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Progeria and related syndromes

George E. Lewis Jr
University of Nebraska Medical Center

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George E. Lewis, Jr.

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The name "progeria" historically was given to posterity by Hastings Gilford (1) at the suggestion of two colleagues, Mr. James Rhoades and Professor Arthur Sidgwick, although Gilford's report is not the first in literature of this rare malady. In his paper are presented three cases, two of which had previously been presented to the Royal Society of Medicine and Surgery in London, one by Jonathan Hutchinson (2) in 1886 and the other, by Gilford (3), himself. However, progeria as we know it today became a clinical entity through the initiative of the latter. The first report in American literature was by Rand (4) in 1904 but it was not of a typical progeria.

Progeria, as an etymologist could readily tell, comes from the Greek prefix "pro" meaning "before" or, more liberally, "to come prior in position or chronologically" and the Greek base "geron" meaning "old man." Hence, progeria, or premature aging which is pathological as opposed to that more often thought of as being a normal process.

The disease process is a rare and peculiar combination of dwarfism and premature senility of unknown etiology. There have been to date, as near as can be ascertained without study of relatively recent foreign medical publications, twenty-two cases reported in the literature (Cooke-5).

Liberally speaking it is recognized that the rate of physical body development is inconstant; grossly we observe this daily in noticing both patients and associates socially. It is

a medically accepted fact that bone age in a given group of chronologically same-aged individuals may vary anywhere from one to six years (Vickers-Harding-6), and soft tissues may vary likewise. Such variation is generally accepted as natural, but if the body oversteps some ill-defined levels of growth thereby results unduly delayed or accelerated growth manifested by anomalies unacceptable to these standards of normalcy. The results of such variation may be called to the attention of the medical profession at any age, but for presentation we shall say largely are seen as compatible with supposed infantilism or prematurity, e.g., premature sexual development.

In much the same manner the degenerative processes which because of inability to inhibit we humbly accept as a normal phenomenon may proceed too slow or too rapidly. We may then academically have delayed or premature senility. Progeria may be regarded as the latter. Unfortunately, progeria may be identified with infantilism which exists in three main forms. These are 1) existing apart from any disease as a mere variation, excessive in degree, i.e., normal infantilism 2) as a manifestation of a disease, e.g., cretenism, syphilis, etc. 3) as a singularly pronounced form apparently the sole symptom initially of the disease, e.g., ateleiosis (Gilford-7).

Until Gilford gave us a name as above mentioned there was no word to describe the process of accelerated senile decay which may be 1) mere natural variation excessive in degree 2) a symptom

of another disease 3) the outstanding feature, so as to be a disease itself. Once again, it is the latter form which is to be considered. One of the two case histories first published by Gilford (1) was fourteen years old when first recognized and was followed until death at the age of eighteen. The second was seen by Hutchinson (2) when three and one-half years old and was followed again by Gilford from age fifteen to age seventeen when he died. Because these are classical and historical we shall briefly note some of the features before going into the more refined studies that have been made by use of modern medical methods and techniques.

In the first case it is reported that there was no intermarriage or familial abnormality. (These contributing factors will be referred to later as being significant when we consider some other supposedly related syndromes.) The patient at fourteen resembled in face only a photo of his paternal grandfather. The birth history is non-contributory. At the age of six months his parents noticed that he was rather emaciated, anodentic, had atrophy of the nails and was becoming alopecic. When eighteen months of age he was already half bald, had rounded shoulders and a narrow chest, and his head appeared large in proportion to his other body parts. At seven he had persistent buccal suckling pads and his hands were "by no means devoid of fat" (Gilford-1). The latter statement, as we shall later see, points out a difference from other syndromes.

The child was reportedly good natured but was easily fatigued and found it obligatory to take frequent rest periods. When age twelve his face was sedate. At no time was there any evidence to implicate the presence of syphilis or rickets. The child walked when two years old but was rather delayed in learning to speak. As previously mentioned his first dentition was slow; this is a not-infrequent occurrence according to case histories reported in the literature. The time at which the second dentition started was not known. The boy had measles when four and was ill with bronchopneumonia when eleven, but neither of these diseases left any directly relatable complications. He suffered from early life with a flatulent dyspepsia accompanied by epigastric distress as well as occasional nausea and vomiting which seemed to become more frequent and lasted the balance of his life.

The first appearance of active disease came with the onset of non-exertional shortness of breath, asthmatic in type, and at this time Gilford first examined the patient (age fourteen). He found that the appearance was suggestive of a child of five or a wizened and dwarfish old man whose height was 1.04 meters and weight was 16.34 kilograms. A sister, who appeared normal in every respect, brought him to the doctor in a mailcart. He was bald, had wrinkled skin and faulty carriage. (The latter is significant because of a supposed constant feature of progeria, as reported by Cooke (5), to be emphasized later.)

The thighs were very thin with an increased width at the fork; he looked as if he were "straddling" (Gilford-1). The patient stood with a slight stoop apparently starting from the hips and had rather atrophic buttocks. His gait was stiff.

The veins of his head were large and conspicuous to the point of being almost varicose on the scalp. There were present a few scattered hairs of eyebrows and eyelashes as were there a few on the backs of the hands and wrists, but no hairs were observed elsewhere on the body. The outline of the cartilage of the nose was particularly conspicuous and although the cartilage of the ears was well formed, the lobules were absent.

The nails of the digits, both upper and lower, were short, flat, and membranous. Peculiarly enough, there was not even a vestige of the mammary glands and the nipples were extremely small. The umbilicus was but a small dimple without the normal folds. The skin at the time of this examination was thin, soft and pliable. It was also found to be unusually dry, this being attributed to his very quiet habitus. In hot weather it was noted that the patient perspired, which fact attested to the presence of sweat glands which functioned normally. Sensation was thought to be normal. The skin had areas of a brownish pigmentation and areas of depigmentation.

His temperature was normal although the tendon and superficial reflexes were absent. The middle ear was abnormal in so far as otoscopic examination could reveal that the umbo was

prominent and the other visible part of the ossicle was somewhat enlarged while the tympanic membrane was rather retracted. The eyes were protuberant enough to be called exophthalmic and were also hypermetropic bilaterally; otherwise they seemed to be normal.

The patient was so mentally advanced to be considered highly intelligent, "bright" in the author's words. The musculature generally was underdeveloped and was easily given over to fatigue. The anterior fontanel was still open, but only a distance of five millimeters. The patellae were large and prominent. The patient was unable to tie his shoes because of the stiffness of his hips. The teeth were in a state of poor hygiene revealing many caries and the mouth could not be opened wide enough to permit examination of the fauces.

The patient was wont to eat small amounts of soft food, and fats caused considerable eructation, flatulence and general "biliousness." The abdomen was particularly prominent and protuberant. The liver was readily palpable with its lower margin at a point one-half the distance between the right lower costal margin anteriorly and the umbilicus. There were no palpable hypertrophic lymph nodes. The thyroid, although palpable, was not thought to be abnormal. The heart was definitely enlarged to percussion with the presence of a persisting soft systolic murmur noted at the apex. There also was a systolic bruit in the aortic area with the pulse generally of 112-120 beats per

minute. The blood was "polycythemic by six per cent;" the balance of studies on the blood demonstrated no irregularities. The rate of growth was one inch per year. The circumference of the head and abdomen remained constant although the chest grew two inches.

When aged sixteen the patient had occasional intermittent nocturnal emissions. It was noted at the time that there had been no change or alteration in the peculiar pitch and tone of his voice. He began now to complain of sporadic joint pains, migratory in type, interpreted as rheumatic in nature. In December of that year he went into cardiac decompensation and liver size increased. Death was not long in arriving.

The autopsy performed showed the skull to be equivalent to that of a one year old with a normal sella tursica. The thymus was enlarged, weighing 48.3 grams. (Normal weight is 26 grams when largest.) The trachea was slightly flattened in the antero-posterior diameter, presumably from the enlarged thymus. The thyroid was grossly normal, as were the lungs, except near the right base which showed an old pleuritic change. The most outstanding pathology was demonstrated in the heart where both mitral leaves were atheromatous, but not stenosed. The posterior leaf was incompetent. The aortic valve was calciferous and the coronary arteries were completely blocked not too far distal to the aortic os. The spleen was negative; kidneys were fibrosed from arteriosclerotic changes. The adrenals were atrophic. The mucosa and epithelial elements of stomach and intestine were

paper-thin. The liver, surprisingly, was not congested.

The over-all pathology could be broken down as follows:

1. Indications of old age-

The general expression and attitude of the body including the manner of walking, baldness, gray hair, atrophy and dryness of skin, absence of fat in certain portions, muscular emaciation and, above all, death probably resulting from extreme angina pectoris with co-existing atheroma of the cardiac valves and of the arteries, the fibrous atrophy of the kidneys and shrivelled suprarenal bodies point to the condition of senility.

2. Indications of delayed development-

The height and proportions of the patient being standard of a seven and a six year old respectively, persistence of some decidual teeth, the thinness and absence of diploe of the cranial bones, the general appearance of the long bones, the absence of facial, axillary and pubic hairs as well as the presence of the enlarged thymus all point to delayed development.

3. Indications of normal development-

The large size of liver and relatively large ends of some of the long bones as well as the cartilages of the clavicle, the size of the sexual organs and the ossicles of the ears point in some degree toward an attempt on the part of the body to develop normally.

In passing, it is interesting to note that the author felt that those long bones examined showed three phases of development.

The shafts were small and delicate as would be expected in those of a child. The epiphyseal ends were indicative of the process of growth in progress while the fusion of the epiphyses of all the bones were equal to his age at death. Further, the reader's attention will take particular note that no peculiar germ layer was reportedly affected any more than another, consequently, the disease process was in all probability not of fetal origin, and may it be repeated for sake of emphasis, that nowhere in the literature an incidence of familial or hereditary transferral appears.

Some special studies of interest have been done by various investigators in an attempt to throw some light on this strange disease process. Cooke (5) in her studies on growth in progeria states that growth and development appear normal during the first year of life. General progress is somewhat below normal. The studies of the case reports in literature reveal that talking and walking are usually not delayed. Early in the second year much of the scalp hair is lost and is slowly replaced by a scant amount of downy fuzz. It should be stated before we advance chronologically that most of these patients are normal children at birth although there is a tendency for birth weight to be less than 2500 grams. There is no mention made as to whether these were term births. If they were, the children could be considered immature by weight. The eyebrows are often lost about the same time the disappearance of the scalp hair takes place, and

frequently the eyelashes are scant. The weight remains almost stationary at the first year level and increases slightly during the first decade; meanwhile, there is a gradual increase in height which may eventually reach that of a normal three year old child. According to Cooke (5) food intake remains low. (This will be reported more extensively later.) Mental development continues at a normal level and may be slightly above normal even though the head circumference is often two to four centimeters less than the average for the given age. (No implication of relationship between head size and mentality is intended.)

Appearance in early childhood is characteristic and very striking. Because of the short stature the illusion of a large head is given, this being accentuated by the lack of normal hair, the presence of a downy growth on the scalp and the prominent scalp veins. The eyes are normal, but seem large in relation to the face which is thin and somewhat drawn out because of the decreased size of the facial bones. An atrophic mandible and receding chin often give the nose a beak-like appearance. The ears are small and without definite lobules. Subcutaneous fat tissue shows a progressive decrease so that later it appears entirely lacking and musculature generally is poorly developed. Within a few years the interphalangeal joints of the digits in the upper extremities become thickened with limitation of extension and, later, flexion. This also often happens to the spine, elbows and knees so that standing posture is somewhat stooped

with the knees slightly bent. The skin is thin, atrophic, and areas of yellowish-brown pigmentation are not uncommon. The nails of both extremities become atrophic, thin and brittle.

The general physical and neurological examinations are usually negative. Laboratory findings are normal and mental tests point to superior intelligence. The peripheral arteries are firm and palpable but demonstrate no constant characteristic changes such as ulcerative gangrene or vascular dermal sclerosis. No constant cardiac abnormalities have been noted. Roentgenographic studies show normal or only slightly retarded epiphyseal calcification and the only constant abnormality in addition to the above mentioned atrophic mandibles is bilateral coxae valgae with the femoral neck in almost a straight line with the shaft.

In the second decade, if the child survives to this age group, the abnormal physical characteristics are accentuated and only minimal growth occurs. The voice remains childish and high pitched. Gnome-like, grotesque appearance with prominence of the eyes, almost complete lack of hair, beak-like nose, absence or decreased amount of subcutaneous fat tissue, wrinkled thin skin, gnarled fingers, stooped posture and prominent arthritic knees create the picture of advanced senility.

The terminal stage may develop as early as the age of seven years or may be delayed until the second decade. One subject is reported to have lived to the age of twenty-six (Schippers-8). This end stage is characterized by manifestations of arterio-

sclerotic disease, especially of the coronaries. Customarily, after a short period of dyspnea and severe precordial pain with the appearance of electrocardiographic changes of myocarditis and myocardial infarction, death occurs suddenly.

Following is a self-explanatory table of those cases of supposedly true progeria with one exception. Thomson and Forfar reported twenty-two cases that were not typical of true progeria, but rather a pseudoprogeria. Their one case which is typical of progeria is listed. The charted listing is taken from the work of Cooke (5).

TABLE I

CASE	OBSERVATIONS MADE--AUTHOR	YEAR REPORTED	SEX	AGE	HEIGHT (CM)	WEIGHT (KG)	BIRTH WEIGHT (GM)	AGE AT DEATH (YR)
1	Hutchinson	1886	M	3				
	Gilford			14	107.2			
				15	109.6	17.2		17
2	Gilford	1904	M	14	104.0	16.3		18
				18	113.0			
3	Variot and Pironneau	1910	F	15	102.0	11.6		
4	Keith	1913	M	18	115.0		2750	
5	Schippers	1916	M	4	84.0	11.3		
	Manshot	1950		5	88.0	11.9		
				26	115.0	15.5		26
6	Orrico	1918	M	19	113.0	15.4		
	Orrico and Strada	1927						21
7	Nasso	1925	F	4	83.0			
8	Curtin and Kotzen	1929	F	7	96.0	11.7	3500	9

TABLE I (cont.)

CASE	OBSERVATIONS MADE--AUTHOR	YEAR REPORTED	SEX	AGE	HEIGHT (CM)	WEIGHT (KG)	BIRTH WEIGHT (GM)	AGE AT DEATH (YR)
9	Strunz	1929	F	2	70.0	6.4		
				3	77.0	7.5		
				4	84.0	8.7		
				6	90.0	9.4		
10	Skiff	1934	F	6			2500	
11	Exchaquet	1935	F	14	113.0	12.9		
				17	108.0	15.0		
12	Broc and Assoc.	1935	F	11	110.0	14.0	2000	
13	Papek and Hadlik	1938	F	8	99.0	11.2		
14	Mitchell and Gottman	1940	F	10	105.0	12.7	3855	
15	Zeder	1940	M	5	83.0	7.6	2000	
16	Schondel	1942	F	5	93.0	10.9	1750	
17	Schondel	1943	M	7	102.0	15.3	2250	
18	Talbot and Assoc.	1945	M	1		7.4	2340	$7\frac{1}{2}$
				6	94.7	10.9		
19	Moehlig	1946	M	5	96.5	12.0	1366	
20	Thomson and Forfar	1950	M	4	88.9	9.0	2380	
21	Cooke	1952	F	1		8.2	2300	
				2		9.5		
				6	96.0	11.0		
				8	100.0	11.0		
				13	110.0	13.2		13
22	Schwartz and Cooke	1945	M	4	81.2	9.8	3400	
		1952		6	86.0	10.0		
				7	89.0	10.4		
				8	91.0	10.7		8

Certain studies have also been made regarding the metabolic phases of progeria. It has been stated by Cooke (4) that glucose tolerance tests and basal metabolic rates using Talbot's standard for children are grossly within normal range. Talbot et al (9) ran some interesting studies on a patient with the diagnosis of progeria which, although they do not cast diagnostic insight nor establish etiology, are definitely contributory to the study of progeria. The patient was of a healthy family and had a normal younger brother. He was delivered of Caesarean section after seven and one-half months intrauterine gestation due to an android maternal pelvis. The birth and growth statistics are included in Table I so will not be mentioned here.

His first year was normal with the exception that his teeth failed to erupt as anticipated. However, the first hint of disturbance or disease was given when he failed to gain weight or gain in stature. Shortly, his scalp hair fell out and the facies seemed to change, probably as described previously. The physician examining him at the age of two years thought that he was suffering from ectodermal dysplasia. His teeth, incidentally, first began to appear about that time. He started to walk between the first and second year but it was noted that his gait was extremely odd in that he seemed behooved to sway sideways as he took his steps. When four years old his fingers were bent and could not be drawn out straight. From the age of two years until the age of six years he only gained approximately

five hundred grams per year. There was no pathologic or pathognomic history that would establish an etiologic agent for the above.

The significant physical findings on his first admission to the hospital for study at the age of six years and four months were as follows:

He could not move his joints well. There seemed to be no periarticular or intrinsic joint disease but instead a ligamentous thickening as in arthrogryposis. There was a systolic bruit heard over the entire skull, especially loud in the temporal area. Surprisingly enough, there were twenty teeth, the full complement of decidual teeth--if these were of that nature--in excellent condition. His blood pressure had a systolic value of 25 millimeters of Hemoglobin and diastolic value of 25 millimeters of Hemoglobin. The pulse was 110. Peripheral circulation was poor, causing the extremities to have a dull gray-pink hue. The arteries were extremely easy to palpate. The abdomen was full and tense.

Laboratory studies showed urine, blood, electrocardiogram, electroencephalogram, phosphatase, serum calcium levels, serum phosphorous levels, serum protein levels to all be within normal limits.

Roentgenographic studies of bone demonstrated that the mandible was small, skull sutures were narrowed and the extremities were underdeveloped. The epiphyseal lines were narrower than

usual. Intelligence tests were superior, even suggestive of genius.

The main features that this author wishes to point out are the results and conclusions implied from the metabolic studies. The above brief contributory history and physical examination report are mainly background for this feature. The metabolic studies reveal that the patient was given and ate a diet of 1,120 Calories which would be 103 Calories per kilogram of body weight. The stools contained 0.56 grams of nitrogen, equalling seven percent (7%) of daily nitrogen intake (8.29 grams). The fecal fat (7.6 grams) was thirteen percent (13%) of the daily fat intake (57.2 grams). The stool of normal infants of the six to eight kilogram body weight contains seven to seventeen percent of the daily nitrogen intake and fourteen to twenty percent of daily fat ingested (Levine et al-10). Although the patient weighed slightly more than the weight range cited above, it appears that he easily assimilated these two types of nutrients. The patient was using all the energy from the diet for daily activity and had no surplus for growth. He had hypermetabolism therefore, but by basal metabolic studies and other clinical findings had no typical hyperthroidism nor thyrotoxicosis.

In attempt to promote body growth the patient was put on methyl testosterone in a dosage of fifty milligrams daily for one month; later this was changed to twenty-five milligrams of

testosterone propriónate. Iodine was also administered to inhibit thyroid function and reduce energy output. This did produce growth, but only one kilogram per year, and did increase body nitrogen as measured by the previously mentioned methods. However, the weight gain was thought to be due in some degree to the myxedematous condition which developed. Propyl thiouracil was given and then discontinued because of a reaction in the submaxillary salivary gland. On this therapy there was not noted any increase in subcutaneous weight or tissue. During the course of the one and one-half years of testosterone the skeletal development advanced to that of a fifteen year old body. This could be anticipated provided that sufficient estrogenic levels, calcium and protein in sufficient quantities were present to allow somewhat advanced bone growth beyond that of the patient's age.

The high pitched voice seemed to deepen as if maturing but the alopecia persisted. Skin changed to a pinker, healthier appearance, but did not totally change in its gross abnormal characteristics.

Four months after the above studies, the patient developed, rather acutely, dyspnea and epigastric pain giving the impression of coronary heart disease. Orthopnea gradually ensued and at the age of seven and one-half years the patient expired of a coronary thrombosis. The pathological diagnoses when the autopsy report returned were:

1. Progeria

2. Coronary sclerosis, severe with probably occlusions
3. Myocardial infarctions, recent and old
4. Infarction of left parietal lobe of brain, slight
5. Subdural hematoma
6. Arteriosclerosis, severe, generalized
7. Pulmonary edema and congestion
8. Meckel's diverticulum, small
9. Osteomalacia with fishmouth deformity of vertebral column
10. Postpubertal prostate
11. Thyroid hyperplasia, slight, not significant.

The skin was normal except that there were no hair or fat cells in the abdominal subcutaneous tissue. The skin of the scalp was thin with many veins. The fact that the basal metabolic rate and the insensible weight loss were not below normal when the serum protein bound iodine levels fell to low values was suggestive that something other than thyroid might have been responsible for excessive production of energy.

SUMMARY OF PROGERIA

Progeria, a rare non-hereditary, acquired disease, usually insiduous in onset but rendering itself diagnostic to the astute observer in the age range of two to four years, is customarily characterized by a birth weight indicative of immaturity or prematurity. The first year is uneventfully normal; however thereafter changes appear rather rapidly. These include an incomplete alopecia, stationary weight, subnormal height increase, increased energy output not attributable to thyrotoxicosis, atrophy of the mandible, which is a facet of old age (Gray-11), subcutaneous fat decrease, arthrogrypoic changes, bilateral coxae valgae of a congenital nature, atrophic brittle nails, and the skin is thin and atrophic having pigmentation. As previously stated, there are concomitantly present indications of old age, delayed development and normal development. The voice is peculiarly high pitched and childish, although there is no report of changes noted in the intrinsic vocal apparatus. There is about equal incidence reported in the literature between the sexes. Males have been afflicted in twelve reported cases while females are recorded to be ten in number.

Death seems to occur usually in the second decade and predominantly from cardiovascular disease, usually compatible with arteriosclerosis and especially of the coronary arteries. Laboratory studies showed hypermetabolism most probably extrathyroid in origin. Otherwise, changes noted in such things as electro-

cardiograms are terminal. Autopsy reports merely confirm the pre-mortem diagnosis of cardiac deaths and add nothing more of significance that might aid in establishing the etiology.

A few possibilities as to etiology have been entertained, but none as yet have satisfactorily explained the intricacies of this disease process. Hence, before very briefly discussing two possibilities, it is right to emphasize that the etiology is unknown. One possibility that immediately comes to mind in any disease which is manifested generally throughout the organism and which also is not respective of any particular germ layer is that of a pluriglandular deficiency. However, post mortem examinations have not confirmed this. Gilford's (1) report on enlarged thymus has been an inconstant finding.

The next possibility might be considered to be the pituitary since we attribute body growth to its stimulus and, grossly, progeria is a drastic upset of normal growth processes. Orrico and Strada (12) found a small cyst in the pars intermedia of the pituitary to which was not attached any particular significance as concerns progeria. Manshot (13) believed that the number of eosinophilic cells in the pituitary were decreased, but this claim has not been substantiated by other investigators. No other specific organs have been found abnormal in a degree sufficient to indict them; the organs being referred to, of course, are those of internal secretion. Still it is theoretically conceivable that some pituitary dysfunction could exist unbeknown to

medical science which would bring about the possible early arrival of the normal growth inhibiting factors which are affected at normal maturity beginning senescence, the grand inevitable disease which is mankind's ultimate manifest destiny.

The following facet, as the last possibility to be considered is more readily determinable today whereas the former, in all probability, is something to pass on to medical posterity. The development of dwarfing, skeletal changes, loss of subcutaneous tissue and arteriosclerosis of the progeric patient indicates that an excess total energy output may be a characteristic of the disease. Further, the probability is high that the loss of subcutaneous tissue is due to an over-all negative caloric balance much the same as obesity is probably due to an over-all positive caloric balance. This subject is beyond the scope of this paper and hence shall be dropped here.

WERNER'S SYNDROME (14)

The next subject which we shall investigate to a degree and attempt to correlate with progeria, also known as "Hutchinson Gilford's Syndrome," "Progeria of children with nanism," "nanism senile" or "progero nanie," will be that of Werner's syndrome (Werner-14). The name was given to the disease process by Oppenheimer and Kugel (15) in American literature as they, in 1934, were the first to report of cases occurring in America. However, Bloch and Stauffer (16) reported earlier in our literature two Swiss cases.

Studying the continental cases of Werner's syndrome Oppenheimer and Kugel found ten, occurring in three families, to be identical with their own two cases. These reports were scattered in the literature, depending primarily on the interest of the author, and were variously found in journals of such specialties as dermatology, ophthalmology and neurology.

As near as can be ascertained by this author there have been today twenty-three cases reported in the world literature of true Werner's syndrome, including the so-called "forme fruste" (Krebs et al-17).

Werner's syndrome, as first described in 1904 by Otto Werner in his Doctor's thesis from the Ophthalmological Clinic in Kriel under the title, "Cataract in Connection with Scleraderma," is a peculiar heredofamilial dermatosis characterized by:

Shortness of stature, characteristic habitus.

Canities (premature graying of scalp hairs)

Premature alopecia (balding of scalp)

Scleropoikiloderma

Trophic ulcers of the legs

Juvenile cataracts

Hypogonadism

Tendency to diabetes

Calcification of blood vessels

Osteoporosis

Tendency to occur in brothers and sisters

Metastatic calcification

The above characteristics, it should be emphasized, are classical, and some modern writers are convinced that such should not be taken literally, but rather need revision. Further, the author, Thannhauser (18), feels that the classification is not appropriate; references to this will appear later.

Werner's dissertation was written concerning the appearance of the above group of signs in four brothers and sisters, two females and two males. A fifth sibling was considered normal and healthy. There were no interfamilial marriages and no blood relationship; at the same time it was reported that a cousin of the patients on the maternal side was already showing graying of hair at the age of twenty.

In place of presenting a case history which, in view of the hereditary aspect, would involve presentation of at least two

case histories or more, it seems advisable to abstract the salient clinical features and thereafter to merely refer to specific cases for information.

Skin: The typical changes are degenerative and non-inflammatory in nature and have been called scleraderma with or without scleradactyly by previous authors with a few exceptions (Oppenheimer and Kugel, Thannhauser--15, 18). In certain cases, however, poikilodermatous changes predominate over the scleradermatous although both are present. Skin changes are symmetrical occurring on the face and distal portions of the extremities, particularly on the feet, where chronic recurrent ulcers are a prominent feature.

Hair: Canities develops in the Caucasian on the average at 34.2 years plus or minus 8.6 years statistically (Oppenheimer and Kugel-15). In Werner's the onset is considerably earlier, even at eight years of age; several have been complete in the second decade. Subsequent whitening or alopecia is the rule. Axillary and pubic hair is sparse as is the hair in the affected skin areas.

Cataract: These are always bilateral, beginning usually in the third decade and are sometimes very rapid in progression. The patient may become blind within six months of onset. The type differs from the usual senile cataract in that it is cortical and usually spares the nucleus of the lens. This resemblance to the endocrine cataract has been emphasized thoroughly by

Mamou (19). Senile cataracts customarily involve the nucleus and are distributed in other lens elements.

Larynx and Voice: The voice is rough, hoarse, falsetto and weak. The laryngeal involvement in typical scleraderma is well known. Although fairly rare, the abnormal changes in Werner's are fixation of the epiglottis, inability to approximate the edges of the cords perfectly in phonation, and thinning of the vocal cords. These changes, where occurring, are almost identical in patients.

Constitution and Endocrine: There are frequent peculiarities related to abnormal ductless glands. Shortness of stature, gracile build with some features of juvenility which suggest a retarded or arrested development, i.e., wrinkled skin, canities and vascular changes indicating a premature senescence. Sometimes a dysproportion between the trunk and torso with abdominal fat and thin, spindly limbs are present. Some males have features typus femininus. Hallux valgus and pes valgus and increased bony prominences are not uncommon. Some patients are small, asthenic, slender, shrivelled, infantile or underdeveloped while others are senile. The intelligence may be normal, infantile or poor. As concerns the gonads--in the female there is usually ovarian insufficiency with delayed puberty and infrequent or scanty menses with premature amenorrhea, sometimes at the sixteenth year. In males there is hypogonadism, delayed puberty, failure to develop fully and there are secondary sex characteristic

changes, e.g., occasional gynecomastia, a large broad pelvis or eunuchism. Thyroid disorder in the form of goiter or frank Grave's disease or merely Basedow form symptoms have been described in patients and members of their families.

The original observations made by Werner, a medical student on an ophthalmology ward, of four brothers and sisters represent the first description of a unique clinical entity. Naturally, Werner was concerned primarily with the juvenile cataracts, but his description, especially the details of the appearance of skin changes, give the impression that the described disease should be of general medical interest since the whole body is involved. Without repeating each of the cases Werner published we shall mention some observations by way of comment. All symptoms developed in the patients in the second and third decades of life. All patients had a reportedly normal birth. The development in childhood was also normal, but in adolescence they all remained short in stature. Strikingly similar, almost to the least detail, are the reports of the appearance of the other features. At age twenty graying of the hair commenced, and later the skin on the lower legs became taut, atrophic, stretched over underlying tissues which had meager fat and atrophic muscles. Areas of hyperkeratosis were present which were painful and, after the horny layer was removed, became ulcerated. At the same time, the second decade, bilateral cataracts developed and the whole physiognomy became more senile in appearance. The once

appropriate physical capabilities were inadequate and the patients could not do heavy work, partially because of the immobility of ankles and feet (due to tightness and ulcers) and partially because of the total reduced nutritional status of the body. Signs of arteriosclerosis became evident and completed the picture of presenility.

It is of interest only and not the purpose of this paper to point out other reports in the world literature concerning this syndrome. In 1920 Vossius (20) reported two cases with scleraderma and cataracts. In the first instance the patient was the only one in the family so afflicted. The second case had a sister small in stature. Both cases showed manifestations of Werner's syndrome.

G. Guillain, Alajouanine and Marquezy (21) published an isolated case, and Manjoukowa's (22) case also fits into this syndrome; but Papastratiyakais's (23) patient with complete alopecia, atrophy of nails, and cataracts is probably better classified as "Hereditary Ectodermal Dysplasia." Barbot (24), in a paper, the subjects of which were written up and published by Monier-Vinard and Barbot (25), told of a family that had four members showing signs compatible with this syndrome under discussion. Hasimoto (26), Bau-Prussak (27), Sainton and Mamou (28), and Eguchi (29) all published cases of Werner's, but the cases of Segarry, Favory and Mamou (30) plus the case of Mamou (19) do not belong in this syndrome. The best attestation of the familial

incidence of Werner's syndrome is to be found in the publication of Krebs, Hartmann and Thiebaut (17) wherein is presented the family tree. The syndrome under discussion was present in all its features in three members of the second generation and in three members of the third. But some features occurred interchangeably as abortive ("forme fruste") also in other members in three generations. These observations are important because they prove 1) a recessive inheritance of the syndrome, 2) abortive features may occur as "forme fruste" which might easily be overlooked by an examiner not familiar with the disorder. Oppenheimer and Kugel (15) also demonstrate the occurrence of "forme fruste" in their report of a genealogic table.

Because many of the clinical laboratory facilities were not available to many of those studying Werner's syndrome, not a great amount of laboratory data is to be found in the older reports. However, Thannhauser (18) ran many tests on two patients of his own, Sidney, O. and Nathan, O., which have been published and will be recorded for their value and important place in modern medicine. It is Thannhauser's belief that these cases are typical and consequently, it may be implied that these laboratory data might be anticipated in a patient with Werner's. The data is from Sidney O.'s case.

The basal metabolic rate was a minus fifteen, test satisfactory. Total cholesterol was 172 milligrams percent; free cholesterol was 39.5 milligrams percent; cholesterol esters were 132.5

milligrams percent. Follicle stimulating hormone in the blood was reported negative and 3.24 milligrams of 17-ketosteroids per twenty-four hour urine specimen were excreted. Creatine levels were 0.8 and 0.61 milligrams percent in twenty-four hour urine specimen. Sugar was present in random urines and reported as traces. Glucose tolerance curve; fasting 150 milligrams percent; one half hour, 274 milligrams percent; one hour, 286 milligrams percent; two hours, 278 milligrams percent; three hours, 272 milligrams percent. Serum calcium was 11.8 milligrams percent and serum phosphorus was 3.6 milligrams percent. The alkaline phosphatase was 2.2 Bodansky Units. The total serum protein was 8 grams per 100 cubic centimeters; albumin fraction, 5.5 grams, and globulin fraction, 3.2 grams. The erythrocyte sedimentation rate was 28 millimeters in twenty minutes and 74 millimeters in one hour. Serology was negative. Hemoglobin, 75 percent; Erythrocyte count, 2.24 million; color index, 0.9. Leucocytes, 10,000 with a differential; Band Forms, 5 percent; Adult polymorphonucleocytes, 63 percent; Eosinophiles 3 percent; Basophiles, one percent; Lymphocytes, 16 percent; and Monocytes, 12 percent. Platelet count was normal. Appetite, normal; while in the hospital this patient ate 2500 to 3000 Calories each day without weight gain.

The interrelation of scleraderma, cataract of the endocrine type, disturbances of calcium metabolism, and of parathyroid function both increased and decreased, is a problem which is

fully discussed in Mamou's thesis, but still needs further classification. The major clinical manifestations such as scleraderma, cataract and changes in skin and appendages indicate a primary involvement of the ectoderm which is known to be under the rather direct control of the parathyroids. Disturbances of calcium metabolism and disorders of the sympathetic innervators also point to participation by the parathyroids. If there is agreement with Von Arady (31) in interpreting the symptoms as evidence of pituitary relationship, one may say in reviewing the endocrine involvement of Werner's that there is evidence of pluriglandular disturbance and most significantly perhaps, the parathyroid. However, Oppenheimer and Kugel were very careful to evaluate this phase and ran tests to ascertain parathyroid function in two of their cases.

The total calcium picture was determined in both cases simultaneously. The study consisted of measuring the urinary and fecal output of calcium resulting from a diet low in calcium. A quantitive diet, well balanced otherwise, containing an estimated daily calcium content of 100 milligrams (actual determinations of diet content proved about 50 milligrams) was given to each case and a duplicate diet preserved for estimation. After a preliminary seven day period on this diet to obtain basal conditions as nearly as possible, the experimental period of six days was instituted. Results are given in the following table as two three-day periods:

TABLE II CALCIUM STUDIES

PERIOD	CALCIUM INTAKE IN MG.	URINARY CAL. IN MG.		FECAL CAL. IN MG.		TOTAL OUTPUT IN MG.		BALANCE	
		I	II	I	II	I	II	I	II
1 (3 days)	150	174	282	312	612	486	894	-336	-744
2 (3 days)	150	144	306	240	522	384	828	-234	-678

Normally the diet results in a moderatively negative calcium balance (the output being two to three times the intake) with a one to three ratio of urinary to fecal calcium. In both instances the ratio of urinary to fecal calcium is not significantly altered. Case I reveals a negative calcium balance within the normal range. Case II seems to have an abnormal negative calcium balance. However, according to Kugel, who personally helped to run the test, this second case was a mild diabetic who usually received 15 units of insulin daily and received no insulin during the preliminary and experimental periods. On this regime the urine contained 15-25 grams of glucose daily and at no time were acidotic changes detected either clinically or by laboratory procedures. Several blood calcium determinations on both patients were normal. From the above careful studies and the absence of pathology in the parathyroids at autopsy, it would appear that they are not too readily incriminated.

One other portion of the presenting picture of Werner's syndrome has come into the fore, especially with the later investigations. This is in regard to the actual presence of

scleraderma or poikiloscleraderma. The present concept of true scleraderma is based on a histological picture exhibitory of the characteristic features of 1) homogenization and sclerosis of the subcutaneous tissue, 2) inflammatory changes of the arteries of the subcutaneous tissue revealing perivascular infiltration and obliterative vascular changes. Thannhauser (18) was unable to find any familial incidence of true scleraderma in the literature on that subject, particularly as a familial recessive trait. Diffuse scleraderma usually involves the skin and tissue beneath the lower eyelid, the skin covering the nose, nostrils and the vicinity of the mouth and chin. In the majority of cases there is involvement of the skin of the neck, thorax, abdomen and the extremities. Likewise, more recently, the involvement of the esophagus and a tendency toward frequent intrathoracic pulmonary complications has been stressed. Interstitial fibrosis in the lungs with gross and microscopic cystic structures of bronchiolar-epithelium have been found in a significant number of cases. The incidence of dysphagia with esophagal involvement in true scleraderma has been reported at about fifty percent (Mahrer et al-32).

In many cases of true scleraderma an intensive melanotic pigmentation is seen in some areas of the body, especially on the neck, in the axilla, on the trunk or on the buttocks. Areas of circumscribed hyperkeratosis occurring in the distal lower extremities and around the elbows are not a feature of true scleraderma. In Werner's, in contrast to scleraderma, the skin

changes begin with circumscribed areas of hyperkeratosis beneath the heels, beneath the large toes, on the lateral portions of the feet as well as in the instep and over the Achilles tendon. There has not been reported any significant incidence of cardiospasm, esophageal fibrosing, dysphagia or pulmonary fibrosis as being co-existent or concurring with skin changes in Werner's syndrome. There are never areas of melanotic pigmentation seen in Werner's. Scaling, however, along fine faintly colored strips of skin may be found occasionally. The skin generally has been reported to be white and waxy in appearance with areas of reddish color developing at the pressure points of clothing.

The above gross clinical features of true scleraderma as differing from the pseudoscleraderma in Werner's are supported by the histological examination. The previously mentioned three microscopic characteristics of true scleraderma have not been reported as such in the examinations made of biopsies in Werner's.

In a typical case which was examined by H. Montgomery, M.D. (Oppenheimer and Kugel-15), a dermatologist at the Mayo Clinic, he reported, "No evidence of so-called senile skin, no inflammatory reaction, no appreciable obliterative changes in vessels. The connective tissue appears essentially normal and there is no decrease in the thickness of the cutis."

This is all in opposition to a diagnosis of scleraderma. In view of acrodermatitis chronica atrophicans it has been suggested that the skin changes in Werner's syndrome be labelled as

"heredofamilial atrophic dermatoses with ulcers" (Oppenheimer and Kugel-15). This seems notable and adequate in so far as can be determined by evaluating the literature.

SUMMARY OF WERNER'S SYNDROME

This relatively rare heredofamilial disease, transmitted by a recessive Mendelian character, first manifests itself in the second or third decade. Until this time, those afflicted usually have no complaints in regard to this disease process to send them to a doctor, and one would be hard pressed to make a diagnosis until many of the characteristics are present. A typical case has early graying, premature balding, tight atropic skin over the ankles with or without ulcers, hyperkeratoses of the lower extremities, bilateral cataracts of the endocrine type before the age of thirty, high pitched voice, short stature and some endocrine disorders as manifested by an enlarged thyroid. In general, signs of arteriosclerosis and premature aging are present. An incomplete development or part, without all, of the signs may appear, this being known as "forme fruste." There is no particular sex affinity although in the literature the males seem predominant.

The skin changes which have been reported are variously classified as scleraderma, poikiloscleraderma, scleraderma-like, and poikiloscleraderma-like. However, from the preceding discussion it seems more plausible to adopt as a characteristic of the disease or as a description of the skin lesions the phrase, "heredofamilial atrophic dermatosis with skin ulcers" (Thannhauser-18).

There have been no consistent endocrine disorders, however, there is usually reference made to the thyroid and its function, be it hyper-, hypo- or normal. Mild diabetes has been noted in some cases and a tendency toward diabetes as attested by fasting blood sugar and/or sugar tolerance curves is not an uncommon finding. Osteoporosis is frequently present.

The mechanism of death, nor the age at which death occurs is not referred to, although in looking over family histories of afflicted patients and paying note to those relatives who reportedly had similar signs, it is found that those relatives have died from diabetic gangrene or heart trouble.

The etiology has been mentioned in so far as it seems to be known today, i.e., heredity.

ROTHMUND'S SYNDROME

The next syndrome to come under discussion as being related to the previous two is that of Rothmund's (33). Rothmund wrote and published in 1868 of a previously unpublished clinical picture. This syndrome occurred in three families in the Breganz Valley, an isolated area which had not allowed much commercial intercourse. This implied intermarriage and/or a hereditary feature. The disease process was brought to his attention when he saw a boy of five years in the ophthalmological clinic in Munich. This boy had a cataract of one eye which was not due to trauma and had gradually developed during a period of two weeks. Rothmund also noticed at this time a peculiar skin degeneration. The skin changes were described as a peculiar teliangiectatic condition which began in infancy, and from the report it is difficult to evaluate the skin condition adequately. It was discovered that these children came from the same area. Rothmund asked his colleagues in the field of dermatology to examine these cases and was assured that they had never seen such a disorder. For this reason when his vacation came he decided to visit the "Kleine Walsertal" (Rothmund-33) in the Austrian Bregenzerwald in Voralberg. This is a small dead end valley; the only road to it is through the Bavarian Allgau mountains. In this valley are located three little villages with a total population of about fifteen hundred. Almost all of the families were related and intermarriage was not infrequent.

In Rothmund's no other organs outside of the skin and eyes are involved generally. Cataracts usually are noted as developing in the age range of four to six years. They develop rapidly in both eyes and show star-like opacities at the lower pole of the lens with extensions in short time to the center of the lens; resultant blindness occurs frequently. Skin changes are not, as a rule, present at birth, but marmorization of the skin first becomes visible on the face approximately three months after birth. Later the skin on the knees, ears, buttocks and extremities (first on the extensor surfaces, later, the flexor surfaces) are involved. The skin grossly shows red lines like teliangiectasis and scar tissue simultaneously present. There is not present any itching, vesiculation, ulcers or crusts and the areas of skin involved are extremely fine, soft, white and transparent such that the veins just beneath the skin are easily visible. The histology picture demonstrates the diseased piece of skin to be somewhat inconsequential. The essential findings are that of fatty degeneration of the rete Malpighi and the disappearance of pars papillaris.

The follow-up of Rothmund's three families with the disease showed that the children lived to an average or old age. In these families there were normal children who married and had normal children. In some the skin changes only were present and one with no cataracts and only slight skin changes married producing thirteen children. One patient with both skin changes and

bilateral cataracts did not marry and had no children. In thinking back to Werner's syndrome it is interesting to note that only one of the patients Rothmund examined originally remained short, had short extremities, small hands and feet and became gray and bald at the age of forty.

There have been seventeen cases of this syndrome reported as nearly as can be ascertained with no particular sex dominant trend. Nieden (34), Terrien and Prelat (35), Siegrist (36) and Schnyder (37) (reporting on the brother of Siegrist's patient) and Bloch and Stauffer (16) all have reported cases that are Rothmund's syndrome. Further it appears that much like Werner's, Rothmund's syndrome can occur as a "forme fruste." The reports of Zinsser (38) in 1910 and Janovsky (39) in 1921 are indicative of this.

Of importance is the publication of Seefelder (40) who reported the case of an adult giving a history of Rothmund's. In the family were six children, two with skin changes, teliangiectasis and bilateral cataracts, one with skin changes alone and the other three normal. The parents were second cousins from a secluded valley. The skin changes were described as identically developing in all three between the ages of six and twelve months. The balance of the report will not be recorded but the similarity to Rothmund's syndrome is sufficient to obviate the diagnosis and to point out that it may be differentiated from the signs and symptoms in Werner's syndrome.

SUMMARY OF ROTHMUND'S SYNDROME

This heredofamilial disease usually starts in early childhood with skin changes becoming noticeable from three to six months of age. Until such time the child is considered normal, but a family history, if carefully taken, should reveal the presence of this disease somewhere previously. Bilateral cataracts which may occur simultaneously or in sequence appear between the ages of three and five years. The skin changes consist of teliangiectic areas appearing first on the face and progressively later, ears and extremities, first, extensor, then flexor surfaces. The microscopic pathology shows flattening of the papillae with or without complete disappearance of the rete pegs and atrophy of the panniculus adiposus. There may be an occurrence of the disease as "forme fruste." Patients live to an average or old age. The endocrine involvement is minimal and usually is limited to the male patients who show hypogonadism with the onset of this being at puberty. Females have had children if skin changes were the only manifestation of the syndrome, otherwise they were childless.

There has been in this syndrome, and in Werner's, considerable debate as to the skin changes. Some authors have been wont to call the lesions poikiloderma atrophic vasculare (Jacobi-41) because of the color and the formation of the teliangiectasis, which on closer inspection are small white atrophic areas of pigmentation. Bloch (Bloch and Stauffer-16) thoroughly debates

this but Thannhauser (18) has suggested the name, "heredofamilial atrophic dermatoses with teliangiectasia," on the basis of the above findings. The latter, in view of the literature, seems the most adequate and accurate to this author.

The diseases which are related to the previous three discussed are in all probability, several, but there remain three entities which might more often be confused with the syndromes Hutchinson-Gilford, Werner and Rothmund. With these we shall attempt to mention facts which show that they are different syndromes or diseases and leave the absolute differentiation for the conclusion.

1. Cataracta dermatogenes (Neurodermatitis) type Andogsky (42)--Andogsky published in 1914 an article on four different and unrelated patients with chronic eczemoid skin lesions present from childhood. In the third decade these patients all developed bilateral cataracts. Similar cases, some with, some without cataracts, have been published by Vogt (43), Lowenstein (44), Siegrist (37), Ollendorf and Levy (45), Metzger (46), Laslo (47), Oltmann (48) and Franceschetti (49, 50). To these fifteen cases Kugelberg (51) has added two more in an extensive study. This process produces lichenification of skin, neck and flexor surfaces of the extremities especially at the elbow and knee bends. The skin in the bends shows chagrinization, and facies leontina may be resultant from the disease process. No histopathologic report

has been published and only one case where heredity was involved has been reported (Thannhauser-52). It is, however, possible that this may represent a heredofamilial dermatosis with occasional cataracts. The picture is obviously totally different from the previous syndromes discussed and only one out of seventeen cases has shown any hereditary relationship.

2. Hereditary Ectodermal Dysplasia, dystrophy of hair and nails (type McKay and Davidson-53), "anhydrotic type," (type Widderburn)--is an anomaly described as being characterized by complete inability to perspire, a deficiency of the scalp, axillary and pubic hairs (hypotrichosis), and incomplete development of the teeth (anodontia). From this McKay and Davidson (53) have differentiated a type with functioning sebaceous glands and sweat glands with atrophy of the hair and nails. In these are a keratoderma plantaris and palmaris. In this syndrome, it is noted, there are only defects in the ectodermal germinal layer wherein other germinal layers have been indicted in previously discussed disease processes.

3. Myotonic Dystrophy--This disease was first differentiated from Congenital Myotony as a separate clinical entity in 1900 by Hoffman (54). It was Steinert (55), Curschmann (56), Hauptmann (57), Naegeli (58) and Rohrer (59) who thought of it as a general dystrophy in which myotonic reaction was not

essential. Wasting of the entire body, and weakening of some of the muscle group are present. In reviewing the literature consisting of thirty-five case reports and in fifteen cases of his own Rohrer (59) reported a significant heredofamilial incidence, especially the collateral occurrence in brothers and sisters of one generation. It is realized also that general weakness, wasting of subcutaneous fat tissue, skin atrophy, loss of scalp hair, sexual dysfunction, and testicular atrophy are as characteristic of this disease as is atrophy of some muscle groups with the occurrence of occasional myotonic reaction. However, in most of the cases the latter is the outstanding feature.

GENERAL SUMMARY

As seen above and in the various publications in the world literature, there is considerable confusion in differentiating Werner's syndrome from Rothmund's. Although they are related clinical entities, understood because of the similarities of the families in both instances, the striking differences are as follows:

1. Werner's starts between 20-30 years beginning with gray hair and progressing with skin changes and cataracts. Rothmund's starts in early childhood with skin changes visible from three to six months of age, and cataracts develop in childhood from three to five years of age.

2. Shortness of stature is more pronounced in Werner's than in Rothmund's.

3. The skin changes differ:

Werner's	Rothmund's
1) Skin draws tight over underlying structures which are poor in fat tissue.	1) Skin lesions appear in first six months of life.
2) Localized on legs and feet and to a lesser degree on forearms, hands and face.	2) No stretching of skin or ulcers.
3) Ears only slightly deformed and few skin changes in ears.	3) First change appears on face, ears, cheeks, buttocks, extensor and then flexor surfaces.
4) Circumscribed areas of hyperkeratoses on soles and beneath big toes and heels.	4) First stage of skin change is a livedo reticularis progressing to a red color and then to teliangiectasis.

Werner's (cont.)	Rothmund's (cont.)
5) Pressure ulcers especially near Achilles tendon.	5) Skin appears yellow, becomes scarred in appearance, then scales. Finally looks fine and is translucent and thin.
6) That skin grafts "take" is proof that this is not entirely atrophic in origin but due to pressure.	6) Areas of pigmentation and depigmentation are much more noticeable.
7) Classification of skin changes as sclero- or poikilosclerodema is not proven by histological examination.	
8) Calcification in blood vessels is seen.	

4. The histological difference lies in the fact that in Rothmund's there is a distension of vessel walls often forming pools; in Werner's, there is none.

5. The muscular and subcutaneous fat are less atrophic in Rothmund's than in Werner's.

6. Cataracts bilaterally are present in both, but with different ages of onset.

7. Canities appears early in Werner's and may not appear at all in Rothmund's.

8. Diffuse arteriosclerosis appears in all of Werner's and can result in early complication. In Rothmund's it is not observed in youth, but may appear in the fourth decade.

9. Osteoporosis is common in Werner's and uncommon in Rothmund's.

10. Thyroid dysfunction may be present in Werner's, not so in Rothmund's.

11. Underdevelopment sexually is present in Werner's and post pubertal atrophy, in Rothmund's.

12. Hoarse, high pitched voice occurs in Werner's due to changes of epithelium of vocal cords and if present in Rothmund's, is due to sex retardation.

13. Tendency toward diabetes or diabetic glycosuria is present in Werner's, not in Rothmund's.

14. Both syndromes may occur as "forme fruste."

15. Both syndromes are related in causality to a recessive heredity factor.

It is also important to distinguish the differences between the Hutchinson-Gilford syndrome (progeria with nanism) and Werner's syndrome:

1. In Werner's there is a tendency toward dwarfism, and in Hutchinson-Gilford's patients are definitely dwarfs.

2. Both have short extremities with increased protuberance of the abdomen. Hutchinson-Gilford's patients consistently have bilateral coxae valgae, and Werner's do not.

3. The lack of scalp hair is more pronounced in the child progeric than the patient of Werner's syndrome.

4. There is no familial occurrence in Hutchinson-Gilford's; there is in Werner's.

5. There are no ulcers in the Hutchinson-Gilford syndrome,

nor are there cataracts. This, too, differs from Werner's.

6. The abnormal features develop much earlier in the progero nanie patient, and death occurs before most of those patients with Werner's show their characteristic signs.

It is suggested in both of the above that they may result from multiple germ plasm defects manifesting themselves at different ages in abiotrophic features of the genotypic variety.

In order to facilitate the reader's comparison of these various entities Table III is included as taken from Thannhauser (18). From the signs and symptoms presented the major ones are enumerated, and values as to the presence, absence, frequency and age of occurrence are recorded. The chart is further self-explanatory.

TABLE III COMPARISON OF DISCUSSED SYNDROMES

SYMPTOMS	WERNER'S	ROTHMUND'S	CATARACTA DERMATO-GENES WITH NEURODER-MATITIS	PROGERIA OF CHIL-DREN WITH NANISM	MYOTONIC DYSTROPHY	ECTODERMAL DYOPLASIA WITH DYSTRO-PHY OF HAIRS, NAILS
Heredofamilial occurrence	+++	+++	±	o	++	+++
~~Age~~ at ~~beginning~~ of disease	20-30 years	3 mo. - 3 yrs.	3-20 yrs.	2-5 mo.	20-30 years	shortly after birth
Shortness of stature	+++	+	o	++++	+	o
Skin changes	++++	++++	++++	+	+	++
a) tightly drawn over underlying tissue	++++ 20-30yr.	o	o 3-20 yrs.	+ 2-5 mo.	+ 20-30yr.	o shortly after birth
b) atrophic thin skin	++++	++	++	++	++	+
c) teliangiectasis	+	++++ 3 mo.	o	o	o	o
d) scaling	++	++++	++++	+	o	o
e) pigmentation and depigmentation	+	+++	++	+	+	o
f) ulcers	++++	o	o	o	+	o
Canities and age	++++ 20-30 yrs.	± 40 yrs.	o	++++ 2-5 mo.	+++ 20-30 yrs.	bald
Sparse sex hair	+++	++	o	+++	+++	o
Muscular atrophy on distal parts and extremities	+++	±	o	+++	+++	o

TABLE III (cont.) COMPARISON OF DISCUSSED SYNDROMES

SYMPTOMS	WERNER'S	ROTHMUND'S	CATARACTA DERMATO-GENES WITH NEURODER-MATITIS	PROGERIA OF CHIL-DREN WITH NANISM	MYOTONIC DYSTROPHY	ECTODERMAL DYOPLASIA WITH DYSTRO-PHY OF HAIRS, NAILS
Atrophy of subcutaneous fat	+++	±	o	+++	+++	o
Bilateral cataract	++++ 20-30 yrs.	++++ 3-4	±	o	+++ 20-30 yrs.	o
Diffuse Arterio-sclerosis	+++	±	o	++++	++	o
Osteoporosis	+++	o	o	++	+	o
Joint deformity	+++	+	o	+++	+	o
Thyroid	+	o	o	o	+	o
Proptosis	+++	o	o	++++	o	o
Sex underdevelopment	++++	++	o	+++	+++	o
Myotonic Rx	o	o	o	o	++	o

CONCLUSION

If a medical examiner is confronted with a group of signs and symptoms which make a patient appear twenty to thirty years older, it brings to mind arteriosclerosis, Simmond's disease, carcinoma, emphysema, malnutrition and a host of other diseases. A group of syndromes such as those presented also formulates the picture of premature aging. And the problem of premature aging, in turn, arouses interest in such questions as 1) what comprises growing old, 2) the nature of arteriosclerosis has what as an etiology, and 3) what actually is the effect on the human organism of the dynamic equilibrium of the endocrine systems? These questions have not been answered to date, but modern medical investigation is daily attempting to formulate their answers.

As concerns the syndromes discussed there is little to conclude other than what has been referred to previously. However, it seems to this author that one item should be resolved, that is a classification of the terminology used in naming these disease processes. The term progeria was first coined as a specific title for that syndrome, since variously referred to as Hutchinson-Gilford syndrome, progero nanie and progeria with nanism. By rights of priority the name, progeria, as instituted belongs to this syndrome. However, the term has been generalized and now is descriptive of many processes. The term of "progeria in the adult" has been applied to those patients with Werner's syndrome, as has the title of "heredofamilial atrophic dermatoses

with ulcers and cataracts." The term of "progeria in the child" has been applied to those patients with Hutchinson-Gilford's syndrome as has the title of "heredofamilial atrophic dermatoses with teliangiectasia and cataracts."

In this author's opinion and in view of the present medical trend to have done with eponyms, it seems appropriate to forget the terms such as Hutchinson-Gilford's syndrome, Werner's syndrome and Rothmund's syndrome, dismissing them as of historical interest only. Descriptive phrases should replace these terms and because progeria is general in meaning, it should represent a class of diseases. Under this classification a listing of separate entities would suffice, i.e.:

Progeria--

1. Associated with nanism (Hutchinson-Gilford's syndrome).
2. Associated with heredofamilial atrophic dermatoses with ulcers and cataracts (Werner's syndrome).
3. Associated with heredofamilial atrophic dermatoses with teliangiectasia and cataracts (Rothmund's syndrome).
4. Associated with familial ectodermal dysplasia (dystrophy of the hair and nails--type, McKay and Davidson).
5. Associated with neurodermatitis (cataracta dermatogenes--type Andogsky).
6. Associated with myotonic dystrophy (myotonic dystrophy).

The balance of the features of these disease processes, such

etiology and treatment is not as yet thoroughly understood; this is not a conclusion, but remains for medical science as a challenge.

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It is only fitting that the foremost expression of gratitude be attributed to my parents, without whose aid and assistance the very writing of this paper would never have been possible. To them, then, a deep and sincerely heartfelt thank you.

In sequence I should next express my indebtedness to E. L. MacQuiddy, Jr., M.D., who first aroused and stimulated my interest in the subject of "Werner's Syndrome." I was introduced to this syndrome when, as a junior student on medical ward rounds, I presented one of my assigned patients. The patient had signs and symptoms suggestive of this disease entity and Dr. MacQuiddy asked me to define the above; this I was unable to do. By this experience my interest was aroused, hence, my decision to write on the subject which is the title of this thesis. Dr. MacQuiddy kindly consented to be my sponsor and was very helpful in directing my review of the literature. Further, he helped by reading the completed rough draft and by presenting constructive criticism of the thesis.

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To the above cited, "Aren't we glad it is finished?"

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