapy can apparently be influenced by calcium phosphate. The mongoloid needs the latter as much as thyroid. If the child becomes irritated and restless, the dose of calcium phosphate can be increased without decreasing the amount of thyroid. On the other hand, too much calcium phosphate suppresses the influence of thyroid.

There is no doubt in my mind that the mongoloid child who has been treated for more than a year is physically and mentally in better shape than the untreated one. The parents notice the changes very quickly and usually insist on further treatment. The children have a less conspicuous expression and are able to keep their tongue inside the mouth. Their skin has a better turgor and less skin blemishes. Constipation disappears. If the child gets "nervous," and the dose is too high, this is no proof that the administration of thyroid can be dispensed with entirely. In any outpatient clinic, one can easily observe that the relatively higher grade mongoloids are the ones who have been treated, at least for some time, in infancy.

Thyroid treatment alone is never sufficient to reach optimal results. It needs to be supported by other medications.

Pituitary Extracts

The therapy of choice is an efficient pituitary treatment. Unfortunately, just this treatment is not available at the present. The influence of the pituitary upon the other glands of the organism, to maintain their metabolic levels, calls for a generally effective pituitary substance, which has to be adjusted to the changing requirements of a fast growing body. It is obvious that a newborn baby does not need a powerful gonadotropic action, and thyrotropic and adrenocorticotropic hormones have to be tuned to the rhythm of development. What is needed is a "growth hormone" having a beneficial chondrotropic action upon the bone cartilages and having, at the same time, a mild stimulating influence upon the body cells and the other endocrine glands.

A few remarks may be permitted in regard to the present situation. The "growth hormone" which is so much needed for application in children is sought in extracts from adult animal glands. These extracts are from the pituitaries of full sized animals who were mature, fat, and heavy, and who have stopped growing. Although some physiologists seem to think that the pituitary produces "growth hormones" throughout life, the observations reported in this book suggest that normal growth in children after puberty not only stops, because their bodies have matured and their cartilage is used up in the process of ossification, but that the pituitary has a different composition after puberty, owing to the changing endocrine milieu and the changing requirements of the body. We really need pituitary extracts from immature animals, but it is not possible to get sufficient amounts in that way to provide for general use.* It is possible that the chondrotropic agent of the pituitary may be isolated in the near future. This would represent a great progress, but even with such a hormone available, the treatment of "congenital acromicria" must always be "polyglandular," because all endocrine glands are slow in starting and are likely to degenerate before they develop any activity.

At the present, no pituitary anterior lobe substitute is available. Some of the isolated fractions have proved to be generally effective, but one which is much needed for the treatment of mongoloids is little available and is still in an experimental stage. The material which I offered in Chapter V indicates that the use of thyrotropic hormones is indicated in mongolism more than in any other known condition. One case under observation may be briefly reported. Although one case is not of much significance,

* Due to the cooperation of the Armour Company, Chicago, Ill., and especially its Director of Research, Dr. Frederick Fenger, the Armour Company has manufactured pituitary capsules for me from immature animals for the last few years. More than 50 infants and children are now under treatment with these capsules and the results are quite promising. The physical development is much improved and the mongoloid features much less conspicuous than in untreated control cases. I have recently been advised by The Armour Laboratories that sufficient supplies of this special material are now available for distribution.

the child has been under careful observation for more than two years, and the experiment seems to be of considerable general interest.

A mongoloid girl was first seen by her physician at the age of 2 years and 4 months. From November 1942 to October 1943, she received ½ gr. thyroid daily. When I saw her in October 1943, at the age of 3 years and 3 months, x-ray examination of the wrists showed a bone age of 12 months. Only the hamate, capitate, and the radial epiphysis were present and small. The middle phalanx of the little finger was markedly hypoplastic. The child was then given injections with thyrotropic hormone.* The first injection, in November 1943, was 2½ cc., but it was felt that this was too much and it was changed to 1 cc. each week. Thyroid was given by mouth in addition, but after the fourth injection, thyroid by mouth was discontinued. After 12 injections the child appeared a little brighter. When another x-ray examination was made after five months of treatment, the picture of the hands had not changed and the bone age was still 12 months. It was felt that the amount given was too small and that the injections should be increased to 2 cc. weekly. When the child was again seen, in October 1944, at the age of 4 years and 3 weeks, the bone age had increased to 3 years and 9 months, and the ossification centers and the carpal bones had improved a good deal. At the age of 4 years and 6 months the child had a bone age of 4 years and 3 months, and at the last examination, in July 1945, she had a bone age of 4 years and 9 months, with a chronological age of 5 years. The child had a mental age of at least 3 years. She is active, happy, rides a tricycle, and has a good vocabulary, although the pronunciation is not too distinct. Her susceptibility to colds was less marked during the last winter than in the previous winters. There is a slight suggestion of exophthalmus. The capillary microscopy showed normal capillaries. The blood cholesterol was 320 mg. per cent in January 1945 and was 286 mg. per cent in July 1945. Serum cholesterol esther was 239 mg. per cent, esther percentage of total 84 per cent. It may be noted that these values are unusually high. There is no suggestion of myxedema. The diagnosis of mongolism is beyond doubt.

The case is of interest because it shows that the thyroid therapy, which was carried out for a whole year with ½ gr. thyroid each day, was not effective in increasing the bone age before treatment with thyrotropic hormones was given. The best progress was made when the thyrotropic hormone was administered alone, but the best results may be achieved when courses are alternated with periods in which thyroid extract is administered.

The injections should be given twice weekly, 1½ cc., rather than once only. In babies of 1 month of age, one may start with ½ cc. once or twice weekly. At 6 months 1 cc. may be tolerated, and at 1 year I would suggest 1½ cc. twice weekly. These, however, are only suggestions, and one will have to find the right dose in each case. Experiments of that kind should be made under periodic x-ray control and, if possible, metabolism tests.

* The "thyrotropic factor" of Ayerst, McKenna, and Harrison was used. According to the manufacturers, "the material is prepared from the anterior lobe of the hypophysis after the technique of Dr. J. B. Collip and supplied with the approval of the Department of Biochemistry, McGill University. It contains also small amount of other hypophyseal factors. The potency is standardized to contain 50 units per cc."

The difficulties of this treatment consist, however, of the fact that the patient has to get injections two or three times weekly and this constitutes a great burden. In many instances, it is impossible to carry out such intensive treatment. Moreover, children become resistant to this treatment and some have developed unpleasant abscesses in their muscles.

In animal experiments the effect of thyrotropic hormones is quickly exhausted and antihormones are said to be formed. It needs to be studied whether the same is true for children.

Other Hormones

Adrenocorticotropic hormones are not yet available and would have to be used with great care, since the infantile adrenal is different from the adult one and may be damaged instead of being stimulated.

Some physicians who have observed the signs of chronic adrenal insufficiency in mongolism have made trials with adrenal cortex extracts. The effect is not encouraging. The available preparations may be helpful in Addison's disease, but they appear too crude to cope with the difficult situation in mongolism. The damage may be greater than the benefit, because adrenal cortical hormones are known to counteract the adrenocorticotropic hormones of the pituitary, and their administration leads to adrenal atrophy.

There are, however, signs of insufficient adrenalin action also. Following a suggestion which has been expressed by Cramer in his studies on the adrenals, I tried the use of ephedrine sulfate (U.S.P. capsules $\frac{1}{4}$ gr.). This dose appears very high for infants of 6 months or less, but the responsivity of infants to sympathetic stimuli is minimal and such a dose is well tolerated. Ephedrine may be given every second day for a limited period of weeks or every third day for a month. The use of ephedrine in some mongoloid infants was encouraging. The circulation improved, and the susceptibility to respiratory infections diminished.

Gonadotropic hormones are the most efficient pituitary-like hormones offered by the industry. Beyond their specific gonadotropic action, they have a general stimulating effect on the whole organism. In mongolism where hypogonadism is so conspicuous, the administration of these hormones seems indicated but at the same time, there are many reasons against the use. It is not advisable to stimulate sexual development in a mentally deficient child, and one of the reasons that so many mongoloids can be kept at home in their teen ages is that none shows heterosexual interests. The management of gonadotropic hormones is, therefore, rather difficult and application has to be made with caution. There will be no need for administration before the age of 10 years when one is in a position to form a definite conclusion as to the potentialities of the patient. Only if mental development is fairly high can anything beneficial be expected.

Glutamic Acid

Looking for substances which may directly influence brain metabolism, the effect of which would manifest itself in improved learning ability and in an increased rate of maturation, F. T. Zimmerman and S. Ross believe that they have discovered such an agent in glutamic acid. The rationale for the use of l (+) glutamic acid is based on a number of experiments which seem to indicate a particular relationship to cerebral metabolism. Weil-Malherbe has reported that l (+) glutamic acid is the only amino acid metabolized by the brain. Nachmansohn found that glutamic acid has a catalyzing effect on the rate of production of choline acetylase. There seems general agreement that l (+) glutamic acid can be used as a metabolic factor by the brain if energy is supplied by glucose oxidation. d (−) glutamic acid, the one natural isomerid is not oxidized. Although a great variety of foods, for instance meat broth, contain a high amount of glutamic acid, it is possible that, in certain deficiencies, glutamic acid cannot be sufficiently utilized from natural food sources and administration of l (+) glutamic acid is necessary. F. T. Zimmerman, B. B. Burgemeister and T. J. Putnam have published two communications in which they claim an improvement of the mental developmental rate in mongoloid children. The dosage of glutamic acid must be worked out empirically for each individual case. There is no relationship between the age of the patient and the effective doses. Two patients, age 8, required each 24 Gm. of glutamic acid daily to produce the maximum effect, while another child 4 years of age likewise required the same dosage. In general, the efficient dosages varied between 12 Gm. and 48 Gm. Glutamic acid is administered in gradually increasing doses to the point where an optimum increase in motor and psychic activity is apparent. This dose is then maintained or reduced slightly if too much activity is evoked. The optimal dose is just short of the amount required to produce distractability or aimless physical activity.

These authors claim a gain in mental age after six months of treatment which was equal to that of children having average intelligence. The gain represented an increase in rate of development which was twice as great as that formerly achieved.

While these results are not yet confirmed by other investigators, and similar experiments in treatment, which were made in several state schools over a one year period, were not encouraging, it is certainly true that one needs to look for new medications which increase mental development and l (+) glutamic acid may be one of those substances which will open a new field of therapy. In infants and children below the age of 4 years, I would assume that endocrine therapy, as outlined before, is more advisable because at that age the general somatic deficiency is so striking

that it needs primarily medical attention. After the ages of 4 to 6 years, endocrine therapy is much less effective and other approaches are necessary. Then an attempt with glutamic acid seems advisable. It is possible that some of the negative results in other places are due to the fact that few patients have received such a high dosage (about 24–48 Gm.) as was used by Zimmerman and co-workers.

X-Ray

It should be mentioned that the x-ray therapy of mongolism, which was introduced by von Wieser in 1928, has attracted some attention for several years. Some reports appeared promising; others saw no results. If one reads the unfavorable reports, one has to admit that trials on children of 8 to 15 years of age are not of great significance. I am not aware that anyone has tried this type of treatment in recent years. No one knows whether the radiation which was suggested by von Wieser* had a stimulating effect on the pituitary or a destructive one. Until such a fundamental question is decided, the application of x-rays is in a state of experimentation.

Recently Ira I. Kaplan has used x-ray irradiation in the treatment of married women for amenorrhea and sterility and felt that the irradiation of the pituitary had a beneficial effect in restoring regular menstruation and normal fertility in a large percentage of cases. If the same treatment could be worked out for mongoloid children, some results may be expected and a trial is, at least, worthwhile. The treatment which Kaplan offered on adult women was with high voltage x-rays: 200 kv., not exceeding 5–10 ma., 0.5 mm., Cu plus 1 mm., Al. filter. The target distance used was 50 cm. The pituitary region was irradiated through a 6 by 8 cm. field. Three treatments were given, consisting of 75 r to the anterior pituitary field.

General Care

Besides specific therapy, the general management is of equal importance. From a biological point of view, the mongoloid newborn is immature, regardless of whether born at full term or premature. Mongoloid infants have very poor heat regulation. They have to be kept warmer than normal children, and exposure to cold must be avoided. The inactivity of the baby should be overcome by turning it frequently onto the stomach for sleep.

The feeding has to be rich in carbohydrates and salts and low in fat. The amount of feeding must be smaller than usual, but the number of

* Von Wieser suggested the following dose: two temporal fields 6 x 8 cm.; distance 40 cm. (18 ins.); 5 per cent H.E.D.; exposure 1–5 min. six times monthly, later on one to six times per month.

meals should be increased. When the infant is weaned, some feeding should be given at three hour intervals, and the sugar ratio should be kept high. A diet rich in salt, as in chronic adrenal insufficiency, is also indicated.

Most of the chronic eczemas, colds, and respiratory infections of the mongoloid can be kept down with such a management. In bacterial infections, sulfa drugs are well tolerated and help to clear up an infection which might otherwise last over several months.

Education

Hormonal and chemotherapy alone are not sufficient to produce the optimal mental development of the mongoloid child. Special attention has to be given to his emotional needs and to his peculiarities in learning. It has to be remembered that the mongoloid child is influenced by the same emotional factors which psychodynamic psychiatry has discovered as essential in the upbringing of normal children. The needs of the mongoloid child for affection, love and consideration are great, and lack of these manifestations of being accepted influence the development of a mongoloid in an unfortunate way. Mongoloid children who are loved, usually are trusting, quiet and loving, and have no difficulties in establishing contact with their surroundings and securing interest and affection from others. Some mongoloid children are restless and destructive little creatures, who run from one place to another, tearing everything down and are the despair of everyone who comes in contact with them. Analysis of the latter cases shows that the parents of these children often reject the defective child because a physician told them that "the mongolian idiot" would never amount to anything and should be "put" into an institution immediately after birth. The parents feel guilty and wish to hide the fact that the child is not normal. They constantly correct the child and fight a losing battle. The influence of the parental attitude upon the child can often be recognized from the behavior of the patient. The parental attitude is also reflected in that of the siblings. If the mongoloid is the youngest child and the parents train their older children in understanding of the fact that their little brother or sister is not so well, is suffering from some "glandular deficiency" and needs to have special attention, the older siblings will usually be quite willing to accept such a fact and bestow their affection upon the youngest. If, however, the older children witness parental quarrels over the defective patient and feel that the presence of such a child is considered something shameful, they adopt such an attitude quickly as their own. Of course, neighborhood children and friends are frequently of no help and difficulties may arise from the unfriendly attitude of a neighborhood.

The decision whether a mongoloid child should be placed outside of a home or should stay in the family depends on a consideration of the overall family situation. As far as the mongoloid child is concerned, there is no doubt that it develops better and to a higher degree if kept within its own family for the first ten years. The advice of many physicians to place the mongoloid, immediately after birth, in an institution is rather shortsighted and takes into consideration neither the feelings of the parents nor the possibilities of development in the child. If the parents accept the fact that the child will not be perfectly normal but will learn to walk and to talk and live a rather happy life within its family, the child can well stay within the family for many years, after which time a further decision can be made. If the mongoloid child is the oldest child and younger siblings are by-passing their elder in physical and mental development, the presence of the mongoloid frequently represents a difficult problem and institutionalization may alleviate the situation. Sometimes, older siblings, especially in their teens, feel that their friends do not like to come to their home, and girls may think that their chances for marriage are lessened. These feelings should be recognized. Some parents sacrifice the whole family for the sake of the unfortunate child, neglecting the healthy children who, in their opinion, don't need so much care. This does not seem fair to the other siblings who will enter society and will then have to make their own contributions to the life of the community. It is the duty of the physician to remind the parents of their obligation to all of their offspring. If the affected child, however, is the only child, or the age interval between the siblings is great, the child can easily stay at home and benefit from the attention and affection given to him.

During the preschool years, the upbringing of the mongoloid child has to include consideration of the fact that the child is developing slower and needs, as was previously emphasized, more time for each step than the average. Up to the age of about 8 years, the mongoloid has to be considered a preschool child, handled as any normal child who is in reality younger than his chronologic age. By realizing that the average developmental quotient is about 50 per cent or less, parents will be governed as to what to expect and how to handle their child. The well-cared-for mongoloid learns to walk between 2 and $2\frac{1}{2}$ years, and some earlier. They learn to talk between $2\frac{1}{2}$ and $3\frac{1}{2}$ years. The mongoloid cannot be expected to enter school at an age of 6; nevertheless, some are on a kindergarten level at that time and may be on first grade level after 8 years of age.

The scholastic capacities of the mongoloid are less developed than are his potentialities for social maturation. Many mongoloids have a good memory, acquire a large vocabulary and learn to spell well. Arithmetic and the concept of quantities are the least developed, and offer the greatest

difficulties. In the handling of money the child will, therefore, be most handicapped. As a whole, education should utilize everyday material and concentrate on the development of concrete conceptions. Abstract thinking will always be limited In the teaching of language and reading the above facts have also to be taken into consideration. The bringing-up should have as its main goal the development of practical skills and parents should not be too ambitious to press reading and arithmetic. A mongoloid adolescent with a pleasing personality can be quite helpful around the house, especially in rural environments, and may be able to remain in the community. If, however, in the early teens observations indicate that the youngster will not be able to stay outside of an institution, or final provisions have to be made, it is better to admit the child to an institution in his teens rather than to wait until the patient is in his twenties or over. At that time, adjustment may be very difficult. Moreover, the psychologic and emotional isolation of some of these patients makes it preferable to have them join an institutional group where they find other responsive patients and a wealth of occupational facilities and entertainment.

The attitude of many doctors, considering any effort useless if a child is not perfectly normal, is by no means justified. The great successes achieved recently in the field of cerebral palsy offer a promising goal through giving the mongoloid more consideration. Many of their capacities are trainable. The association of mongoloid children with other feebleminded children, usually of lower intelligence, retards the former's development. They learn by imitation and from the example of others—it is amazing how much they can develop if special attention is given their needs.

Cretinism

Thyroid Treatment

In contrast to the treatment of mongolism, which is still in an experimental state, the treatment of cretinism is based on experience which has been gained over a period of more than two generations. With thyroid (U.S.P.) available in all strengths and in tiny tablets which can be powdered and mixed into the feeding of an infant, the treatment of cretinism is standardized. In small infants one starts with one tenth of a grain daily and increases the dose until the optimal level is reached. The requirement in each case is different. The dose should be kept not at the lowest possible level, but at the highest level which is tolerated without untoward effects. Irritability, loss of sleep, restlessness, sweating, and acceleration of the pulse rate are sure indications that the optimal level is overstepped.

In a case which is well under medical supervision, it is advisable to determine the highest dose by gradual increases until symptoms of thyroidism appear. The writer has called attention to the fact that increase of the pulse rate alone is no indication of hyperthyroidism (p. 44). As long as the temperature is subnormal, a fast pulse rate may be a symptom of myxedema. The effect of the right dosage of thyroid will appear within a few days to weeks. The treatment should be controlled, if possible, by periodic x-rays, cholesterol determinations, and metabolism tests. The therapy can thus be carried out with the greatest scientific accuracy.

As soon as cretinism is discovered, thyroid treatment should be initiated. In the infant one should start with one-tenth grain 3 times daily, and gradually increase from week to week until an optimal dosage is achieved which may be as much as one grain or more daily in the first half year of life. In the second half year, requirements of two grains daily in the thyroid aplastic cretin are not rare. After the first year, requirements of three grains daily are frequently encountered. This dosage has to be controlled and the physician should insist that the parents not discontinue treatment and keep appointments at regular intervals. The increase of the thyroid dosage has to be made gradually and too quick dehydration must be avoided. On the other hand, many cretins and hypothyroid patients are treated with too small amounts and unsatisfactory results are due to improper medications.

In the general management of the cretin, his high carbohydrate demands and low fat requirements have to be taken into consideration. The diet should be rich in sugar and proteins and low in fat. Too much milk is not indicated.

It may be stated that an early treatment of athyroidism, and especially hypothyroidism, can bring the infant back to his natural personality level. There can be, however, no improvement above the level of hereditary endowment. Many physicians start the treatment of a cretin with too much optimism. Congenital thyroid aplasia is frequently associated with damage to the central nervous system which is beyond repair.

The treatment of the endemic cretin requires special attention. It has been pointed out that most endemic cretins are not goiterous cretins. The endemic cretin with the small, inadequate thyroid has to be treated according to his hypothyroidism. The cretin with goiter is nowadays recognized as a surgical problem. Total thyroidectomy seems to be indicated, followed by the usual thyroid substitute therapy. It is, however, important to prevent the goiterous patient from becoming a cretin. The introduction of iodinization of table salt, which has been advocated by Swiss authorities and in this country, seems to be a preventive measure of paramount importance and great promise.

BIBLIOGRAPHY

Cramer, W.: Fever, Heat Regulation, Climate and the Thyroid Adrenal Apparatus. Longmans, Green, London, 1928.

Dunn, Charles W.: Endocrine Therapy in Mongolian Idiocy. Delaware State M. J., May 1940.

Freud, J., Levie, L. H., and Kroon, D. B.: Observations on Growth (Chondrotrophic) Hormone and Localization of Its Point of Attack. J. Endocrinol. **1**, 56, 1939.

Kaplan, Ira I.: The Use of High Voltage Roentgen Therapy in the Treatment of Amenorrhea and Sterility in Women. Am. J. Roentgenol. **59:** 370, 1948. Year Book of Radiology, Chicago, 1948.

Means, J. H.: The Thyroid and Its Diseases. Lippincott, Philadelphia, 1937.

Nachmansohn, D., and Machado, A. L.: The Formation of Acetylcholine; A New Enzyme: Choline Acetylase. J. Neurophysiol. **6:** 397, 1943.

——, John, H. M., and Waelsch, H.: Effect of Glutamic Acid on the Formation of Acetylcholine. J. Biol. Chem. **150:** 485, 1943.

Nobel, E., and Rosenbluth, A.: Über die Dosierung des Thyreodins bei Kindern. Ztschr. Kinderh. **39,** 1925.

——: Zehn Jahre systematischer Schilddrusenbehandlung beim kindlichen Myxoedem. Acta paediat. **16:** 213, 1933.

Page, Irvine H.: Chemistry of the Brain. Springfield, Ill., Charles C. Thomas, 1937.

Smith, Philip M.: Relationship of Anterior Lobe of the Hypophysis to Other Endocrine Glands. J. A. M. A., Dec. 7, 1940.

Timme, Walter: Mongolism and Its Treatment. Bull. Massachusetts Dept. Ment. Dis., April 1930.

Von Wieser: Roentgentherapie des Schwachsinns bei Kindern. Radiolog. Præcticæ lo, 1928, and Verhandl. d. deutsch. Gesellsch. Roentg. 19, 1928.

Weil-Malherbe, H.: Studies on Brain Metabolism: Mechanism of Glutamic Acid in Brain. Biochem. J. **30:** 665, 1936.

Zimmerman, Frederic T., Burgemeister, Bessie B., and Putnam, Tracy J.: Effect of Glutamic Acid on the Intelligence of Patients with Mongolism. Arch. Neurol. & Psychiat. **61:** 275, 1949.

——, ——, and ——: The Effect of Glutamic Acid upon the Mental and Physical Growth of Mongols. Am. J. Psychiat. **105:** 661, 1949.

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