Reticuloendotheliosis: Eosinophilic Granuloma; Non-lipoid Reticuloendotheliosis (Letterer-siwe Disease); Lipoid Histiocytosis Of Cholesterol Type (Hand-schuller-christian Disease)

Brenton M. Hamil
RETICULOENDOTHELIOSIS

Eosinophilic Granuloma; Non-Lipoid Reticulendotheliosis (Letterer-Siwe Disease); Lipoid Histiocytosis of Cholesterol Type (Hand-Schüller-Christian Disease)

BRENTON M. HAMIL, M.D.*

The terminology for this condition has been in continuous confusion since the first published material by Hand in 1893. Cases are reported from the literature which are said to fit this classification as far back as 1836.

The earliest reports dealt with a triad of symptoms. Hand1 described the triad of diabetes insipidus, exophthalmos and membranous lesions of bone occurring in a case diagnosed as tuberculosis. Schüller2 reported two cases in 1916 with this triad, and Christian3 reported one case in 1919. Thompson, Keegan and Dunn4 reported a complete autopsy of a case with the triad of symptoms described by Hand, Schüller and Christian, and the conclusion was drawn that the lesions demonstrated caused the symptoms by the physical mechanics of their location. Denzer5 in 1926 also supported this thesis. Since this time the anonymous Hand-Schüller-Christian Disease is used.

Rowland6 in 1928 based a treatise on the assumption that the so-called "foam cells", which were considered by pathologists as essential in pathological material to show reticuloendothelial involvement in the pathologic lesions in this disease, were the result of overloading because of a primary disturbance of lipoid metabolism and was similar to the other described storage diseases. This analogy is summarized in Table 1. The attention was thus focused upon lipoid fractions, and in 1930 Epstein and

<table>
<thead>
<tr>
<th>Name</th>
<th>Type of lipoid</th>
<th>Blood findings</th>
<th>Eye grounds.</th>
<th>Spleen, liver glands</th>
<th>Age.</th>
<th>Bones.</th>
<th>Pathognomonic features</th>
<th>Skin.</th>
<th>Treatment</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Gaucher's disease (90-95 cases)</td>
<td>Cerebroside or lipoid</td>
<td>1. Hypertrichosis</td>
<td>Spleen markedly enlarged</td>
<td>Infancy to adult</td>
<td>Subcutaneous pigmentation of exposed parts in 40%; leukopenia in 15%</td>
<td>Common in Jews.</td>
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<tr>
<td>B. Niemann-Pick's disease or lipoid</td>
<td>Phospholipid, lecithin</td>
<td>1. Moderate secondary anemia</td>
<td>Spleen and liver, very large, splenomegaly</td>
<td>Spleenic puncture</td>
<td>Brown-yellow discolouration</td>
<td>No treatment, all fatal.</td>
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<tr>
<td>C. Hand-Schüller-Christian disease (18-39 cases)</td>
<td>Cholesterol and inclusions</td>
<td>There may be a hypercholesteremia</td>
<td>Negative</td>
<td>Not enlarged</td>
<td>Any age</td>
<td>Membranous bone involved</td>
<td>Negative</td>
<td>X-ray treatment of involved area causes prompt local healing and arrest the progress of the disease.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D. Tay-Sachs' disease or amaurotic familial idiocy</td>
<td>A precipit</td>
<td>Negative</td>
<td>Cherry-red spots, mentally dull</td>
<td>Usually negative</td>
<td>Infant</td>
<td>Not involved</td>
<td>1. Eye grounds</td>
<td>Mental retardation</td>
<td>All-visual</td>
<td></td>
</tr>
<tr>
<td>E. Xanthomatoses of skin, etc.</td>
<td>Cholesterol and inclusions</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Any age</td>
<td>Any bone may be involved</td>
<td>Xanthomatoses of any part of skin</td>
<td>Regression, if too soon.</td>
<td></td>
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</table>
Lorenz\textsuperscript{4} presented some brilliant work showing the specificity of lecithin, cholesterin and neutral fat in these different endothelial storage diseases. Cowie and Magee\textsuperscript{5} did some similar work in 1934 and showed the variability in the lipoid fractions according to the tissue site of the lesions studied; that is, dura as compared with periosteum and bone marrow with viscera. Histologically these lesions are said to consist, early in their development, of a mass of lipoid-laden histiocytes known as “foam cells” which make up more or less rubbery masses arising from the dura in the skull lesions or from the periosteum in the long bones. Scattered throughout the bone marrow and viscera are small lesions which are histologically similar to the bone lesions.\textsuperscript{10}

Letterer\textsuperscript{11} in 1924 described a case of generalized endotheliosis due to proliferation of the reticuloendothelial apparatus and Siwe\textsuperscript{12} reported similar findings in 1933. The so-called “foam cell” was not a feature of this pathology. Abt and Denenholz\textsuperscript{13} reported a case in 1936 which showed the clinical and pathological features identified by both of the two authors just mentioned and called it Letterer-Siwe Disease. Since that time “Abts Disease” or Letterer-Siwe Disease has been applied to this group which is characterized by more fulminating over-growth of the reticuloendothelial tissue. There are some eosinophiles such as are found in the pathologic lesion of eosinophilia granuloma but with no foam cells which were considered to be diagnostic of Hand-Schüller-Christian Disease. Merritt and Paige\textsuperscript{14} in 1933 had reported a case with exophthalmos, diabetes insipidus, characteristic bone lesions, and severe cutaneous involvement such as characterizes Letterer-Siwe Disease. Pathologic changes were found in the bones, dura, infandibulum of the hypophysis, periosteum, orbits, skin, thymus, pleura, lungs, heart, peritoneum, spleen, liver, pancreas, lymph glands and peritoneal adipose tissue. There was extensive hyperplasia of the reticuloendothelial cells in the spleen and lymph glands without any evidence of lipoid storage but in many sites, such as the dura, bones, lungs and thymus there were typical xanthomatous lesions. The corium in the skin contained localized accumulations of large mononuclear cells similar in morphology to the reticuloendothelial cells found in other regions, but in these cutaneous infiltrations few cells contained fat or lipoid.

It is readily seen that the transition of terminology necessarily had to evolve through the recognition of a symptom complex, the physical aspects of production of the symptoms, then the phases of the lipoid distribution of its characteristic lesions. Most recently interest has been directed toward grouping cells of these conditions which are characterized pathologically by some greater or less degree of inflammatory reaction of the reticuloendothelial system, either as the result of infection or physical trauma, under one general terminology. Cases observed by Green and Farber\textsuperscript{15} concerning the nature of “certain benign, destructive, solitary or multiple lesions” in the bones of 10 children whose progress had been followed from 3 to 10 years, led Farber\textsuperscript{16} to discuss a comparison of the pathological material obtained from these 10 patients who had solitary or multiple lesions known as solitary eosinophilic granuloma, with the lesions in the skeleton and viscera in Hand-Schüller-Christian Disease. He also compared them with several examples of what has been known as Letterer-Siwe Disease. He stated that a study of the evolution of the bone lesion in Hand-Schüller-Disease led to the conclusion that all of these conditions represent variations in degree, stage of involvement and localization of the same basic disease process. He did not
imply that any one of these three conditions is a primary xanthomatous process or a secondary manifestation of a primary alteration in lipoid metabolism. He did feel definitely and did so state that "eosinophilic or solitary granuloma of bone is not a new or a separate disease entity." Kennedy and co-workers\textsuperscript{17,18} in a report of the treatment of 12 children who had extensive involvement with reticuloendotheliosis of Hand-Schuller-Christian type stated that roentgen radiation in multiple small doses proved effective and suggested its use in all cases.\textsuperscript{9} They suggested that the term "reticuloendothelial group" be used to cover the three conditions under dispute as being similar, and to specify the type as a subtitle, that is, Hand-Schüller-Christian Disease, Letterer-Siwe Disease or Eosinophilic Granuloma. Wallgren\textsuperscript{20} has suggested the term "systemic reticuloendothelial granulomatosis" for this group of diseases. Epstein and Pinkus\textsuperscript{21} proposed the name "reticulo granuloma" for the granulomatous manifestation of reticulosis. Lichtenstein and Jaffe\textsuperscript{22,23} who first called attention to and described the eosinophilic granuloma of bone, suggested the term Histiocytosis X\textsuperscript{24} to cover this group of three conditions which have seemed to have an inflammatory inciting cause to stimulate the endothelial cells or histiocytes to abundant proliferation, but since he did not know the exact cause, the "X" was added as a qualifying or compromising factor. Table II shows this classification as prepared after Lichtenstein's presentation. Table III presents the standard nomenclature as used at the Henry Ford Hospital for indexing purposes. Some of the other nomenclature which have been used in the literature to designate one or more of these pathologic conditions are also presented.

Excellent bibliographies have been published in the evolution of the approach to our present attitude toward these pathologic states of the reticuloendothelial tissue at various periods.

<table>
<thead>
<tr>
<th>Distribution of lesions</th>
<th>Clinical Expressions</th>
<th>Age Incidence</th>
<th>Treatment</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>localized in bone (one, several, or many foci); no discernible visceral involvement</td>
<td>Eosinophilic Granuloma of bone</td>
<td>Infants, Children, and younger adults (Occasionally older adults)</td>
<td>Curettage or X-ray therapy</td>
<td>Cure (although additional skeletal lesions may sometimes appear)</td>
</tr>
<tr>
<td>Acute or sub-acute course of disease</td>
<td>Letterer-Siwe syndrome</td>
<td>Infants and younger children below age of 3 years; occasional younger adults (adult counterpart of L-S syndrome)</td>
<td>As yet non-specific; Supportive Antibiotics for secondary infections; X-ray therapy for skeletal and cutaneous lesions</td>
<td>Serious, though probably not invariably fatal; in occasional children, disease may become chronic or go into remission</td>
</tr>
<tr>
<td>Disseminated</td>
<td>Schuller-Christian syndrome (not necessarily Christian triad)</td>
<td>Children and young adults; occasional older adults.</td>
<td>As for L-S syndrome; also x-ray therapy or B-hy pophamide for diabetes insipidus; x-ray therapy for early pulmonary infiltration; cortisone?</td>
<td>Guarded, especially for children showing active progression and for patients with diabetes insipidus; included with pulmonary fibrosis and/or pituitary involvement.</td>
</tr>
</tbody>
</table>

\textsuperscript{*}Kennedy\textsuperscript{19} has had in his experience a total of 46 patients; 9 with skull lesions only, 32 with combined skull and other bones involved, and 5 with no lesions observed in the skull; the mortality was slightly over 23 per cent and x-ray therapy is still being used.
TABLE III
Reticuloendotheliosis Listed According to Standard Nomenclature of American Medical Association

Rowland (1928); Lichty (1934); Abt and Denenholz (1936); Wallgren (1940); Green and Farber (1942); Hodgson, Kennedy and Camp (1951); Freud (1951); and recently Lichtenstein (1953); Christie and co-workers (1954); and most recently Merman and Dargeon (1955) and Batson, Shapero, Christie and Riley (1955). All of the reported cases have been accompanied by lengthy discussion of the descriptive pathology as to the gross character of involved organs and the microscopic examination of tissues, with particular emphasis upon the overgrowth of elements of the reticuloendothelial system. Christie and co-workers have ably and thoroughly presented such data and give as references to the excellent description of the pathology, the papers of Abt and Denenholz; Foot and Olcott; Wallgren; Mallory; and Schafer. Christie and co-authors agree with the conclusion of other authors that the large mononuclears seen in disseminated reticuloendotheliosis may in one instance resemble the large phagocytic cells and in another may appear neoplastic. He states that the diagnosis may be suggested by any one of the described lesions in the skin; the lymphoid tissue (lymphnodes, spleen, thymus); bone marrow; infiltration into lungs, liver and kidney periglomerular interstitial tissue. These manifestations were all the result of endothelial proliferation and infiltration. Careful search could not determine an etiological factor but infection was considered to be of “direct or indirect importance.” The manifestations were stated to be “fortuitous”, depending only upon the “age of the subject” and the chance distribution of lesions, thus accounting for transitional forms. A diagram is presented to show the age distribution of this “spectrum”, age 0-15 months for “disseminated reticuloendotheliosis” (Letterer-Siwe Disease), 2-6 years for Hand-Schüller-Christian Disease and over 6 years for eosinophilic granuloma. When this material was presented before the American Pediatric Society among the discussants was Dr. Arthur E. Abt (Baltimore) who mentioned that in the
era of the middle 1930's when he presented his material, reticuloendotheliosis was in
the medical spotlight, much as gamma globulin is today. He also mentioned that the
term reticuloendotheliosis is derived from the fact that whenever a small or large part
of the mesenchyme of the body has been found to react, this will be either in phagocytic
or hemopoietic activity.

Dr. Sidney Farber (Boston) also discussed the paper. He suggested that names
were given usually at the period of greatest ignorance concerning the nature of a
disease. He was in agreement with Dr. Abt, that the word reticuloendotheliosis would
serve only to continue what was a useful term 30 years ago and that the lymphocytes,
plasma cells and mononuclear cells described in lesions should not be included in the
reticuloendothelial system. He mentioned the use of antibiotics, ACTH, cortisone,
nitrogen mustard and folic acid antagonists in use in supportive treatment. He called
attention to work being done to show no evidence of any single etiologic agent. He
stated that if a comparison was to be made it would be with the exudative and
proliferative forms of rheumatic fever or with the protean manifestations of tuberculosis,
particularly the lesions which are not produced by the tubercle bacilli actually at the
site of the lesion. Recent editorials show wide support for this opinion but indicate
that there is neither uniformity of opinion about the pathogenesis of these conditions
or of the possible etiology; in fact, of the descriptive pathology or terminology. There
seems still to be a dispute among the pathologists who comprise the tumor nomen­
clature committee of the American Medical Association as to whether the pathology
is essentially neoplastic or inflammatory.

MATERIAL

This paper is presented at this time in order to put on record for the first time
a report of the cases which have been indexed under this terminology at this clinic
which have shown either pathological, laboratory or strong clinical confirmation of
this diagnosis. This, therefore, indicates the approximate occurrence in a series of
850,000 admissions to this clinic and hospital service in all age groups and from a
cross section of economic, racial and industrial population, and represents direct
voluntary practice as well as some referral cases. Some have come from social
agencies in this community as well as from other doctors and have been referred to
various members of a staff which at present consists of 137 permanent full time
physicians and 216 residents and internes in all specialties. The cases indexed with
this diagnosis affirmed by x-ray or biopsy are briefly presented in the following table
(Table IV). Those with a diagnosis of solitary eosinophilic granuloma are grouped
together; those with a confirmed diagnosis of Hand-Schüller-Christian Disease (lipoid
histiocytosis of cholesterol type) are listed together and those with proven diagnosis
of Letterer-Siwe Disease (non-lipoid reticuloendotheliosis) are presented together. The
earliest records of any cases fitting this classification in general indexing was in January
1942.

All of these cases had a history of inflammation, either trauma or infection,
which may have been primary. The histology of these conditions has been adequately
dealt with in the references given for the descriptive pathology. Treatment has con­
sisted of various recognized practices consistent with the period of occurrence of the
disease. Currettment or roentgen therapy was used for bone lesions. Antibiotics have

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# Eosinophilic Granuloma;

<table>
<thead>
<tr>
<th>Pt.</th>
<th>Case No.</th>
<th>ONSET SYMPTOMS</th>
<th>X-RAY</th>
<th>BIOPSY</th>
<th>DIAGNOSIS</th>
<th>RESULTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>T. D.</td>
<td>66 61 26</td>
<td>1. 12-31-51 Pain and tenderness Rt. side of head for about 2 years. 2. 4-16-46 Age 5½ years</td>
<td>12-2-52 Biopsy from currettments. Eosin. gran.</td>
<td>Eosinophilic granuloma Shaft Rt. Femur.</td>
<td>No return visit recorded.</td>
<td></td>
</tr>
<tr>
<td>H. K.</td>
<td>77 57 7</td>
<td>1. 12-6-54 Pain and tenderness rt. thigh especially at night for several months. 2. 12-6-54 Possible lesion of Eosinophilic gran. middle of shaft of Rt. femur.</td>
<td>3-21-53 Path report of currettments Eosinophilic gran.</td>
<td>Eosinophilic granuloma left parietal bone.</td>
<td>No return visit recorded.</td>
<td></td>
</tr>
<tr>
<td>M. D.</td>
<td>71 75 9</td>
<td>1. 3-17-53 Pain and tenderness left side of head for several months. 2. 4-16-16 Age 39 years</td>
<td>3-17-53 Chest norm. Skull Eosinophilic gran. lesion left parietal bone.</td>
<td>Eosinophilic granuloma left parietal bone.</td>
<td>Roentgen therapy weekly, 4-4-53 to 6-6-53. Progress x-ray 7-11-53 healing. Blood smear normal.</td>
<td></td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Pt.</th>
<th>Case No.</th>
<th>C &amp; S</th>
<th>BIRTH DATE</th>
<th>ONSET SYMPTOMS</th>
<th>X-RAY</th>
<th>BIOPSY</th>
<th>DIAGNOSIS</th>
<th>RESULTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>M. M.</td>
<td>31 63 87 w. f.</td>
<td>9-20-17</td>
<td>Age 39 years</td>
<td>12-23-55 Headache. Referred to Neurology. Findings negative except for tenderness left side of skull.</td>
<td>12-27-55 Area of bone destruction left temporal bone suggests Eosinophilic gran.</td>
<td>1-5-56 Pathology exam. from currentments Eosinophilic gran.</td>
<td>Eosinophilic granuloma left temporal bone.</td>
<td>Roentgen therapy weekly 1-17-56 to 4-10-56. X-ray 1-31-56; 3-20-56; 5-1-56. No further growth of lesion.</td>
</tr>
<tr>
<td>Name</td>
<td>DOB</td>
<td>Age</td>
<td>Diagnosis</td>
<td>Treatment and Outcomes</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>M. McD.</td>
<td>50 67 83</td>
<td>7 months</td>
<td>Ad. 4-26-47, Ex. eryth., cursted eruption. 7-30-47, Rt. mastoiditis, 8-27-47 skull lesion, rt. temporal. 9-29-47 Spon. fracture, Rt. humerus.</td>
<td>Lymph node and bone marrow 6-7-47. Chronic lymphadenitis. Extensive miliary infection in lung, skull, xanthomata, rt. mastoid, rt. temporal, left post parietal, left mandible</td>
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<tr>
<td>C. B.</td>
<td>80 30 64</td>
<td>16 months</td>
<td>8-26-55, History of rash from age 3 mos. Draining ears from 6 mos. Infection, mastoidectomy recurrent high fevers, poor nutrition, poor appetite. Whining and fretting and itching all of time. Rash crusted, purpuric at base and generalized.</td>
<td>Roentgen therapy to skull and to both hips 5-15-56 to 6-19-56 daily. Staph. aureus resistant to most antibiotics, sensitive to Chloramphenicol and less so to Erythromycin. These have been alternated in treatment. Cortisone, ACTH or mecostin given continuouslly to suppress histiocyte overgrowth and help in some way with immune response. Good skin care. At home most of last 6 mos. Two admissions for about 1 week each for blood. Think she will grow out of her disease.</td>
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*443169 Dr. Wulff Zuelzer, Children's Hospital of Michigan kindly supplied report of biopsy, lymph gland and tissue taken from coroner's autopsy.
been used liberally and not always specifically. ACTH, cortisone and antifolic acid
drugs or nitrogen mustard have been used or their use has been considered in the
more serious cases. This table for these cases needs no further elaboration except
for two considerations. Those cases which have shown the best response, even to the
point of complete recovery, have had attention given to purposeful treatment with
surgery, x-ray, steroid therapy, antibiotics, antihistamines or vaccines with effort directed
toward the use of whole blood or packed cell transfusions and other supportive
parenteral therapy as it seemed to be indicated. Vitamin supplements and supportive
blood tonics were used when they could be tolerated. An attempt was made toward
good dietary and nutritional therapy. No familial occurrence was observed.

Necropsy pathological reports were available from four cases. Three of these
cases were diagnosed Letterer-Siwe Disease (non-lipoid reticuloendotheliosis) and one
age 15 months was called Hand-Schüller-Christian Disease (lipoid histiocytosis). In
this case there was extensive bone involvement with spontaneous fracture of the right
humerus although there was generalized organ involvement. This represents the
“transitional” type.

Three cases have not had tissue removed for biopsy. One (#720619) has been
observed for 18 months with a diagnosis of eosinophilic granuloma of the skull. The
two other cases have shown at some time the Hand-Schüller-Christian triad of symptoms
and have had at some time extensive bone involvement. Both have been observed
closely and one without symptoms except for the diabetes insipidus, (#393557) for
13 years and (#519207) for 10 years. Both patients are now in early puberty. The
other case of Hand-Schüller-Christian Disease (#779617) with the typical triad of
symptoms has been treated for about 18 months. The diabetes insipidus is well
controlled with a snuff of a selected small amount of posterior pituitary gland powder
which is used once or twice daily. This is a preparation made from beef pituitary
gland. We have not experienced the recurrence of any of the solitary eosinophilic
granulomata which have been successfully treated and neither has there been re­
currence in other skeletal locations.

The patient with severe Letterer-Siwe Disease (non-lipoid reticuloendotheliosis)
(#803064) has been under continuous treatment for one year from age 18 months,
having had some degree of her illness from the age of 3 months. She has had
continuous treatment with cortisone, hydrocortisone, ACTH or meticorten (Prednisone,
Schering) as well as the continuous use of antibiotics during this time. She has had
roentgen treatment for her bone lesions and has had the organism which was obtained
from her ear pus, skin lesions, urine and blood stream treated with the antibiotics
to which it was most sensitive. This is important not because of the organism, since
a large variety have been associated with this disease, but because of the possible
effect upon the plasma and tissue factors operative in the immune response if the
organism is made only static or if its metabolism is reduced and the organism is not

*This preparation now marketed by Armour Laboratories is a posterior pituitary gland powder in
40 milligram capsules together with an insufflator to make more convenient its use as a snuff. The
trade number for the capsule is 3080 and that for the insufflator is 3082. Directions for use are given.
killed. The steroid preparations have been used in sufficient dosage to suppress the histiocytic overgrowth but it also has been reported to have some action toward the function of the immune mechanism. Mutation of microorganisms and types of resistance that develop by gene mutations in the organism have been shown experimentally.

Steroids also contribute to a sense of well being, and there is improvement in the appetite of the patient. This patient has spent most of the last 6 months in her home and is clinically improved although there is extensive organ involvement. This case is to be presented with greater detail in another publication as will also be the patient #519207 who has had the triad of symptoms which characterize the group of cases called Hand-Schlüller-Christian Disease (lipoid histiocytosis) and has no evidence of tissue involvement or effect from the disease after 10 years of observation from its onset. The patient (#393557) has had symptoms of allergy during much of his 13 years of observation. This symptom and its treatment is interesting to me because of its involvement with the mechanism of immunity and the cross reactions observed with fungi. As his allergies have been treated his Hand-Schlüller-Christian Disease has improved.

CONSIDERATIONS

The rationale which governs our thinking in regard to the pathologic cytology or the cytologic histology of these three conditions must be liberal. They all have similarities but at the same time they have profound differences. They all have some cellular elements in different occurrences that are recognized as not being a part of the so-called reticuloendothelial system. Certainly all of these cellular elements must be bathed in plasma for their nutritional and physiologic exchange of ions, hormones and fractionated proteins which have been shown to contribute to the immune response. This may also apply to the presence of plasma and other cells, said not to be a part of the reticuloendothelial response. There is one thing which the clinician and the physiologist and the biological chemist realize: a cell, an organ, and organism, a group of animals or people are subject to constant change. Nothing is static that lives.

The least serious of these conditions, the eosinophilic granulomata are usually solitary, slow growing, easily healed by the effect of roentgen therapy or simple currettment and are characteristically found in older children and adults who have their hormonal physiology adjusted to act as a matter of regular routine. Hand-Schlüller-Christian type is most common to the middle age group of children or poorly nourished young adults and the most serious cases are found in those patients who have the onset in the early years of childhood when their body defenses including all of the elements which participate in such mechanisms, cellular or otherwise, are less patterned in their response. Letterer-Siwe Disease is the most serious and often fulminating, showing its onset in middle or late infancy at a time when the infant has recently liberated itself from its required excess storages of intrauterine life. The same hormonal unloading can be anticipated, as is true in regard to vitamins and steroids and the effect upon “resistance” will consequently be altered.

*Klein stated that the blood corticosteroid levels in several babies who died of infection were very high except one who was in vascular collapse. Talbot stated that data would seem to indicate that death from overwhelming infection, or Waterhouse-Friderichsen Syndrome, is not due to adrenocortical insufficiency.
It is logical in the present state of our knowledge, to which the laboratory scientists have brought us, to know that the physiologic and pathologic functions, as at present learned by histochemical methods, is not a matter of arithmetic in the interpretation of mineral and essential amino acids as determined by intake and outgo. Neither is our knowledge yet to the place that the pathologist can look at a stained, fixed section of tissue and tell from the size and number of granules in cytoplasm or nucleus or vacuoles gorged with phosphatids, cholesterol and its esters or lecithin and tell whether this condition is beneficial or harmful in the enzyme chemistry of the cell.

Changing environments have altered the behavior of bacteria and viruses as well as the mechanism of response of the cell to inflammation from that observed before the introduction of antibiotics and steroids now known. Goodman has presented ultramicroscope photography to show that leucocytes disintegrate in their attempt to digest virulent bacteria. Nonvirulent strains of bacteria succumb to phagocytosis or remain as bacterial remnants in the cells.

The early works of Sabin, Doan and Forkner called attention in their animal experiments to some of the basic facts which are elaborated upon now by the steroid and histochemists. The emphasis to the reticuloendothelial system in the early 1930's as being all important to immunity and disease processes was only the ground work for such investigations as are being done with electrophoresis and chromatography by Janeway and others in the study of gamma globulin and/or its fraction relationship to antibody. Gardner in excellent reports of studies of steroids and their fractionation, their synthesis, and their active constituents put a different interpretation upon the factors commonly mentioned in the earlier consideration of "alarm reaction."

These three conditions and also other disease processes involving a response of mesenchymal cells and their relation to the processes of inflammation will find an easier and more logical explanation with improvement of our knowledge in this direction. We will then not be so dependent upon the acuteness with which one person sees and describes characteristics as he observes them grossly or under a microscope in the light of what someone else has described or pictured for him. Eosinophilic granuloma, Hand-Schüller-Christian Disease and Letterer-Siwe Disease are all seen as different degrees of a similar reaction to a lack or decrease, allergy or tiredness of a substance necessary for a response that will maintain good tissue function. This seems to be more logical for consideration than a relative comparison of tissue architecture. The names just mentioned seem adequate and are time-seasoned, if the cause of the reaction that results in the pathology observed is considered from these stand points.

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