

5-1-1942

## Hand-Schueller-Christian disease

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HAND-SCHULLER-CHRISTIAN DISEASE

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Senior thesis presented to College of Medicine

University of Nebraska

Omaha, Nebraska

April 6, 1942

F O R E W A R D

In this thesis there is no pretense toward originality. I have attempted only to accumulate most of the important work done on this disease and assemble it into one paper.

It is with great pleasure that I present this thesis on "Hand-Schuller-Christian Disease" to the University of Nebraska College of Medicine.

Richard F. Brendel

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### DEFINITION

Horsfall and Smith (22) consider Hand-Schuller-Christian disease a clinical syndrome of defects in the bone, exophthalmos, and diabetes insipidus and is thought to be one of the sticking but not characteristic manifestations of lipoid granulomatosis.

Numerous men who have studied the disease agree that it is a disease entity in itself in that it is a disturbance of the lipoid metabolism characterized by 1.-the deposition of lipoid in the reticulo-endothelial system and 2.- the presence of one or more signs of the triad making up the Hand-Schuller-Christian syndrome -- namely 1.- bony defects, 2.- diabetes insipidus and 3.- exophthalmos.

Jason and Abraham (23) consider it a disease of the reticulo-endothelial system. This idea has been more or less excepted by various men (38, 27, 40, and others)

### HISTORY

In 1865 a Thomas Smith (1) in one of his writings describes a condition which is now thought to have been Hand-Schuller-Christian disease. He tells of a child four and one-half years that had a soft fluctuant pulsating swelling on the head. Other swellings developed later. At autopsy Thomas found what he called a "dried up abscess formation. He looked upon the case as a Medical curiosity and gave no further particulars

concerning the case.

Hand (17) is credited with describing the first case in 1893. However he did not realize he was describing a disease entity for the first time. The characteristic triad of exophthalmos, bony defects and diabetes insipidus was present. He thought that it was a rare form of tuberculosis or syphilis, in other words on an infectious basis.

Kay (11) in 1905 described a case which had the characteristic triad. He thought that it was due to a lesion in the neighborhood of the 4th ventricle.

Schuller (4) in 1915 described three cases of hypophyseal dysostosis in which he described the characteristic triad.

In 1919 Christian (4) brought to light a case in which the triad was present.

Thompson, Keegan, and Dunn (36) in 1925 described a case in which a very complete autopsy report was given.

In 1928 Rowland (29) reported a case and reviewed the literature very completely up to the time the article was written. He is the one to whom the credit is given as definitely classifying it as a disturbance in lipid metabolism.

Since Rowland's contribution, numerous cases have been reported by various men.

In my opinion there have been many cases of Hand-Schuller-Christian disease which have been diagnosed as some other disease and likewise there have been cases reported of Hand-Schuller-Christian disease which after reading I would hesitate to call them that.

#### ETIOLOGY

The actual etiology is unknown. In reviewing numerous cases I've found that climate and locality in no way influences the disease. There is no evidence that season or occupation affects the frequency of the disease. According to the cases I reviewed and to numerous authors there is no correlation between race and the frequency of the disease, however. Chester and Kugel (3) say that the disease has no familial or hereditary tendencies, (20) however, Herzenberg reported two cases in one family (3). This is the only report of two in the same family.

Age seems to be a relatively important factor. Chester and Kugel (3) state that fifty percent of the cases are children less than 5 years old. In averaging the age of onset Horsfall and Smith (22) found that six and fifty six one hundredth years is the average age of onset. The oldest case in their report being forty years old and the youngest being 21 months.

Males seem to be affected more often than females. Horsfall and Smith (22) found the ratio to be males 3.1 to females 1.0. Chester and Kugel (3) found the ratio

to be 2:1 with males predominating. I did not compute male-female ratio, but the incidence of the disease in cases I reviewed there was a predominance of the disease in the male.

There is no immunity to the disease. In reviewing the literature I found no reference to immunity and most case reports stated the condition but none reported a complete cure and recurrence.

There seems to be two predominant excitatory factors, that of an infectious nature and that of a traumatic nature. As one reviews the cases one finds that this condition is preceded by some infectious disease. The first case reported by Hand (17) was preceded by an infection. His second case had scarlet fever six months preceding this disease. Schuller (4) had two cases preceded by whooping cough 6 months before. Christian's (4) case had mumps four months before the case became under his care. Groch and Stifel's (15) case had had a draining left mastoid for seven weeks before their attention was called to the case. Thompson, Keegan and Dunn (36) reported a case which had never completely recovered from the measles. The preceding reported cases are among the first cases reported, and all show evidence that infection might be an exciting factor. Numerous other reports since that time has shown an infectious disease preceding the Hand-Schuller-Christian disease.

Numerous other reports make no mention of any infectious disease preceding the disease. However it appears to be an important excitatory factor.

Trauma especially of bony skeleton seems to be an important excitatory factor. Griffith, (12) Kellogg, (24) Wynkoop and Hadley, (41) and many others reported the presence of a bony defect at the site which had previously been traumatized. This leads one to believe that trauma plays an important role as an excitatory factor.

Christian and Schuller (4) thought it to be a disturbance in the secretion of the pituitary that was responsible for the condition. This was based on the fact that pituitary extract controlled the diabetes insipidus.

Several theories have been put forth as the cause. (8)

#### 1.- Neoplastic Theory

Conclusions were drawn from the character and disposition of the tumor masses in various organs. Kyrklund and Dietrich (8) considered lesions in the organs to be tumors of sarcomatous growth. Dietrich (8) considered them malignant tumors which had the ability to metastasize, and that the neoplasm was secondary to trauma.

#### 2.- Inflammatory disease

Hand-Schuller-Christian disease usually follows some intercurrent infection of childhood and that it is a change of inflammatory foci and fibrosis in conjunction



with the deposition of lipid cells.

The inflammation is considered to be primary and the fibrosis and neoplasm secondary to some toxic or infectious agent. (8)

### 3.- Lipoid Metabolism Disturbance

The disease is now thought to be a lipid metabolism disturbance and allied to Gaucher's disease, Niemann-Pick disease, and Amaurotic family idiocy. (8)

Rowland (29) was the first to state that it was a disorder of the lipid metabolism which was the primary phenomenon and that the infiltration of the reticulum cells was a secondary phenomenon due to the lipoidemia of his patient. He was of the opinion that lipoids and other substances when in excess in the body fluids become pathogenic to the individual. At first irritation of the vessel walls occurred, then a perivascular cell infiltration took place, the lesions increasing in size as a result of a progressive blockage of the reticulo-endothelial system.

Epstein and Lorenz found that Hand-Schuller-Christian disease could be distinguished chemically from the other diseases resulting in lipid granulomatosis. Upon examination of a lesion they found that it contained a large amount of cholesterol and by fractional analysis that the lipid content showed a reversal of the usual phospholipid: cholesterol ratio. These findings were

later confirmed by Kleinman and Cowie - Magee. (6)

The other diseases which are characterized by a disturbance in the lipoid metabolism are; 1.- Gauchers syndrome, a lipoprotien of the cerebroside type which initiates the morbid anatomy. 2.- Neiman Picks syndrome, which is associated with a phospholipid tissue deposit and 3.- Tay Saches syndrome, based on a cerebroside protien derangement. (1)

Rowland (29) from his own findings and those of Epstein and Lorinz (29) came to the following conclusion. 1.- The reticulo-endothelial system is infiltrated by certain substances. According to this interpretation the change is essentially chemical. Lipoid and in fact all sorts of metabolic products, find particularly receptive cells in one part or another of the system, but the lipoids because of their physio chemical nature are the most often observed. 2.- The idea of abnormal activity of the system in connection with lipoid metabolism is purely speculative. 3.- The changes depend primarily on an increase of lipoids in the body fluids and secondarily on the duration of the condition of the blood and local blood and lymph supply. 4.- A rise in amount of lipoid in the body fluids or an increase through stasis may result in storage and even after sufficient length of time, when the lipoid content of the body fluids is

so low as to appear normal, the lipophilic substances sometimes come into view. 5.- Trauma and inflammation predisposes to storage and there is without a doubt other underlying factors. Storage occurs when there is increased activity of the cells. 6.- Disturbances of circulation of the most varied kinds play a part. This is evidenced by the fact that a reversibility of the process with the decrease in hypercholesterolemia is occasionally observed. The tissues are not necessarily injured by such storage, unless secondary reactions in lesions have already taken place. Certain accessory factors predispose to localization, but hypercholesterolemia itself suffices to produce lipid storage. 7.- Even the considerable hypercholesterolemia does not always provoke lipid storage. This indicates that there are unknown elements in the problem. The biological agents in taking up of lipid substances are the reticulo-endothelial macrophages. The chemical nature of these cells are variable and the extent of infiltration varies in each case. (29)

According to Aschoff, the reticulo-endothelial system is an intermediate agent of metabolism between the blood and the tissues. Besides playing a prominent part in metabolism and especially in lipid metabolism, it is probable that this system of cells is concerned

in the formation and distruction of blood.

The question immediately arises as to whether Hand-Schuller-Christian disease was a disturbance in the Cholesterol metabolism or was it due to some disturbance in the reticuloendothelial system. Kaiserling and Orgler(29) were the first to describe the double refractory bodies in the cell,they believed that the double refractory bodies originated there.

Virchow (29) was of the belief that the fatty changes were a mark of degeneration.

Pick and Pinkus, (29) Aschoff,(29), Kawamura, (29) and Anitschow (29) noted that the xanthoma cells had phagocytic properties and regarded the change as an infiltrative one. Aschoff noted that reticulo-endothelial cells had a special affinity for lipoids.

Heck (29) expressed the opinion that the appearance of cholesterol in the tissues and the appearance in the blood have a common origin. A fundamental principle of retention of cholesterol is a physiological change in state which differs in every case. (29)

Thamhauser and Mafendantz (35) contended that this condition is due to a disturbance of the cholesterol metabolism within the cell. Jason and Abraham (23) believed that the development is first a focal hyperplasia of the reticulo-endothelial elements of the bone marrow.

Turner, Davidson and White (37) concluded that there was no evidence that xanthomatous reaction is primarily an irritative hyperplasia of the fibrous tissue followed by a fatty or lipoid infiltration of the connective tissue. The change may be due to the presence in the tissues of cholesterol fatty acid esters deposited from the blood, but the first reaction noted in these areas was the appearance of numbers of mononucleated cells resembling endothelial cells. These cells gradually change into large cells which are multinucleated and finally these multinucleated giant cells correspond morphologically to the multinucleated foreign body giant cell. These cells are found in the vicinity of blood vessels, the xanthomatous nodules being very vascular. Lipoid and fatty substances are taken up by both large mononucleated and multinucleated cells which gradually become vacuolated until the typical foam cells are produced. Davidson (40) again raises the question - "Is the fat and lipoids in these cells due to simple ingestion of infiltration or that of degeneration of the cytoplasm?" There is more evidence in favor of infiltration. The nucleus shows no degeneration during the process of vacuolation of the cytoplasm. The nucleus remains more or less intact for a considerable time after the whole cytoplasm becomes replaced by fat. The presence of plasma cells also indicates some reaction to extracellular disturbance.

All of these findings are evidence of a process of infiltration (37)

White (37) found that in normal fat absorption there is first a variable but steady increase in fatty acid accompanied by an increase in lecithin. At a later stage of absorption the cholesterol is increased. In persistent lipemia, cholesterol becomes more prevalent than the lecithin. What ever the defect it seems to result in the deposition of fat in certain areas in such an altered physiochemical relationship that the re-transportation and ultimate utilization is hindered by the fact that the melting points of cholesterol fatty acid deposits in the skin are considerably higher than that of normal temperatures of the body and as a result would be less subject to agents which normally affect the transport of fats at body temperature.(37)

Sparrow and Fetner (32) conclude that if the xanthoma cell is of reticulo-endothelial origin and the xanthomatous lesion is a hyperplastic reaction of the reticulo-endothelial system resulting from an infiltration of lipoids in excess in body fluids is true, then one should expect repeated manifestations of the disease until a fundamental change has occurred in the lipid metabolism.

Weber (27) states that histocytes give rise to both foamy cells and giant cells and suggests that these wandering phagocytic cells accumulate in a tumor

like mass merely in response to a call to the phagocytosis of foreign bodies, some of them fusing together to form foreign body giant cells. The phagocytes remain until either the foreign body is removed or they themselves die in the attempt to remove it or render it innocuous.

Morrison (27) from his findings concluded that Hand-Schuller-Christian disease is a response of the reticulo-endothelial system to an unknown infective agent which has a predilection for the bones of the skull and other flat bones.

Grady and Stewart (14) say that this condition is a disturbance of the lipid metabolism or of lipid excretion resulting in the storage of lipid substance in granulomatous lesions of various organs and tissue. There is a phagocytic activity on the part of the cells of the reticulo-endothelial system which remove an excess of lipoids in certain area in which infection or trauma, particularly of the bone or skin may stimulate a collection of histocytes.

In reviewing the literature, Lichty (25) said that the avidity of the cells for lipid or a compensatory mechanism resulting from the fat metabolism is problematical.

Hertzog, Anderson and Biebe (21) reported a case that resembled reticulo-endotheliosis both clinical and histological but it also resembled Hand-Schuller-Christian's disease in the wide spread storage of cholesterol. They regard Hand-Schuller-Christian

disease as primarily a disease. Possible consideration was given to the fact that 1.- This case may have been a transitional stage between Hand-Schuller-Christian disease and a malignant lymphoblastoma. 2.- or that this case was an atypical case of Hand-Schuller-Christian disease. These men also considered the fact that it is to be expected to encounter a condition that presents a condition common to more than one of the recognized syndromes.

If the reticulo-endothelial system was the primary involvement in Hand-Schuller-Christian disease then the cells throughout the reticulo-endothelial system should contain a large amount of cholesterol. This is not true, the reason being that while the proliferation of the reticulum cells in Hand-Schuller-Christian disease show large numbers of cholesterol containing foam cells in certain organs. These cells may be absent altogether in the proliferation of the reticulum cells in other organs. (14, 26) Thus the proliferation of reticulum cells can obviously take place without a trace of any local accumulation of lipid in the unaffected organ. (38)

Hypercholesteremia concomitant with Rowlands theory is certainly not demonstrable in every case of Hand-Schuller-Christian disease, and on the other hand it may be present in other cases of reticulo-endotheliosis that are not classified as Hand-Schuller-Christian disease.



In those cases in which hypercholesterolemia is present it may well be a secondary phenomenon resulting from the proliferation of the reticulum cells (38) I think that Wunkoap and Hadleys(41) conclusions will agree with most authors. They believe that Hand-Schuller-Christian disease is due to a disturbance of the lipid metabolism, with occassional but inconstant increase in the blood cholesterol and with subsequent deposition of lipoids, chiefly in the form of cholesterol or its esters in the various organs and tissues of the body as well as the reticulo-endothelial system. Local trauma or infection may determine the location of the deposition of the lipid material but apparently neither is necessary.

PATHOLOGY

Grossly in the early stages the lesion is a yellowish rubbery mass and variable in size and is fairly well demarkated. The lesion in a late stage shows a connective tissue proliferation with fibrotic replacement of the foam cells. Eventually there is a complete fibrosis of the lesion (25) If the lesion is in a bone, the area has an impaired blood supply and eventually becomes necrotic and dissolution of the bone results.(5) The marked fibrosis which occurs is due to the irritation of the abnormal presence of a fat deposition (37)

The basic lesion is a chronic noninfectuous abacterial, inflammatory granuloma due to the deposition of various lipoid substances in the involved tissue and should be termed "lipoid granula." This lesion is thought to be as characteristic of the Hand-Schuller-Christian disease as the gumma and tubercle are for syphilis and tuberculosis respectively.

Microscopically the lesions are characterized by

- 1.- Characteristic foamy lipoid cells, the specific element that contains the lipoid substance.
- 2.- Inflammatory cellular elements, a response of the tissue to the lipoid tissue.
- 3.- Connective tissue proliferation (3).

Other characteristics listed by Turner, Davidson and White (37) are:

- 1.- Appearance of numbers of mononucleated cells, endothelial in type. Their nuclei were either round, oval or elongated with considerable cytoplasm.
- 2.- Cells increased in size and the number of nuclei increase until they have an appearance of multinucleated foreign-body cells.
- 3.- Vacuolation is not seen in the commencing mononucleated cells which have not yet changed to the multinucleated cells.
- 4.- Vacuolated cells or foam cells showing no degeneration of the nuclei are found.

In a fresh state the protoplasm of the typical "foam cell" is filled with small droplets of lipoid substance which dissolves when treated with ordinary fixing reagents. This leaves a fine areolar network within the protoplasm and gives the cell a vacuolated or a foamy appearance (28)

The greatest number of foam cells are found in fairly old granulomas, especially those showing necrosis. On the other hand foam cells are missing or occur only singly in the more recent proliferations of the reticulum cells.

If the lesion is healed or in old lesions the cholesterol is carried away, and the necrosis is replaced by connective tissue and the final stage is a collagenic scar. (38)

Chemically the lipoids show no marked difference from those of normal persons, except in the xanthomatous masses. Epstein, Lorenz and Kleinman, and Cowie and Magee (6) obtained the same result upon the analysis of the material in the masses. The lipid content was high - 6.96 to 10.37 gm./ 100 gm. of tissue, at least 40 - 50 % of total lipid content. The phospho lipid content is much lower than in normal tissues. The lipid content and cholesterol content were very similar in the xanthoma of bone and of the dura. The phospholipoid content of the xanthoma of the bone marrow was twice as high as that of the dura xanthoma. No explanation can be given for this.

Kleinman (6) reported a high cholesterol content in the liver and spleen. Cowie and Magee's findings were normal. Kleinman also found the phospholipoid to be much lower in the liver and spleen than did Cowie and Magee.

The phospholipoid ratio is reversed in the xanthomous masses. Normally the phospholipoid is higher than the cholesterol. (6) At autopsy lesions are found in various parts of the body. Probably the earliest and still the most complete report of the autopsy findings is that by Thompson, Keegan, and Dunn. (36) The frontal and parietal bones of the skull are the most commonly involved bones of the skull. The skull is the most common bony structure involved and is frequently the only area of the skeleton which shows bony defects.(22) The destruction of the membranous bone of the skull may not be extensive or it may be massive. In the case of Thompson, Keegan, and Dunn (36) there was a massive destruction of the membranous bone. The edges of the bone were abrupt and sharp and only a bony framework was left of the calvarium. The membranous calvarium could be cut with the scissors or a knife. The dura mater of this area was rather firmly adherent to the cranium, and the inner surface of the dura mater was mottled by a dull yellowish tissue.

Microscopic examination of this area revealed a lining layer of large oval cells with sharp borders, with clear slightly granular cytoplasm and a small compact centrally placed nuclei. The cytoplasm contained a variable amount of lipoid material in finely divided forms.

The cranial membrane that this fatty layer lined consisted of a typical dense white fibrous tissue with no evident lines of cleavage between the dura proper, the endostium, the absorbed cranial bone, and the periostium. The dura of the falx cerebri and that beneath the normal bone had a normal smooth, white glistening appearance and stripped away from the bone easy.

Microscopic examination of the bone edge of the lesion revealed a highly cellular tissue composed chiefly of large cells with eosinophilic cytoplasm and large reticular nuclei. These cells appeared to have fused to form large multinuclear foreign body giant cells. The nuclei were mainly located centrally, however some were located peripherally. The remaining cells of this soft tissue consisted of lymphocytes, plasma cells and polymorphonuclear cells and eosinophilic cells. The larger areas of bone by transmitted light showed round or oval decalcified areas of variable size, bound by the same cellular tissue at the border. The dura and periostium were adherent over these areas. (36) Chester and Kugel (3) found osteoclasts throughout the edge of the lesion and osteoblasts in the contiguous bone.

In the case of Thompson, Keegan and Dunn (36) the floor of the skull showed extensive defects in the anterior and middle fossae. The destruction of bone was

so distributed in the anterior fossa that the entire medial borders of the supra orbital plates were freed and could be depressed easily by a finger. The left orbital plate was loosened by the extensive bone destruction. The temporal portion of the frontal bone was also involved. The posterior fossa was of normal shape except the anterior clinoid processes. The anterior clinoids appeared to be depressed, due to the lesser wing of the sphenoid bone and the supra orbital plates. There was an area of bone about 8-x 5 mm. decalcified in the right anterior inferior region of the pituitary fossa. This decalcification extended forward under the lesser wing of the sphenoid bone. Dr. Thompson, Keegan and Dunn thought that the exophthalmos could be accounted for by the loosening and depression of the supra orbital plate. (36) Atkinson (1) agreed with the above men as to the cause of the exophthalmos but also added that part of it was do to a lipoid mass at the base of the orbit in the orbital fossa. (1)

In the greater wings of the sphenoid the decalcification was extensive and occurred in an irregular manner. A mixture of dense yellowish white fibrous tissue filled the large defects. A grayish cellular tissue was present at the bone margins. Microscopic examination of the lesion showed it to be the same as the lesions in the other areas of the skull.

There was extensive decalcification of squamous portion of both temporal bones, however the petrous portion, the mastoids, and the middle ear were not involved.

There was a dense white fibrous tissue filling the sphenoid sinus. The tissue growth also obliterated the ethmoid cells.

The sella turcica is the next most common area, for bony defects to occur. Rarification of this area is reported many times in the X-ray findings of the case reports, however in most cases, the X-ray findings were not confirmed by autopsy as the case had not gone to autopsy at the time the article was written. (36) Christian (4) found that the sella turcica was enlarged somewhat and was slightly flattened. He thought that there was a bony defect which involved the sella turcica. Schuller reported the sella turcica quite changed. He found that only the dorsum of the sella was present, and that the anterior portion of the floor was noticeably deepened. (36) Thompson, Keegan and Dunn noticed no marked change in the contour but there was a defect in the floor of the sella. (36) Chester and Kugel, and Davidson reported the sella turcica to be normal. (3,8)

The bony defects are alike microscopically no matter what bones they may be present in. According to Horsfall and Smith (22) the skull is the most commonly involved of all bony structures. By the survey of the cases recorded they listed the bony areas according to the frequency which they were involved. They found that it

occured in the following order - skull, pelvis, long bones, mandible, sella turcica, ribs, vertebrae, maxilla and scapula.

I found no case history reports which mentioned pathological fractures occurring. There were numerous cases mentioned various bony deformities and changes in gait and stature due to bony defects in various parts of the osseous system.

The region of the hypophysis is probably the second most common area of involvement. The hypophysis was thought to be the source of the diabetes insipidus since the first case of the disease was reported and it was suggested by some that the sole source of the condition causing the common triad of bony defects, diabetes insipidus and exophthalmos. Hand (17) thought that endocrine disturbance of the pituitary was the cause. Schuller and Christian had the same idea as to the cause. The reason for their belief was that pituitary extract would relieve the diabetes insipidus but there would be a reoccurrence of the disease when the pituitary extract was discontinued. (4)

Thompson, Keegan and Dunn (36) pointed out that the pituitary had something to do with the laying down of bone in the skeletal growth and that there was no evidence that by a reverse process it could cause a massive destruction of disseminated areas of normally built bone.



Thompson, Keegan, and Dunn (36) found the hypophysis to be of normal size and of reddish color. The infundibulum was of normal size and appearance at its junction with the gland. It was 1--2 mm in diameter. A saggital section of the pituitary gland had a normal appearance.

Microscopically the anterior lobe was normal. The pars intermedia appeared to be rather poorly defined. It was identified by its position and the fibrous stroma, indefinite cell elements and a few alveoli containing colloid. The pars posterior was not entirely normal. There was an increase of fibrous tissue with a slight infiltration of polymorphonuclear cells and eosinophilic leukocytes. Small foci of degenerated cells were scattered throughout the pars posterior. Foci of basophilic mononuclear cells resembling lymphoid follicles were found at the periphery. This condition present was considered a subacute degenerative and inflammatory process of a rather recent origin. At the base of the infundibulum there was a rather dense, white fibrous stroma. Extending into it there were the normal cellular elements of the pars posterior and the glandular elements of the pars anterior. There was a tissue composed chiefly of faintly stained large eosinophilic giant cells with a moderate infiltration of smaller mononuclear cells surrounding the stroma. This tissue was thickened on the anterior surface of the infundibulum and had a few glandular

cord and alveoli embedded in it. It could be traced a short distance into the superior portion of the pars anterior of the hypophysis.

The dura was intact and surrounded the hypophysis. It was a dense white fibrous tissue. Attached anteriorly to its outer surface there was a cellular tissue composed of pale eosinophilic cells and a varying amount of fibrous stroma. This cellular tissue was infiltrated with mononuclear cells, polymorphonuclear cells and eosinophilic cells. Apparently this tissue had arisen from an adjacent decalcified area of bone in the right anterior wall of the pituitary fossa. It did not extend through the dura. The dura surrounded a rather narrow extension of the pars posterior. The center of this extension showed some necrosis. There was quite a thick fibrous layer above the pars posterior. This layer was continuous with the fibrous layer which was continuous with the fibrous septum of the pars intermedia and also with the central fibrous strand of the infundibulum. (36)

Davison (8) reported loose areolar tissue surrounding the pituitary gland. This tissue contained the characteristic "foam cells" with occasional lymphocytes. In the anterior lobe there was a striking decrease of the oxyphilic cells. The region of the pars intermedia and posterior

lobe was invaded by groups and islets of acidophilic and basophilic cells. Chester and Kugel (3) in their article state that the areolar structure was well preserved in their case. The eosinophils were reduced in number, irregular and diffusely scattered throughout the anterior lobe. Eosinophils were present in great numbers in the posterior lobe. Some of the chromophilic cells contained isotropic fat droplets. Basophils were present in large numbers in the posterior lobe.

Posterior and lateral to the anterior lobe, there were several small cysts lined with squamous columnar and occasionally ciliated epithelium. These cysts contained a gelatinous material. The neuroglial elements of the posterior lobe were closely compressed. The interneuroglial spaces were practically obliterated. The entire lobe was atrophic and fibrotic with a marked round cell infiltration (3) The tuber cinereum was involved in both Thompson, Keegan's and Dunn's (36) case and also in Davison's (8) case.

Thompson's Keegan's and Dunn's (36) case showed a yellowish involvement extending as a bulbous enlargement from the infundibulum into the tuber cinereum. This enlargement was distinctly outlined in the median sagittal section from the optic chiasma in front and the gray brain substance above. The region of the pathological condition was darker stained and was 3 mm. in diameter.

The upper border was somewhat indistinct and was histologically similar to the soft tissue at the cranial bone edge. There were very few blood vessels in this area and the process of fibrosis appeared to be underway. Further up into the tuber cinereum microscopic examination showed a central strand of dense fibrous tissue. This was continuous with a very dense fibrosis which compressed the entire area of junction with the nervous tissue.

There was a marked perivascular mononuclear cell infiltration, where the pathological condition extended into the brain tissue. The perivascular infiltration extended a short distance into the nervous tissue beyond the fibrosis. The characteristic eosinophilic cellular tissue surrounded the dense fibrous tissue of the tuber cinereum and extended upward to the same level as the perivascular infiltration in the nervous tissue. Multinuclear giant cell formation was quite prominent in this region. A focus of dense small mononuclear cell infiltration was present at the base of the fibrous one. There was a sharp line of separation anteriorly between the optic chiasma and the cellular zone. The upper and lateral part of the chiasma showed a slight perivascular cell infiltration. (36)

Davison's(8) case showed areas in the tuber cinereum which were replaced by fibrosis and gliosis. In some

areas, the fibroblasts had a parallel arrangement, in other areas they appeared in whorls. At the periphery there was a lymphocytic infiltration. A few vessels showed perivascular infiltration and there was some new vessel formation. No giant cells were seen.

The ganglion cells in the substantia grisea, periventricular nuclei, nuclei tuberis and nuclei supra optici were diminished or destroyed. They contained no pigment and were replaced or surrounded by fibroblasts.

(8). Grossly cerebral vessels were congested. The convolutions appeared normal. In the parietal region the convolutions had a slight spongy appearance (8). Thompson, Keegan, and Dunn reported the cerebral hemispheres to be entirely normal in color conformation and size. (36)

Microscopic examination showed scattered plaques of demyelination in the white matter of most of the cerebral convolutions and particularly those of the parietal region. The myelin had completely disappeared and was replaced by irregular shaped swollen cells.

Fragmentation of the myelin sheaths were at the periphery of the demyelinated areas. The cytoplasm of the cells was pale and the nuclei were irregular and dark stained. Multinucleated cells and mitosis were occasionally seen.

The destructive changes in the axis cylinders were not marked as those seen in the myelin sheath. Healthy axis cylinders were seen in areas of complete demyelination. Some axis cylinders appeared to be slightly swollen while others were fragmented and had corkscrew shapes.

Glia tissue replaced the destroyed areas. The glia cells were large, irregular in shape and had processes. These cells were surrounded by glia fibers which had a criss cross arrangement. There were demyelinated plaques in the superior and inferior parietal, inferior temporal, hippocampal, dentate and fusiform gyri. The splenium of the corpus callosum and the optic radiations showed demyelinated plaques.

Small plaques were found throughout the corpus callosum, internal capsule, anterior commissure, thalamus, globus pallidus, fornix and the columnar fornices. Glia cells were found in the substantia nigra, globus pallidus and corpus luyii. The glia cells had replaced some of the ganglion cells of these regions. There was a warty outgrowth in the third ventricle and ependymal lining was slightly thickened. In the mid brain and pons there were scattered demyelinated plaques in the lateral lamniscus, brachium conjunctiva, medial lamniscus, brachium pontis and pontile fibers. The ependyma of the aqueduct was thickened and contained

cells which looked like multinucleated giant cells. The decussation of the brachium conjunctivum, left sensory nucleus of the fifth cranial nerve, and right and left fifth cranial nerve as emerged from the pons, contained small plaques. The ganglion cells of the left fifth cranial nerve nuclei were diminished in number. Some cells contained poor chromatin material and in others it was destroyed.

Sections of the cerebellum and medulla oblongata showed plaques in the brachium pontis, brachium conjunctivum, posterior longitudinal bundles and the right pyramid. (8) The plaques contained compound granular corpuscles and giant glia cells. The giant glia cells are known to originate from the plasma giant cells. The microglia gives rise to the compound granular corpuscles. It was difficult to tell if these cells were related to the foam cells of other organs. (8) Upon further investigation Davison found the typical "foam cells" in the plaques (9).

Lipoid lesions have been found surrounding the optic nerve by Horsfall and Smith, and Wheeler. (22,39) Similar lipoid lesions were found in the middle and internal ear.

The lungs are frequently involved. Horsfall and Smith found the pleurae smooth and glistening with a

few small firm yellow nodules on the visceral surface. (22) Davison found the lungs to be a grayish yellow with stellate shaped nodules. He found "foam cells" in the lung. (8) Thompson, Keegan and Dunn(36) found the pleurae to be free from adhesions and no nodules. Upon microscopic examination they found extreme interstitial fibrosis. The alveolar walls were thickened to a point of obliterating normal lung architecture. There was a moderate infiltration of mononuclear cells into these alveolar walls. Only a few polymorphonuclear cells were present. Some of the thickened septum were covered with a single layer of cuboidal epithelium. In places it appeared to be desquamated and formed masses of cells.

The bronchioles were slightly enlarged and lined with a hyperplastic layer of columnar epithelium. There were no cellular elements in the lumen. Turner, Davidson and White (37) found lesions in the right apex. There was an avascular fibrous tissue which was infiltrating the lung and was gradually replacing the alveoli and bronchioles. Cells containing fatty material were at the advancing margin of the fibrotic area. Areas of numerous small round mononucleated lymph cells were seen. The heart doesn't seem to be involved with lesions. I could not find any records of lesions being present in the heart. Horsfall and Smith (22) reports that the



myocardium was firm and of a granish red color and no valvular defects. Thompson, Keegan and Dunn (36) reported that the heart was slightly enlarged and was otherwise normal.

Of the liver, Thompson, Keegan and Dunn (36) found the liver cells well defined with little degeneration or vacuolation. The sinuses were dilated and contained a few polymorphonuclear cells. There was no fibrosis of the portal system. The gall bladder and ducts were normal.

Horsfall and Smith (22) found the liver cut surfaces a yellowish brown and the normal markings poorly defined. Chester and Kugel (3) found parenchymatous degeneration of the liver. The stomach and intestines were found to be normal by Thompson, Keegan, and Dunn, (36) Chester and Kugel (3) and Horsfall and Smith (22) I found no other reports of pathology in the stomach and intestine.

Chester and Kugel (3) reported a slight autolysis of the pancreas. I could find no other reports of pathology of the pancreas.

Slight enlargement and engorgment of the spleen was reported by Thompson, Keegan and Dunn (36). Worsfall and Smith (22) reported an irregular increase of the reticular tissue of the spleen with scattered infiltration

of large lipid containing cells. There were no focal aggregation of cells and no giant cells. Lymph follicles appeared numerous, small, irregular, and compressed. A moderate amount of parenchymal degeneration of the kidneys was reported by Chester and Kugel (3) Slight enlargement of the kidneys was reported by Thompson, Keegan and Dunn.(36)

Suprarenal gland pathology was reported only by Chester and Kugel. (3) They found two definite ganglionic masses in the medulla, the muscular coat of the vein hypertrophied, the fascicular layer markedly atrophied, and a moderate amount of lipid substance in the glomerular layer.

General enlargement of the lymph nodes was reported by Horsfall and Smith (22) Chester and Kugel (3) reported a cellular infiltration of the gums, consisting of plasma cells, lymphocytes and enlarged cells with vesicular nuclei. No lipid substance was present.

The skin lesions found at autopsy were described by Horsfall and Smith.(22) They found that there were two distinctive types, 1.-the old papular lesions and 2.- the recent lesions. In the old papular lesion there were closely packed pleomorphic cells which had infiltrated and replaced focal portions of the dermis and subcutaneous tissue. The characteristic cell type was a large, pale, oval or round cell with a very abundant vacuolated cytoplasm. The nucleus was well stained and was frequently eccentric.

Scattered among the characteristic cells were lymphocytes, plasma cells, eosinophils, and large polymorpho nuclear cells, and numerous large multinuclear giant cells. There was a moderate amount of fibrous tissue. There were a few capillaries seen. In the recent lesion there were focal collections of relative large pale staining cells of oval, polygonal or fusiform shape. The nuclei of these cells were large, well stained and had prominent nucleoli. The cells were closely packed with only a small amount of loose fibrillar tissue. No giant cells were seen. The lesions were consistently found surrounding hair follicles or coil glands which they compressed. The overlying epidermis was frequently invaded and replaced. In many instances the epidermis remained simply as thin flattened layer of homogeneous and keratinized cells.

SYMPTOMATOLOGY

The clinical manifestations of the disease depend upon two things; 1.- The local effect of the lesion, which may become large, 2.- the degree of the associated general metabolic disturbance (28)

Henachen gave seven clinical groups or variations of the disease. One of these variations is always present plus other inconstant symptoms. (19)

The seven clinical groupings are:

1. Skeletal transformation, exophthalmos and diabetes insipidus. This triad is known as the Hand-Schuller\*

Christian Syndrome.

2. Skeletal transformation, exophthalmos without diabetes insipidus.
3. Skeletal transformation, diabetes insipidus without exophthalmos.
4. Skeletal transformation without exophthalmos and diabetes insipidus.
5. Diabetes without skeletal transformation.
6. Disturbance in growth.
7. So called xanthosarcomatosis without skeletal transformation and diabetes insipidus.

The onset of the disease is very insidious and the symptoms and signs develop very slowly.(25) The complaints first told to the doctor are variable within the group of symptoms common of this disease.

Fraser's (11) case came in with the complaint of limp, the left hip being involved. Headaches, tenderness on top of the head, buzzing of the ears,(worse at night) polyurea and polydypsia were complaints in the case of Dauksy's .(7)

Fraser's (11) second case complained of an extensive infectuous condition of the teeth. Polydypsia and polyurea was among the first complaints on the cases of Chester and Kugel,(3) Wortis, Wolf and Dyke, (40), Fraser,(11) Davison,(8) Hemblen, arena and Cayler,(16), Thompson, Griffith, Keegan,(12) and Dunn. (36) Infected teeth were one of the first complaints of

Grosh and Stifel's (15) case, also Hankey's (18) case.

Failure to gain weight, weight loss, under development, and irritability are other early complaints. (11,12,22,&3) Exophthalmos was one of the early complaints also.

(34,4,40) "Lumps" on the head is another common early complaint. (11,12,34,40,41,18) (Hankey, Wynkoop, Hadley, Griffith, Strong, Fraser, and others.) Kellog's (24) case complained of intermittent soreness in temporoparietal area of the right side. Grosh and Stifel's case (15) also complained of a painless discharge from an ear. In discussing the signs and symptoms in order of their appearance according to Strong, (34) Skull defects occur the most frequently. The patient may not notice any lump or depression over the area of the defect but might complain of a soreness or tenderness over the involved area. (7,24)

There may be a "lump" appear on the skull. It can occur in any area. It may be painless (11,40) or it can also be quite painful. (24,18,40,12,41) It is not uncommon for the lump to appear for the first time shortly after a blow or some other form of trauma. (41,24,34,12)

The bony defects are progressive. The lumps may recede then reoccur. (34) The lump appears to be a rather soft mass just beneath the skin. It has an appearance of a sebaceous cyst. (34) The defect may be neither depressed or bulging, however it is soft and

in some cases pulsations of the brain may be in the defect, This has caused some surgeons to refuse to touch them.(4) The bony defects may occur in either membranous bone or cartilagenous bones. (3)

The skeletal pains are caused by the lipoid granulomatous changes and are particularly marked when the lesions are near the periostium.

Diabetes Insipidus may appear as the only complaint (36) or it may follow the bony defects, the interval of time varies considerable. (10)

A pituitary disturbance was thought to be the cause of the diabetes insipidus by several men who first reported cases. (17,4)

There were two views as to the cause of this condition 1.- That it was due to some pituitary disease although it was never demonstrated at autopsy. 2.- that it was due to an extrahypophyseal or basilar origin. (36)

The first view has now fallen into discard since the work of Bailey and Bremer. They have shown that lesions of the hypophysis cause temporary diabetes insipidus while lesions of the hypothalamus and tuber cinereum cause permemant diabetes insipidus. (2) Camus and Roussy (36)(French) carried out the same experiments as Bailey and Bremer and got exactly the same results. With this experimental evidence and the pathological lesions of the tuber cinereum and hypothalamus

found by Thompson, Keegan and Dunn (36) in their case, The second view of the cause of diabetes insipidus has become the most popular. The lesion causing diabetes insipidus is assumed to be in the para infundibular region of the hypothalamus. Grosh and Stifel (15) found that the water balance is maintained well in diabetes insipidus.

Pressure of bone on the pituitary has been considered a cause for the diabetes insipidus. (10,15) However, there is no evidence of intracranial pressure.

It has been pointed out that there is question as to whether the neural centers are directly responsible for the general lipoid metabolism and the diabetes insipidus or if a lipoid metabolic disturbance or an infection acts upon the neural centers. (8)

Exophthalmos is the third most important symptom of Hand-Schuller-Christian syndrome. Exophthalmos usually appears after the bony defects, however, it can appear before. This condition may be so slight that it is found only at the time of the examination. (7,15,11) or it may be one of the complaints that brings the patient to the doctor. (22,40) Excessive protrusion of the eye may make one eye look smaller than the other. (1) Exophthalmos can be so great that on crying or coughing the eye looks as though it might pop out of the socket. (20) This condition may be unilateral but it is rarely absent. (3)

Several reasons are given for the exophthalmos.

- 1.- It is the result of the flattening and linking down of the orbital bone from the bone deficiency and formation of lipoid granuloma at the base of the orbit.(1)
- 2.- Lipoid granulomatous involvement of the sympathetic fibers to the mullerian muscle may be a factor.(3)
- 3.- Intraorbital lipoid granulomas may be a factor. (22)

The triad of skull defects, exophthalmos and diabetes insipidus commonly occur together, as has been mentioned previously. The bony defects usually appear first and later as the disease progresses the exophthalmos and diabetes insipidus appear. (10)

Pelvic defects are of the same type of lesion as those found in the skull except that they can not be found during a physical examination. The ilium and sacrum are probably the bones most often involved. (36,3,11,15)

Cutaneous defects may appear as an eczematous rash. The rash consists of small hemorrhagic papules, pinhead size and pustules, which are very persistent to treatment.(40) Hamblen, Arena, and Cuyler (16) reported yellowish nodular skin lesions with a dermatitis. Biopsy showed a lipoid granuloma with typical foam cells present.

Arrest in growth is a rather common complaint of the parents when the victim is a child.

Jaw lesions and gingivitis is rather common also.



When there is involvement of the jaw there is usually a gingivitis. The patient gives a history of having lost teeth and his remaining teeth being loose.(8,15,3,18) Early oral manifestations are 1.- Pain in the tooth. 2.- Multiple areas of decalcification. 3.- Stomatitis. 4.- Looseness of teeth. Dentists should always be on the alert for this condition and probably more of these cases would be diagnosed.(30) Femur defects are bony defects which are of the same character as the bony defects of the skull. Numerous cases have been reported where the disease is more generalized. Temporal bone defects are common. The mastoid bone is frequently the area of involvement when the temporal bone is affected.(28) A common complaint is that of a draining ear. (3,8,22,40) The Hand-Schuller-Christian disease seems to be associated with chronic otitis media and mastoiditis when the ear is involved. (14, 31, 5, 28)

The wound following a mastoidectomy, when the area is involved with a lipoid granuloma, is slow healing and drains for long periods of time.(28)

Pulmonary involvement is invariably fatal and the death is in the form of cardiac failure due to impairment of circulation. (36, 17)

Lymphadenopathy may or may not be present and when it is it is in a variable degree.

Fever is noticeably absent when one reviews the cases. This was my observation as I could find no reference as to how common it was. I found fever to be present in patients who had secondary infections complicating the condition and in those patients who were in the last stages just before death, in the cases I reviewed.

Vertebral defects are the same as the bony defects of the skull and other bones of the body. (36)

Dystrophia Adiposa genitalis is not a common condition. Thompson, Keegan and Dunn (36) reported this condition to be present in their case. Davison (8) reports that one of his cases (male 27 yrs) had a typical female hair distribution.

Other bone defects include defects of the humerus, clavicle, ribs and other bones occasionally. They are usually present when the disease is generalized. The pathology of the lesions are the same as for all bony lesions- lipoid granuloma and are discovered by means of X-ray

Neurological findings are extremely rare.

Merrit and Page (26) reports:

1. Lower extremities hyperactive
2. Briefly sustained ankle clonus.(Chester and Kugel (3))
3. Plurred vision.
4. Unsteady gait and generalized tremor increased on the right side.

5. Inconstant ataxia in the upper extremities.
6. Tremor- more marked when pituitary extract was withdrawn.
7. Ankle clonus--right side.
8. Equivocal Babinsky sign.
9. Positive Hoffman--right side.
10. Concentric restriction of visual field.
11. Sensory disturbance --Left fifth cranial nerve area due to an old seventh nerve lesion or involvement of the gasserian ganglion.

The neurological consultants decided that the above findings were due to the extension of the pathology to the adjacent portion of the cerebral hemisphere on the left side.

Davison (8) reported:

Early finding:

1. Horizontal nystagmoid twitching in both directions.
2. Peripheral paralysis of the left side.
3. Loss of taste--left anterior 2/3 of tongue.

Later findings: (15 months later)

1. Dragging of right lower extremity. Osteomyelitis of the femur.
2. Diminished power - all extremities - mostly on rt. side.
3. Generalized hyperreflexia
4. Bilateral ataxia

5. Suggestive Gordon Holmes sign - right side.
6. Dys diadokokinesis bilaterally.
7. Coarse tremor - in outstretched hand.
8. Slight intention tremor of hands.
9. Normal sensation throughout body.
10. Left palpebral fissure
11. Left pupil - smaller than the right.
12. Nystagmoid jerks on extreme gaze to right.
13. Questionable pallor of right optic nerve head.
14. Hypalgesia, thermhypesthesia, hypethesia over distribution of left fifth cranial nerve.
15. Impaired taste - left anterior 2/3 of tongue.
16. Peripheral paralysis of the left side of face.
17. Slight involvement of the eighth cranial nerve.
18. Polyurea and polydypsia.
19. Libido and potency impaired.

#### LABORATORY FINDINGS

##### X-ray Findings -

The bony defects appear as decalcified areas.(22)  
 There are usually areas of decreased density. The size of the defects vary from 1 -2 mm. to 10 cm. (40) The lesions have a somewhat irregular margin and are more or less circular in shape. It suggests a punched out or a trephine like appearance. (22) Hand liked it to a moth eaten hole in a cloth or a hole chewed in a paste-board card by a mouse. (17) Defects can be in any bone in the body. (22)

### Blood Findings

There is no typical blood picture. There is usually a secondary anemia. This anemia does not occur until there has been a considerable amount of bone involvement. The white count is usually normal but may be 30,000 if there is a secondary infection present. (25) Aplastic anemia develops in a few due to the great amount of bone involvement. The red blood corpuscle appears to be normal and the differential count is not remarkable usually. (1) No foam cell has been found in the blood. (25) The blood wasserman was negative in all the cases I reviewed and there were no reports of a positive wasserman. The blood cholesterol varies from 40 mgm % to 1039 mgm %. The calcium phosphorus ratio is normal. (5)

### Urine Findings

The specific gravity varies from 1.000 to 1.010 and is albumen free. (8) Sparrow and Fetner (33) reported the only case which had sugar in the urine. Hamblen, Arena and Cuyler (16) thought that since cholesterol is the most likely precursor to various sex sterols within the blood that it would be likely to expect some alteration in the metabolism of sex sterol in a patient with this disease. The normal daily excretion is 2.7-4.0 androgenic units per day. Their patients excreted 40 units per day. They thought that this might be due to an adrenal tumor, however they ran a sodium preandiol glucuronidate (a metabolic excretion product of progesterone) test. This test was negative.

There is normally no sodium prenandiol glucuronidate in male urine unless there is an adrenal tumor. This test being negative proved that the excessive excretion of androgens in the urine was related to the general disturbance of lipid metabolism rather than to an excessive activity of the gonads or adrenal cortex. (16)

The laboratory is of no diagnostic aid with the exception of the X-ray. (22)

### DIAGNOSIS

This disease should concern many specialists namely the general practitioner, radiologist, internist, pediatrition, physiological chemist, ophthalmologist, dermatologist, neurologist, neuro-surgeon, and the pathologist as the disease involves all of these fields.(33)

The diagnosis may be made in the absence of any one or more of the symptoms. However, the defects of the skull should be made a dispensable condition for the diagnosis of Hand-Schuller-Christian disease. (41)

No one of the triad is essential to the diagnosis. Neither are gingivitis or stomatitis, which is so common early in the cases. Adiposogenital dystrophy is also non essential to the diagnosis. Any combination of symptoms or signs is possible in this disease. (33)

## DIFFERENTIAL DIAGNOSIS

Diseases to be considered in the differential diagnosis are: (3)

1. Various types of neoplasm with skeletal metastasis.
  - a. Ewings sarcoma
  - b. Sarcoma of the reticulo endothelial system.
  - c. Primary pituitary neoplasm.
  - d. Multiple Myeloma. (13) Hand-Schuller-Christian can be differentiated by the presence of one or more **signs** of the triad plus the other inconstant findings.
2. Hodgkin's Disease.
3. Various types of granulomas.
  - a. Syphilis.
  - b. Tuberculosis.
  - c. Actinomycosis.
  - d. Glanders.
4. Chronic non specific granulomas.
5. Carcinoma of prostate, thyroid, bronchus, breast, or hypernephroma.
6. The various other types of lipoid metabolic disturbances (34)
  - a. Gauchers Disease.

This disease can be differentiated by the chemical analysis of a lesion as there is an increase in lecithin. There is always a splenic involvement. It can occur at any age

and is familial disease. It is fairly benign. Females are most often afflicted with the disease.

b. Niemann-Pick Disease.

There is a hepatosplenomegaly and it is most often found in the Jewish infants.

It is rapidly fatal.

7. Osteoporosis circumscripta. (24)

This condition is an early phase of Paget's disease, it being the demineralization before the sclerotic stage. It is similar to Hand-Schuller-Christian disease but occurs primarily between the ages of 40 to 60 years.

8. Cholestratoma. (24)

Slower in the development than Hand-Schuller\* Christian disease. There is extensive involvement but usually is regular in its general contour. There may be a dense trabeculae separating destroyed areas, giving a somewhat polycystic appearance. It does not respond to radiation.

9. Non Specific Osteomyelitis. (24)

This disease simulates xanthomatosis in the presence of irregular contour. The development is more rapid and the symptoms are quite marked. There



is an attempted bone repair as well as bone destruction, also sequestration often occurs. There is no spectacular response to radiation as xanthomatosis does.

### PROGNOSIS

The condition is usually fatal especially in children. There have been a few cases that have continued from childhood into adult age. (22) At the best the prognosis is always questionable.

When the condition presents cutaneous lesions it seems to progress more slowly and tends to become chronic.

Types having visceral or neurological lesions are more fulminating. The disease probably never disappears but it may have spontaneous remissions. (33)

The mortality varies from 30 - 50 %. The death may be due to, (5)

1. Cachexia.
2. Cirrhosis of the liver.
3. Endocarditis.
4. Aplastic anemia.
5. Intercurrent disease.

There is some evidence that older people tolerate the disease better than the younger do. (40)

## TREATMENT

According to Kellogg (24) radiation is the treatment of choice. From reviewing the literature I believe that all the men, who have studied this disease since radiation therapy has come into use, agree.

Cignoline (41) was the first to use radiation for treatment of this disease (1928)

Surgery is not curative and may be dangerous. (1)

Diet should be of the type to build up the general condition of the patient. Rowland (29) used a low fat diet to reduce the hypercholesteremia. He also gave insulin and other drugs to stimulate the appetite.

Pituitary extract in doses from 0.5 cc. to 1 cc. relieves the diabetes insipidus. The effect and use of pituitary extract for the diabetes insipidus is agreed upon by all the men who have studied this disease.

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