FIG. I. PHILIPPE CHARLES ERNEST GAUCHER 1854-1918

"It is safe to presume that to avoid needless suffering is a legitimate rule of life".

Gustafson J.M. (1974)

GAUCHER DISEASE

IN

THE ASHKENAZI-JEWISH

COMMUNITY OF SOUTH AFRICA

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This thesis is submitted for the degree of Doctor of Medicine of the University of Cape Town. The study was performed by the author under the supervision of Professor P. Beighton of the Department of Human Genetics, University of Cape Town.

Jack Goldblatt, M.B. Ch.B.

February, 1980.

DEDICATION

TO MY WIFE AND OUR PARENTS

A C K N O W L E D G E M E N T S

I am most grateful to Professor Peter Beighton, my supervisor, for giving me the opportunities and facilities to work in the field of human genetics. His guidance throughout the project is much appreciated and it is doubtful whether this thesis would ever have been completed were it not for his constant help, encouragement, constructive criticism and reassurance.

I wish to express my thanks to the patients, without whose active participation this study could not have taken place. I am especially grateful to their respective doctors for referring affected individuals and making available their clinical data. I acknowledge with special gratitude the invaluable help of Dr Sidney Sacks for access to his patients and for always giving generously of his time and advice. My thanks are due to Professor L. Solomon for referral of patients and for the use of his departmental facilities during my visits to Johannesburg. In this respect, the secretarial help of Mrs Ruth Norman and Mrs Fifi Cloete is gratefully acknowledged.

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D E F I N I T I O N

In modern terminology the designation 'Gaucher disease' is used in preference to the traditional possessive form 'Gaucher's disease'. For this reason, the contemporary form will be used throughout the thesis when alluding to the condition.

There are great semantic problems in the classification of the various clinical types encountered under the general category of 'Gaucher disease'. This nosological confusion will be discussed at length in a later chapter, (Chapter 4). For the sake of clarity, however, it should be stressed that the form of Gaucher disease with which this study is concerned is the chronic adult, non-neuropathic type which is characteristically encountered in high prevalence in the Ashkenazi-Jewish population. Unless otherwise defined, the term 'Gaucher disease' in this thesis will, at all times, refer to this form of the disorder.

ABSTRACT

GAUCHER DISEASE

Gaucher disease is a biochemical genetic disorder of the lipid storage group. It is characterised by an accumulation of a glycosphingolipid, glycosyl ceramide in the reticulo-endothelial system. The condition presents clinically with hepatosplenomegaly, haematologic and orthopaedic problems. Affected individuals suffer from chronic ill-health and debility, with a clinical course of acute exacerbations, remissions and relapses. The basic defect has been shown to be a genetically determined abnormality in the enzyme beta-glucosidase, (Brady *et al*, 1965; Patrick, 1965). The diagnosis can now be accurately confirmed by laboratory procedures, which also enable determination of carrier status.

Of particular interest is the high prevalence of the condition in the Ashkenazi-Jews. Fried, (1958), in a survey of cases in Jerusalem, estimated the minimal carrier or heterozygote rate to be 1 in 25. Other studies of Ashkenazi-Jews have revealed carrier frequencies ranging from 1 in 25 to about 1 in 40. This stimulated the investigation which was initially undertaken under the supervision of Professor Beighton in the Department of Human Genetics, University of Cape Town Medical School in 1975 and 1976. Further data has been accumulated by the author as a medical registrar at Groote Schuur Hospital in the ensuing period until 1979.

SOUTH AFRICAN SURVEY

There are presently approximately 120 000 Jews in South Africa, of whom an overwhelming majority are of Ashkenazi origin and the survey which forms the subject of this thesis

was undertaken on the assumption that a significant number of them suffer from Gaucher disease. An attempt was made to investigate every Gaucher disease patient in South Africa, with special reference to those of Ashkenazi-Jewish stock. These individuals were carefully clinically documented with full history and systemic examination. They were then investigated radiologically, haematologically, biochemically and genetically. Studies of the kindreds were undertaken by means of discussions with members of the families regarding the ancestral origins of their progenitors and the original immigrants.

SPECIAL INVESTIGATIONS

The author personally travelled throughout the Republic in order to examine the respondents and collect blood samples. These samples were flown to the Cape Town laboratory and assayed on the day of venesection. The biochemical assay for beta-glucosidase was established by Dr H. Henderson in the biochemical laboratory of the Department of Human Genetics. The author repeated the enzyme assay and some of the preliminary experiments in order to obtain proficiency in this specific laboratory procedure. The actual testing of samples from the patients and kindreds was then performed by a technician under the author's direction and Dr Henderson's supervision. Simultaneously, blood specimens were collected for haematologic and 12/channel biochemical analyses, which were performed in the Groote Schuur Hospital routine laboratories. Radiographic studies on the patients were carried out by arrangement with their own practitioners.

RESULTS

Twenty-one affected Ashkenazi-Jewish individuals, from eighteen kindreds, were ascertained, fully investigated and documented. A further twelve Ashkenazi-Jewish Gaucher disease patients were diagnosed and investigated by their attendant physicians. Although the author had access to their clinical notes and investigations, for various reasons the patients were not personally seen.

During the course of the survey ten Afrikaners, two Englishmen, two Sephardic Jews, two African Negroes and four patients of mixed ancestry were also extensively studied.

This thesis is confined to a survey of Gaucher disease in the South African Jewish population and the non-Jewish patients who were encountered will only be considered where necessary to illuminate points of comparison and contrast.

AIMS

The intentions of the author were to:-

i Confirm the mode of genetic transmission of Gaucher disease from a large scale population study;

ii determine the local prevalence;

iii further elucidate the reason for the high frequency of the gene in the Ashkenazi-Jewish community;

iv document the clinical course and prognosis of affected individuals and assess responses to regimes of management;

v investigate the feasibility of population screening for this genetic disorder in a well-defined population group;

vi establish a working laboratory procedure for beta-glucosidase enzyme assays for the screening of carriers and affected individuals.

PRACTICAL BENEFITS OF THE INVESTIGATION

Numerous positive results which were of assistance to both patients and medical practitioners were obtained. These included the possibility of easily confirming the diagnosis of Gaucher disease through blood testing and thus avoiding the performance of a biopsy to obtain material for histological examination. The availability of a practical screening procedure enables differentiation of clinically identical phenotypes into separate and distinct genotypes. It therefore becomes possible to base genetic

counselling on direct ascertainment of individual Gaucher disease genotypes. This obviates the risk of inaccurate counselling on the basis of statistical chance. An analysis of the variability of the clinical manifestations, course and prognosis of the condition, together with an assessment of responses to current regimes of management, could be made on the basis of the information obtained. The availability of heterozygote screening and pre-natal diagnostic procedures also enable detection of Gaucher disease in early foetal life. The future holds exciting prospects for effective therapy for Gaucher disease and it may be foreseen that appropriate therapy will eventually be available to keep the condition in remission and prevent the later destructive clinical complications.

SYNOPSIS OF THESIS

The aims of the survey and the nature of the disease process are outlined in the introduction. Historical factors leading to the evolution of current thought and understanding of Gaucher disease and the origins of the Ashkenazi-Jews are then described and the methodology of all aspects of the survey is presented.

Case reports of three representative patients are given in detail together with clinical summaries of 18 other affected individuals. The results of the clinical, radiological and biochemical examinations are tabulated and discussed in relation to world literature.

Genetic findings on a basis of the data from all the cases ascertained during the survey are analysed from a viewpoint of population genetics, in order to determine the local distribution and prevalence of the condition. Theories concerning the historical reasons for the very high prevalence of Gaucher disease in the Ashkenazi-Jewish population are discussed.

Finally, the practical implications of the survey are considered, followed by concluding comments, a list of references and an appendix.

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HISTORICAL PERSPECTIVES

CHAPTER I

ASHKENAZI JEWRY

INTRODUCTION

As in most world series Gaucher disease in South Africa reaches maximal prevalence in individuals of Ashkenazi-Jewish stock. Consideration is given as to the emergence of the Ashkenazi community as a distinct entity within the Jewish people. The history of this group is then traced from its initial division up till the establishment of the Ashkenazi-Jewish community in South Africa.

THE ASHKENAZIM

As is often the case with historical origins, those of Ashkenazi-Jewry cannot be pinpointed with any accuracy. The name "Ashkenazi" itself points to the middle ages, for it was only in medieval days that the German lands came to be called "Ashkenazi" in Hebrew. Over the last three or four centuries this group has numerically been the largest of the three major divisions, i.e. Ashkenazim, Sephardim and Oriental, which comprise the Jewish people. The Ashkenazi community has therefore only emerged as a historically and culturally important component late in the history of the Jewish people.

The Ashkenazim have a heterogeneous background on the basis of mass migrations and conversions, both voluntary and forced, and large-scale intermarriage, (Groen,1964; Sheba,1968; Adam, 1973; Goodman, 1974). The exact origins of this presently well-defined group bear further elucidation.

2000 to 586 B.C.

Earliest Jewish migrations were into the Middle-eastern region in about 2000 B.C. The Jewish people were then forcibly taken en masse into slavery in Egypt. Subsequently under the guidance of Moses they returned to their "promised land", which was subdivided into regions by the 12 tribes of Israel. From 1000 to 925 B.C. this territory became the Kingdom of David and then Solomon. The Assyrian invasion and conquests, 850 to 722 B.C., destroyed this Jewish independent state and were associated with the division of the nation into the separate regions of Israel and Judah, from 850 B.C. These Assyrian conquests and annexure, 722 B.C., and the Babylonian siege with destruction of the Temple, 587 to 586 B.C., resulted in fragmentation and local dispersion of the Jewish nation. The Assyrian deportations, 740 to 722 B.C., also resulted in ten of the twelve tribes becoming lost. The location of the descendants of the "ten lost tribes" remains a mystery which has over the years stimulated much research and theoretical debate.

586 B.C. to 73 A.D.

With the subsequent development of further Empires, the Jews gradually settled throughout the territories of the respective imperial powers, i.e. Babylonian 586 to 550 B.C., Persian 550 to 333 B.C., Alexander the Great 323 B.C., Ptolemaic 270 B.C. Minor movement of the Jews then took place in approximately 200 years B.C. when many were taken into captivity as slaves in the mediterranean regions, especially Greece and Italy. Their numbers were augmented by the Jewish Judean captives brought back to Rome by Trajan after conclusion of the Jewish-Roman war in 70 A.D. The last Jewish defenders were in fact killed at Masada in 73 A.D.

Early European Diaspora

These captives, who were predominantly males, became slaves in Rome during the first centuries A.D. At this time there was also a major migration of Jews following the destruction of the second Temple in 70 A.D. by Titus, son of the Roman emperor. These Jews made poor slaves and, freed from bondage, proceeded into Roman-occupied Europe in the second and third centuries A.D. In this manner Jewish communities were founded in Spain, Portugal, France, the Rhinelands, Italy, Greece, Rumania and in fact throughout the Roman empire, except Britain. It is estimated that by 300 A.D. there were approximately three million Jews, a third of whom lived West of Macedonia, (M. Gilbert, 1969).

This early migration was almost solely of originally Jewish males. They were forced by circumstances to marry indigenous non-Jewesses during the course of their migrations. The majority of these women converted to Judaism and raised Jewish families, (Adam, 1973). This substantial resettlement then led to the founding of Jewish communities who remained geographically, as well as culturally and religiously isolated. However the original intermarriage of the founding settlers resulted in these later communities also having the characteristics of their respective autochthonous populations, (Shapiro, 1960), in contrast with the homogeneity of the ancestral Jewish groups.

Some of the Jewish settlements, founded in Roman times, had become established in France and Italy by 500 A.D. when their inhabitants began migrating Northwards across the Alps into Germany. These early beginnings of a Jewish diaspora in Central and Eastern Europe were followed by a long period in which practically nothing is known about the fate and circumstances of these Jews, who were to be the forerunners of the present-day Ashkenazim. This period which lasted till the middle ages, was periodically punctuated by mass Jewish conversions, massacres and expulsions.

Khazars

Some Jews moved up from Anatolia to the North shore of the Black Sea even prior to the end of the second Jewish commonwealth, 200 to 400 A.D. This new region in which they settled became the Khazar Jewish kingdom in about 700 A.D. when Bulan, king of a Heathen nomadic people, was converted to Judaism. In 723 they were joined by Jewish fugitives from Greece. The Khazars were initially attacked by the Russians in 970 and then restricted to the Crimea. They were finally destroyed by a joint Russo-Byzantine expedition in 1016 and subsequently dispersed into Russia, Byzantium and the Mediterranean ports. However, accurate historical data is not available regarding their migrations and their contribution to the Ashkenazim is generally thought to be minimal, (Goodman, 1979).

Middle Ages

By the year 1000 large Jewish communities had developed in central Europe, especially in Germany and France. The principal cities inhabited by them were Cologne, Magdeburg, Merseburg, Wurzburg, Frankfurt, Mainz, Worms, Speyer, Ratisbon and Augsburg in Germany and the regions of Provence, the Loire Valley, Bordeaux, Bayonne, Paris and adjoining cities along the Seine river in France. The German crusades which began in 1096 initiated a period of Jewish history characterised by anti-Jewish violence, forcible conversions, restrictive laws and expulsions. The Crusader kingdoms, 1098 to 1489, resulted in a great reduction in the number of Jews. The relatively small groups of people who chose to remain Jewish were driven out of central Europe by the Crusaders, and migrated en masse to Eastern European countries, especially the region of Greater Lithuania which incorporated Poland, Latvia, and White Russia, during the thirteenth and fourteenth centuries A.D. These expulsions initially began in the Rhinelands and then spread all over Germany, France, Bavaria, Switzerland, Hungary and Austria. It was at this time that the ethnic designation

"Ashkenazi" was first coined. These individuals were the presumed medieval founders of the present-day Ashkenazi-Jewish communities,(Adams, 1973).

Some of the German refugees initially fled to France, where they were joined by Jewish refugees expelled from England in 1290. Following a period of flourishing Jewish literacy and scientific activity in France, 1200-1500, these French Jews were also driven out into Eastern Europe. The Jews of Spain and Portugal were forced to migrate during the inquisitions and finally settled in Amsterdam in 1492 and Hamburg in 1497, respectively.

Eastern European Jewry

The Jews of Poland, Lithuania and Russia therefore originated from refugees initially from Germany in 1096 and then from the remainder of Central Europe throughout the 12th, 13th and 14th centuries; and possibly a minor contribution from the Khazar Jewish Kingdom, in 1016, and from the Crimea in the 14th century (*vide supra*).

Some of these Ashkenazi-Jews settled in Brazil, North Africa, Holland, Italy and throughout the Ottoman Empire. For this reason there were Ashkenazim in Holland during the period of the Dutch East Indies Company's voyages of exploration to South Africa,(Jenkins *et al*, 1977). The Eastern European Ashkenazi-Jews, usually migrating and settling in relatively small groups, formed an intensely isolated and community-based society during this period and there was very little gene interchange with the indigenous non-Jewish peoples. Belligerent and antagonistic local rulers enhanced this isolation by promulgating anti-semitic edicts. The first persecution of Jews in Poland took place in 1399. In 1648 the Cossacks revolted against the Polish gentry and defeated the Polish army. The Polish peasants then joined forces with the Cossacks to attack the Jews and perpetrate the Chmielnicki massacres from 1648 to 1656. From this isolation and threat of aggression arose a need on the part of the Jews to establish a capability for defence and self-preservation.

Ghettoes

The indigenous population was influenced to remain aloof from this so-called "inferior group of potential subvertors". Restrictive laws further isolated the Jews geographically with the introduction of Jewish ghettoes. The first Polish ghetto was created in 1494 when the Jews were restricted to a suburb of Cracow.

Russian Jewry

The annexations of 1654 then gave Russia its first substantial Jewish community, which was greatly enlarged by the Westward expansion of Russia with the three partitions of Poland in 1772, 1793 and 1795 and the defeat of Napoleon in 1815. It is estimated that approximately 1 200 000 Jews were thus transferred from Polish to Russian sovereignty, (Gilbert M, 1969). The Russians considered this to be a "Jewish problem" and confined the Jews to a "pale of settlement". By laws of 1795 and 1835 the Jews were compelled to live within a region with precisely determined boundaries and they were subjected to a particular jurisdiction separate from non-Jewish Russians. The Jews were not allowed to travel or trade beyond the boundaries of the "pale". By 1885 more than 4 million Ashkenazi-Jews lived in this "pale of settlement", mostly under conditions of marked poverty.

In the latter part of the 19th century and the first half of the 20th century, these Eastern European and German Jews migrated en masse to South Africa, Israel, North and South America and Australia, because of extreme hardships and persecutions in their home countries. (*Vide infra.*, Chapter 2).

CHAPTER 2

SOUTH AFRICAN ASHKENAZI-JEWISH COMMUNITY

ORIGINS

The immigration patterns of South Africa's emerging Jewish community fall into a number of distinct periods. Before 1800 a number of individual Jews were known to have settled in this country. They were not professing Jews and readily assimilated with the rest of the Christian community. These early Jewish settlers came with the exploratory voyages of the Dutch East Indies Company which as a matter of policy forbade Jews to accompany these expeditions. There were also thought to be a number of Jews amongst the first permanent settlers to the Cape sent out by the Dutch East Indies Company in 1652, (Herrman,1935).

However, Herrman,1935, considers that there are no present day Jewish descendants of these seventeenth or eighteenth century settlers of the Cape.

1800 to 1979

Jewish immigration from 1800 to 1880 was of a few thousand from Germany, Holland and England. They were more communally orientated than the earlier Jewish settlers and organised fledgling Jewish congregations. However, these early settlers also assimilated fairly rapidly into the non-Jewish majority, so that few, if any, practising Jewish descendants of these families remain today, (Saron, 1965).

The Jewish community of South Africa, as it exists at the present time, was largely fashioned by the next mass emigration of Eastern European Jews between 1881 and 1910. This was the first immigration of whole communities who brought with them

their distinctive Jewish traditions and culture. The earlier Jewish immigrants were just part of the general stream of immigration to this country, and bore no distinctive Jewish character. However these Eastern European Jews were the first to come as part of a purely Jewish immigration because of prejudicial hardships and persecution in their countries of origin. They brought with them certain features which characterise the South African Jewish community to-day. These include the recognition of the importance of education, a deep attachment to Jewish customs, traditions of generosity and charitableness, and strong family and community ties.

They came from the intensely Jewish environment of the ghettoes and isolated villages where they had suffered many years of political, economic and cultural discrimination. Pogroms, Russian for "violent mass attack" against a section of the community, prevalent in the 1880's, coupled with a rash of natural disasters, which included the great fires in the cities of Kovno (1881), Ponevez (1882), Shadowa, Wilkomir, Krok and Mikalishok (1884), further impoverished the lot of these people. These pogroms, often officially instigated, allowed the Russian peasants to vent their economic discontent and frustration in the form of anti-Jewish violence.

Reports of a new life of political freedom and economic security in distant South Africa instilled a desire for mass immigration in these communities. This immigration continued unabated until the passing of the Aliens Act in 1937 placed restrictions on this previously unlimited entry of these Jewish immigrants. Further Jewish immigration from other regions took place in the last two decades of the 19th century when Western Jews joined groups of immigrant fortune seekers in the search for diamonds and gold. In the 1930's a further immigration of Jews occurred from Germany and other Nazi occupied countries. Minor immigration of individual Jews since that time has been a very insignificant factor in population growth of the Jewish community.

Saron, 1965, calculated that between 1880 and 1910 about 40 000 Ashkenazi-Jews entered this country from Eastern Europe and perhaps a further 30 000 entered from 1910 to 1960. He further estimated the number of German Jewish refugees during the 1930's at 5 000 to 6 000 and subsequent post-war immigration at "only a couple of hundred per annum". His periodic estimates of the size of the Jewish population are as follows:

YEAR	APPROXIMATE SIZE OF JEWISH POPULATION	
1880	4 000	
1890	10 000	
1900	25 000	
1904	38 101	(first official census)
1911	46 919	
1921	62 103	
1926	71 816	
1936	90 645	
1946	104 156	
1960	114 762	
1970	117 990	

Dubb, (1973), emphasised that the relative magnitude of each wave of immigration could only be estimated and he confirmed that the Jewish community of South Africa to-day is largely derived from Eastern European ancestors.

CHAPTER 3

GAUCHER DISEASE

P.C.E. Gaucher

Philippe Charles Ernest Gaucher described the disease which later bore his name in his doctoral thesis entitled "*de l'epithelioma primitif de la râte, hypertrophie idiopathique de la râte sans leucemie*", in 1882. The microscopic appearance of the enlarged spleen packed with abnormal cells led Gaucher to the theory that the primary pathology was a splenic tumour.

Gaucher was born at Champfleury, Nievre, France, on July 26, 1854 and was educated in Paris. After graduation in 1882, he was appointed "*Medicin des hôpitaux*" in 1886 and in 1902 he became professor of dermatology at the University of Paris. He published work on dermatology, the cutaneous, ocular and nasal manifestations of syphilis and on renal diseases. Gaucher died in Paris on January 25, 1918.

Historical Reviews

Reich *et al*, 1951; Crone and Bergin, 1958; Brinn and Glabman, 1962; Fredrickson and Sloan, 1972, give excellent summaries of further historical data leading up to the current understanding of the disease process. Some of these studies are cited in the following review of the literature.

1895 to 1910

Many years elapsed before the extent of involvement of organs other than the spleen was documented. Collier, (1895), and Picou and Raymond, (1896), described extrasplenic reticulo-endothelial system involvement and they noted Gaucher disease cells in retroperitoneal lymph nodes.

Bovaird, (1900), was the first to comment on the familial nature of the disease and also noted these same abnormal, large cells in the liver. He considered that a systemic poison might be the causative factor in these affected kindreds. After Brill *et al*, (1904), had reported on skeletal infiltration, the disease was generally classified under the "systemic" disorders of spleen, liver and bone marrow. It was thought to be related to the leukaemias.

Marchand, (1907), described the Gaucher disease cells as being filled with a semi-solid hyaline substance. He suggested that the microscopic appearance might be the result of the deposition of a "foreign substance". The belief that Gaucher disease was a condition involving the reticulo-endothelial system was emphasised by Schlagenhaufer, (1907), and shortly thereafter documented by others, notably Mandlebaum and Downey, (1916).

1910 to 1930

Mandlebaum and Downey, (1916), set the course for further elucidation of the origins of the disease. They concluded that the abnormal Gaucher disease cells were in fact swollen reticular cells, which probably resulted from a metabolic disturbance. The next positive step was the chemical analysis of a Gaucher disease spleen by Lieb, (1924), and Epstein, (1924). They showed that the cerebroside kerasin was the most important lipid constituent. In the same year, Reuben, (1924), noted the relative frequency of the disease in childhood and three years later Oberling and Woringer, (1927), observed in detail the acute form of the disease in infancy. It was at this time that nosological confusion developed, (*vide* Chapter 4). Concurrently Junghagen, (1926), and Klercker, (1927), made important observations on skeletal manifestations. Junghagen described in detail the morphological bone changes and Klercker followed with the first complete radiographic studies.

1950 to 1979

Subsequent discoveries were mainly in the biochemical field. Uzman, (1951), suggested that there might be a defect in the protein-synthesising matrix of the reticulo-endothelial cell which leads to resistance of kerasin to enzymatic hydrolysis. Tuchman *et al*, (1956), noted elevated serum acid phosphatase levels in Gaucher disease patients and Sobotka *et al*, (1959), postulated that these might be indicative of a more elusive enzyme disturbance.

In this period the concept developed that the abnormal quantities of cerebroside were formed and stored in the reticulum cells and histiocytes of the involved organs. This contradicted previous theories that the cerebrosides were transported by the serum or red blood cells to be deposited in the involved tissues. Thannhauser, (1958), also suggested that there might be an imbalance of an enzyme concerned with lipid metabolism in the affected cells.

Thoughts on the primary factor responsible for the disease process were now proceeding in the direction of the modern concept. Further investigation of the enzyme abnormality resulted in an important practical advance which related to all aspects of the condition from diagnosis to prevention and possible therapy. This occurred when Brady and his colleagues, (1965), and Patrick, (1965), published evidence that the livers and spleens of Gaucher disease patients were deficient in their ability to hydrolyse glucocerebroside.

The following ten years saw a rapid evolution of diagnostic tests for assaying the deficient enzyme and procedures for isolation and purification of the enzyme itself. Far from the first description by P.C.E.Gaucher, (1882), of a disease "characterised by primary epithelioma of the spleen", an exciting era has been entered and the possibility now exists for control, prevention and therapy of this genetically determined condition.

CHAPTER 4

NOSOLOGY OF GAUCHER DISEASE

INTRODUCTION

The nosology of Gaucher disease first became a problem when Reuben, (1924), recognised the relatively high frequency of Gaucher disease in childhood. He also noted that the clinical course and prognosis were related to the age of onset. Three years later Oberling and Woringer, (1927), reported on diverse manifestations in infants, children and adults. Although the condition in all age groups generally met the accepted diagnostic criteria for Gaucher disease, there were marked differences in certain important features.

On this basis the following classification formulated by Fredrickson and Sloan, (1972), in accord with the earlier suggestion by Knudson and Kaplan, (1962), is generally accepted:-

Type 1: Chronic, adult, non-neuropathic.
Type 2: Acute, infantile, neuropathic.
Type 3: Subacute, juvenile, neuropathic.

There is some confusion as to which numerical type corresponds to each form of the condition. This could best be avoided by discarding these numerical designations. Also, in view of the frequent presentation of the "chronic, adult, non-neuropathic" form in adolescence and the occasional rapid course, the designation "non-neuropathic" is to be preferred for this form of the disorder. The classification of the three types in this thesis is listed as follows:

Non-neuropathic.
Acute, infantile neuropathic.
Subacute juvenile neuropathic.

The clinical variability regarding course, severity, systemic involvement and prognosis presents difficulties with the formulation of a classification. All these conditions merit classification under the heading of Gaucher disease because of their similarities in basic pathology and aetiology. At present there is no explanation as to how the common factor of defective activity of the enzyme beta-glucosidase leads to such variable clinical manifestations.

The various types of Gaucher disease share the common clinical features of:-

i Hepatosplenomegaly.
ii Gaucher cells in bone marrow.
iii Raised serum acid phosphatase.
iv Deficiency of beta-glucosidase.

The basic differences leading to their separate classification are:-

i Evidence of neurological involvement as a primary manifestation of Gaucher disease cell-infiltrates in the infantile and juvenile forms.
ii Temporal evolution of characteristic clinical features.

NON-NEUROPATHIC GAUCHER DISEASE

Although presenting with great variability in respect of onset, clinical course and prognosis, this type tends to run the mildest course. It occurs with maximal frequency in individuals of Ashkenazi-Jewish stock and presents clinically with splenomegaly, orthopaedic and haematologic complications. This variety is the original form first described by P.C.E. Gaucher in his thesis.

ACUTE, INFANTILE, NEUROPATHIC GAUCHER DISEASE

This condition was first documented by Reuben, (1924). It is a rare disorder which shows no ethnic predilection and very few Jewish cases have been described in the literature. It is a distinct clinical entity characterised by onset in infancy of hepatosplenomegaly, failure to thrive and neurological complications. The course is rapidly progressive, with neurological degeneration and death at an early age. There is no conclusive experimental evidence to explain why this deficiency of beta-glucosidase should so aggressively affect the central nervous system in contrast to the non-neuropathic condition.

No Jewish patients with this type of the condition have been documented in South Africa. The condition has been reported locally in a Rhodesian individual of African Negro stock, (Buchanan and Forbes, 1970).

SUBACUTE, JUVENILE, NEUROPATHIC GAUCHER DISEASE

This is the least well defined of the three varieties, as it presents with a mixed picture of types 1 and 2. Although severe and neuropathic, it tends to appear later than type 2 and runs a more protracted course. The clinical picture is one of mild hepatosplenomegaly with progressive dementia, cerebellar ataxia and extrapyramidal involvement. The condition is extremely rare, but reaches a maximum prevalence in four interrelated families in Sweden, (Hillborg , 1959). No cases of this type have been reported in South Africa.

Marginal clinical overlap of these types does occur in certain cases reported in the literature. However, the classification is acceptable in most respects, especially as a basis for consideration of the clinical course, prognosis, therapy, counselling and control.

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It must be emphasised that the author's investigation was restricted to non-neuropathic Gaucher disease, and the term 'Gaucher disease' in this thesis will only refer to this form of the condition, unless otherwise stated. Although the patients in this series showed some variability in clinical course and severity, they all fulfilled the criteria for inclusion in this category. Care was taken to exclude any doubtful cases.

DISCUSSION

Even within each individual group in this classification there is great variability. For instance, patients with the "adult" non-neuropathic variety sometimes present clinically in early childhood. As the biochemical complexities are unravelled it is possible that further division into sub-types will be achieved. The problem remains as to why the fundamental abnormality of a beta-glucosidase deficiency, as presently assayed in the laboratory, should present with such diverse clinical manifestations.

This could occur for three primary reasons:-

i genetic heterogeneity

ii the effect of epistatic factors, i.e. unrelated genes which have an indirect influence on the phenotypic expression of the primary genetic abnormality

iii the presence of specific environmental circumstances

The latter two possibilities are unlikely as the complete absence of any involvement of the central nervous system in the non-neuropathic variety mitigates against the activity of a modifying factor. No biochemical evidence for this phenomenon has ever been discovered in cerebral tissue or serum. The consistent finding of ethnic specificity of the various types is also against the differential action of an environmental, dietary or epistatic genetic mechanism. In the present state of knowledge genetic heterogeneity is the most likely explanation.

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S E C T I O N II

METHODOLOGY

CHAPTER 5

ASCERTAINMENT

PATIENTS

Initially, affected individuals were investigated following routine referrals to the genetic department of the University of Cape Town. Subsequently the author, in collaboration with Professor Beighton, attempted to investigate every patient with Gaucher disease in South Africa. This step involved extensive contact and correspondence with orthopaedic surgeons, physicians, general practitioners, haematologists and pathologists throughout the Republic of South Africa. This ensured that the author's interest in the condition was made known to medical practitioners who would be most likely to see the condition in the course of their practice. By this method the great majority of patients were ascertained and subsequently referred to the department for further investigation.

A large number of patients had been under the orthopaedic care of Mr Sidney Sacks of Johannesburg. The author had access to these patients by the further courtesy of Professor Louis Solomon of the Department of Orthopaedic Surgery of the University of the Witwatersrand. A few affected individuals were referred through Professor Jenkins' clinic at the Johannesburg Genetic department.

Contact was maintained with the referring doctors, and all patients, with permission from their family practitioners, were followed-up and investigated. Where possible, mention of the research project was made at medical meetings, research congresses and in publications and review articles by both the author and Professor Beighton.

With the knowledge that 90% of the South African Jewish population lives in Johannesburg, Cape Town and Durban, 63%, 22% and 15% respectively according to the 1970 Census, (Figure 1), these were the areas most extensively searched. Communication was established with Jewish physicians as they see the great majority of Jewish patients requiring specialist care. Further contact with practitioners in Port Elizabeth, East London and Kimberley failed to reveal any affected individuals.

Finally, a few affected persons were ascertained through Gaucher disease patients themselves. This was primarily through the discovery of other members of a patient's family who were already known to have the disease or by their being diagnosed following clinical screening. Some of the patients also knew of other Gaucher disease patients not related to themselves. These individuals were contacted through their medical practitioners and subsequently investigated.

In this way 53 affected individuals were ascertained. Five of these patients were seen and documented but have since died. Three known affected sibs of cases had died before the survey was undertaken. The ethnic distribution of the 45 living patients is:-

27	Ashkenazi-Jews	(60%)
2	Sephardic Jews	(4%)
8	Afrikaners	(18%)
2	English	(4%)
2	African Negros	(4%)
4	Mixed Ancestry	(9%)

The 8 deceased patients were:-

6	Ashkenazi-Jews
2	Afrikaners

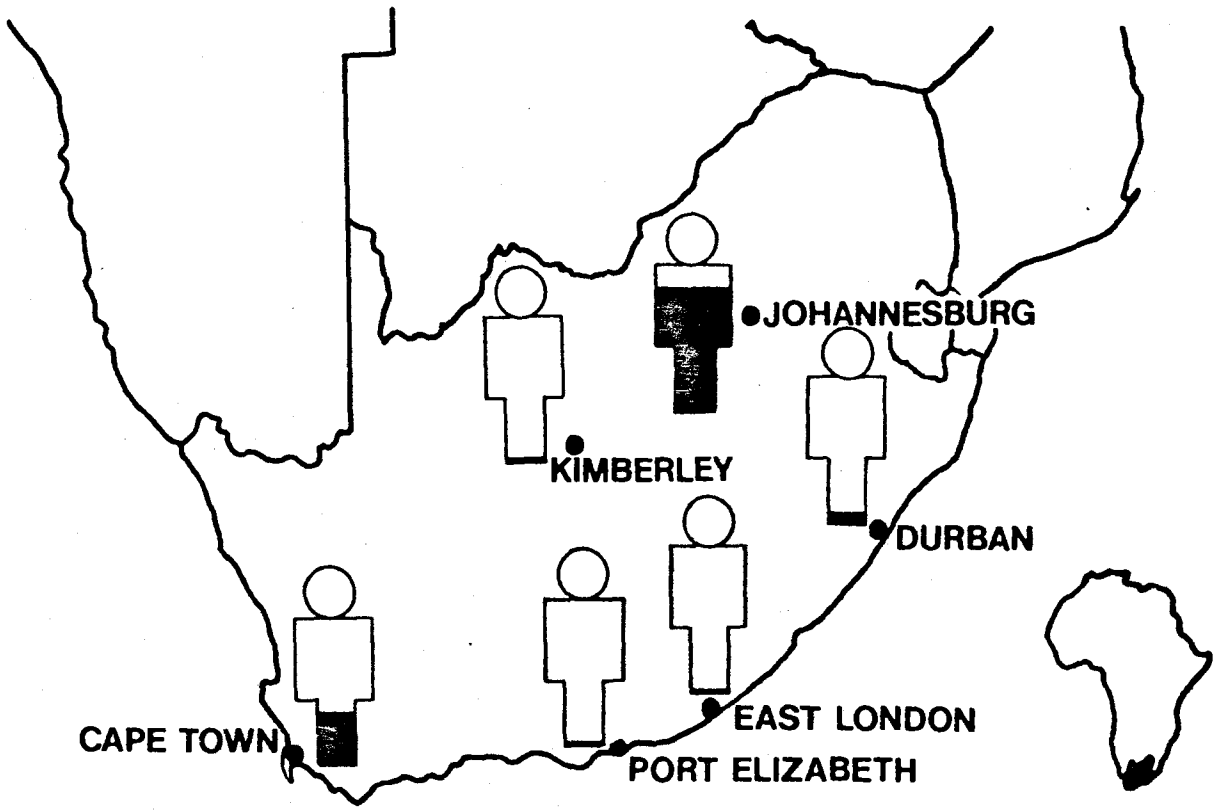

FIGURE 1: GEOGRAPHICAL DISTRIBUTION OF SOUTH AFRICAN ASHKENZI-JEWISH POPULATION

In all these affected individuals the diagnosis was made clinically and confirmed with the use of special investigations. These involved radiographic studies, histological examination of either the bone marrow, liver of spleen and biochemical analyses.

The author personally examined and investigated 30 of these affected individuals. A further 12 were not seen by the author, but were documented by Professor Beighton. The other 11 individuals were not seen for diverse reasons, for example: three refused to take part in the study, but fortunately had very co-operative attending practitioners; one patient was unavailable for the investigation as her parents chose not to reveal the diagnosis to her. Three patients died before the survey was undertaken (*vide supra*). They were all diagnosed as suffering from Gaucher disease by specialist physicians with the use of appropriate investigations and their inclusion in the survey is therefore valid.

The methods of ascertainment have been very thorough and extensive. It is therefore reasonable to assume that a significant proportion of currently diagnosed patients with Gaucher disease in South Africa have been seen in the course of the survey. However, it should be emphasised that there must be a number of affected individuals who are still in the presymptomatic stage of their disorder and who have, therefore, escaped ascertainment.

CHAPTER 6

CLINICAL

The author travelled extensively to see the affected individuals. The majority lived in Johannesburg and Cape Town and the distribution of the remainder was as follows:-

Durban	-	2
Margate	-	1
Springs	-	1
Pietersburg	-	1
Rustenburg	-	1
Kimberley	-	1

The Cape Town patients were seen in their homes and in the Department of Human Genetics. The Johannesburg patients were visited at home and examined in the orthopaedic department of the Medical School. Detailed clinical histories were recorded and the affected individuals were fully examined with special reference to ocular, dermal, skeletal and abdominal systems. Fundoscopy was performed and blood pressure readings were recorded on all patients.

Where possible, patients were examined and then seen together with the available kindred. The whole family would join the discussion relating to pedigrees and historical origins. Patients were followed up during the course of the investigation, with most being seen on an average of three times. Communication by post was constantly maintained and in this way further valuable information was gleaned.

Radiographic examinations had already been carried out in many instances by the family practitioner or referring specialist. The films were collected, copied and personally reassessed. Radiographic studies were performed on the skull, spine, chest, pelvis and long bones. Laboratory procedures carried out on specimens from these patients will be detailed in the next section.

CHAPTER 7

BIOCHEMISTRY

INTRODUCTION

The basic intention was to establish a satisfactory laboratory procedure for the detection of homozygotes and heterozygotes, or carriers, and to assess the feasibility of population screening for Gaucher disease.

Beutler and Kuhl, (1970), described a method for "the diagnosis of the adult type of Gaucher disease and its carrier state by the demonstration of beta-glucosidase activity in peripheral blood leucocytes". This appeared to be the most satisfactory biochemical procedure for the above-mentioned purpose. The initial laboratory studies, methodological refinements and establishment of a working assay were performed by Dr Howard Henderson, Biochemist in the Department of Human Genetics. The author's plan was therefore to reproduce Beutler and Kuhl's results by performing the assay, according to Dr Henderson's modifications of their specific method, on the kindreds ascertained in this survey.

COLLECTION OF SAMPLES

Blood samples were collected from 21 patients with adult type Gaucher disease and 24 members of their families who were obligate heterozygotes. Control blood specimens were drawn from 38 non-Jewish adults and 7 Jews with no history of Gaucher disease in the family.

The patients were spread throughout the Republic, and problems were encountered as it was essential to transport the blood speciments to the Cape Town laboratory within 4 hours of venesection. This was estimated to be a suitable delay with regard to the extracellular leak and decay of the beta-glucosidase enzyme which might cause abnormal results on the assay. Earlier experiments had been performed on the same samples at varying periods following venesection.

These difficulties were solved by venesecting the patients at their homes early in the morning and immediately express airfreighting the blood in polystyrene boxes to Cape Town. A technician would receive these samples at the Cape Town airport within two and a half hours and they would thus be available for investigation in the laboratory within the allotted time period.

Blood specimens from the Gaucher disease patients were simultaneously tested haematologically and biochemically. The haematology investigations were performed as part of the routine in the Groote Schuur Hospital haematology laboratory. This work-up included the haemoglobin estimation, full blood, platelet and differential counts, and a peripheral smear. The biochemical studies involved routine 12/60 and 6/60 channel analysis, as performed in the Groote Schuur Hospital biochemistry department. These results, which are expressed in S.I. units, will be discussed in a later section.

ENZYME ASSAY

The technique followed in the assay for beta-glucosidase activity was that of Beutler and Kuhl, (1970), with minor modifications. A 20ml specimen of blood was taken before breakfast and mixed with 5% w/v sodium citrate in normal saline (7ml) in 50ml plastic tubes. These samples were kept at room temperature and transported to the laboratory within a period of 4 hours. The tubes were inverted to resuspend

all cells and the erythrocytes allowed to settle for 45 minutes at 37 degrees centigrade (^{o}C), after which the supernatant suspension of leucocytes and platelets was drawn off and centrifuged (100g; 10 min) in order to harvest the former.

The leucocyte pellet was gently suspended in saline (0,9%; 10ml) and aliquots (5ml) layered on ficol-hypaque (4ML; S.G. 1 077 at 22^{o}C) in plastic test tubes. Centrifugation (1 000g; 10 min) gave an interphase layer consisting mainly of lymphocytes (90%) and free of erythrocytes. The interphase cell suspension was removed, mixed with an equal volume of saline (0,9%) and the cells were recovered by centrifugation (400g; 10 min). After washing in saline (0,9%, 2 x 3ml), the pelleted cells were carefully suspended in saline (0,2ml), and counted by means of a haemocytometer. All suspensions were diluted to a concentration of 75 x 10^{6} cells/ml and immediately assayed for beta-glucosidase activity.

The assay system for beta-glucosidase activity consisted of sodium acetate buffer (20μl; 0,2M; ph 4,0), lymphocyte suspension (20μl; 1,5 x 10^{6} cells) and substrate (50μl; 1mM 4-methylumbelliferyl- -D glucopyranoside; Koch-Light). The mixture was incubated for 60 minutes at 37^{o}C in a shaking waterbath, enzyme activity was stopped by addition of glycine buffer (3ml; 0,2M; ph 10,7) and fluorescence read on an Amino SP 125 fluorimeter (excitation wavelength 365mμ - emission wavelength 448mμ). A freshly prepared 4-methylumbelliferone standard (100mg/ml) was included in each run. All assays were carried out in duplicate with cell and reagent blanks included. Beta-glucosidase activity was similarly assayed at pH 5,3 by altering the pH of the acetate buffer.

The results obtained by this method are presented in Chapter 21.

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The results obtained by this method are presented in Chapter 21.

CHAPTER 8

CORRELATION OF DATA

The data collected and results obtained by the above methods will be presented and analysed in a subsequent section of this thesis. These results will then be compared to those published in other series reported in the world literature. This will initially involve a discussion of the clinical results and their compatibility with accepted theories. Only the Ashkenazi-Jewish patients have been considered for more detailed observations in this series. Data concerning the non-Jewish patients has only been introduced into the discussion where necessary for clarification.

The biochemical results will be tabulated and statistically analysed to assess their suitability for discriminating genotypes. This was undertaken to determine the possibility for biochemical detection of affected individuals and for population screening. Aspects of population screening relevant to the prevalence of Gaucher disease in the local communities will then be considered.

The formal genetics of Gaucher disease as it occurs in the South African Ashkenazi-Jewish population will be statistically analysed. The results will be correlated from the findings on 18 extensive family pedigrees and the estimated population size according to the Census of 1970 (Department of Statistics, 1970). These figures will then be extrapolated in an attempt to assess the present situation with regard to prevalence and heterozygote frequency.

S E C T I O N III

CASE REPORTS

CHAPTER 9

CASE REPORTS

INTRODUCTION

Three case reports are given in detail in this section in order to exemplify the different clinical manifestations. Concise case studies of the other 18 patients are presented in the appendix for the sake of completion.

CASE 1

History

This Ashkenazi-Jewish male aged 34 years was diagnosed as having Gaucher disease at the age of 21 years. At that time he presented with persistent, non-specific pains in both thighs and clinical examination revealed hepato-splenomegaly. Histological examination of the bone marrow confirmed the diagnosis of Gaucher disease.

He had previously led a normal existence with no childhood illnesses of note. His initial limb pains subsided on symptomatic therapy and he subsequently performed strenuous physical work as a truck driver, remaining asymptomatic for the next seven years. He then developed an acute severe pain in the left hip which was diagnosed as an acute attack of Gaucher pseudo-osteomyelitis of the hip joint. This problem resolved after 2 weeks of conservative management with traction, antibiotics and analgesics.

He was discharged from hospital only to be re-admitted three weeks later with a hot, tender swelling above the left knee. A diagnosis of septic osteomyelitis was made and the left femur was surgically drilled. Following this operation the pain disappeared, but sinuses formed at the operation site.

These sinuses persisted through the post-operative period, continuously discharging a yellow blood-stained material. He was re-admitted to hospital on several occasions for multiple curettages at the operation site. However, these procedures had no effect on the sinuses.

At the age of 29 years, he was admitted to hospital for intensive therapy in an attempt to heal the persistent sinuses. Despite a six month stay and multiple therapeutic measures, the sinuses remained patent and discharging. Bacteriological studies on the discharged material always failed to show an infective agent. Further therapy consisted of nightly sterile cleansing and dressing of the sinuses by the patient, a practice he has strenuously maintained up until the present time. Every six months to a year the sinuses obstruct with formation of an acutely painful swelling. These flare-ups are managed by surgical curettage, with subsequent resolution of the swelling. Unfortunately the sinuses always recanalise during the remission despite the discharge consistently remaining sterile.

He is presently well except for discomfort in his left leg and an ankylosed left knee joint, consequent upon these recurrent problems. He suffers from a moderate bleeding tendency, but has steadfastly refused splenectomy whenever advocated over the last five years.

There is no family history of Gaucher disease, but his father suffers from cholelithiasis. He is married with a daughter of 5 years, who is well. His ancestors originally emigrated to this country from Eastern Europe.

Examination

Examination revealed a thin, fit-looking man of 34 years who walked with a left-sided limp. He was 180cms tall and weighed 60 kilograms. His skin had a generalised yellow-bronzed hyperpigmentation with no localised abnormality. He had marked

bilateral pingueculae, which were raised and nodular. There was also a left congenital ptosis which bore no apparent relationship to his Gaucher disease. No suferficial lymphadenopathy was present. Examination of the cardiovascular, respiratory and central nervous systems revealed no abnormality of note.

He had a 4cm non-tender, firm splenomegaly and a 3cm hepatomegaly. The left knee was fixed in extension. There were two sinuses in the distal region of the left thigh which were discharging a gelatinous, yellow material. He had full and painless movements of all other joints.

Special Investigations

Radiographic studies revealed bilateral Erlenmeyer flask deformity of his lower femora and aseptic necrosis of the left femoral head. The skeletal survey was otherwise normal.

Laboratory Investigations: His beta-glucosidase assay was 1,26 micro-units per 10^7 cells. This value is consistent with a diagnosis of homozygosity for Gaucher disease. Haematology revealed a platelet count of 91 x $10^9/\ell$, a haemoglobin level of 15,3g% and white cell count of 9.3 x $10^9/\ell$.

Comment

This individual presents a classical example of a patient with severe bony complications of Gaucher disease and he illustrates some of the problems of management of these acute orthopaedic attacks. Similarly it is evident that surgery carries the risk of post-operative chronic sinus formation. As in this patient these sinuses are most resistant to any form of therapy. He is otherwise mildly affected with slow, progressive enlargement of his liver and spleen.

CASE 2

History

This Ashkenazi-Jewish male, aged 42 years, was found to have splenic enlargement in early childhood and when 8 years old underwent a laparotomy, at which no splenectomy was performed.

Gaucher disease was suspected at the age of 22 years, when he was investigated for splenomegaly, and the diagnosis was confirmed on histological examination of the bone marrow and by the demonstration of a raised serum acid-phosphatase level.

He was recurrently found to be anaemic and from the age of twenty-six was treated conservatively on long-term haematinics. Over the years he developed a marked kyphoscoliosis due to collapse and wedging of the lower thoracic vertebrae, from Gaucher cell infiltration. This had been a slow process and he never experienced any acute bone or joint symptoms.

He was managed conservatively by his general practitioner until the age of 42 years when he was referred to the respiratory clinic because of congestive cardiac failure and for assessment of his respiratory function. His complaints at that time were of severe weakness, grade three dyspnoea on effort (N.Y.H.A. classification), orthopnoea and paroxysmal nocturnal dyspnoea. A marked loss of appetite, unrecorded weight loss and abdominal swelling were other features. There was no history of abnormal bleeding.

His family came from Eastern Europe and his brother had died at the age of 24 years, having suffered from Gaucher disease. The patient himself was a bachelor and had no other family history of Gaucher disease.

Examination

Examination during his admission to Groote Schuur Hospital in 1974 revealed a thin, wasted man with a generalised yellow-bronze hyperpigmentation. There were multiple spider naevi over the arms, chest and face, but no dermal evidence of a bleeding tendency. He had marked bilateral pingueculae but neither xanthelasmata nor other ocular abnormalities. He appeared polycythaemic but was not clubbed, jaundiced or anaemic and no superficial lymphadenopathy was palpable. Marked ankle oedema was present but apart from a right ventricular heave there was no cardiac abnormality. The chest was deformed as a result of the kyphoscoliosis and percussion revealed an elevated upper edge of liver dullness as well as splenic dullness. Bilateral basal crepitations were audible but the lung fields were otherwise clinically clear. The abdomen was entirely occupied by a massive liver and spleen. This barely separable organomegaly was palpated as a huge, rock-hard mass extending from the costal margin down to the iliac fossae with numerous large nodules projecting from the surface.

Apart from the generalised weakness of all limbs the central nervous system was clinically normal with no focal signs.

Special Investigations

Radiographic studies revealed that the liver and spleen were calcified. There was bilateral Erlenmeyer flask deformity of the lower femora and misshapen femoral heads due to aseptic necrosis. The lower thoracic vertebrae were wedged and kyphoscoliosis was present. The lung fields were grossly reduced in volume by the kyphoscoliosis and an elevated diaphragm due to the hepatosplenomegaly.

The electrocardiogram showed right ventricular hypertrophy with right axis deviation as the only abnormalities.

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The Astrup showed a mild respiratory acidosis with hypoxia. The forced vital capacity of the lungs was greatly reduced from a predicted forced vital capacity of 3 900ccs down to an actual value of 580ccs. Bronchodilators had no effect on the lung function tests. This showed very severe restrictive lung disease which confirmed the clinical findings.

The full blood count showed a haemoglobin of 18,4g%, a haematocrit of 53,8, a white cell count of 9 x $10^9/\ell$ and a platelet count of 62 x $10^9/\ell$.

Beta-glucosidase enzyme assay confirmed the diagnosis of Gaucher disease. The rest of the biochemical studies were normal.

Subsequent Course

He was discharged from hospital on conservative management of his cardiac failure but was readmitted two months later from a convalescent home because of the development of gangrene in his feet and hands.

He was less dyspnoeic than before but still showed evidence of central and peripheral cyanosis. There were signs of arterial insufficiency in the extremities, with superficial gangrene involving the left foot, the right leg up to the knee, the finger tips of both hands and the tip of the right ear. No pulses were felt in the right lower limb, and in the left leg only the femoral and popliteal pulses were palpable. Otherwise all the clinical findings and special investigations were similar to those of the previous admission. Low platelet counts, a prolonged kaolin cephalin time (P.T.T.) and the low prothrombin index suggested possible multiple haemostatic defects.

Despite intensive investigations no obvious cause for the arterial insufficiency was found. His condition deteriorated

rapidly and he died a week after admission. No post-mortem was performed.

Comment

This patient was severely affected with Gaucher disease and presented with superficial gangrene as a preterminal event. This is not a recognised complication of Gaucher disease and no other obvious cause for it was found. However, it is possible that Gaucher cells had infiltrated the small peripheral vessels and his polycythaemia might also have contributed to the clinical picture.

Severe pulmonary restriction and chronic congestive cardiac failure were also secondary results of his Gaucher disease. The lung capacity was greatly reduced by the hepatosplenomegaly forcing up the diaphragm and the deformity of the bony chest secondary to the kyphoscoliosis.

CASE 3

History

This Ashkenazi-Jewish school teacher, aged 39 years, was diagnosed as having Gaucher disease at the age of 23 years. She was 16 weeks pregnant at the time and presented with an influenza-like illness. She was found to be severely anaemic and required a transfusion of 3 units of blood. The patient was asplenomegalic at the time but the diagnosis of Gaucher disease was confirmed following histological examination of the bone marrow. The pregnancy was otherwise uneventful and she had a normal labour and delivery. The post-partum course was also entirely normal and she maintained an adequate haemoglobin level without therapy. Mild anaemia has recurred but has responded well to intermittent haematinic therapy.

A year after this first pregnancy she started experiencing a generalised myalgic pain. This was of gradual onset and her shoulders and hips were most severely affected. The pain progressed to such an extent that she became severely incapacitated. Muscle spasm and subsequent soft-tissue changes led to secondary contractures around the hip joints and she was eventually confined to a wheelchair.

Radiographic studies at this stage showed bilateral destruction of femoral and humeral heads and flaring of the lower ends of the femora. She spent the next 4 years in a wheelchair, her treatment consisting of analgesics and conservative orthopaedic procedures aimed at preserving joint and muscle function.
No operation was performed but at the age of twenty-nine years she was treated with extensive physiotherapy in an attempt to regain mobility. This initially involved shortwave diathermy, gentle graduated exercises and hydrotherapy. Her condition gradually improved and she was eventually able to walk unaided.

When thirty-one years of age she became pregnant again. This was entirely uneventful from an obstetric, haematological and

orthopaedic point of view. In fact, the patient claims that she felt generally much better during the course of her pregnancy. Her labour was uncomplicated and she had a normal vaginal delivery of a healthy full-term infant. The mild anaemia was easily controlled with haematinics. The post-partum course was entirely normal with no excessive bleeding. The patient has continued to improve and there have been no further acute exacerbations of her Gaucher disease. She still has radiographic evidence of gross residual hip and shoulder joint destruction, but manages to walk unaided and has minimal symptoms in her shoulders. She does, however, tire very easily and experiences occasional non-specific muscle spasms.

She still has manifestations of a bleeding tendency, in that she bruises easily and occasionally has noticed crops of dermal petechiae but she has no symptoms referable to other bodily systems.

Her siblings are normal and there is no family history of Gaucher disease. Her non-consanguinous parents are both of Eastern European origin.

Examination

Examination revealed a fit-looking, pale woman who walked with a severe limp. She was 166cms tall and weighed 53 kilograms. She had small bilateral pingueculae and no skin changes. Her spleen at this stage was 3cms enlarged and no clinical hepatomegaly was detected. She had full, painless movement of shoulder joints but there was bilateral gross limitation of hip movement. Flexion-extension was only possible in a 40 degree arc and abduction-adduction in a 30 degree arc bilaterally.

There was no superficial lymphadenopathy and systemic examination revealed no other clinical evidence of involvement by the Gaucher disease process.

Special Investigations

Radiographic studies demonstrated bilateral humeral and femoral head necrosis and a mild Erlenmeyer flask deformity of the lower ends of the femora. There were also mottled areas of rarefaction in the femoral shafts.

The beta-glucosidase level was 2,1 micro-units per 10^7 cells. This value was well within the range for a diagnosis of Gaucher disease. The haemoglobin was 11,4gms % and the peripheral smear revealed a normochromic, normocytic anaemia. The platelet count was 112 x $10^9/\ell$ and the white cell count was 7.5 x $10^9/\ell$.

Routine biochemical investigations were normal except for hypocholesterolaemia of 3,2mmol/ℓ (normal 3,6 - 7,8mmol/ℓ).

Comment

This patient had severe osseous complications of her Gaucher disease. She has marked residual orthopaedic damage from the acute process, which appears to be in remission at the present time. Interestingly, enlargement of the spleen has always been slight.

She has had two relatively uncomplicated pregnancies. This fact emphasises the minimal reciprocal effects of Gaucher disease and pregnancy, especially from a haematological viewpoint. Also of importance was the subjective feeling of increased wellbeing during the second pregnancy. This situation has been described in rheumatoid arthritis, (Persellin, 1976), but only rarely in Gaucher disease, (Bromberg *et al*, 1953).

OTHER PATIENTS

In addition to these three patients and the eighteen affected individuals detailed in the Appendix, Section XI, the positive diagnosis of Gaucher disease on multiple criteria has also been established on eight other Ashkenazi-Jews, cases 22 to 29. These patients are all under the care of specialist physicians and orthopaedic surgeons and there is no doubt as to the validity of the diagnoses.

Their clinical findings are not detailed in this thesis as they have not been personally investigated by the author. However, clinical data has been made available by their attendant physicians and they have, therefore, been considered in the statistical analyses. In addition, where relevant, significant facets of their clinical histories have been described.

S E C T I O N IV

ANALYSIS OF CLINICAL MANIFESTATIONS

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CHAPTER 10

COURSE AND PROGNOSIS

The great variability in the presentation of Gaucher disease has been discussed in an earlier chapter (Chapter 4). Even within the well-defined clinical group described in this survey a variety in modes of expression is found to occur with regard to clinical manifestations, course and prognosis. There are, consequently, wide differences in the degree of suffering experienced by affected individuals and in interference with their normal existence. Unfortunately, this study, as with all the other world series for Gaucher disease, is not large enough to permit accurate compilation of prognosis and mortality tables. This discussion is therefore based on impressions, rather than strict statistical criteria, as they have been gained from analysis of a relatively small group of patients.

The most important general feature is the complete absence, in all patients, of organic central nervous system involvement during the entire course of the disease. The other outstanding feature is the impression that the patients in this series generally have Gaucher disease in a mild form. The condition presents, therefore, with varying degrees of physical disability and an intact intellect.

The majority of patients adapted readily to their physical impairment and coped with their family and professional roles in an admirable fashion. As a group they appeared to be of above average intelligence and generally emulated their healthier counterparts in their respective fields.

Of the 21 patients, occupational distribution was as follows: 2 medical practitioners, 3 teachers, 2 accountants, 5 successful businessmen, 1 business woman, 1 qualified librarian and

1 commercial traveller. Three of the women were housewives and 3 patients were schoolchildren and all were near the top of their classes.

No problems were encountered in marrying and raising normal families. It was obvious, therefore, that despite their handicap, these patients can fulfil a valuable role in society. However, there was still a dilemma in the prediction of the course and prognosis in each affected individual.

There were no strict clinical or biochemical parameters to help clarify the problem. The magnitude of the enzyme defect in the patients in the author's study was no value as a prognostic indicator and showed no correlation with the severity of clinical disease. In fact, one of the most mildly affected patients (Case 15) showed the greatest enzyme deficit. Another patient (Case 13) was severely affected and died at the age of 35, yet her enzyme level was at the upper limit of the homozygous abnormal range.

Multiple modifying factors were probably operative, and the quantitative enzyme deficit within each particular range evidently had no real bearing on the clinical manifestations.

The most important factors affecting the future clinical course were:

i the age at presentation of symptoms
ii severity of symptoms at presentation
iii extent of splenomegaly at presentation.

The average age of presentation in this series was 23 .33 years. The older the patient at presentation, the milder were the symptoms which developed. The worst prognosis was in those patients presenting in the first decade of life. The rate of splenic enlargement was also found to be a significant factor and young patients presenting with large spleens appeared to have the worst prognosis. Table I, however, illustrates that this was not a clear-cut relationship and confirms the great difficulty in prognosticating for each individual patient. Another important feature was that the orthopaedic symptoms often showed a tendency to diminish with advancing age.

KEY TO TABLE I:

KEY WHERE EXACT SPLENIC SIZE NOT RECORDED

N.K.	=	NOT KNOWN
+	=	ENLARGED
++	=	MODERATELY ENLARGED
+++	=	MASSIVELY ENLARGED
SPL.	=	SPLENECTOMY

TABLE 1: RELATIONSHIP OF MODE OF PRESENTATION TO COURSE AND PROGNOSIS

PATIENT	PRESENTATION			CURRENT STATUS		
	AGE Years	INITIAL SEVERITY	SPLENIC SIZE	AGE Years	HEALTH AND COURSE	SPLEEN SIZE
1	21	moderate orthopaedic problems	+	34	severe recurrent orthopaedic problems	4cms
2	8	severe generalised involvement	++	died aged 42	severely affected. Died	reached iliac crest
3	23	severe orthopaedic problems	1cm	39	variable - recurrent arthritic problems stormy course	3cms.
4	11	mild haematology problems	1cm.	18	mild course with increasing haematology problems, well	4cms.
5	4	mild abdominal discomfort	+	18	recurrent orthopaedic and bleeding problems	spl.
6	10	bone pain and orthopaedic symptoms	5cms.	49	recurrent orthopaedic problems	7cms.
7	6	recurrent moderate orthopaedic	+	53	arthritic problems stormy course	10cms.
8	10	mild orthopaedic problems	0cm.	33	mild recurrent orthopaedic problems, well at present	1cm.
9	15	mild orthopaedic symptoms	1cm.	16	mild course, well at present	2cms.
10	50	mild arthritic problems	N.K.	58	mild course, well at present	3cms.
11	20	moderate arthritic pain and severe anaemia	+++	37	recurrent orthopaedic problems, well at present	spl.
12	30	mild haematology problems	+	65	mild course, well at present	spl.
14	7	moderate orthopaedic and bleeding problems	+	39	recurrent moderate orthopaedic attacks and haematology problems	spl.
13	18	severe orthopaedic problems, abdominal discomfort	+++	died aged 35	severe recurrent orthopaedic attacks and generalised debility, died	spl.
15	38	mild arthritic problem	0cm.	44	mild course, well at present	1cm.
16	32	mild haematology problems	N.K.	37	mild course, well	3cms.
18	30	asymptomatic screened	N.K.	32	mild arthritic problems, well	3cms.
17	31	mild abomdinal pain	+	35	mild course with minimal orthopaedic and abdominal symptoms	7cms.
20	44	mild abomdinal discomfort	3cms.	63	excellent, mild course	spl.
19	72	mild	+	72	excellent, mild course	0
21	11	severe arthritic and orthopaedic problems	+	24	recurrent severe orthopaedic problems	7cms.

The more severely affected young patients, with significant haematologic complications, will usually be found to have had early splenectomies. This often leads to the erroneous belief that splenectomy worsens the clinical course and hastens orthopaedic problems, (Schein and Arkin, 1942; Matoth and Fried, 1965; Silverstein and Kelly, 1967). This study did not confirm that view, as shown in Table 2. The majority of splenectomised patients had osseous symptoms pre-dating their splenectomy. They were also the more severely affected group and were, therefore, more likely to develop later orthopaedic problems. Reich *et al*, 1951, and Marks *et al*, 1971, also found no evidence for a worsening of their Gaucher patients' orthopaedic manifestations after splenectomy.

TABLE 2: THE INFLUENCE OF SPLENECTOMY ON ORTHOPAEDIC COMPLICATIONS

PATIENT	AGE IN YEARS				ORTHOPAEDIC COMPLICATIONS	
	PRESENTATION	COMMENCEMENT OF ORTHOPAEDIC COMPLICATIONS	SPLENECTOMY	PRESENT	PRE-OP	POST-OP
1	21	21	-	34	++++	-
2	8	20	-	42	++++	-
3	23	24	-	39	+++	-
4	15	-	-	18	0	-
5	4	10	10	18	++	++++
6	10	10	-	49	++++	-
7	6	12	-	53	+++	-
8	10	10	-	33	++	-
9	15	15	-	16	+	-
10	50	51	-	58	+	-
11	20	20	20	37	++	++++
12	30	63	31	65	0	0
13	18	21	19	35	0	++
14	7	7	12	37	++	+++
15	38	38	-	44	++++	-
16	32	35	-	37	+	-
17	31	34	-	35	+	-
18	30	32	-	32	+	-
19	40	-	-	72	0	-
20	44	-	57	63	0	0
21	11	16	-	24	++++	-

KEY TO ORTHOPAEDIC COMPLICATIONS:

\+ = non-specific bone joint pain

++ = acute aseptic osteomyelitis, recurrent severe attacks

+++ = pathological fractures, collapse of femoral heads

++++ = incapacitating recurrent osteomyelitis, operations, spinal problems, chronic sinuses

Another impression was of the aggregation of similarly affected cases in the same family. In all of the families with more than one affected sibling, the disease ran a similar clinical course, as shown in Table 3.

It would appear then that the most satisfactory indication of future clinical course and severity are those described on page 39, together with a knowledge of the prior family history.

TABLE 3: CLINICAL COURSE IN AFFECTED SIBLINGS

PATIENT	AGE OF DIAGNOSIS	SEVERITY OF SYMPTOMS	CURRENT	
			AGE	HEALTH
2	22	Severely affected	Died 42 yrs.	-
2a	?	Severely affected	Died 24 yrs.	-
6	28	Moderate orthopaedic complications	48	Mild arthritic symptoms
6a	53	Asymptomatic splenomegaly	Died 55 yrs.	of C.A ovary
10	50	Asymptomatic splenomegaly	57	Mildly affected
10a	27	Mildly affected	Died 28 yrs.	of Osteogenic sarcoma
13	18	Severely affected	Died 34 yrs.	-
14	10	Haematological and orthopaedic complications	38	Persistent orthopaedic problems. Post-splenectomy.
17	31	Abdominal pain splenomegaly	33	Mildly affected
18	29	Asymptomatic	31	Mildly affected
19	72	Splenomegaly	72	Asymptomatic
20	57	Mild thrombocytopenia splenomegaly	61	Asymptomatic following splenectomy

very few affected individuals presently found in the over 40 age group. The three patients who died during the course of this series bear out the above impression. Their respective ages of presentation and death were:

Patient 1:	8 years	42 years
Patient 13:	18 years	35 years
Patient 27:	6 years	45 years

LE 4(a): AGE OF PATIENTS AT PRESENTATION

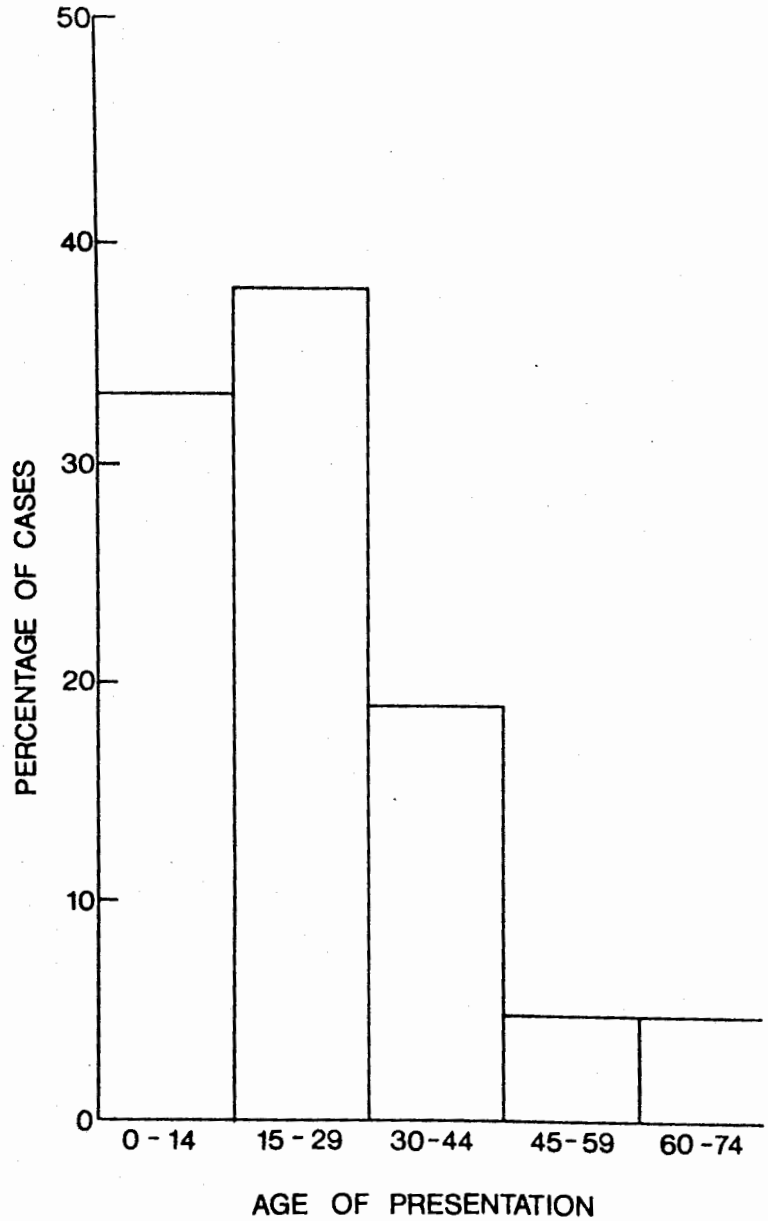


TABLE 4(b): AGE OF PATIENTS AT DIAGNOSIS

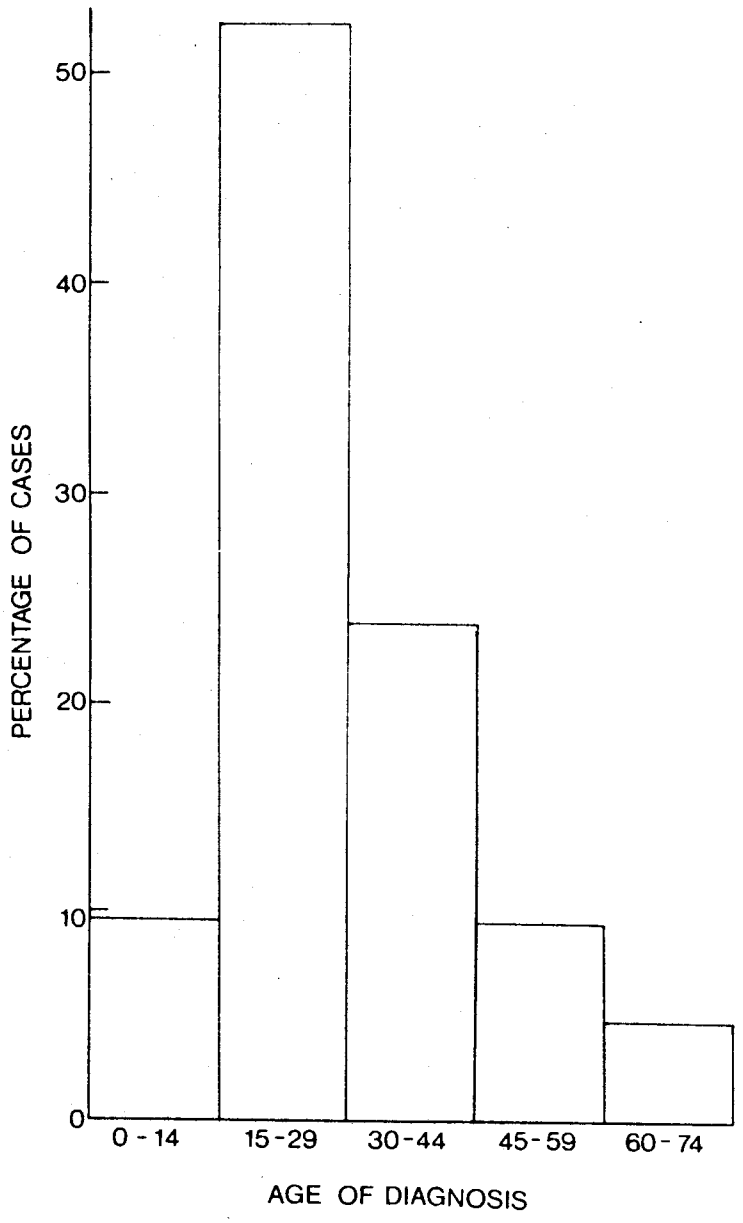


TABLE 4(c): AGE OF PATIENTS AT PRESENT

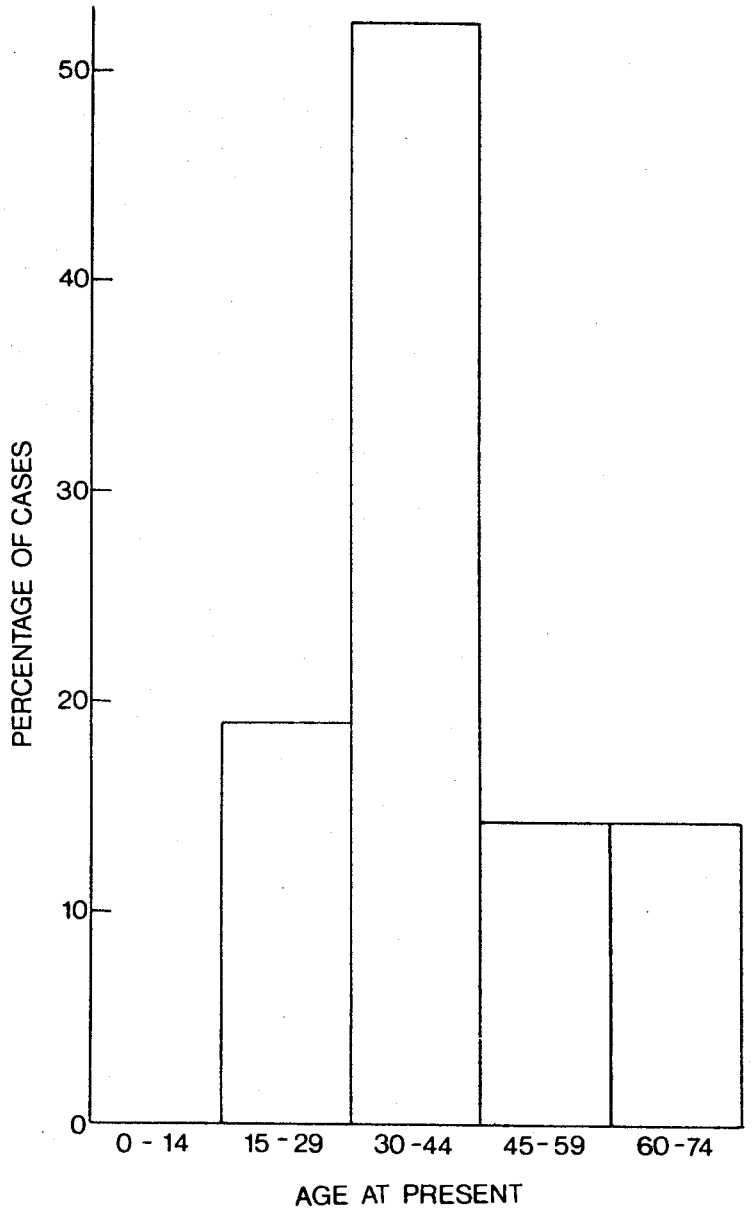
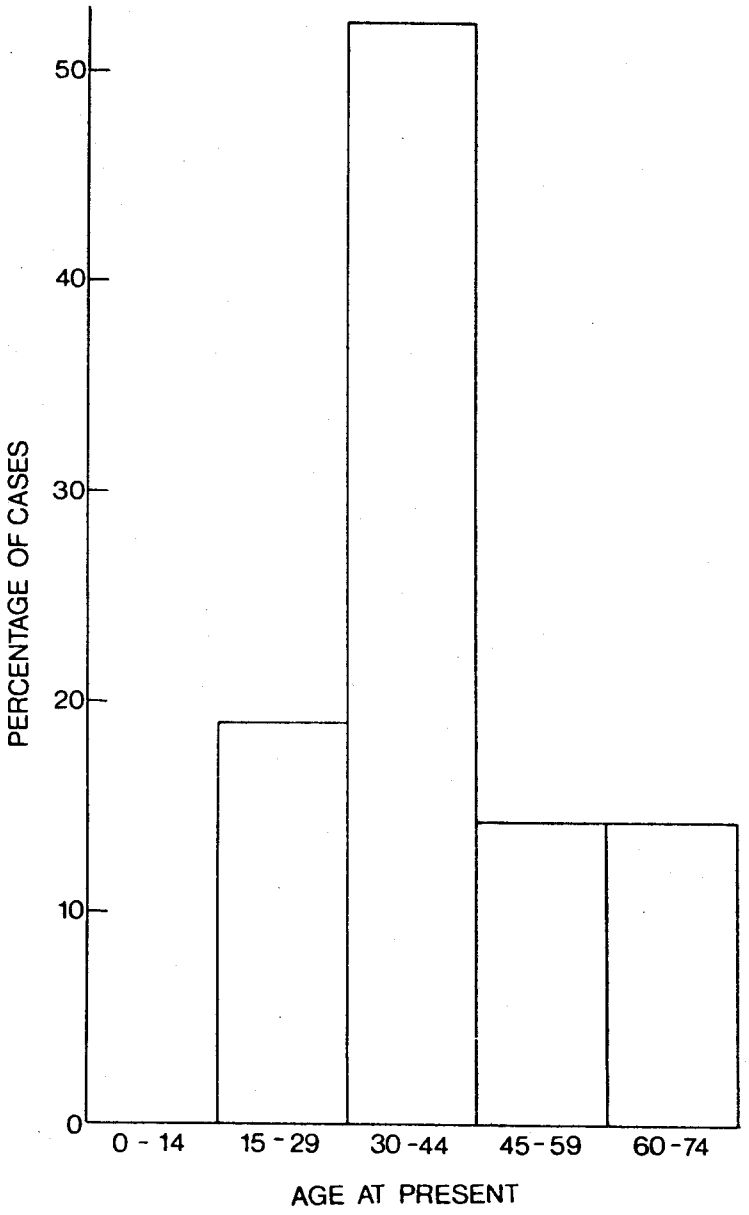


TABLE 4(c): AGE OF PATIENTS AT PRESENT



SUMMARY

The condition in all the patients runs a chronic and progressive course characterised by acute exacerbations, relapses and remissions. Prognosis and mortality tables cannot be constructed with any accuracy, within the framework of the present undertaking, because of the great clinical variability and insufficient patient numbers. However, the impression from analysis of this series is that prognosis can be based on certain features with obvious limitations. These criteria are dependent on the age of onset of symptoms and initial severity of signs, the extent of splenomegaly and the relevant family history.

It would seem that patients presenting in the first three decades of life do have a shortened life span. This is not grossly curtailed, but they do not appear to survive beyond the fifth decade of life. A final complicating factor is the possible presence of a pool of minimally affected, asymptomatic individuals, living normal lives and dying of unrelated illnesses. The present study might represent the tip of the iceberg due to ascertainment of only maximally affected individuals. The solution to this question would lie in population screening.

Despite the inherent severity of the condition, the patients easily adapt and cope with environmental stresses. The majority of them overcome their physical handicaps and are socially successful, capable and highly intelligent individuals.

CHAPTER II

SPLENOMEGALY

INTRODUCTION

Splenic enlargement is the most consistent clinical feature and asymptomatic splenic enlargement in an Ashkenazi-Jew should immediately alert the clinician to the possibility of a diagnosis of Gaucher disease.

RESULTS

Eighteen of the patients (86%) in this study were found to have an enlarged spleen as part of their initial clinical presentation. They were all Ashkenazi-Jews and the majority also showed associated clinical signs of Gaucher disease when first examined. However, in 48% of these individuals the positive diagnosis of Gaucher disease was only confirmed by their attendant practitioners after more than a year of follow-up examinations and investigations. This duration from presentation to diagnosis, as shown in Table 5, again underlies the lack of appreciation of the significance of this condition and its ethnic distribution.

Every patient in this study was found to have an enlarged spleen during the course of the disease and only one patient, Patient 19, was asplenomegalic when examined by the author. She did, however, have an enlarged spleen when originally seen by her personal physician.

TABLE 5: INITIAL PRESENTATION AND DELAY IN DIAGNOSIS

PATIENT	AGE	PRESENTATION SIGNS AND SYMPTOMS	AGE AT DIAGNOSIS	PRESENTATION - DIAGNOSIS DELAY
1	21 yrs.	pseudo-osteomyelitis	21 yrs.	minimal
2	8 yrs.	splenomegaly	22 yrs.	14 yrs.
3	23 yrs.	anaemia with pregnancy splenomegaly	23 yrs.	minimal
4	11 yrs.	splenomegaly	17 yrs.	6 yrs.
5	4 yrs.	abdominal pain splenomegaly	4 yrs.	minimal
6	10 yrs.	pseudo-osteomyelitis splenomegaly	28 yrs.	18 yrs.
7	6 yrs.	acute arthritis splenomegaly	38 yrs.	32 yrs.
8	10 yrs.	pseudo-osteomyelitis hepatomegaly	21 yrs.	11 yrs.
9	15 yrs.	acute abdominal pain splenomegaly	15 yrs.	4 months
10	50 yrs.	Raynauds phenomenon splenomegaly	50 yrs.	minimal
11	20 yrs.	acute arthritis splenomegaly	20 yrs.	minimal
12	25 yrs.	splenomegaly	30 yrs.	5 yrs.
13	18 yrs.	amenorrhoea splenomegaly	18 yrs.	4 months
14	7 yrs.	acute arthritis splenomegaly	10 yrs.	3 yrs.
15	38 yrs.	acute arthritis	40 yrs.	2 yrs.
16	32 yrs.	thrombocytopenia splenomegaly	32 yrs.	minimal
17	31 yrs.	left upper quadrant pain splenomegaly	31 yrs.	6 weeks
18	29 yrs.	splenomegaly, bone marrow following sibling detection	29 yrs.	minimal
19	72 yrs.	splenomegaly	72 yrs.	minimal
20	44 yrs.	thrombocytopenia splenomegaly	57 yrs.	13 yrs.
21	16 yrs.	acute arthritis splenomegaly	17 yrs.	1 yr.

In the majority of individuals the enlarged spleen was non-tender and painless. The only symptoms were of mild abdominal discomfort, usually related to distension from a grossly enlarged spleen. However, three patients presented with episodes of severe pain in the left upper abdominal quadrant which appeared to be related to the spleen, (Patients 5, 9 and 17). No other cause was found for these acute abdominal crises and they resolved spontaneously following conservative management with bed rest and analgesics. It seems reasonable to postulate a diagnosis of splenic infarction in these instances.

The extent of splenic enlargement correlated well with the severity of the disease in these patients. The earlier the presentation with splenic enlargement the more severe was the course of the disease. Also the rate of splenic enlargement was a good index of future course and prognosis, Table I. As a significant number of patients underwent splenectomy, often early in the course of their condition, this assessment cannot be confirmed statistically.

The other interesting facet was the concomitant severity of orthopaedic and haematologic complications in the same individual. The patient with a large spleen and haematologic problems also suffered marked osseous complications. There was no evidence for the existence of distinct, specific osseous or haematologic disease types.

DISCUSSION

Gaucher disease should be high on the list of differential diagnoses of splenic enlargement in this population group. Today the diagnosis can be easily established by histological examination of bone marrow and assaying the deficient enzyme in the laboratory.

Enlargement

The spleen enlarges at varying rates in different patients. Although no absolute values are available, the rate of splenic enlargement usually parallels the severity of Gaucher disease in the affected individual. The spleen may reach mammoth proportions; indeed, the largest reported in the literature weighed 8910 grams, (Appel and Markowitz, 1971).

Symptoms

The initial splenomegaly is usually asymptomatic but gradual enlargement leads to symptoms of abdominal discomfort and distension. Occasionally the patient complains of a vague, dull ache in the splenic area of the left upper abdominal quadrant. Rarely an acute attack of severe abdominal pain is associated with the enlarged spleen. The acute abdomen is characterised by an apyrexial course with signs of focal peritoneal irritation, and by complete resolution on conservative management with bed rest and analgesics. These attacks appear to be incidents of splenic infarction.

Haematologic Complications

With increasing splenic enlargement the patient begins to have haematological problems as evidenced by a bleeding diathesis and a persistent low-grade anaemia. The easy fatiguability described by numerous patients is probably based mainly on the anaemia.

Rupture

Rupture of the spleen has been described in almost all conditions associated with splenomegaly, only two such cases have been reported in Gaucher disease in the English literature, (Mallory *et al*, 1945; Hancock, 1971).

Asplenomegalic Gaucher Disease

A very mild form of Gaucher disease which appears to be compatible with a long life and relative freedom from the incapacitating symptoms and haematologic sequelae of splenic enlargement might exist. In this respect a few cases of asplenomegalic Gaucher disease have been reported in the literature, (Erf, 1938; Petit and Schleicher, 1943; Fienberg and Quigley, 1946; Morgans, 1947; Block and Jacobson, 1948; Reich *et al*, 1951; Snapper and Goldberg, 1957; Matoth and Fried, 1965; Brady, 1978). Brinn and Glabmann, 1962, wrote of a man of 86 years with Gaucher disease who represents the oldest reported asplenomegalic case. Current biochemical analysis reveals an identical deficiency of beta-glucosidase enzyme in these patients. It is possible that an allelic mutation produces a different isoenzyme defect which has minimal osseous and haematological effects.

CHAPTER 12

HAEMATOLOGY

THROMBOCYTOPAENIA

Results

The peripheral blood picture is classically of a varying degree of pancytopenia. The most consistently abnormal finding is a thrombocytopaenia, which occurs in the majority of the patients studied in most series, (Medoff and Bayrd, 1954; Matoth and Fried, 1965).

Platelet studies were performed on 18 of the patients in this survey, Table 6. Six of these individuals underwent splenectomy and presently have normal platelet counts, however they were all markedly thrombocytopenic preoperatively. Eleven of the remaining twelve (92%) patients suffered from thrombocytopaenia of varying severity. Only Patient 9 has persistently had a normal platelet count, the normal range being 140 to 420 x $10^9/\ell$.

TABLE 6: PLATELET COUNTS (Normal Range = 140-420x$10^9/\ell$)

PATIENT	PLATELET COUNT ($10^9/\ell$)	BLEEDING TENDENCY	SPLENECTOMY STATUS	YEARS POST-SPLENECTOMY	SIZE	
					SPLEEN (cms)	LIVER (cms)
1	91	+	-	-	4	3
2	62	+	-	-	25	18
3	112	+	-	-	3	-
4	Not done	+	-	-	4	-
5	164	-	+	7	-	15
6	Not done	-	-	-	7	-
7	69	+	-	-	3	-
8	107	+	-	-	1	5
9	182	-	-	-	2	-
10	52	+	-	-	2	2
11	185	-	+	16	-	7
12	Not done	-	+	34	-	2
13	240	-	+	26	-	20
14	230	+	+	15	-	35
15	85	-	-	-	1	-
16	60	+	-	-	3	2
17	98	+	-	-	7	-
18	60	+	-	-	3	-
19	151	-	-	-	-	2
20	218	+	+	6	-	3
21	101	-	-	-	7	4

Discussion

The main factor responsible for the deficiency in the blood cellular elements is the hypersplenism due to splenic enlargement. This is evident from the following studies reported in the literature:

i Green *et al*, (1971), experimented with chromium-51 ($Cr.^{51}$) labelled platelets. He initially observed that megakaryocyte formation proceeded normally in the bone marrow.
He then injected $Cr.^{51}$ labelled platelets and measured their survival time in peripheral blood. He found a diminution of survival time from a normal of 5,1 days to 0,8 days. There was also a major uptake of $Cr.^{51}$ by the spleen.

ii The presence of intact platelets in Gaucher splenic cells seen on electron microscopy is further evidence of this hypersplenic phenomenon.

iii Finally, the dramatic response of the thrombocytopaenia to splenectomy confirms that this complication arises as a direct result of the hypersplenism. There is usually no later, post-operative recurrence of the thrombocytopaenia.
The Gaucher bone marrow infiltrate is thought to contribute in a minor degree to the dyshaemopoiesis. However, the bone marrow usually functions adequately until the condition has progressed to an advanced stage.

ANAEMIA

Results

The red blood cells were not as severely affected as the platelets and anaemia, when present, tended to be of a very mild nature, (Table 7). It was usually a normocytic, normochromic anaemia and was controlled by haematinic therapy. The majority of patients only required blood transfusion when the anaemia was aggravated by pregnancy, as with Patients 3, 8 and 11. Patient 11 also required pre-splenectomy blood replacement because of her marked anaemia. One individual, Patient 13, experienced a more severe anaemia and the peripheral red blood cells were macrocytic in appearance. No other cause was found for this abnormality. The affected individuals who underwent splenectomy showed no post-operative rise in their haemaglobin levels and these anaemias have persisted for many years after the operation.

TABLE 7: RED CELL INDICES

PATIENT	SPLEN-ECTOMY	HAEMOGLOBIN(g/dℓ) (n: m 13.2-17.2) (f 11.6-15.6)	H.C.T. (n: m 40-50) (f 35-45)	M.C.V. (Fℓ) (n: m81-93) (f81-95)	M.C.H.C.(g/dℓ) (n: 33-35)	M.C.H.(pg) (n: 28-30)
1	-	15.3	45.9	89	33.3	29.9
3	-	11.4	33.5	83	33.7	28.5
5	+	13.3	39.5	93	31.9	29.1
6	-	14.6	40.3	88	35.0	32.5
8	-	14.3	42.0	94	34.0	31.6
9	-	13.7	36.1	92	38.6	34.1
10	-	13.9	40.5	87	34.2	29.5
11	+	12.0	43.2	95	26.4	27.5
13	+	10.7	34.1	106	29.9	31.2
14	+	14.3	42.2	96	33.9	33.1
15	-	13.2	40.2	90	32.8	29.9
17	-	15.6	44.5	80	34.0	28.7
18	-	13.7	39.6	82	33.6	29.2
19	-	12.7	37.8	91	33.5	30.5
20	+	13.0	39.3	96	33.9	32.6
21	-	14.8	47.)	-	-	-

Discussion

The anaemia occurs as a result of several mechanisms:

i A normal red cell mass with an elevated plasma volume leading to a dilutional anaemia.

ii Ineffective erythropoiesis due to Gaucher bone marrow infiltration and abnormal ferrokinetics.

iii An increased peripheral loss of red blood cells due to:

(a) pooling in the enlarged splenic vascular spaces;

(b) phagocytosis by altered splenic Gaucher cells.

Other more rare contributory factors are:

iv Loss through haemorrhages conditioned by the thrombocytopaenia.

v An acquired haemolytic anaemia.

Haemodilution occurs because the greatly increased vascularity of the spleen leads to a disproportionate increase in the plasma volume. The bone marrow infiltration and ineffective erythropoiesis prevent production of sufficient red blood cells to compensate for the increased plasma volume. Bowdler, (1963), reported on a patient with Gaucher disease and a dilutional anaemia which was corrected by splenectomy.

Matoth and Fried, (1965), differentiated the anaemias, according to their different morphology, into a hypochromic variety which responds to iron therapy, and a megaloblastic anaemia which responds to folic acid. The macrocytic nature of the anaemia has also been described by Bloem *et al*, (1936); Melamed and Chester, (1938); Fienberg and Quigley, (1946).

Krim *et al*, (1951), postulated that the megaloblastic bone marrow probably occurred as a result of increased uptake of folic acid by the Gaucher cells. This would result in a relative deficiency of folic acid which was available for red cell maturation. Fienberg and Quigley, (1946), theorised that the Gaucher cell infiltrate would have the same effect on the bone marrow as a neoplastic infiltrate.

The Gaucher cell might also interfere with normal iron utilisation in the maturing red cells, comparable with Mollin's, (1965), description of a failure of haem synthesis in the sideroblastic anaemias. Gaucher cells have been found to have large stores of iron, which was not available for erythropoiesis, possibly on the basis of a release-blockade phenomenon, (Van Slyck *et al*, 1974). Lee *et al*, (1967), also described a degree of ineffective erythropoiesis associated with decreased incorporation of radio-iron into the developing red blood cells. He postulated that this might result in a moderately reduced red blood cell survival time and that this phenomenon was not altered by splenectomy.

The anaemia is predominantly due to the combination of the mildly ineffective erythropoiesis and a peripheral loss due to splenic pooling and the decreased red blood cell survival time.

WHITE BLOOD CELLS

Results

Gaucher disease had little quantitative effect on the white blood cells, Table 8, and where present, the leucopenia was of a very mild degree. Only two of the patients tested had white cell counts less than $4 \times 10^9/\ell$ and all were above $3 \times 10^9/\ell$. No qualitative tests of white blood cell function were undertaken. Three of the six patients showed a leucocytosis following splenectomy.

Discussion

A mild degree of leucopenia is sometimes present, but its clinical importance has not been fully evaluated. It probably occurs as a result of Gaucher bone marrow infiltration and increased peripheral, hypersplenic consumption. There is also some evidence of a decreased resistance to infection in patients with Gaucher disease. This phenomenon is discussed in Chapter 19. The two leukopenic patients in this survey, Cases 10 and 21, experienced no increased incidence of infections.

TABLE 8: WHITE CELL COUNTS

PATIENT	SPLENECTOMY	WHITE CELL COUNT ($10^9/\ell$) (n: 4-11)
1	-	9,3
3	-	7,5
5	+	11,3
6	-	5,4
8	-	12,5
9	-	7,8
10	-	3,1
11	+	14,4
13	+	21,8
14	+	10,1
15	-	4,5
17	-	5,3
18	-	5,1
19	-	8,0
20	+	7,1
21	-	3,9

HAEMOSTASIS

Results

Seventeen of the patients (81%) experienced abnormal bleeding during the course of their disease, (Table 6). Six of these patients underwent splenectomy with resolution of this problem in all but one, (Case 14). This patient still displays a bleeding diathesis despite a post-splenectomy platelet count of 230 x $10^9/\ell$. Unfortunately no coagulation screen was performed on this patient. The main symptoms were epistaxes, easy spontaneous bruising, prolonged bleeding, dermal purpura, menorrhagia and post-partum haemorrhages. The course of their bleeding diatheses showed great fluctuations in severity, and appeared to be worse in association with acute bone or joint attacks. This conforms with the usual course of the condition; that is a chronic persistent disability with acute relapses and crises. The bleeding was usually easy to control and only required transfusion in the event of post-partum haemorrhaging. However, the more severely affected patients underwent splenectomy before the bleeding tendency had advanced to a potentially dangerous degree.

Discussion

The bleeding problem was essentially due to the thrombocytopaenia and the severity of the abnormal bleeding correlated well with the extent of the platelet deficit. Further supportive evidence was the reversal of the bleeding problem following splenectomy and the subsequent rise of platelets to a normal level. However, there was not always a definite relationship between the quantity of platelets and the degree of the haemostatic defect. The possibility of qualitative platelet alterations or coagulation factor deficiencies should therefore always be considered.

Effects on coagulation factors have also been described. Sawitsky and Boklan, (1972), discuss their findings of a commonly occurring defect in factor IX. Sporadic deficiencies of factors V, VIII and X have also been reported in Gaucher disease, (Sawitsky and Boklan, 1972).

RARE HAEMATOLOGICAL PHENOMENA

Haemolytic Anaemia

Mandlebaum *et al*, (1942), described the rare phenomenon of auto-immune haemolytic anaemia in a patient with Gaucher disease. Their patient showed an acute exacerbation of anaemia with leucocytosis, increased erythrogenic activity of the bone marrow, and an increased serum bilirubin. Improvement of the condition occurred following splenectomy. This has also been discussed by Carling *et al*, (1953), and Wasserman *et al*, (1955).

Leucoerythroblastic Reaction

A leucoerythroblastic reaction is also rarely encountered, (Melamed and Chester, 1938; Zlotnick and Groen, 1961), as a result of gross replacement of bone marrow by the Gaucher cell infiltrate. This usually occurs after splenectomy where there is a reactive increase in circulating white cells. Simultaneously increased extra-medullary haemopoiesis, in the presence of an infiltrated bone marrow, leads to the presence of erythroblasts in the peripheral circulation.

MANAGEMENT OF HAEMATOLOGICAL COMPLICATIONS

Introduction

As with other complications of Gaucher disease, there is at present no available therapy to cure the underlying process causing the haematological problems. Treatment is therefore aimed at alleviating the symptoms or correcting the secondary effects. The mild anaemia is rarely symptomatic and therapy with haematinics is only indicated when specific deficiencies occur. Blood transfusions are only occasionally necessary when the anaemia is aggravated by pregnancy or following a severe bleeding episode.

It is the thrombocytopaenia and consequent bleeding diathesis which usually demands more active therapy. Steroids have been tried, but are only claimed to be successful as short term therapy in a grossly affected, inoperable patient, (Decker and McWhorter, 1955). Prolonged steroid administration has not proved to be an acceptable therapeutic measure and the mainstay of management in these severely affected persons is therefore splenectomy.

Splenectomy

The ideal haematological management involves accurate assessment both clinically and by laboratory testing at regular intervals in a specialist hospital department. Crucial timing of splenectomy is then possible; that is neither too early in the course of the disease, nor too late to control the bleeding problems.

The main indication for splenectomy is the severe thrombocytopaenia with consequent bleeding problems. Less commonly, splenectomy is performed to relieve the discomfort from abdominal distension due to massive splenomegaly. Splenectomy itself is not a completely safe procedure and besides the operative problems when removing a grossly enlarged spleen there are definite post-operative risks:

i An increased risk of infection - especially by pneumococcal organisms. This is important in individuals with Gaucher disease who may already show a measure of immunological incompetence. Pneumococcal vaccine should, therefore, be given pre-operatively to these patients.

ii The removal of a potential storehouse for the glycolipid, which accumulates due to the beta-glucosidase enzyme deficiency. There must, therefore, be some post-operative extra-splenic, reticulo-endothelial system expansion to accommodate the abnormal quantity of glycolipid produced.

iii The removal of a site of extra-medullary haemopoiesis in an individual with a progressively increasing bone marrow infiltration.

Post-splenectomy course

Following splenectomy, the patients in this study showed very good post-operative recovery. Their platelet counts rapidly rose to normal levels and no further bleeding problems were experienced. There is a post-operative leucocytosis, but no effect on the red blood cells. The greatly improved haematologic status of these patients has persisted for many years after splenectomy, (Tables 6, 7 and 8).

Some authors have reported deterioration in the patient's condition, especially as regards osseous complications, following Splenectomy, (Schein and Arkin, 1942). This was not the impression in this survey, (Table 2), as it was always in the most severely affected individuals that splenectomy was

necessary. In these persons orthopaedic problems pre- and post-dated the splenectomy. This series of splenectomised individuals was small and insufficient for an in-depth analysis. However, there was definite evidence in these patients that the orthopaedic problems were far advanced before the splenectomy and showed no accelerated deterioration post-operatively. Rourke and Heslin, (1965), also denied that splenectomy resulted in a worsening of the orthopaedic complications. This misconception, therefore, probably arose as a result of a false ascertainment bias.

Liver enlargement definitely progressed at a more rapid rate following splenectomy. However, although the livers attained great size, there was no clinical or biochemical evidence of significant hepatic dysfunction in the splenectomised patients, (Table 9), even with long-term follow-up. The liability to post-operative hepatic enlargement appears, therefore, not to be a significant factor when a decision for or against splenectomy is under consideration. Patient 12, interestingly, only showed a two centimetre hepatomegaly when examined thirty-four years after her splenectomy.

Comment

A diagnosis of Gaucher disease must be considered in any Ashkenazi-Jewish individual presenting with an enlarged spleen. The regular assessment of the haematological status by a specialist department is important in the management of all patients, and only in this way can timing of the splenectomy be accurately planned. Satisfactory long-term results are usually obtained in severely affected patients who have undergone splenectomy.

TABLE 9: * HEPATIC FUNCTION AFTER SPLENECTOMY

PATIENT	YEARS POST-SPLENECTOMY	HEPATIC ENLARGEMENT (centimetres)	BILIRUBIN (2-17)	ALBUMIN (35-50)	A.A.T. (10-50)	ALKALINE PHOSPHATASE (30-85)
5	7	15	10	44	50	52
11	16	7	27	45	40	85
12	34	2	-	-	-	-
13	15	20	10	35	29	70
14	26	35	14	39	66	115
20	6	3	10	43	30	55

* Footnote: All the results are in S.I. units and for each biochemical parameter the normal values appear in parenthesis underneath the appropriate heading.

CHAPTER 13

ORTHOPAEDIC MANIFESTATIONS

INTRODUCTION

It was originally thought that there were two types of Gaucher disease, a purely osseous type and a predominantly splenomegalic type, (Pick,1933). It is now known that orthopaedic complications are a concomitant part of the process involving the reticuloendothelial system. This contention is also borne out by analysis of the clinical findings in this study in which eighteen of the patients, (86%), experienced orthopaedic problems during the course of their disease. All these individuals also suffered haematological problems of varying severity, as discussed previously in Chapter 12.

RESULTS

The orthopaedic complications experienced by the patients in this survey are listed in Table 10, and then described in detail. The aetiology of bone pain in these affected individual is then discussed with reference to the reported findings in other series. The final discussion involves the pathogenesis and surgical management of these orthopaedic complications.

TABLE 10: ORTHOPAEDIC MANIFESTATIONS

PATIENT	AGE	SEX	ORTHOPAEDIC COMPLICATIONS					HIP JOINT PROSTHESIS
			NONSPECIFIC BONE PAIN	PSEUDO-OSTEO-MYELITIS	ACUTE ARTH-RITIS	COLLAPSE OF FEMORAL HEADS	OTHERS	
1	33	M	+	+	+	+	-	
2	42	M	-	-	-	+	Kyphoscoliosis	
3	38	F	+	-	+	+	-	
4	18	M	-	-	-	-	-	
5	17	F	+	+	+	+	-	Thompson
6	48	M	+	+	+	+	-	McKee-Farrar
7	51	M	+	+	+	+	-	Charnley
8	32	F	+	+	+	-	-	
9	33	M	+	+	+	+	-	
10	51	M	-	-	+	-	-	
11	36	F	+	-	+	+	-	McKee-Farrar
12	63	F	-	-	+	-	-	
13	35	F	+	+	+	+	-	
14	38	M	-	-	+	+	-	
15	43	M	-	-	+	+	-	Cup Arthro plasty
16	36	F	+	-	-	-	-	
17	33	M	+	-	+	-	-	
18	31	F	-	-	+	-	-	
19	72	F	-	-	-	-	-	
20	61	M	-	-	-	-	-	
21	23	M	+	+	+	+	-	

RESULTS

Orthopaedic problems at presentation

Eight of the patients (38%) in this survey were initially investigated because of orthopaedic problems. Three presented with the syndrome of Gaucher pseudo-osteomyelitis and the other five presented with acute arthritis. In only one of these patients was a correct diagnosis of Gaucher disease made at the initial presentation with orthopaedic complications and the delay in confirming the diagnosis ranged from a few days to 30 years, (Table 5).

There is little consideration given to the inclusion of Gaucher disease in the classification of causes of acute bone and joint pain. The association of splenomegaly and pancytopaenia in an Ashkenazi-Jewish patient should register a high index of suspicion of Gaucher disease. Incorrect initial diagnosis has led to protracted and needless therapeutic regimes. Patient No. 7 spent six months in hospital on anti-tuberculous therapy because of an incorrect diagnosis of tuberculosis of the hip. He had known, undiagnosed splenic enlargment for six years before the development of these orthopaedic problems. Three other patients initially presented with non-specific bone pain resembling osteomyelitis. Fortunately, although the diagnosis of Gaucher disease was not considered, none of these patients was submitted to operation. They were all treated with bed-rest, analgesics and antibiotics and their symptoms resolved. They were all discharged from hospital without a diagnosis of Gaucher disease and were regarded as having mild, responsive forms of a pyogenic osteomyelitis. The patients' ethnic background and the presence of haematologic involvement was not considered to be of diagnostic significance at this stage. The importance of an early diagnosis of Gaucher disease in these individuals is emphasised by the chronic sequelae of injudicious curettage and drainage procedures. (Amstutz and Carey, 1966; Noyes and Smith, 1971).

Bone Pain

Twelve patients (57%) in this series described the phenomenon of non-specific bone pain. This was usually experienced as a persistent, deep-seated dull ache in both thighs. It was rarely of sufficient severity to incapacitate the patient and it resolved spontaneously or following the ingestion of mild analgesics. These phenomena tended to recur at variable intervals and lasted for one to two days. Eight of these individuals also suffered acute attacks of Gaucher 'pseudo-osteomyelitis', (*vide infra*). They presented with varying inflammatory signs and the condition was often difficult to distinguish from acute haematogenous, purulent osteomyelitis. The distal portion of the femur was most commonly affected and the condition resolved following bed rest, antibiotic cover and appropriate analgesics. Only Patient 12 underwent surgical exploration of his femur during an acute attack. The operation site never fully healed and he has since suffered from a persistent, discharging sinus. The discharge has remained aseptic and the sinus is still patent despite various therapeutic measures.

Pathological Fractures

It was noted that none of the Ashkenazi-Jewish patients in this series experienced a pathological fracture. These were however seen in two non-Jewish individuals. Patient A.A. (18) sustained pathological fractures of her right femur and humerus, and Patient W.M. (10) fractured her right humerus and radius following relatively minor trauma.

Collapse of femoral heads

Most of the severe orthopaedic problems which were experienced involved the hip joints. Eight of the patients (38%) had bilateral, and three patients had unilateral, aseptic necrosis of the femoral heads with severe damage to the hip joints. The condition initially presented with pain and limited movement of the hip joint and minimal radiological changes were usually found in the early stages. These radiological signs consisted of a generalised demineralisation or localised cysts and the condition then progressed slowly over a few years with gradual collapse of the femoral heads and destruction of joint cartilage. The gross anatomical changes which develop eventually become irreversible. The position is then reached where operative, corrective therapy must be considered for the abnormally functioning joint.

Growth and stature

There was no evidence of a generalised stunting of skeletal growth in this series, (Table 11). However, the small number of patients, especially when differentiated into sex and age groups, prevents accurate analysis of their average heights or their comparison with accepted norms. When present, dimunition in stature was due to specific, gross, localised bony deformity rather than to an overall growth problem. For example, Patient 2 was short as a result of his vertebral collapse and kyphosis. Matoth and Fried, (1965), also reported their impression that Gaucher disease had no general effect on their patients' growth.

TABLE 11: HEIGHTS AND WEIGHTS

PATIENT	AGE	SEX	HEIGHT (cms)	WEIGHT (Kg)
1	33	M	182	69
3	38	F	167	52,7
4	18	M	173	64
5	17	F	154	49
6	48	M	170	
7	51	M	178	67
8	32	F	153	49
9	16	M	173	60
10	57	M	178	
11	36	F	162	
12	63	F	161	63
13	34	F	169	54,5
14	38	M	178	66
15	43	M	178	73
16	36	F	162	59
17	33	M	184	73
18	31	F	170	52
20	61	M	170	63
21	23	M	173	61,3

Arthritis

Fifteen of the patients (71%) experienced joint symptoms. The typical clinical picture was of chronic joint pain and stiffness, punctuated by acute, severe exacerbations. The symptoms were precipitated and aggravated by a cold climate and exertion and most commonly affected the hips, shoulders and knees. The severe joint problems were usually secondary to underlying bone necrosis. However, in a number of patients the initial acute arthritis was unattended by overt radiological signs. The condition is self-limiting and responds well to bed rest, analgesics, immobilisation and splinting of the joint and physiotherapy to prevent secondary soft tissue contractures. Patient 3, however, suffered from a severe arthritis with associated periarticular muscle spasm. She developed secondary soft tissue contractures around the affected joints which grossly limited her mobility and she was confined to a wheelchair for five years. She eventually achieved full rehabilitation after intensive physiotherapy.

DISCUSSION

Bone Pain

The acute attacks of bone pain can result from multiple causes. These are:

i An episode of Gaucher pseudo-osteomyelitis. These acute bone "crises" present with a very similar picture to an acute haematogenous, pyogenic osteomyelitis. There is a sudden onset of severe, throbbing pain in an extremity. This complication causes a wide spectrum of clinical signs from complete normality to an acute inflammatory picture with localised signs of tenderness, redness, swelling, warmth and inability to use the limb. There may be

an associated pyrexia and haematologic investigations show a raised erythrocyte sedimentation rate and leucocytosis. This pseudo-osteomyelitis most commonly affects the femur and is difficult to differentiate from an infective osteomyelitis. The important differentiating feature is the presence of bacteriological growth from blood cultures obtained from patients with infective osteomyelitis and the absence of toxaemia in 'pseudo-osteomyelitis'. The correct diagnosis of a non-infective Gaucher disease pseudo-osteomyelitis is critical because of the serious sequelae resulting from injudicious operations on these patients.

This pseudo-osteomyelitis is usually self-limiting and resolves on symptomatic therapy and antibiotic cover. The antibiotics are normally given as a precautionary measure to prevent the formation of secondary infection in the affected bone. Operative procedures are only necessary in the presence of superimposed infection or as a corrective measure where bony damage has been established. These should be performed under strict sterile conditions because of the danger of secondary infection, and the tendency to chronicity and intractable sinus formation, (Noyes and Smith, 1971).

These acute attacks usually abate after a few days but may persist for a number of weeks. There is no specific therapeutic regime to control these attacks and the mainstay of treatment is analgesics and bed-rest with immobilisation of the affected bone. It is thought that avoidance of weight-bearing might prevent the development of secondary bone damage, (Schein and Arkin, 1942). This was disputed by Rourke and Heslin, (1965), and they described a patient who had suffered collapse of the femoral head despite six months' immobilisation of the affected hip.

ii The acute attack may be due to a true haematogenous septic osteomyelitis as the avascular, lipid-laden bone is an excellent medium for bacterial proliferation. These affected individuals may be susceptible to infection on the basis of a generalised immunological incompetence. (Chapter 19). This osteomyelitis is treated in the usual manner with the maintenance of careful asepsis during surgical procedures, (Sacks, 1971).

iii Pathological fractures are reported as being a childhood feature of Gaucher disease, (Yossipovitch *et al*, 1965) Matoth and Fried, 1965; Amstutz and Carey, 1966). They are thought to occur because the thin, eroded cortices tend to make the weight-bearing femora susceptible to fractures following minor stress. This phenomenon did not occur in the individuals investigated in this survey. Only Patients A.A. (18) and W.M. (10) of non-Jewish English and Afrikaner extraction, respectively, sustained pathological fractures. (Chapter 29).

iv Articular cartilage collapse occurs, usually as a result of subchondral aseptic bone necrosis. This can produce an acute attack of bone pain usually related to the hip, with referred pain down the femur.

ARTHRITIS

Joint involvement as an initial manifestation of Gaucher disease often presents as a diagnostic problem. There are reports of Gaucher joint disease being misdiagnosed as an acute infective arthritis, Perthe's disease, idiopathic avascular necrosis, Sickle cell anaemia, caisson disease, ochronosis, leukaemia, Hodgkin's disease, syphilis, articular rheumatism, 'growing pains', tuberculosis and rheumatic fever, (Yossipovitch *et al*, 1965; Sacks, 1973). The association of a painful joint with limited movement and hypersplenism should raise the possibility of a diagnosis of Gaucher disease. The clinical features vary from a pure arthralgia to severe joint destruction with grossly restricted movement. The Gaucher cell infiltrate causes avascular necrosis and collapse of the osseous component of the respective joint and the resultant articular cartilage damage renders the joint susceptible to the stress of weight-bearing. Ultimately, the patient is left with a grossly deranged joint which then forms a fibrous or bony ankylosis.

The most commonly affected joint is the hip and shoulder, knee and vertebral joints are less frequently involved. Therapy consists of immobilisation of the affected joint in splints and the application of traction in the hope that prolonged avoidance of stress on the compromised articular surfaces will prevent severe sequelae. In addition, physiotherapy plays a major part in later mobilising affected joints to prevent secondary soft tissue spasm and contracture. Broad-spectrum antibiotics are often administered as a prophylactic measure. Once the disease becomes quiescent, further operative procedures may be necessary to correct joint and bone deformity. Arthroplasty, in particular, has restored full joint mobility to patients who were incapacitated prior to operation.

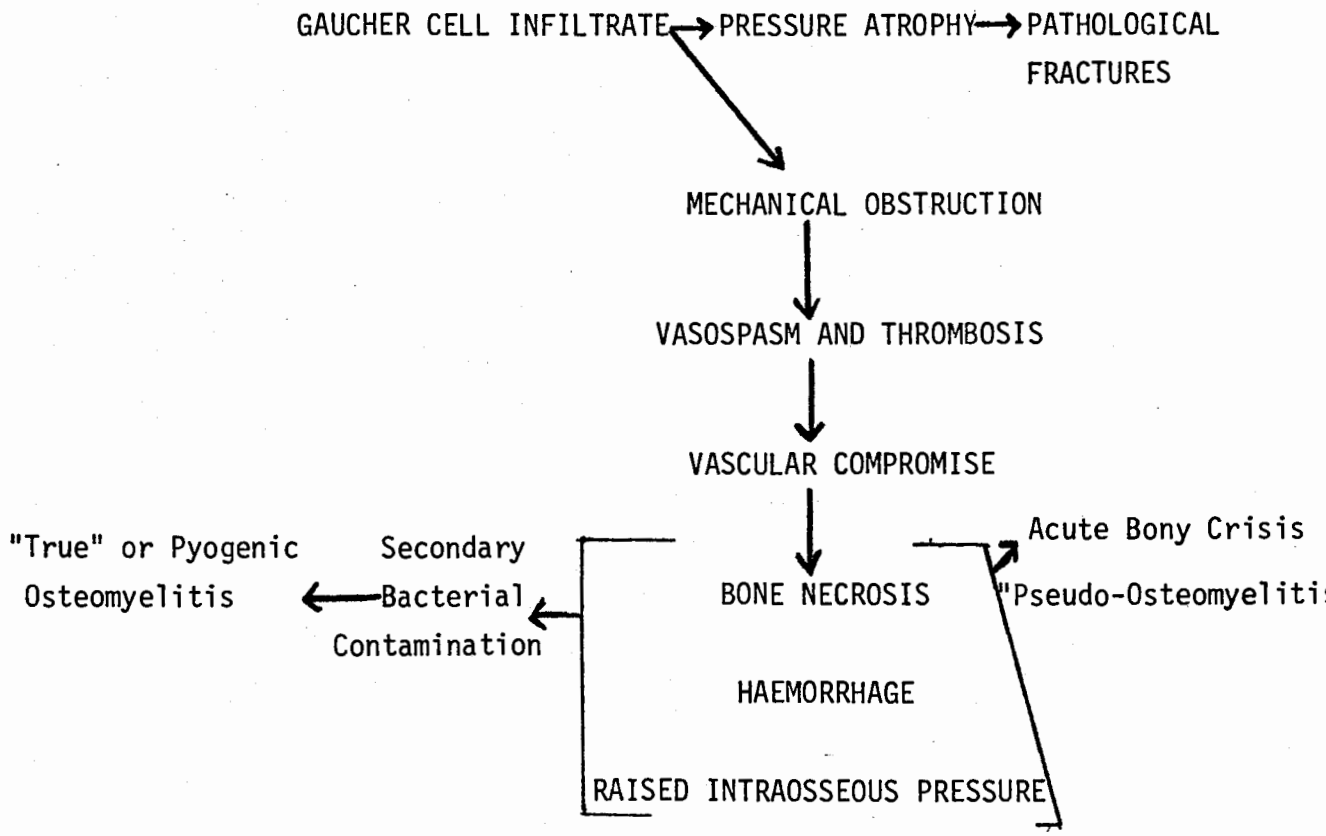
PATHOGENESIS OF ORTHOPAEDIC COMPLICATIONS

The primary aetiology of the bony problems appears to be infiltration of the medullary space by Gaucher cells. The presence of the large Gaucher cell infiltrate compromises the function of the normal bone marrow. The clinical features then result from:

i pressure effects of the expanding, abnormal cell mass.

ii inadequacy of available space for normal marrow functioning.

A very acceptable graphic presentation of the pathogenesis of the orthopaedic complications is a modified version of the flow chart constructed by Noyes and Smith, (1971), *vide infra*.



The initial insult is probably a mechanical interference with normal vascular supply to the affected bone. The vascular abnormality also results in a propensity for local haemorrhage. The resultant necrosed bone and lipid-rich haemorrhagic tissue is theoretically a very good nidus for bacterial proliferation. Although this complication appears to be initiated by a sterile mechanism, the risk of secondary bacterial contamination is present. Besides the mechanical effect of the Gaucher cells on the vascular supply, the sheer mass of the abnormal infiltration causes pressure atrophy on the surrounding bone. The process is slow and appositional bone is laid down on the outer cortical surfaces of the involved areas, giving them an expanded appearance. The process results in thin cortices and a loss of definition between bone cortex and medulla.

The condition usually affects the long bones with the femora most commonly involved. Lesions have, however, been described in the humerus, tibia, fibula, radius, ulna, clavicle, ribs, mandible, vertebrae, pelvis and skull, *vide infra,* Chapter 20. The actual pathological bone changes will be discussed in the section on radiological results, (Chapter 20).

SURGICAL MANAGEMENT OF ORTHOPAEDIC COMPLICATIONS

An important orthopaedic surgical advance has been the replacement of the diseased joints by a prosthesis. Four of the patients in this survey have had prosthetic replacement of diseased hip joints. They have all done exceptionally well and were symptom-free when examined 4, 4, 6, and 8, years respectively after their operations. These results are very encouraging and emphasise the importance of awareness of the orthopaedic manifestations of Gaucher disease and available therapy. The prostheses used were one Charnley prosthesis, two McKee-Farrar prostheses and one Thompson prosthesis, (Figures 2 and 3).

Other operations performed included corrective osteotomies and curettages. Chronic bone infections with intractable, discharging sinuses most commonly result from operative interference during an acute attack of Gaucher pseudo-osteomyelitis. The sinuses discharge a sterile material and are characteristically resistant to any form of therapy. It is therefore evident that, where possible, orthopaedic operations should be limited to the quiescent phase of the osseous disease and performed under antibiotic cover.

CONCLUSION

Bone and joint complications are common in Gaucher disease and cause chronic pain and disability, with the femora, hips and shoulder joints most commonly affected. They are often misdiagnosed when presenting as the initial complaint in an affected individual. It is therefore important to consider Gaucher disease when faced with specific orthopaedic problems in an Ashkenazi-Jew. The hazards of misdiagnosis are protracted incorrect therapy and the performance of unnecessary operations on high infection-risk patients.

FIGURE 2: CHARNLEY PROSTHESIS IN PATIENT 7.

FIGURE 3: THOMPSON PROSTHESIS IN PATIENT 5.

The excellent results obtained following prosthetic replacement of diseased joints are of great practical importance. Finally, there is no evidence of a generalised effect of Gaucher disease on growth and stature.

CHAPTER 14

DERMAL MANIFESTATIONS OF GAUCHER DISEASE

INTRODUCTION

The dermal manifestations of Gaucher disease can be broadly classified into two main groups on the basis of:

i The primary effect of Gaucher disease on the skin.

ii The secondary dermal effects resulting from Gaucher infiltration of other organs, especially bone marrow, liver and spleen, with resultant dysfunction of the affected organ.

RESULTS

Skin manifestations are common and fourteen patients (67%) in this series had some abnormal dermal finding, Table 12. However, the 'classical' clinical picture (page 90) described in the literature was not found in these patients (Bloem *et al*, 1936; Groen and Garrer, 1948). The secondary effects of Gaucher disease leading to skin changes, for example purpura, ecchymoses, pallor and rarely jaundice, were seen in certain individuals.

A substantial number of patients had a diffuse brown or yellow-bronze dermal hyperpigmentation, with no specific peripheral localisation. This characteristic dermal appearance is only significant as an associated clinical feature of Gaucher disease and requires no special management. The generalised nature of this hyperpigmentation possibly reflects the more frequent exposure to the sun experienced by these patients in the warm South African climate.

A few patients initially described the interesting phenomenon of easy tanning and they became deeply tanned even in winter after minimal exposure to the sun. This was eventually found to occur in eight of the affected individuals (38%) in this study.

Other interesting minor dermal features which were found to occur more frequently in these individuals were:-

i Telangiectasia, which were especially numerous over the arms, chest and face. The appearance of these telangiectasia was not associated with underlying organ complications, that is, hepatic dysfunction. Two of these patients did have markedly enlarged livers, but there were no other clinical or biochemical signs of hepatic decompensation. These telangiectasia might theoretically represent a very early sign of liver involvement in the disease process.

ii Non-specific brown macules which tended to be flitting and fluctuant in nature. One patient described an exacerbation of these macules occurring during an acute osseous crisis and anatomically related to the affected bone.

TABLE 12: DERMAL MANIFESTATIONS OF GAUCHER DISEASE

PATIENT	EASY TANNING	YELLOW-BRONZE DIFFUSE HYPERPIGMENTATION	BLEEDING DIATHESIS	TELANGIECTASIA	OTHER
1	-	-	-	-	-
2	-	+	-	arms, chest and face	cyanosis
3	-	-	-	-	-
4	+	+	-	chest	-
5	-	-	-	-	1 centimetre scattered white macules on legs occasionally macules tan brown
6	+	+	-	-	-
7	+	+	-	-	-
8	+	+	scattered purpura	arms and face	-
9	+	-	-	-	Brown macule right ant.thorax
10	-	-	-	-	multiple non-specific freckles
11	+	+	-	-	-
12	-	+	-	-	-
13	-	-	purpura on back,bruises on arms	arms and neck	-
14	-	+	-	-	3x2cm. brown macule over left shoulder blade
15	-	+	-	-	scattered small freckles
16	+	-	-	-	-
17	+	+	bruises easily	-	-
18	-	-	purpuric crops, bruises easily	-	-
19	-	-	-	face	-
20	-	-	-	-	multiple non-specific freckle
21	-	-	-	-	-

DISCUSSION

'Classical' descriptions of dermal signs are found in most reviews, (Reich *et al*, 1951). These include:-

i Chloasma-like patches and streaky pigmentation of non-specific distribution, (Bloem *et al*,1936).

ii Peripheral and symmetrical hyperpigmentation. This is classically described as extending from just below the knees to a sharply defined lower margin just below the ankles and may be glossy, scaly and ulcerated, (Bloem *et al*, 1936; Groen and Garrer, 1948).

iii The rare occurrence of a peculiar malar flush, (Bloem *et al*,1936; Groen and Garrer, 1948).

iv Haemorrhagic furunculosis of the extremities or residual black pigmented scars are reported to occur, (Reich *et al*, 1951).

None of the above-mentioned dermal changes were present in any individuals in this series. Pick, (1933), postulated that the skin pigmentation was a manifestation of an underlying haemochromatosis. However, Wechsler and Gustafson, (1940), found the pigment involved to be melanin or a melanin derivative. Gaucher cells are reported to affect iron metabolism related to erythropoieisis, (page 63). Theoretically, Gaucher cell infiltration might result in the abnormal deposition of iron in the skin. Intradermal iron lifts the inhibitory effect of the glutathione radical on the tyrosinase enzyme. The consequent enhanced tyrosinase activity results in increased melanin formation by accelerating conversion of the precursor tyrosine to dopa. This hypothetical model would explain the finding of hyperpigmentation in these individuals.

SUMMARY

Other than the obvious importance of the secondary dermal changes as an indication of haematological or hepatic problems, skin changes were entirely benign and never presented as a clinical problem nor necessitated any form of therapy.

CHAPTER 15

OCULAR MANIFESTATIONS OF GAUCHER DISEASE

RESULTS

Twenty of the patients (95%) showed ocular involvement of variable clinical significance, Table 13. Nineteen patients had pingueculae, of these eight had bilateral, large, nodular pingueculae and the other eleven had less obvious pingueculae of minimal bulk.

The typical pingueculae were bulbar, subconjunctival, bilateral and involved the nasal and temporal aspects of the eye. They were of a nodular, fleshy appearance and yellowish-brown in colour. The patients experienced only occasional, mild, irritative symptoms from the pingueculae and none progressed to the extent that they needed operative removal. Their interest lies in the clinical association with other stigmata of Gaucher disease. Severe pingueculae in the presence of undiagnosed splenomegaly in an Ashkenazi-Jew should arouse suspicion of Gaucher disease.

Seven of the patients (33%) wore spectacles for myopia; two individuals for marked, and the others for minimal myopia. There were no statistics available for the prevalence of myopia in South African Ashkenazi-Jews, and this finding is therefore of doubtful significance.

None of the patients in the series showed retinal changes which could be attributable to Gaucher disease. Patient 13 had choroid tubercles associated with her disseminated tuberculosis.

TABLE 13: OCULAR MANIFESTATIONS OF GAUCHER DISEASE

PATIENT	PINGUECULAE	MYOPIA	RETINA	OTHER PROBLEMS
1	+	-	-	Left congenital ptosis
2	+	+	-	-
3	+	-	-	-
4	+	-	-	-
5	+	-	-	-
6	+	-	-	-
7	+	+	-	-
8	+	-	-	-
9	+	-	-	-
10	+	-	-	-
11	+	+	-	-
12	+	+	-	-
13	+	-	white discrete, irregular "hard" deposits scattered across posterior polar area and extending into periphery of fundus	-
14	+	-	-	-
15	+	+	-	-
16	+	+	-	-
17	-	-	-	-
18	+	-	-	-
19	+	-	-	-
20	+	-	-	-
21	-	+	-	-

DISCUSSION

Pingueculae of varying grades are the most common ocular manifestations of Gaucher disease. There is very little written on the subject because of its minimal overt importance, except for their diagnostic significance. These are also a relatively common finding in normal individuals, although no exact frequencies are known.

Macroscopically, the pingueculae appear as subconjunctival (usually bulbar) wedge-shaped, yellowish-brown thickenings with bases at the corneal margin and apices at the canthi. Biopsy of a pingueculum revealed a small collection of Gaucher cells according to East and Savin, (1940).

Other exceptionally rare ocular findings have been described by authors cited in J. Francois', (1975), extensive review of the subject. The retinal changes which have been described are retinal haemorrhages associated with the marked anaemia, and rare cases showing macular and perimacular abnormalities, (Carbone and Petrozzi, 1968; Petrohelos *et al*, 1975). The absence of changes of the anaemic type in the patients in this series can be explained by the fact that none had profound anaemia when seen by the author.

Bloem *et al*, (1936), describe myopia as being a constant feature. This is disputed by Thannhauser, (1958), but not discussed by other authors.

CHAPTER 16

OBSTETRIC ASPECTS OF GAUCHER DISEASE

INTRODUCTION

The findings in this series confirmed the contemporary thoughts on pregnancy in Gaucher disease in that the patients experienced no abnormal complications with fertility, spontaneous abortions or premature labours. The outcome in all these pregnancies was excellent for both mother and child.

RESULTS

There were no reciprocal effects of the pregnancy on the Gaucher disease and seven patients tolerated a total of thirteen pregnancies exceptionally well, (Table 14).

One patient (Case 3) had normal vaginal deliveries despite the presence of a severe musculo-skeletal deformity necessitating a prior five year period of wheelchair existence. Haematological effects during the pregnancies were minimal and easily controlled in the majority of patients.

One individual required Caesarean section for pre-eclamptic toxaemia. All the others had normal full-term deliveries, and there were no premature labours. Only Patient 12 aborted spontaneously and this was not associated with gross splenic enlargement nor any other complication of Gaucher disease. Patient 11 was discouraged from further pregnancy because she suffered from severe post-splenectomy bone marrow depression which complicated her first pregnancy.

Post-partum haemorrhage did occur in a substantial number of pregnancies in this series. The exact aetiologies were not documented but in most instances they were easily controlled by conservative measures, a blood transfusion being only necessary in Patient 8.

A number of the patients described a general sense of well-being during their pregnancies which continued into the post-partum period. This was especially noticed in Patient 3. The exception was Patient 11, who experienced an acute exacerbation of orthopaedic and haematologic complications during the course of her pregnancy. Her condition partially remitted again early in the puerperium.

Lactation was normal as was the entire puerperal course in all patients.

TABLE 14: OBSTETRIC ASPECTS OF GAUCHER DISEASE

PATIENT	PREGNANCY NUMBER	PREGNANCY DURATION	DELIVERY	POST-PARTUM COURSE	INFANT	CONDITION DURING PREGNANCY
3	1	full term	N.V.D.	normal	well	severe anaemia - required 3 units transfusion, felt well
	2	full term	N.V.D.	normal	well	well
8	1	full term	forceps	P.P.H.-conservative therapy	well	mild anaemia, felt well
	2	full term	N.V.D.	P.P.H.-one unit blood	HURLER'S syndrome	mild anaemia, felt well
	3	full term	N.V.D.	P.P.H.-conservative therapy	HURLER'S syndrome	mild anaemia, felt well
	4	full term	N.V.D.	P.P.H.-conservative therapy	well	mild anaemia. felt well
11	1	full term	N.V.D.	normal	well	severe anaemia - multiple transfusions severe bone pain during pregnancy
12	1	abortion at 3 months	-	-	-	-
	2	full term	N.V.D.	normal	well	well
16	1	full term	N.V.D.	P.P.H. mild conservative therapy	well	well
	2	full term	N.V.D.	P.P.H. mild conservative therapy	well	well
	3	full term	N.V.D.	P.P.H. mild conservative therapy	well	well
18	1	full term	caesarian section for P.E.T.	normal	well	mild anaemia, responded to Iron therapy felt well
19	1	full term	N.V.D.	normal	well	well

KEY: N.V.D. = Normal Vaginal Delivery
P.P.H. = Post-partum Haemorrhage
P.E.T. = Pre-Eclamptic Toxaemia

DISCUSSION

Genetic Transmission

Contemporary understanding of the mechanism of inheritance of Gaucher disease (Section VII), together with modern prenatal diagnostic and screening procedures, enables fairly accurate prediction of the Gaucher disease status of the unborn child. For this reason, fear of transmitting this genetic disease to future offspring should not enter into the debate concerning the desirability and safety of pregnancy in a woman with Gaucher disease. This should only be discussed with the patient to allay doubts.

Gaucher Disease and Pregnancy

Controversy in the past has revolved around the reciprocal effects of Gaucher disease and the pregnancy. For a long period these were considered to be incompatible and pregnancy was strongly discouraged in an individual with Gaucher disease. It was thought that pregnancy endangered the patient's life as well as presenting a risk of transmitting the condition to the unborn child, and for this reason some practitioners advocated therapeutic abortions, (Bromberg *et al*, 1953). Groen, (1948), and subsequently Teton and Treadwell, (1957), developed the concept of an increased incidence of sterility, spontaneous abortions and neonatal deaths in affected individuals. Following extensive reviews of the literature, Bromberg *et al*, (1953); Greenwald and Fenton, (1959), and Hoja, (1960), denied this increased risk of sterility, abortions and foetal hazard in Gaucher disease. Further successful pregnancies were described by Elliott, (1952); Logan, (1953); Addleman and Gold, (1963); Mendel and McCullough, (1968); Houlton and Jackson, (1978). They all agreed on the need for a change of attitude regarding the advisability of pregnancy in the Gaucher patient and that pregnancy should no longer be discouraged because of the fear of complications.

Bromberg *et al*, (1953), could find no justification for termination of these pregnancies as advocated by previous theorists.

Considering firstly the effect of pregnancy on the Gaucher disease there is no evidence to indicate that pregnancy affects the course and prognosis of Gaucher disease in any way. Bromberg *et al*, (1953), described a subjective feeling of increased well-being experienced by the pregnant patients. The present study tended to confirm this impression. This phenomenon has been reported in a large number of conditions, (Persellin and Rutstein, 1979), and is especially well documented in rheumatoid arthritis, (Persellin, 1976). The subsequent post-partum deterioration in the condition of the rheumatoid arthritis patient has not been found in Gaucher disease.

The enlarging uterus does not appear to compromise the spleen or liver mechanically. Surprisingly, splenic rupture has never been reported during the stress of parturition in these patients. In addition, Teton and Treadwell, (1957), discounted the theory that the hazards of rupture of the uterus or obstruction to labour due to progressive splenomegaly justified termination. There is also no evidence of liver damage because of the metabolic demands of pregnancy and no change in the size of spleen or liver has been described during pregnancy.

Pregnancy and Haematologic Complications

The haematological complications of Gaucher disease require special intra-partum management, but have little overall influence on the pregnancy. The anaemia of Gaucher disease is augmented by the secondary anaemia of pregnancy. This is usually controlled with haematinics but may require the judicious use of blood transfusions. There is a minimally increased bleeding diathesis during pregnancy, labour and the post-partum period. However, there is only one report in the literature of uncontrolled post-partum haemorrhage resulting in the patient's demise, (Groen, 1948). In this case, the exact aetiology of the protracted haemorrhage was not discovered.

The size of the spleen alone is not an indication for ante-partum splenectomy. The operation should only be performed for standard haematological indications as described earlier. If indicated, the second trimester is the optimal time for splenectomy, (Decker and McWhorter, 1956; Hoja, 1960; Watov and Sandre, 1964), because there is the least danger of abortion or premature labour in this phase of pregnancy.

Hoja, (1960), advocated the use of steroid therapy as a temporary measure before splenectomy to induce remission in selected cases of Gaucher disease and co-existent pregnancy. This therapy was never undertaken during the present survey. He also discussed the rare indication for discouraging pregnancy where pancytopaenia and bleeding problems recur due to Gaucher marrow infiltration following splenectomy. This problem arose with Patient 11 in this study and she was counselled against having further pregnancies for haematological reasons.

CONCLUSION

Gaucher disease was found in this series to have little effect on the normal course of pregnancy, labour and the post-partum period and there was normally a successful outcome for both mother and child. Pool and Stillman, (1923), advocated splenectomy for Gaucher disease patients wanting children following one spontaneous abortion, on the basis of their experience with one patient. However, the spleen appears to have no mechanical effect on the enlarging uterus and the previous reports of increased spontaneous abortions due to this factor have been thoroughly disproved. There is also no evidence for decreased fertility of male or female persons with Gaucher disease. The foetus develops normally *in utero* and the infant experiences no specific neonatal problems consequent to the mother's Gaucher disease.

Theoretically, severe osseous complications with resultant hip and pelvic deformity could affect labour through distortion of the bony birth canal. However, obstruction to normal vaginal child-birth is very unusual in affected individuals.

The approach to the Gaucher disease patient's enquiries regarding desirability of pregnancy is therefore on a basis of optimism and encouragement. Each person is individually assessed and carefully observed and managed throughout the pregnancy.

A useful obstetric assessment may be based on the following principles:-

i General condition of the patient.

ii Extent of splenic and hepatic enlargement.

iii Status of haemopoietic system.

iv Osseous deformity of birth canal.

The management of the individual patient is determined by the findings in respect of these criteria and is essentially conservative, with close observation of the patient by the obstetrician and haematologist at all stages of the pregnancy. The anaemia usually responds to haematinic therapy and bleeding problems are rarely encountered if anticipated.

This series showed good correlation with reports in the literature that women with Gaucher disease tolerate pregnancy well and they have no increased incidence of sterility, abortions or still-births.

CHAPTER 17

CARDIO-RESPIRATORY COMPLICATIONS OF GAUCHER DISEASE

INTRODUCTION

Clinically significant cardio-respiratory complications in Gaucher disease are rare. However, histological evidence of Gaucher cell infiltration in the lungs is an occasional post-mortem finding, (Chang-Lo *et al*, 1967; Sharer *et al*, 1974). Minor radiological features may also denote respiratory infiltration in asymptomatic individuals. Cardio-pulmonary symptomatology is usually a very late feature in a severely affected patient.

RESPIRATORY

Patient 1 in this series suffered severe respiratory decompensation due to a combination of his skeletal deformity and an elevated diaphragm, (Figure 4). The lung volumes were markedly diminished due to impairment of normal pulmonary expansion. Patient 13 exhibited peripheral cyanosis with no clinical evidence of respiratory problems, although she complained of mild shortness of breath accentuated by effort. Chest radiographs were normal but no other tests were performed to exclude an interstitial infiltrate in the lung.

Patient 7 suffered respiratory problems which appeared to be a result of both his Gaucher disease and prolonged heavy smoking. His chest radiograph revealed a non-specific picture of diffuse interstitial infiltration, (Figure 5). A lung biopsy was not performed; however no other cause for the infiltration was found on special investigations. None of the other patients had clinical or radiographic evidence of respiratory involvement.

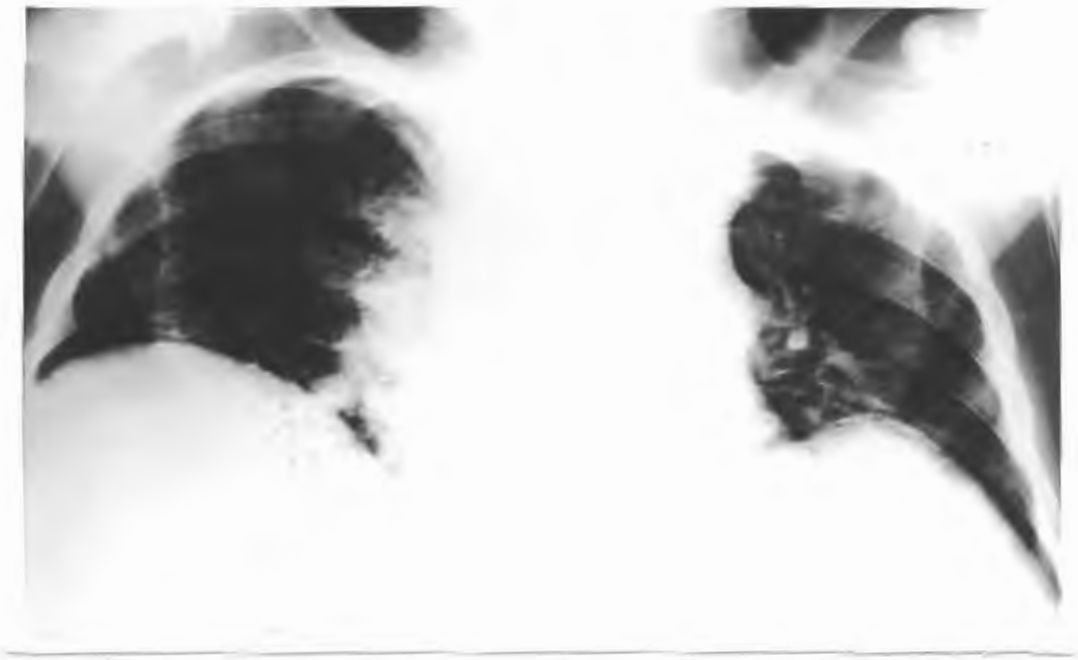


FIGURE 4: CHEST RADIOGRAPH OF PATIENT 1.

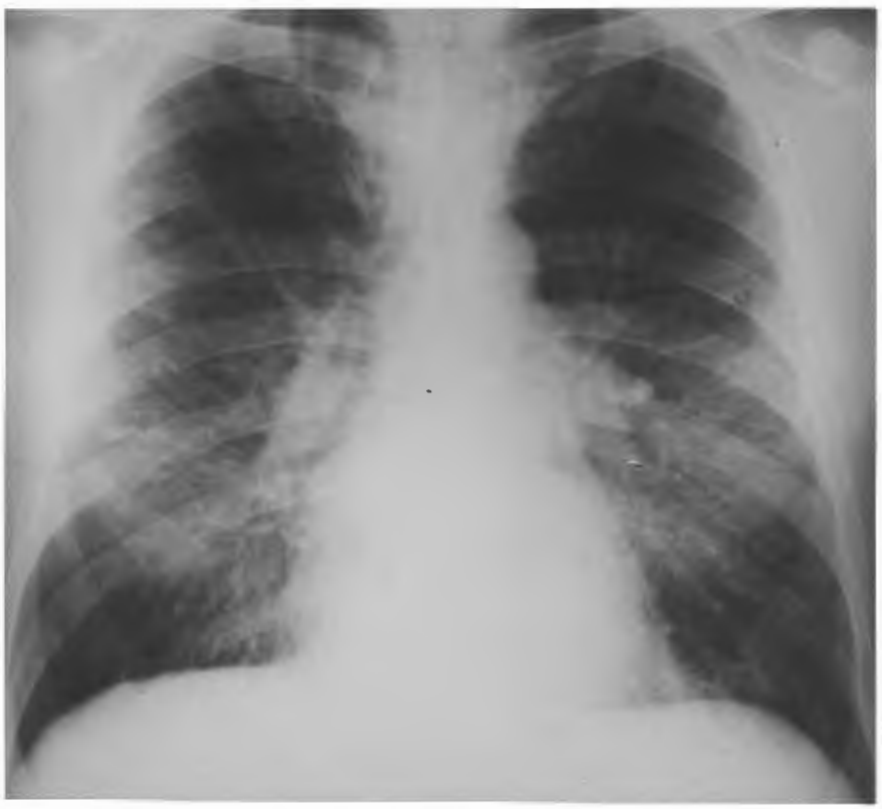


FIGURE 5: CHEST RADIOGRAPH OF PATIENT 7.

DISCUSSION

The extreme picture of respiratory involvement in Gaucher disease is of emphysema-like changes due to a chronic, diffuse, interstitial fibrosis. The mildly affected patient usually has no clinical signs and respiratory complications are only diagnosed on the radiographic findings. These changes are on the basis of the interstitial and alveolar infiltration with Gaucher cells. Gross respiratory involvement is more common in the infantile variety and has only rarely been reported in chronic, non-neuropathic Gaucher disease, (Levin, 1961; Zlotnick and Groen, 1961; Chang-Lo *et al*, 1967; Schneider *et al*, 1977). Roberts and Fredrickson,(1967), reported on the rare occurrence of pulmonary hypertension as a consequence of lung involvement in Gaucher disease.

Elevation of the diaphragm due to a markedly enlarged spleen and liver is the commoner cause of respiratory embarrassment. Occasionally severe vertebral involvement and consequent kypho-scoliosis will also secondarily impair cardio-respiratory function.

CARDIAC

RESULTS

Patient 1 suffered from persistent congestive cardiac failure from an early age. His gross kypho-scoliosis and markedly reduced pulmonary volume appeared to be major causative factors by reducing venous return to the heart. No cause was found for the terminal occurrence of peripheral, superficial gangrene in this individual but it was suggested that the underlying factor might well have been Gaucher cell infiltration of the peripheral circulation. This phenomenon has not been previously reported in Gaucher disease.

Patient 10 initially presented with Raynaud's phenomena of the hands for which no cause was found but these could have occurred on the same basis as the gangrene described for Patient 1.

DISCUSSION

Cardiac complications are exceedingly rare. Where present, these tend to be pericardial in nature. Patients with pericardial haemorrhagic effusions and even constrictive pericarditis have been reported by Brill *et al*, (1904); Welt *et al*, (1929); Zlotnick and Groen, (1961); Roberts and Fredrickson, (1967); Benbassat *et al*, (1968); Harvey *et al*, (1969), and Davies and Foreman, (1970). Rosenfeld and Epstein's, (1961), patient with Gaucher disease had a haemorrhagic pericardial effusion caused by a malignant infiltration.

The exact aetiology of the pericardial problem has not been discovered. Pericardial effusion probably occurs as a result of:-

i Intrapericardial haemorrhage due to the bleeding tendency. This may eventually go on to fibrosis and calcification.

ii Glucocerebroside deposition in the pericardial space stimulating fibrous tissue proliferation. There is no proof of this process on available histochemical evidence.

iii Gaucher cell infiltration with secondary effusion and fibrosis.

Cardiac problems may also occur secondarily to the anaemia, respiratory impairment and skeletal deformities, i.e. the kypho-scoliosis due to vertebral collapse.

CHAPTER 18

GASTRO-INTESTINAL TRACT MANIFESTATIONS OF GAUCHER DISEASE

INTRODUCTION

Except for liver and splenic complications, the gastro-intestinal system is rarely involved in the Gaucher disease process. Problems due to splenomegaly have already been discussed in Chapter 11.

HEPATIC COMPLICATIONS

Results

Thirteen of the patients in this series (62%) were found to have enlarged livers, (Table 6.). Gross, asymptomatic hepatomegaly was particularly evident in those patients who had previously undergone splenectomy, (Table 9). None of the patients showed any significant clinical or biochemical evidence of hepatic damage, (Table 9), ascites or portal hypertension.

Discussion

The majority of the patients in this series presented with asymptomatic liver enlargement during the course of their disease. Gaucher cells are reported to be found in the liver capillaries in children, whereas in adults they are found in addition in the portal spaces and sinusoids, (Chang-Lo *et al*, 1967). The Gaucher cell infiltration and consequent fibrous connective tissue response eventually

results in an obliteration of central veins and sinusoids and a compression of portal tracts and in rare instances this might contribute to the formation of portal hypertension and ascites. However the occurrence of portal hypertension has been reported in only 6 patients. (Meriel *et al*, 1954; Morriso and Lane, 1955; Imparato, 1960; Javett *et al*, 1966; Sales and Hunt, 1970, and Kozower *et al*, 1974). No clinical evidence for ascites or portal hypertension was found in the author's series despite the fact that some individuals suffered from long-standing gross hepatic enlargement.

The portal hypertension is due to intrahepatic venous obstructio by extensive deposits of Gaucher cells and the increased volume of portal blood flow as a result of the markedly increased vascular capacity of the enlarged spleen.

Hepatic decompensation due to derangement of liver function from cellular infiltration and destruction is exceedingly rare and did not occur in this survey.

ASSOCIATED GASTRO-INTESTINAL PROBLEMS

The other gastro-intestinal complaints encountered in this series did not appear to be related to the Gaucher disease. Three patients had indirect inguinal herniae, two suffered from duodenal ulcers and two complained of chronic diarrhoeas of unknown aetiology. However the patients with chronic diarrhoea have not been fully investigated, so the possibility exists of Gaucher cell infiltration of the intestinal tract causing this complication.

The association of gall-bladder disease with Gaucher disease in some patients or their kindred is of interest. This problem will be discussed fully in a later chapter, (Chapter 19).

CHAPTER 19

MISCELLANEOUS CLINICAL FEATURES OF GAUCHERS DISEASE

RARE ORGAN INVOLVEMENT

Clinical evidence of involvement of other organs such as renal, endocrine and gonadal is exceptionally rare and was not found in the author's series. However, Gaucher cell infiltrates have been recurrently reported in these sites at autopsy. Prior to their death none of these patients had any clinical symptoms referable to the histologically involved structures.

Ross, (1969), described the histological appearance of a kidney infiltrated with Gaucher cells. He commented that the finding of Gaucher cells in the glomerular endothelial lining reinforces Fredrickson's, (1962), belief that the glucocerebroside accumulates within the reticulo-endothelial cells. The cells appeared, singularly or in clusters, and bulged into the glomerular capillary lumina. Bowman's capsule and the parenchymal interstitium were found to be free from Gaucher cells. Gaucher cells in the kidney have also been reported by Horsley *et al*, (1935); Choisser and Montgomery, (1949); Reich *et al*, (1951), and Chang-Lo *et al*, (1967). Imparato, (1960), commented on Gaucher involvement of the testes and mesenteric nodes.

CONCLUSION

No autopsies were performed during the course of this series and no evidence of unusual organ involvement, as outlined above, was clinically detectable. A lymph node in the region of the parotid gland in Patient 11 was surgically removed and histologically showed a heavy infiltration with Gaucher cells.

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ASSOCIATED DISEASES

Introduction

In this chapter three aspects of conditions associated with Gaucher disease are considered:

i Conditions which occur in patients suffering from Gaucher disease either by coincidence or as a causal relationship.

ii Diseases which probably occur more frequently in families of Gaucher disease patients than in the general population.

iii Conditions producing 'Gaucher cells' in the bone marrow with no evidence of Gaucher disease on clinical grounds or by special investigations.

Immunoglobulin Abnormalities

In the first category the reports of immunoglobulin abnormalities in these individuals are important (Goldfarb *et al*, 1950; Blattner, 1968; Pratt *et al*, 1968).

Pratt *et al*, (1968), subdivided patients with immunoglobulin abnormalities into those with a diffuse increase in serum globulins and those with a homogeneous elevation of immunoglobulin. In their series it was noted that immunoglobulins were always abnormal in patients with hepatosplenomegaly. Homogeneous protein increases were found in all patients with hepatosplenomegaly who were over 50 years of age. Diffuse immunoglobulin elevations were found in patients with hepatosplenomegaly who were under the age of 50 years. Most of these individuals had evidence of chronic or recurrent infections or aseptic bone necrosis.

The exact pathogenesis of this immunoglobulin abnormality is unknown, but is probably related to the reticulo-endothelial system dysfunction as a result of Gaucher cell infiltration of the bone marrow, spleen and lymph nodes. This theoretically could result in a reduced resistance to infection in these individuals. Although this aspect has never been quantitatively analysed, there is certainly an impression of susceptibility to infection in some of the affected individuals in the author's series. A striking example was Patient 13. This person lived a sophisticated urban existence with no overt contact with tuberculosis sufferers, yet she contracted and eventually died from tuberculosis, with cerebral complications.

There is no definite evidence to suggest that the accumulating glucocerebroside contents are antigenic. Joffe *et al*, (1963), confirmed that the glucocerebroside was not antigenic and had no irritant effect on immunoglobulin synthesis, while Brady *et al*, (1965), showed that the galactocerebroside moiety of the accumulating lipid had antigenic properties.

Associated Malignant Disease

These immunoglobulin abnormalities have led authors to postulate an association between Gaucher disease and certain malignant disorders. Cho and Sastre, (1976), reported on a patient with coexistent Gaucher disease and Hodgkins disease; there is a further individual documented by Sharer *et al*, (1974). Turesson and Rausing, (1975), and Wolf, (1973), reported on the association of benign monoclonal gammopathy and Gaucher disease. Osserman and Takatsuki, (1963); Pinkhas *et al*, (1965), and Benjamin *et al*, (1979), described patients with Gaucher disease and associated multiple myeloma. However Scullin *et al*, (1979), have questioned the evidence for diagnosing Gaucher disease in the patient reported by Pinkhas *et al*, (1965). In addition, they report the finding of 'pseudo-Gaucher cells' in a patient with multiple myeloma. These cells had the appearance of Gaucher cells on light microscopy, but were found to be bone marrow macrophages filled with proteinaceous material and easily differentiated from true Gaucher cells when examined under electron microscopy.

Gaucher cells have also been found in the bone marrow of patients suffering from acute myeloblastic leukaemia, (Witzleben *et al*, 1970); chronic granulocytic leukaemia, (Albrecht, 1966; Smith *et al*, 1968; Gerdes *et al*, 1969; Rosner *et al*, 1969); and thalassaemia, (Zaino *et al*, 1971). Lee, (1969), described differences in ultrastructure between the cells found in Gaucher disease and leukaemia. He showed this with high resolution microscopy, negative staining and carbon-platinum shadowing methods. It is therefore important to establish the diagnosis of Gaucher disease on multiple criteria when 'Gaucher cells' are seen in the bone marrow of individuals suffering from haematological malignancies.

There are other sporadic reports in the literature of Gaucher disease patients suffering from co-existent malignancies, for example islet cell carcinoma of pancreas, (Groen and Garrer, 1948); osteogenic sarcoma, (Straus, 1948); giant follicular lymphoblastoma, (Friedman and Grayzel, 1951); thymic carcinoma, (Morrison and Lane, 1955); bronchogenic carcinoma, (Rosenfeld and Epstein, 1961); cerebral astrocytoma, (Davis and Dorfman, 1961).

The majority of these individuals had definite Gaucher disease by many criteria, prior to the onset of the malignant disease. Although co-existence of the two diseases may be coincidental, it is possible, as postulated by Sharer *et al*, (1974), that the histiocytic proliferation in Gaucher disease might be associated with an increased risk of malignancy in this over-stimulated cell line. Interesting examples in the author's series were:-

i The sister of Patient 16. This individual had Gaucher disease and then died from carcinoma of the ovary.

ii The brother of Patient 10. He died of a disseminated osteogenic sarcoma; a diagnosis of Gaucher disease had been confirmed many years previously.

Associated Lipid Disease

Many authors have speculated on an association between Gaucher disease and other lipid diseases. There have been reports of an increased incidence of these disorders in Gaucher disease patients and their unaffected kindred. The most commonly implicated conditions are diabetes mellitus and cholelithiasis, as reported by Rosenthal, (1940); Groen and Garrer, (1948); Gordon, (1950); Reich *et al*, (1951); Brinn and Glabman, (1962). Reich *et al*, (1951) also reported the impression that instances of mental retardation and stunted growth were more common in affected individuals and their families. Three of the patients in this study (Patients 11, 12 and 14) suffered from cholelithiasis. Nine individuals (43%) had a strong family history of diabetes mellitus, but there was no specific inheritance pattern for this condition in any of the kindreds.

Six patients (29%) had a distinct family history of gall-bladder disease. The exact incidence of diabetes mellitus and gall-bladder disease in South African population groups is not known. It is, however, accepted that these diseases occur frequently in individuals of Ashkenazi-Jewish stock. For this reason it is difficult to comment on the significance of the specific association of these conditions in this series.

Also of interest is Patient 8, who has two children with the Hurler's syndrome. Although this condition is also a genetically determined biochemical abnormality this association with Gaucher disease is probably coincidental.

CONCLUSION

There is an impression of an association between Gaucher disease and certain pathological lipid-states in the same kindreds. It is difficult to gauge the significance of this finding with the present lack of population statistics on these conditions. Cells indistinguishable from Gaucher cells on light microscopy are found in the bone marrow of patients with white cell neoplastic conditions. These affected individuals have no other clinical stigmata of Gaucher disease. In some instances these cells have been shown to have distinctive features on ultrastructural studies. Abnormalities in immunological competence of individuals with Gaucher disease appear to contribute to a susceptibility to infection, but do not appear to result in a significant risk of later neoplastic disease.

S E C T I O N V

RADIOGRAPHIC FEATURES OF GAUCHER DISEASE

CHAPTER 20

RADIOGRAPHIC MANIFESTATIONS OF GAUCHER DISEASE

INTRODUCTION

The majority of patients with Gaucher disease have radiographic abnormalities and the extent and distribution of these will depend on the severity of the disease. However, the characteristic radiographic signs, although not pathognomonic, have definite diagnostic significance when in association with the suspicious clinical picture. Indeed, an Ashkenazi-Jew with asymptomatic splenomegaly and classic radiographic changes in the femoral head and lower femoral metaphyses will almost certainly have Gaucher disease.

Extensive radiographic studies were undertaken on seventeen patients in this study but these pictures were not always available to the author. It is, therefore, inappropriate to tabulate the data which is preferentially discussed in relevant sections. Only five of these seventeen individuals had completely normal skeletal surveys.

Almost all of the wide range of commoner radiographic abnormalities found in the course of Gaucher disease, Windholz and Foster, 1948; Strickland, 1958; Levin, 1961; Moseley, 1963; Amstutz and Carey, 1966; Greenfield, 1970, and Myers *et al*, 1975), were seen during this survey. Representative radiographs are shown in Figures 4 to 22.

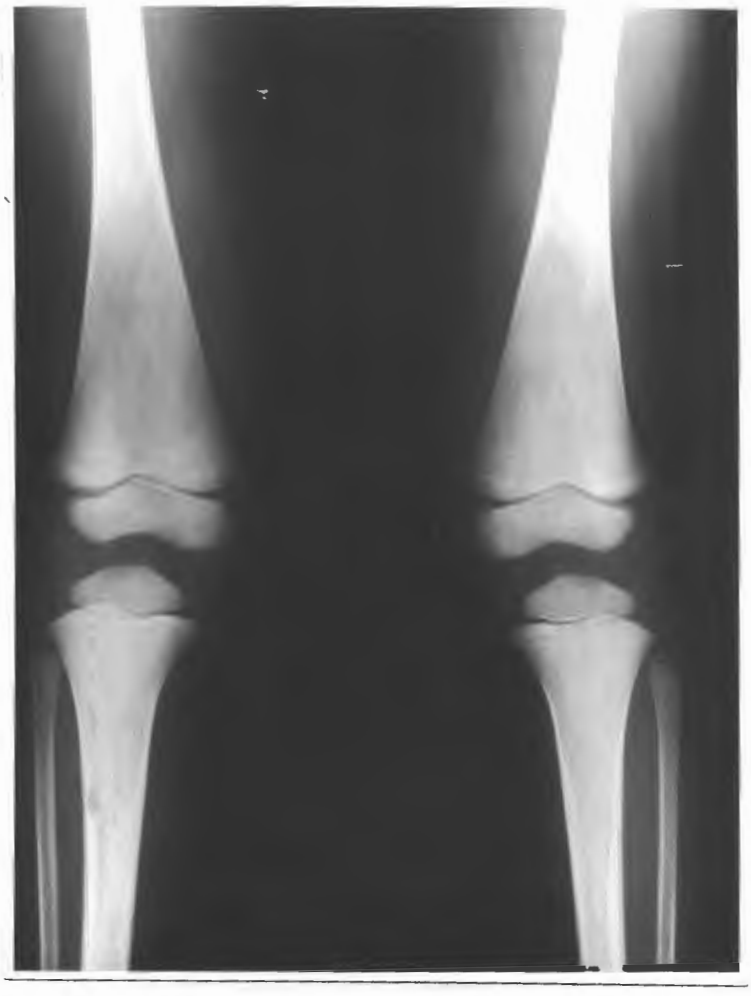


FIGURE 6: ABSENCE OF NORMAL MODELLING OF DISTAL FEMORA PRODUCING AN 'ERLENMEYER FLASK' DEFORMITY IN A 4 YEAR OLD PATIENT.

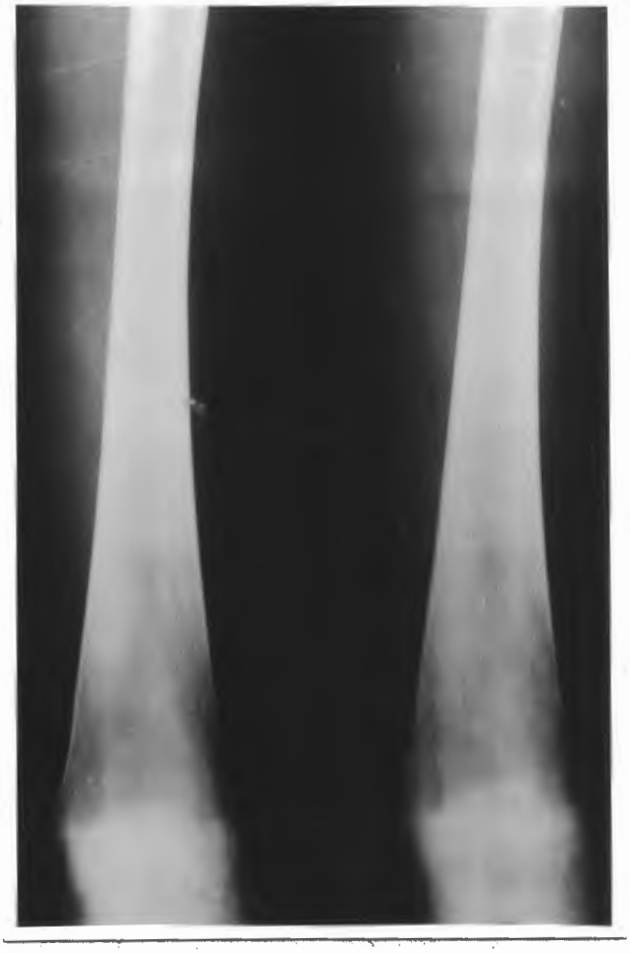


FIGURE 7: CLUBBING OF DISTAL FEMORA, i.e. ABSENCE OF NORMAL SUPRACONDYLAR CONCAVITY PRODUCING AN 'ERLENMEYER FLASK' DEFORMITY.

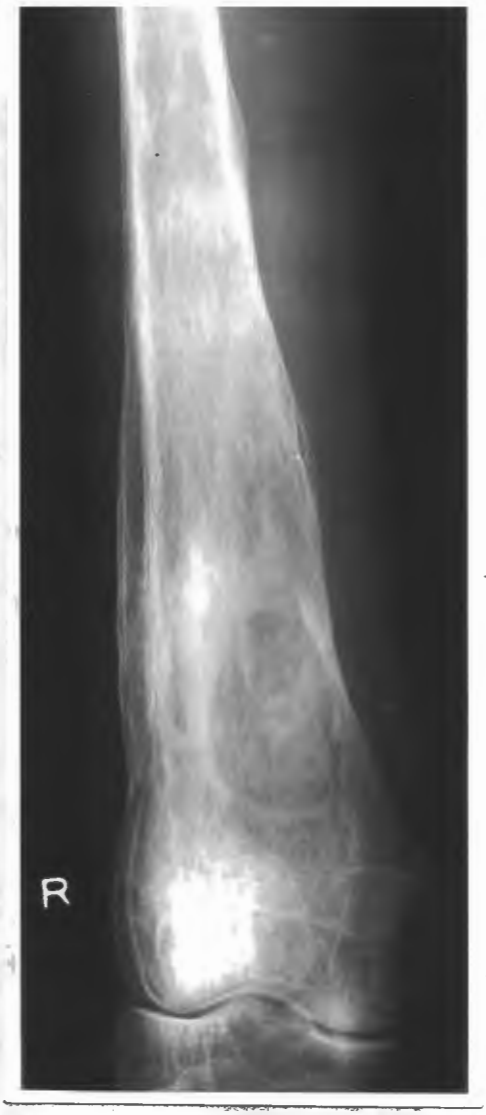


FIGURE 8: ABNORMAL MODELLING, CLUBBED APPEARANCE, OF DISTAL FEMUR WITH PATCHY SCLEROSIS AND POROSIS AND A LARGE LOCALISED LUCENT AREA. PERIOSTEAL REACTION ALONG THE SHAFT.

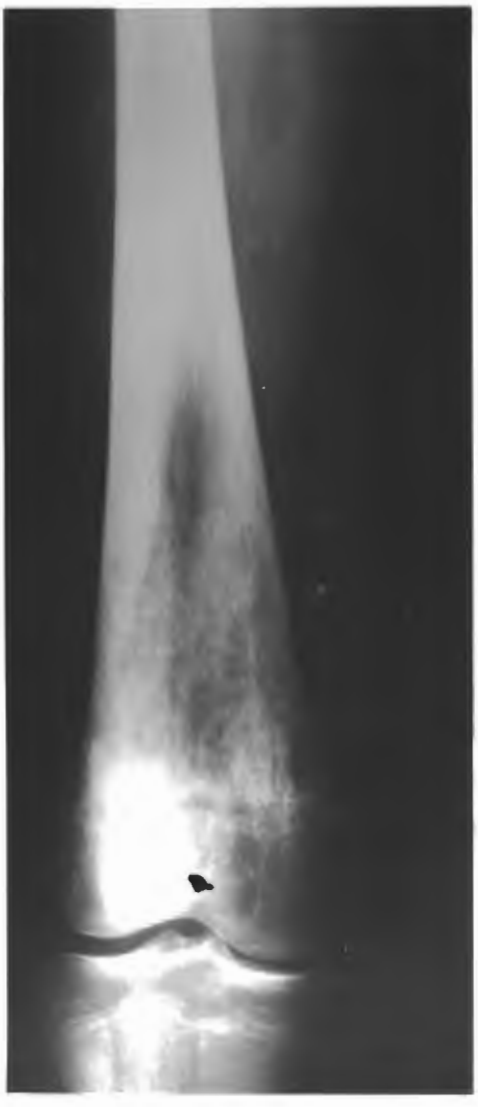


FIGURE 9: CLUBBED APPEARANCE OF DISTAL FEMORAL SHAFT DUE TO DEFECTIVE MODELLING, AND PATCHY SCLEROSIS AND POROSIS.

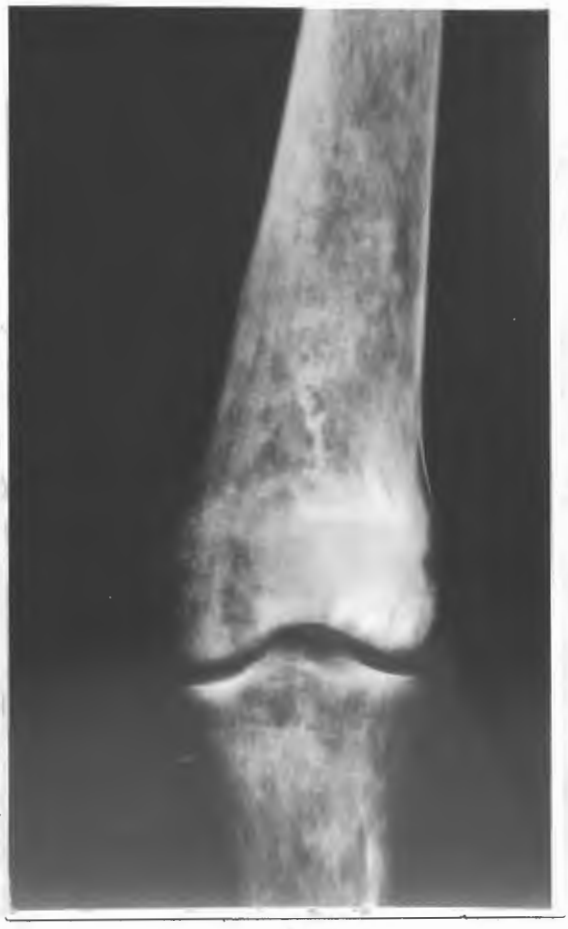


FIGURE 10: 'ERLENMEYER FLASK' DEFORMITY OF DISTAL FEMUR, WITH PATCHY SCLEROSIS AND POROSIS, AND A CENTRAL SERPIGINOUS SCLEROTIC BAND THOUGHT TO BE THE MARGIN OF A LARGE BONE INFARCT. PROXIMAL TIBIA SHOWS PATCHY SCLEROSIS AND POROSIS.

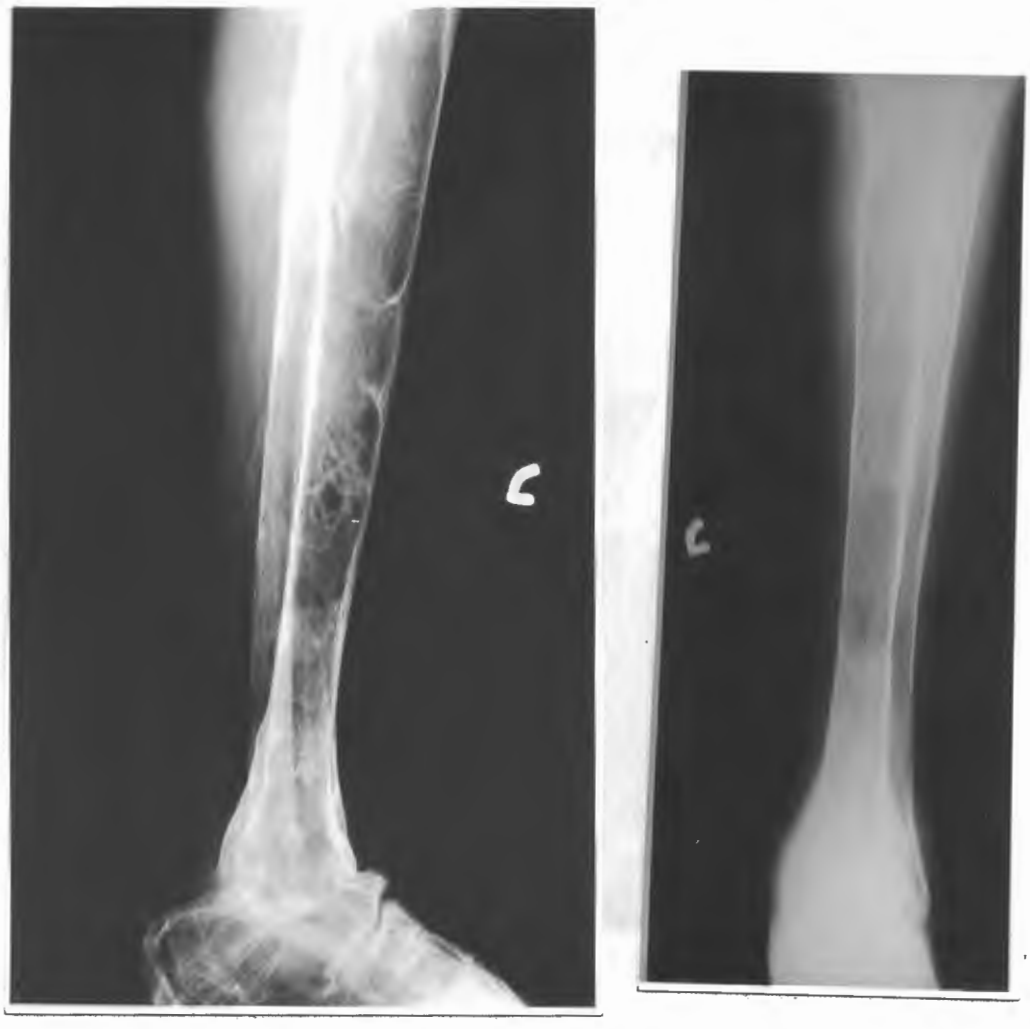


FIGURE 11: TIBIA AND FIBULA DIFFUSELY POROTIC WITH MULTIPLE LUCENCIES CAUSING A 'SOAP BUBBLE' APPEARANCE.

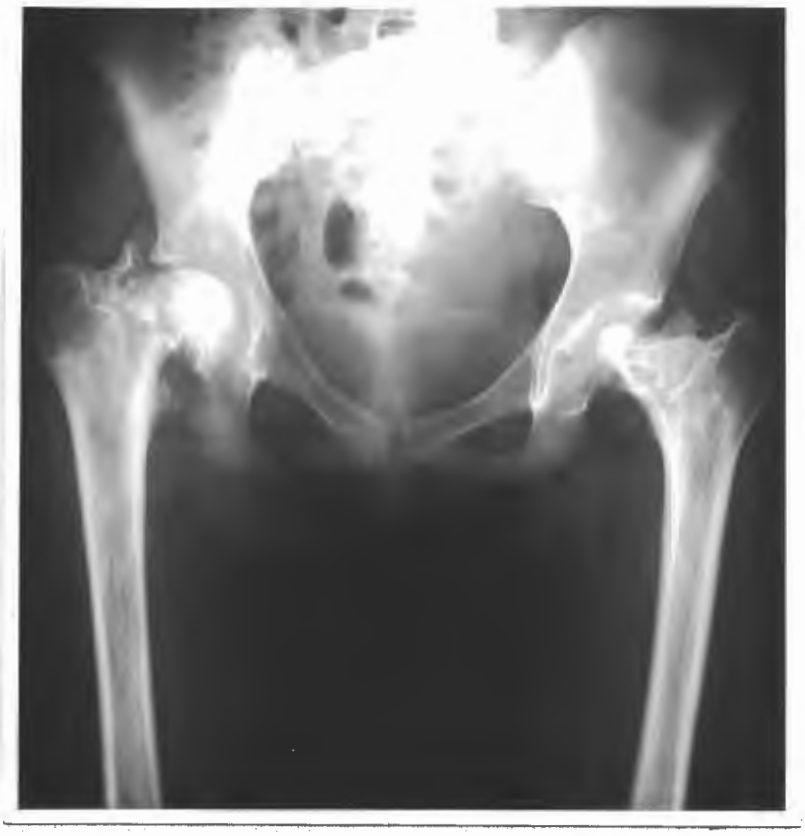


FIGURE 12: BILATERAL SEVERE DESTRUCTION OF FEMORAL HEAD AND NECK WITH PATCHY SCLEROSIS AND POROSIS, AND COXA VARA.

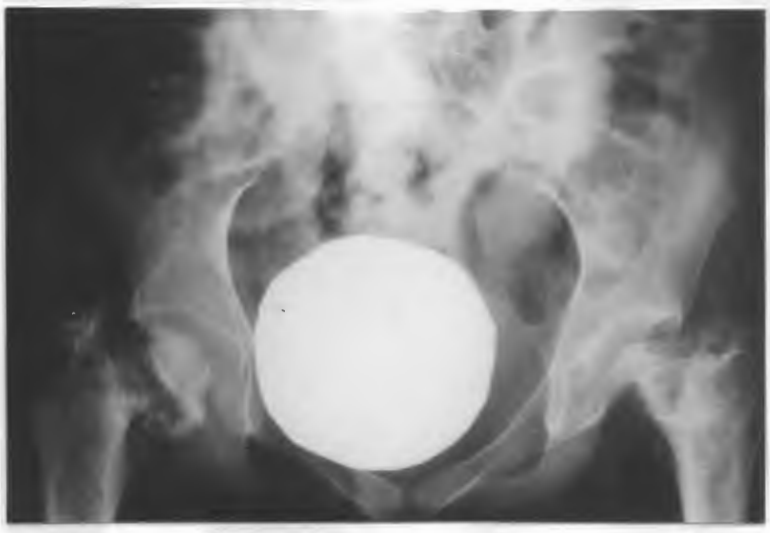


FIGURE 13: BILATERAL SEVERE DESTRUCTION OF FEMORAL HEAD AND NECK, WITH COXA VARA.

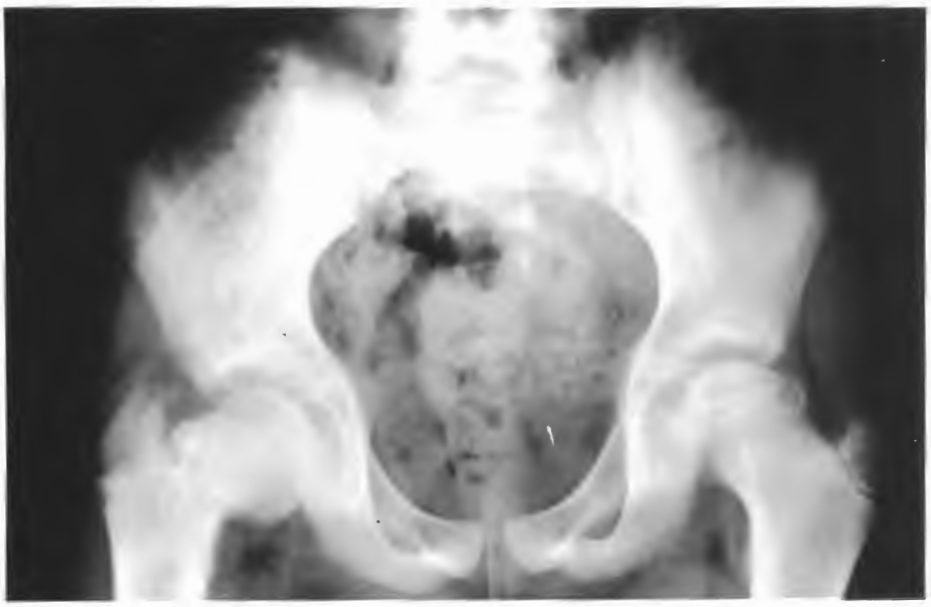


FIGURE 14: FEMORAL HEADS IRREGULARLY CONTOURED AND FLATTENED. RIGHT COXA VARA.

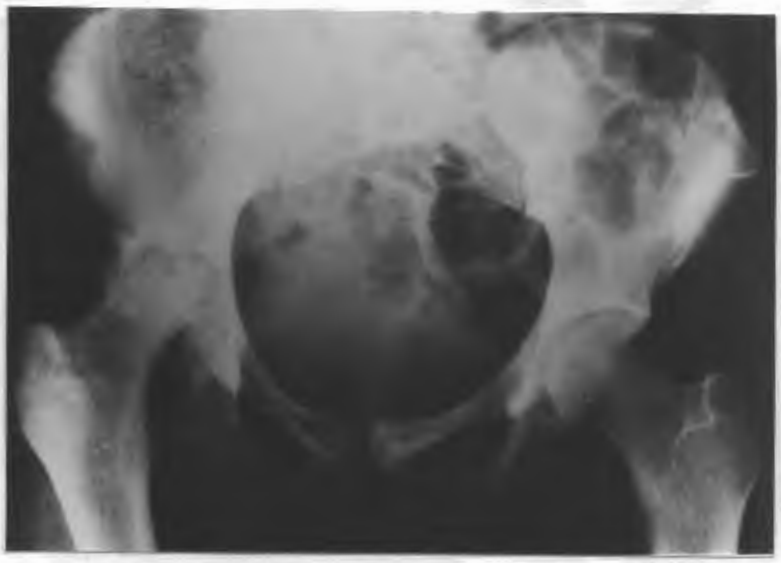


FIGURE 15: RIGHT FEMORAL HEAD DESTRUCTION, PATCHY SCLEROSIS IN REMNANT NECK. ACETABULAR IRREGULARITY AND SCLEROSIS, JOINT SPACE SEVERELY DIMINISHED, AND COXA VALGA.

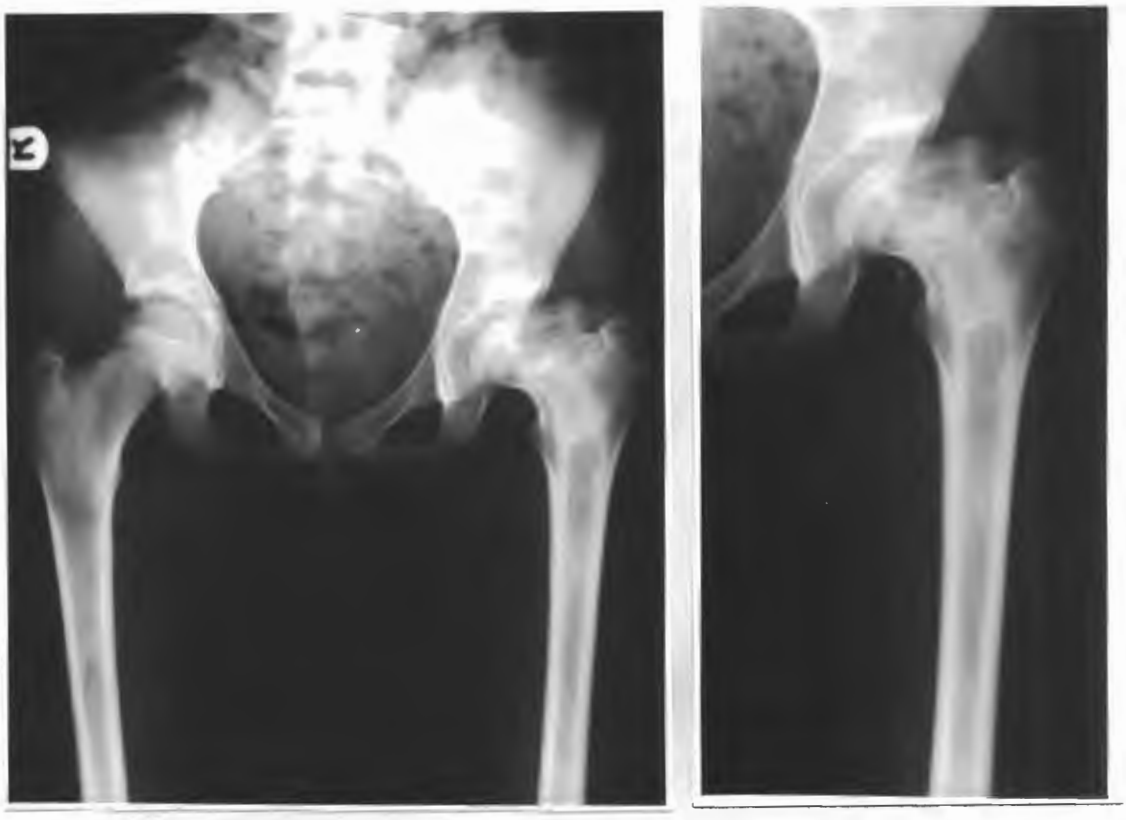


FIGURE 16: FLATTENING DEFORMITY OF LEFT FEMORAL HEAD, WITH SUBLUXATION, COXA VARA DEFORMITY OF FEMORAL NECK, AND 'BONE WITHIN BONE' APPEARANCE OF PROXIMAL FEMORAL SHAFT, DUE TO A NEW SUBCORTICAL LAYER.

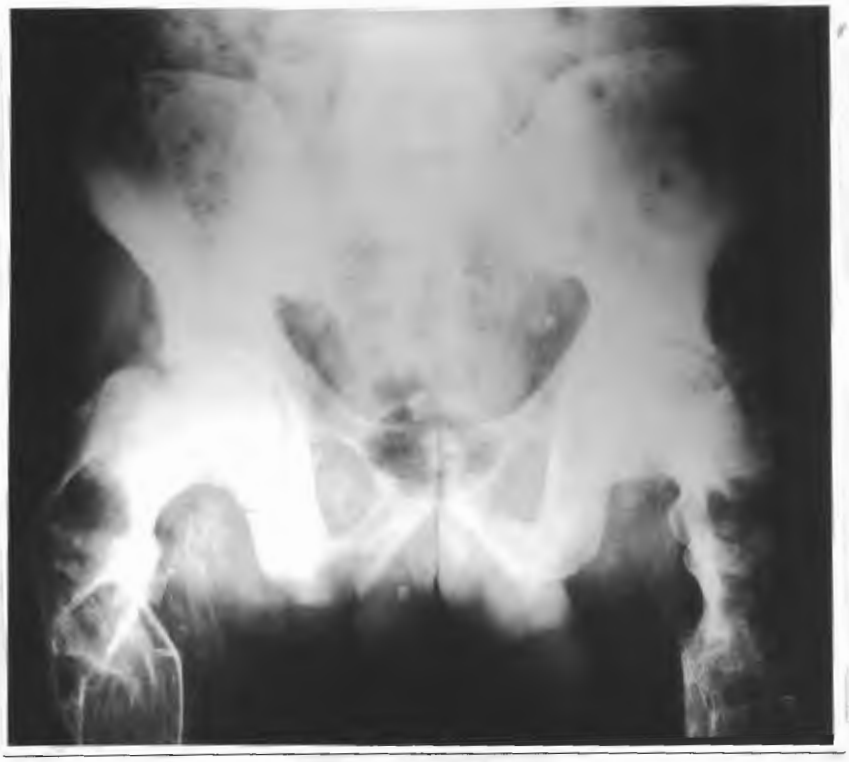
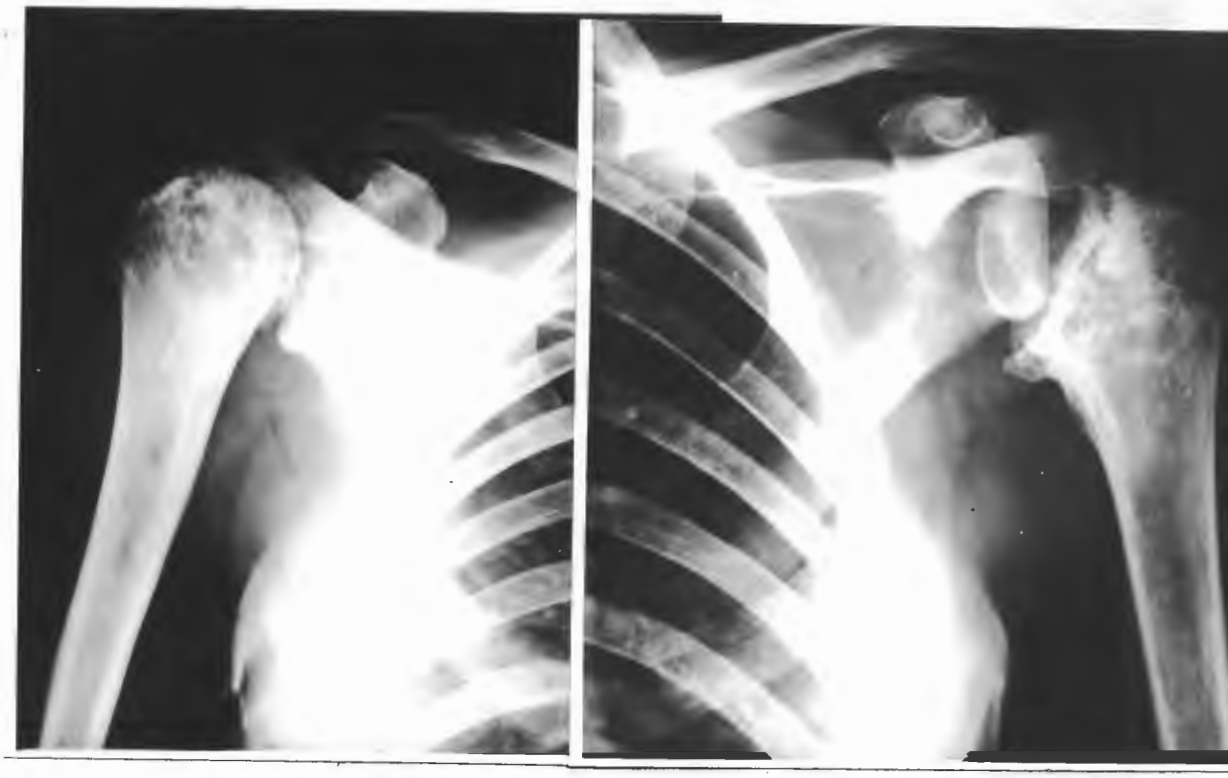


FIGURE 17: BOTH FEMORAL NECKS AND SHAFTS ARE EXPANDED AND DIFFUSELY RAREFIED PRODUCING A 'SOAP BUBBLE' APPEARANCE WITH A COXA VARA DEFORMITY.



FIGURES 18, 19: DEFORMITY AND DESTRUCTION OF HUMERAL HEADS WITH IRREGULAR, PATCHY SCLEROSIS AND POROSIS.

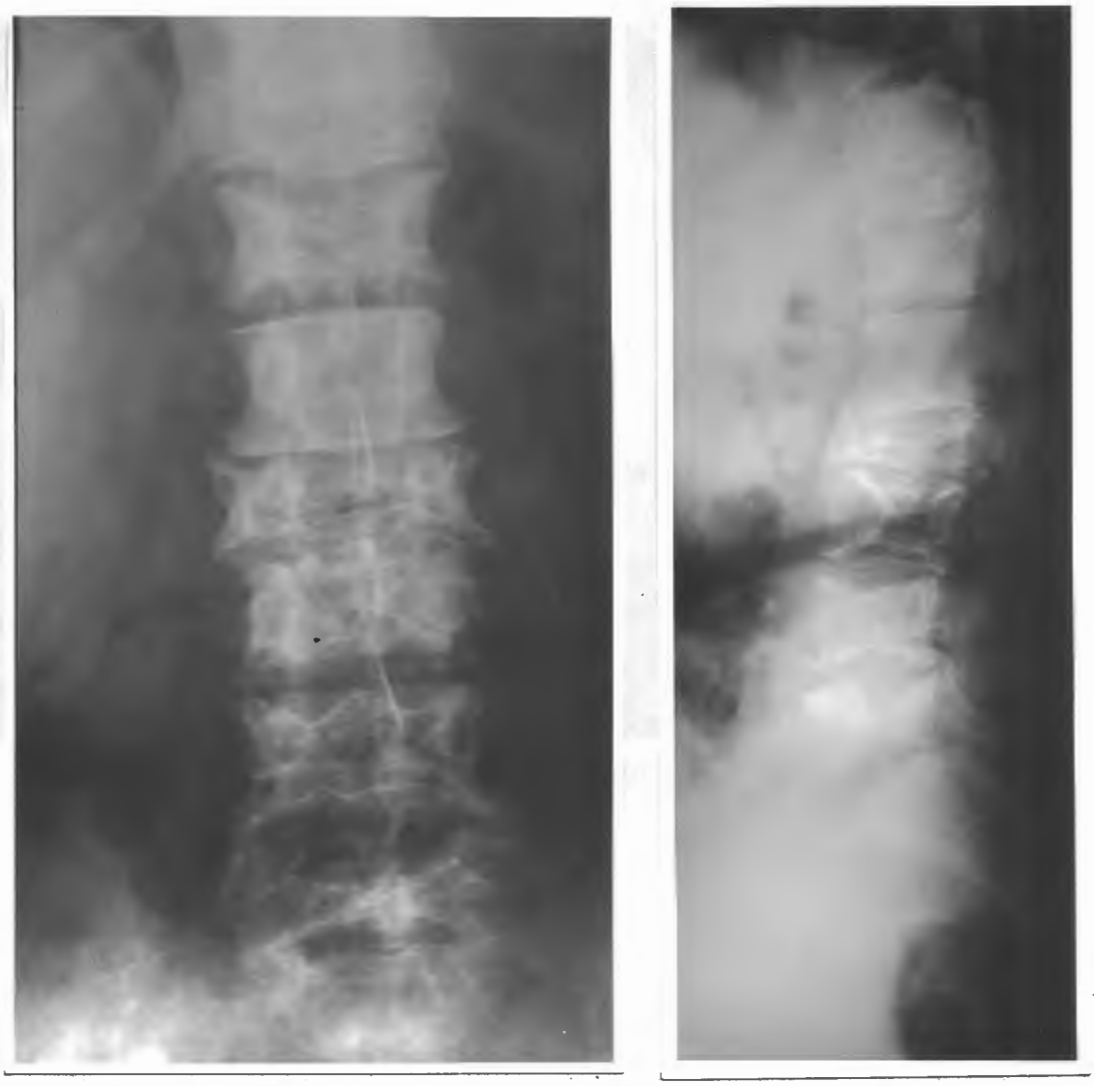


FIGURE 20: MULTIPLE SEVERE VERTEBRAL BODY DEFORMITIES INCLUDING COLLAPSE, BICONCAVITY, WEDGING AND FLATTENING, WITH PATCHY SCLEROSIS AND POROSIS, OSTEOPHYTOSIS AND DISC DAMAGE (SPACES IRREGULARLY NARROWED).

FIGURE 21:

(a) BILATERAL SACROILIAC JOINT SPACES OBLITERATED WITH ADJACENT SCLEROSIS.

(b) BILATERAL SEVERE FEMORAL HEAD DESTRUCTION AND DEFORMITY WITH PATCHY SCLEROSIS AND POROSIS IN THE REMNANTS AND IN THE FEMORAL NECKS.

(c) COXA VARA AND BUTTRESSING OF LEFT FEMORAL NECK.

(d) BILATERAL ACETABULAR IRREGULARITY, SCLEROSIS AND POROSIS WITH JOINT SPACES IRREGULARLY DIMINISHED AND OSTEOPHYTE FORMATION.

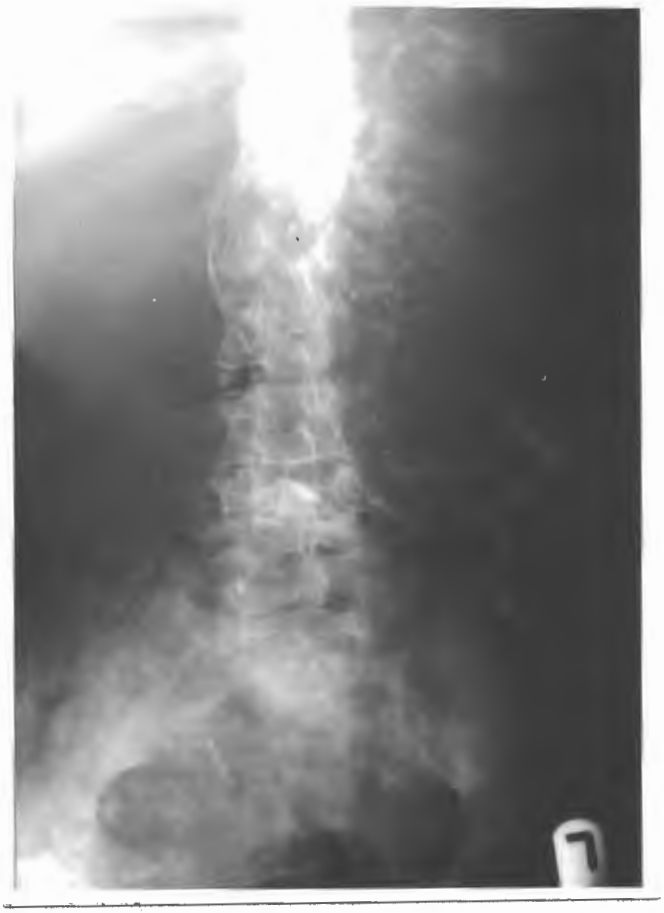


FIGURE 22: MASSIVE CALCIFIED SPLEEN OCCUPYING LEFT UPPER QUADRANT, FLANK AND ILIAC FOSSA AND EXTENDING OVER TO RIGHT FLANK AND RIGHT ILIAC FOSSA.

DISCUSSION

Erlenmeyer Flask Deformity of Femora

Radiographic evidence of Gaucher disease is not usually present in the early stages of the condition. In fact, some patients with clinical manifestations of skeletal involvement have normal radiographic surveys and initial attacks of acute arthritis and pseudo-osteomyelitis may be unaccompanied by radiographic signs.

The earliest, most common finding is expansion and abnormal modelling of the lower femoral shaft, (Tennent, 1945), with loss of normal cortical concavity in the supracondylar region of the femora. The appearance of this expanded region aptly deserves the designation of an 'Erlenmeyer Flask' deformity, (Figures 6 to 10). This description is derived from the laboratory container which is similarly triangular in shape. Further radiographic changes develop with increasing age and Gaucher cell bony infiltration. Twelve of the seventeen patients (70%) who had skeletal surveys in this survey were found to have an Erlenmeyer Flask deformity of the lower femora.

The primary bony pathological process is one of destruction and deformity as the medullary region is progressively replaced and undermined by the infiltrating Gaucher cell mass. The bone matrix is thin and radiographically appears osteoporotic, with areas of rarefaction. Rarely, the medulla has a "soap-bubble" or diffuse "ground glass" appearance, (Figures 11, 17). Localised areas of sclerosis indicate ischaemic necrosis, or subsequent healing, (Figure 10).

Other long tubular bones are less commonly involved, (Figure 11), and show the same radiographic features as described in the femora.

Femoral and Humeral Head Necrosis

As the disease progresses, destruction and deformity of the femoral, (Figures 12 to 17), and, less commonly, humeral heads develops, (Figures 18, 19). The radiographic features in these regions closely resemble aseptic necrosis as produced by any other disease process. Misdiagnoses of Perthe's disease, idiopathic aseptic necrosis and other related conditions are frequently made.

Once destruction of femoral heads has commenced, the process usually progresses relentlessly, ultimately resulting in disintegration of the femoral heads but the condition may become quiescent at any stage.

Eleven patients in this survey had radiographic evidence of femoral head necrosis, of whom eight were bilaterally affected. Only two individuals had bilateral humeral head necrosis, although a number of patients complained of non-specific shoulder joint paints.

Miscellaneous radiographic features

Spine:

Spinal changes consist of vertebral collapse and narrowing, (Figure 20). When present, this complication diffusely involves the thoracic and lumbar vertebrae causing variable kyphoscoliosis. It may also result in diminution in height and respiratory restriction due to deformity of the ribcage. Patient 2 suffered markedly from this problem.

Chest:

Radiographic changes in the chest occur because of diffuse infiltration of pulmonary tissue and lymphatics by Gaucher cells. The picture varies from mild involvement, with increased lung markings, to marked diffuse pulmonary infiltration resembling interstitial fibrosis. Autopsy examination occasionally reveals some degree of pulmonary infiltration, usually with minimal ante-mortem radiographic signs. (Page 103).

Sacroiliac joints:

Radiographic signs of sclerosis are rarely seen in the sacroiliac joints, (Figure 21), (Greenfield, 1970). However, this change was found in three affected individuals in this study.

Splenic calcification:

One patient in this series presented with diffuse splenic calcification on abdominal radiography, (Figure 22).
It is presumed that the calcification had occurred in areas of infarction, haematomata or healed fibrosis.

Skull and mandible:

Skull and mandibular lesions have only been reported in isolated instances, (Reed and Sosman, 1942; Silverstein and Kelly, 1967; Weigler *et al*, 1967; Bildman *et al*, 1972), but these abnormalities were not seen in any of the author's patients.

Cardiac:

An enlarged cardiac shadow may be due to cardiac failure (Patient 2) or to a haemopericardium. Pericardial calcification with constriction has been reported, (Harvey *et al*, 1969).

Hepatic:

Cholelithiasis, varices and other evidence of portal hypertension may be demonstrated, (Sales and Hunt, 1970).

Secondary bone deformities:

Further radiographic abnormalities can occur with secondary orthopaedic complications in the diseased and weakened bones. These changes include coxa vara, genu valgum, pathological fractures and bowed diaphyses.

The acute bone crises of Gaucher disease may be unattended by radiographic signs, but changes which are similar to an acute septic osteomyelitis might develop, and make radiographic differentiation most difficult.

S E C T I O N VI

BIOCHEMISTRY

CHAPTER 21

BETA-GLUCOSIDASE ENZYME ASSAY

INTRODUCTION

Studies were principally involved with assaying the beta-glucosidase activity of pure lymphocytes, derived from individuals of varying genotypes, in kindreds suffering from Gaucher disease. Blood specimens were collected and tested according to the method described earlier, (Chapter 7).

It was decided to establish a working laboratory procedure for biochemical diagnosis of Gaucher disease and screening of potential heterozygotes. The benefit of the former was the development of a safe and easy method for definitive diagnosis, without resorting to biopsy.

Biochemical differentiation of clinically identical phenotypes into distinct and separate genotypes was the ultimate aim. This was most desirable for the following reasons:-

i The detection of clinically normal heterozygous carriers of the mutant gene.

ii Genetic counselling could be based on definitive, accurate discernment of individual genotypes. This avoids the uncertainty of counselling according to statistical estimates and chance.

iii It might eventually become possible to undertake population screening for a disabling genetic disease in a high-risk, well-defined population group.

iv The birth of affected individuals could be predicted and prevented where pre-natal diagnostic methods were available.

v The early initiation of enzyme replacement therapy, when feasible, might prevent later disabling complications of the disease process in affected individuals.

Method

Initially, experiments were undertaken to establish the laboratory procedure and define biochemical ranges for the respective genotypes. For this purpose specimens for testing were obtained from known, obligate genotypes. Random non-Jewish individuals with no history of Gaucher disease were used as homozygous normals. Ashkenazi-Jews with no family history of Gaucher disease were then tested and the findings were incorporated into the normal scale, where applicable.

Parents and children of known patients, who had been diagnosed clinically, radiologically, histologically and biochemically, were used as obligate heterozygotes for range determinations. While setting up the biochemical procedure numerous assays were undertaken to confirm the reliability of the pre-natal test.

Large-scale enzyme assays on fibroblasts have not yet been attempted. Work was performed in this field in order to establish a laboratory procedure should the future need arise. An Amniotic fluid beta-glucosidase assay was only performed on one patient during the course of the survey. The patient was non-Jewish and was therefore not included in this study.

Extensive experiments were performed to establish a satisfactory procedure for storing white cells to maintain their original enzyme activity over extended periods. Unfortunately, all the methods used during the course of this survey failed to produce acceptable results. Freezing at different stages of lymphocyte isolation did not produce repeatable enzyme levels on subsequent thawing and assaying. Enzyme levels diminished markedly following even short-term freezing and thawing, and specimens stored overnight showed diminished enzyme activity on the day immediately following venesection. This produced considerable difficulties in maintaining a standardisation of biochemical technique and no satisfactory method of storage was developed. Low results initially obtained from freeze/thaw experiments were thought to have resulted from thawing at too high a temperature with consequent denaturation of the enzyme. Subsequent freeze/thaw experiments which have been undertaken subsequent to this survey have shown good correlation between enzyme levels assayed after storage and the same specimen studied in the fresh state. All specimens are frozen in 20ML aliquots at a cell concentration of 1.5×10^6 cells/20$\mu\ell$. These experiments are still continuing; the aim is to determine the effect of long-term freezing, as a method of storage, on enzyme standardisation.

Eventually it should be possible to produce standard enzyme solutions for use as controls when screening individuals for carrier status. However, during this survey, for the reasons discussed above, specimens were always tested within four hours of venesection, having been stored at room temperature.

RESULTS

The following results were obtained after testing 45 control, homozygous normals and 24 obligate heterozygotes and 21 individuals homozygous for Gaucher disease. These results are listed in Tables 15, 16 and 17, and graphically represented in Figure 23. The designation $\mu u/10^7$ cells is not repetitively used after each enzyme level. This is included with the heading on each Table, and then the enzyme levels are numerically listed without the appropriate units.

TABLE 15: BETA-GLUCOSIDASE ENZYME ASSAY OF 45 NORMAL CONTROLS

ENZYME LEVEL ($\mu u / 10^7$ CELLS)

9.22	15.30
12.60	16.23
13.38	19.90
21.10.	17.50
12.18	18.10
20.80	20.20
20.46	24.00
16.70	16.45
18.60	27.38
15.20	16.80
15.50	19.70
14.94	20.10
15.05	19.60
16.52	19.80
28.40	20.10
16.40	21.10
15.64	15.10
22.87	23.60
26.55	
15.30	
18.50	
16.50	
14.80	
15.60	
18.60	
18.90	
21.80	

TABLE 16: BETA-GLUCOSIDASE ENZYME ASSAY OF 24 OBLIGATE HETEROZYGOTES

ENZYME LEVEL ($\mu u / 10^7$ CELLS)
8.14
8.08
11.30
6.80
12.90
8.46
10.50
10.98
8.77
9.00
9.70
11.80
12.69
8.90
7.80
6.10
7.10
7.76
6.22
8.50
9.60
8.70
11.80
10.20

TABLE 17: BETA-GLUCOSIDASE ENZYME ASSAY OF 21 GAUCHER DISEASE HOMOZYGOTES

PATIENT	ENZYME LEVEL ($\mu u/10^7$ CELLS)
1	1.26
2	1.50
3	2.10
5	0.95
6	1.45
7	1.30
8	1.33
9	1.77
10	0.95
11	1.64
12	1.58
13	2.27
14	1.30
15	0.57
16	0.88
17	1.30
18	2.00
19	2.30
20	1.50
21	0.95
29	2.00

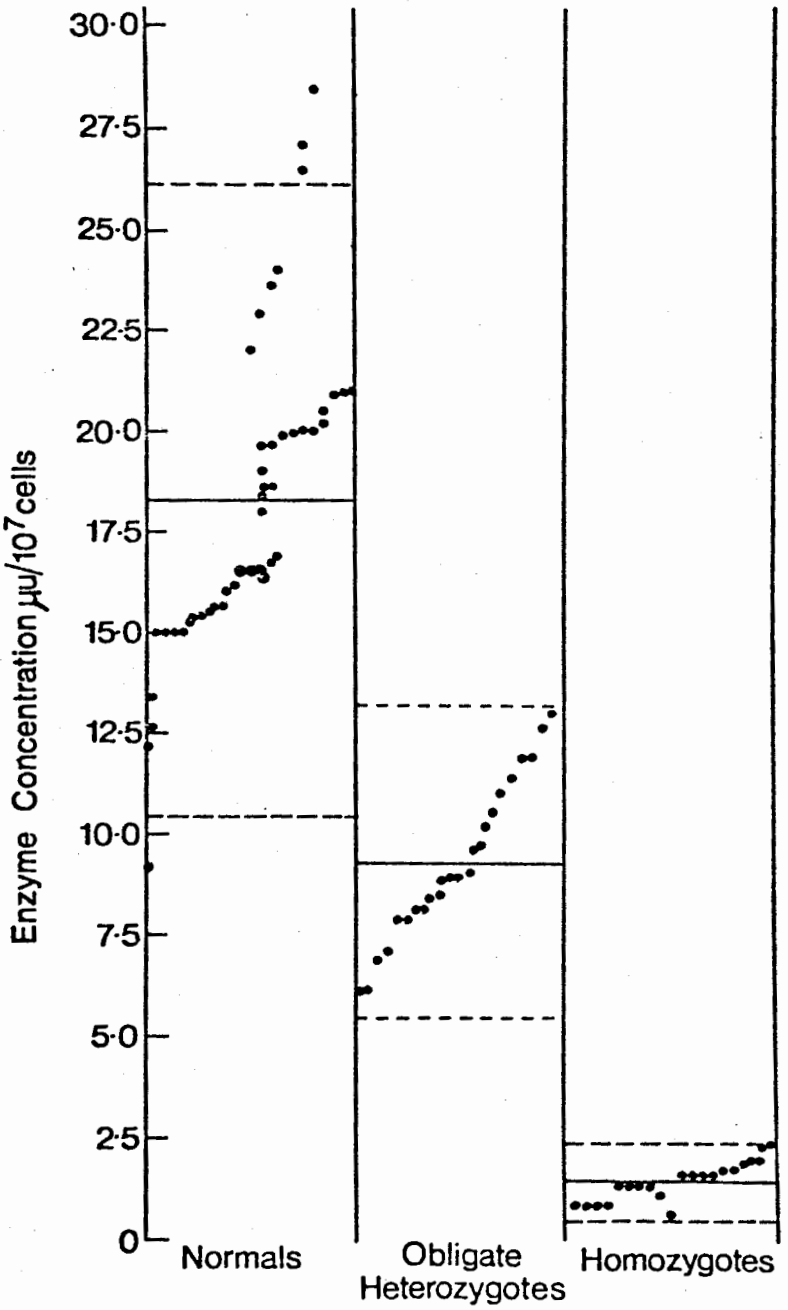


FIGURE 23: GRAPH OF BETA-GLUCOSIDASE ASSAYS OF GAUCHER DISEASE GENOTYPES.

CALCULATIONS

The following enzyme ranges for each genotype were derived on the basis of the mean result and 95% confidence levels, by calculation of twice the standard deviation.

i NORMALS

Number	=	45
Mean	=	18.2904 $\mu u/10^7$ cells
Standard deviation (S.D.)	=	3.9485 $\mu u/10^7$ cells
2 x S.D.	=	7.897 $\mu u/10^7$ cells
∴ 95% confidence range	=	10.3934 to 26.1874 $\mu u/10^7$ cells

ii OBLIGATE HETEROZYGOTES

Number	=	24
Mean	=	9.2416 $\mu u/10^7$ cells
Standard deviation (S.D.)	=	1.9418 $\mu u/10^7$ cells
2 x S.D.	=	3.8836 $\mu u/10^7$ cells
∴ 95% confidence range	=	5.3580 to 13.1252 $\mu u/10^7$ cells

iii GAUCHER DISEASE HOMOZYGOTES

Number	=	21
Mean	=	1.4714 $\mu u/10^7$ cells
Standard deviation (S.D.)	=	0.4765 $\mu u/10^7$ cells
2 x S.D.	=	0.9530 $\mu u/10^7$ cells
∴ 95% confidence range	=	0.5184 to 2.4244 $\mu u/10^7$ cells

DISCUSSION

Biochemical discrimination of genotypes

The results, Figure 23, produce an acceptable spread with regard to differentiating Gaucher disease patients, carriers and homozygous normal individuals. There is some overlap in results obtained for the latter two groups. However, as a diagnostic test for Gaucher disease the enzyme assay has proved to be an excellent procedure. All twenty-one patients tested fell into the range for homozygous affected Gaucher disease and showed a gross deficiency in their beta-glucosidase enzyme levels. The mean for this group was 1.4714$\mu u/10^7$ cells, with a deviation of 0.4765 $\mu u/10^7$ cells. None of the obligate heterozygotes, nor any normal control fell into the 95% confidence range of 0.5184 $\mu u/10^7$ cells to 2.4244 $\mu u/10^7$ cells. The test proved, therefore, to be 100% reliable and repeatable, with no overlap or error.

For detection of heterozygous carriers the results were not entirely reliable. Twenty-four obligate heterozygotes were tested and analysis of these results showed a mean of 9.2416 $\mu u/10^7$ cells and a standard deviation of 1.9418 $\mu u/10^7$ cells. When 95% confidence levels are plotted there is a substantial overlap with the respective limits for the control group. This overlap zone was 10.3934 $\mu u/10^7$ cells to 13.1252 $\mu u/10^7$ cells. 100% of the obligate heterozygotes fell within the 95% confidence levels and there were, therefore, no false negatives amongst the carriers screened. However, 29% of the heterozygote results fell within the overlap zone.

With respect to the normal controls, 4.5% were in the overlap region. A further 2.2% of the normals screened fell in the carrier range at a lower level than the overlap zone,

that is less than 10.3934 $\mu u / 10^7$ cells. If results in the overlap are disregarded, this could be considered as the false positive, percentage error.

The results showed that all the obligate carriers tested fell within the 95% confidence limits for heterozygotes. The problem still remains as to the analysis and categorisation of individual results which fall within the overlap zone.

One factor to consider from the outset is the possibility that some so-called normals were, in fact, carriers of the abnormal gene. This unknown could affect the plotting of a normal range. However, this would only exert a minimal modifying effect, as the controls were randomly collected from a small-risk population group. It is therefore assumed, for analytical purposes, that all the "controls" were in fact homozygous normal individuals. None of the controls had any symptoms, signs, or family history of Gaucher disease.

Statistical discrimination of genotypes

There exist three possibilities for discriminating genotypes where a significant overlap zone occurs, (Westwood and Raine, 1975). These methods involve:

i The arbitrary assignation of a strict dividing line according to the appropriate mean enzyme levels and standard deviations. All results above this line are considered as normal and all the results below the line are considered as falling in the carrier range. With this method a certain fraction of each genotype will be wrongly classified. The magnitude of the error

can be calculated for this series if the total number of obligate carriers and normal controls screened is considered to be a random population. The population screened is then sixty-nine, that is 24 carriers and 45 normals, and the dividing line is 13.1252$\mu u/10^7$ cells, that is the upper limit of 95% confidence level for the heterozygote range. Only three controls fall below this line giving a false positive of 4.34%. There were no heterozygotes above the line giving a zero per cent false negative. Clearly this is not a random population group, but consideration as such allows some estimation of the magnitude of the 'overlap problem' and its possible solution.

ii The definition of limits in terms of standard deviations from the respective means for the two populations as described by Hsia and Steinberg, (1960) and Renwick *et al*, (1960), for phenylketonuria. Their complex, statistical method involving logarithms has not been applied to this series, although their basic principle is utilised. Individuals falling in the overlap zone between the two limits are not classified, thereby excluding statistical estimates and uncertainties.

Considering this series, levels above 13.1252 $\mu u/10^7$ cells would be classified as homozygous normals and results between 5.3580 $\mu u/10^7$ cells and 10.3934$\mu u/10^7$ cells are heterozygotes. Those falling in the overlap zone, i.e. 13.1252 $\mu u/10^7$ cells to 10.3934$\mu u/10^7$ cells would not be classified. The false positive rate would then be 1.44% and the false negative rate stays at zero per cent. However, 13% of the population screened would be unclassifiable, of which 10.1% are carriers. By this method the false positive rate is reduced, however only 90% of the carriers would be correctly ascertained.

iii Statistical and analytical estimation of the probability that any individual result belongs to one or other genotype, no matter where it actually falls, as described by Wilson *et al*, (1965), and Murphy and Mutalik, (1969).
This method involves the use of heterozygote likelihood ratio graphs as described by Westwood and Raine, (1975), for phenylketonuria.
The present discussion assumes that the respective distributions are Gaussian in form, although this was not strictly the case in this series.
With the results from this series a heterozygote likelihood ratio (H.L.R.) graph, Figure 24. was constructed using the appropriate calculation or probability density functions where

$$Y = \frac{1}{\sqrt{2\pi S^2}} \; e^{-\frac{(x-\bar{x})^2}{2S^2}}$$

, Westwood and Raine, (1975).
An example is shown in Figure 24 where a beta-glucosidase result of 12.2 μu /10^7 cells was obtained. Reading off the graph a log result of 0.340 and an antilog of 2.18 is derived. Therefore, the heterozygote likelihood ratio for the value 12.2 μu /10^7 cells is 2.18.

Once a result has been estimated for categorisation in this way, further modifying factors can be considered to improve the accuracy of classification. These modifying factors include:-

i The genetic proximity of the person tested to an affected individual, if a positive family history exists.

ii The gene frequency in the particular population group.

If this person, with the enzyme level of 12.2$\mu u/10^7$ cells (Figure 24), was an Ashkenazi-Jew with no affected relatives his probability of heterozygosity would be 2.18 multiplied by $^1/29$, which equals 0.075. He would therefore have a 7.5% probability for heterozygosity and a 92.5% probability of being homozygous normal. If he was Ashkenazi-Jewish with an affected sibling, his probability of heterozygosity would be 2.18 multiplied by $^2/1$. He would then have an 81.3% probability of being a heterozygote.

Since no random population biochemical screening on Ashkenazi-Jews has yet been performed, the statistical method remains a theoretical possibility. On the basis of the example shown above, it is suitable for more precisely classifying results which fall in the overlap zone.

The present method of enzyme assay is at least 90% accurate for detecting carriers on 'random' screening of a population regardless of the statistical interpretation of the result.

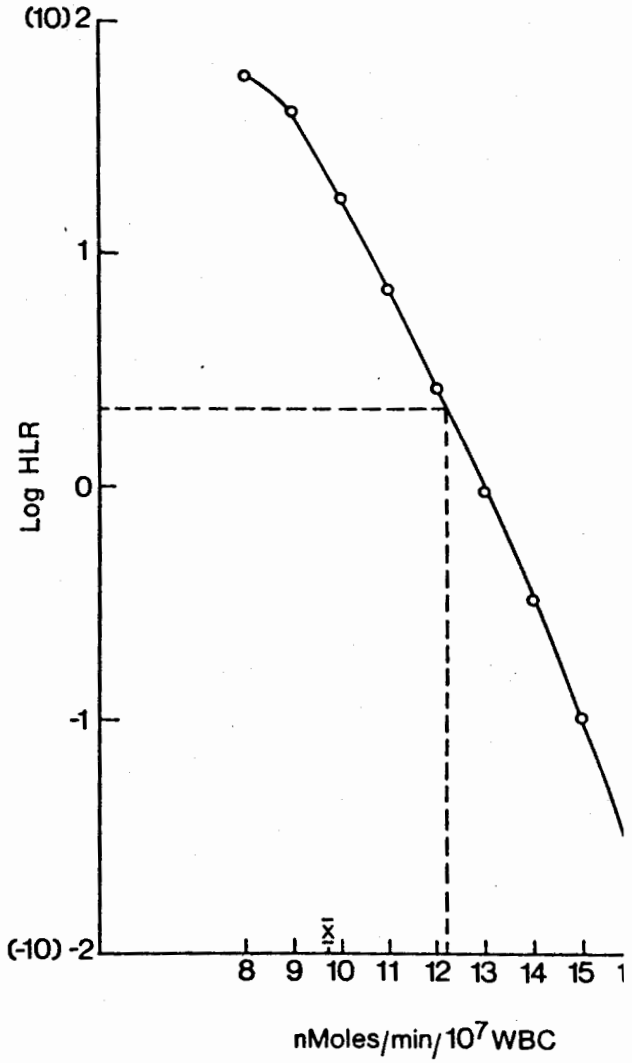


FIGURE 24: BETA-GLUCOSIDASE HETEROZYGOTE LIKELIHOOD RATIO GRAPH FOR GAUCHER DISEASE.

Anomalous results

Certain impressions were gained when attempting to explain anomalous results. It appeared that although individual variations were present, these were not significant. Repeatedly tested individuals always fell in the same range, although the absolute enzyme level might differ from day to day.

The problem lay, therefore, in experimental variation and the lack of a technique control system. There was obviously a need for standard enzyme activity solutions which could be introduced into each test day for quality control. Results could then be more accurately determined as a ratio of the quality standard. It was therefore decided to develop enzyme standards which retained their initial activity over long periods of storage and re-use. Various methods were tested and found to be unsatisfactory, as discussed in the method of enzyme assay.

Another impression was that anomalous results on a single day usually reproduced an acceptable spread, but at a reduced level of activity. The obligate heterozygote assays were always lower than the controls, although respective results were usually too low. There was never a bizarre pattern to the discrepancies and this suggested variations in quality control.

On a few occasions retesting of the same specimens with new, freshly opened substrate reversed the previously abnormal results. A change in substrate activity, which perhaps deteriorates after prolonged exposure to light and air, does appear to be a further significant factor.

Modifying factors

Finally, there is no indication in the literature to suggest dietary, infectious or other factors which might significantly alter enzyme assay results. All the patients in this series were venesected following overnight fasting. Repeatability studies did not suggest any significant variability in results because of associated conditions such as infections or menstruation.

When all these problems are considered, it becomes apparent that the solution lies in the development of more discriminatory tests, rather than in complicated statistical analyses of ambiguous results. The assay, as performed in this laboratory, is producing acceptable results. It is felt that these could be substantially improved by the introduction of known standards for quality control and by modification of the present assay.

Future assay methods

In order to avoid the inaccuracies of the cell count method Mrs L. Peterson, Dr Henderson's successor in the laboratory, has modified the original assay, which is presently being performed on a cellular protein homolysate. The same lymphocyte extraction procedure is used, the cells are then lysed and their protein concentration is calculated according to the Lowry method, (Lowry *et al*, 1951). The method of assay then remains the same except it is now related to the protein concentration.

The preliminary results are encouraging with respect to both accuracy and improved delineation of genotypes. Further testing is necessary to provide new, discriminatory genotype ranges.

Another method for eliminating variation is the simultaneous testing of two lysosymal enzymes in the same individuals's lymphocytes, (Hall and Neufeld, 1973). This was not undertaken during the course of this survey. It has, however, been considered as a future laboratory project. It is hoped that in this way variability of results, due to metabolic factors causing generalised lysosymal enzyme alterations, could be eliminated. The modifying factors would presumably affect both enzyme systems. A more accurate estimate of beta-glucosidase activity could be obtained by expressing the result as a ratio of another stable lysosymal enzyme.

CONCLUSION

It is quite clear that flaws do exist in the biochemical method as discussed. However, within the perspective of this rare genetic disease, with a limited number of patients and obligatory heterozygotes available for study, an acceptable laboratory procedure has been established. It is hoped that by ongoing testing of all genetic subtypes, the biochemical discriminatory possibilities can be further improved by both modification of the procedure and by recalculation of new 95% confidence limits. Preliminary experiments using a protein homolysate, rather than the cell count method, indicate that this aim might be achieved.

CHAPTER 22

ASSOCIATED BIOCHEMICAL STUDIES

TWELVE CHANNEL ANALYSIS

Results

Routine twelve-channel ayalysis of serum was performed on most patients. The routine laboratory screening involved the following parameters:- total protein, albumin, inorganic phosphorus, calcium, cholesterol, urea, uric acid, bilirubin, (total and conjugated), alkaline phosphatase, creatinine phosphokinase, lactate dehydrogenase and amino aspartate transferase.
All the results, which are expressed in S.I. units, are tabulated, (Table 18), but only the relevant ones will be discussed. Normal values for each biochemical parameter appear in parenthesis under the appropriate heading.

TABLE 18: RESULTS OF 12 CHANNEL ANALYSIS

PATIENT	UREA (1.7-6.7)	TOT.PROT. (60-80)	ALB. (35-50)	CHOL. (3.9-7.8)	TOT.BILI. (2-17)	ALK.P. (30-85)	C.P.K. (0-50)	L.D.H. (120-240)	A.A.T. (10-50)
3	6.2	80	43	3.2	10	37	30	175	20
5	4.5	81	44	5.0	10	52	23	193	50
6	6	67	43	5.1	15	77	22	186	50
7	4.6	74	44	4.1	10	44	-	231	59
8	6.6	82	47	4.9	10	40	10	170	46
9	4.5	70	45	3.9	10	158	30	219	48
10	4.8	80	46	3.5	24	38	10	98	47
11	3.1	83	45	5.1	27	85	31	258	40
13	3	66	35	4.0	10	70	28	252	29
14	5.3	75	39	4.8	14	115	40	240	66
17	4.5	81	46	3.6	10	55	31	201	62
18	5	79	49	3.4	10	68	28	240	67
20	6	73	43	6.0	10	55	40	150	30
21	6.1	80	48	3.5	17	49	40	197	47

Discussion

Cholesterol:

Hypercholesterolaemia has been described as occurring more frequently in association with Gaucher disease, (Fredrickson, 1966). This was not confirmed in this series. Although the analysis is only of a small group, the overall impression is, in contrast, of a lowered serum cholesterol level.

Six of the fourteen patients tested had serum cholesterol levels below the lower limit of normal. This was also reported by Zlotnick and Groen, (1961).

Liver function:

Liver function studies from 12 channel analysis revealed no significant abnormality even in those patients with markedly enlarged livers. Unfortunately, serum electrophoresis was not performed on any of the patients. However, unreliable 12-60 channel analysis of total protein and albumin estimations revealed no obvious hypergammaglobulinaemia.

Renal function:

Detailed renal function studies were not performed as all patients had normal serum urea levels and no clinical features to suggest any renal decompensation.

Acid phosphatase:

Acid phosphatase studies were not routinely performed on these patients. Where tested by their general practitioners, it was confirmed that individuals with Gaucher disease show an elevated tartrate stable fraction of serum acid phosphatase. Crocker and Landing, (1960), suggested that the elevated acid phosphatase might represent the initial metabolic derangement. However, this hypothesis has not attracted popular support.

Angiotensin converting enzyme:

Recent reports have shown the presence of elevated serum angiotensin converting enzyme in patients with Gaucher disease. The exact biochemical significance of this finding is still being investigated, (Lieberman and Beutler, 1976).

S E C T I O N VII

GENETICS

CHAPTER 23

HISTORICAL ASPECTS OF GAUCHER DISEASE

REVIEW

When P. C. E. Gaucher originally wrote his "Epithelioma de la spleen" thesis in 1882, he did not suspect the genetic nature of the condition. Collier, (1895), first described the occurrence of the disease in siblings when he diagnosed a six-year old child, whose deceased sister had had splenic enlargement, as having Gaucher disease.

Bovaird, (1900), encountered two sisters with the condition in a family of ten children and Brill, (1901), reported on three affected individuals in one family. Brill *et al*, (1909), described the second of four patients in one generation of a family. In spite of this familial aggregation, Brill and Mandlebaum, (1913), disputed the presence of an hereditary factor. They claimed that none of the seven familial cases which had so far been reported had an affected parent and they held that this mitigated against a genetic mechanism. They did not, however, consider Plehn's, (1909), description of the condition occurring in a father and his daughter as proof of an hereditary factor.

Hoffman and Makler, (1929), reviewed eighty-nine cases and found that one-third had a family history and sixteen per cent were under one year of age. They concluded that the condition was 'both congenital and familial' They knew of no patient who had transmitted Gaucher disease to his children or any other individual. These findings were reconfirmed by Pick, (1933).

Anderson, (1933), reported on the possibility of Gaucher disease affecting individuals in different generations of the same family. In this family, Gaucher disease was diagnosed in four sisters and suspected as being present in their grandparents. These four girls had normal parents and Anderson, (1933), considered a possible genetic mechanism to have caused this familial aggregation. Bloem *et al*, (1936), reported on Gaucher disease patients in two families with a shared healthy grandfather. Groen, (1948), reviewed his series and found that twenty-three of the twenty-five kindreds showed only 'horizontal' spread of the disease in their pedigrees. No parents or grandparents were affected and his cases only involved brothers, sisters and cousins. Two of the families exhibited 'vertical' occurrence. He considered the condition to arise from a sporadic mutation, which was then transmitted as a simple dominant hereditary trait. He postulated that the condition worsened in severity with ensuing generations, manifesting earlier in life until eventually the mutation extinguished itself, by causing the early death of foetuses grossly affected by Gaucher disease. This concept of anticipation is now redundant.

Snyder, (1941), suggested the possibility of autosomal recessive inheritance and Stransky and Dauis-Lawas, (1949), discovered Gaucher cells in the bone marrow of asymptomatic parents of affected individuals. They considered this to be a heterozygous manifestation or proof of autosomal dominant inheritance with incomplete penetrance and variable expressivity.

Herndon and Bender, (1949), analysed the coefficient of inbreeding for infantile, neuropathic Gaucher disease in negro sibships. They concluded that this form of Gaucher disease was inherited as an autosomal recessive condition. This theory has since been substantiated on numerous occasions for non-neuropathic Gaucher disease by the statistical analysis of sibships and the biochemical determination of genotype status.

Similar analyses of the author's series have been undertaken to confirm the mode of inheritance. Beta-glucosidase assays (Chapter 21) on the kindreds consistently showed heterozygosity in both parents and all the children of affected patients. No instance of dominant inheritance was diagnosed biochemically.

CHAPTER 24

PEDIGREES

RESULTS

Four of the pedigrees, involving patients 21, 15, 16 and 17, 18, 4 are presented here, (Figures 25 to 28), because they contain aspects of special interest and the rest are tabulated in an abbreviated form, (Figure 29). The detailed pedigrees of the remainder of the kindreds have been included in the Appendix.

KEY TO PEDIGREES

- ○ normal female
- ● affected female
- □ normal male
- ■ affected male
- ⊘ deceased
- ◧* biochemically confirmed male heterozygote
- ◐* biochemically confirmed female heterozygote
- * genotype confirmed biochemically
- ◇ indeterminate number of male and female siblings

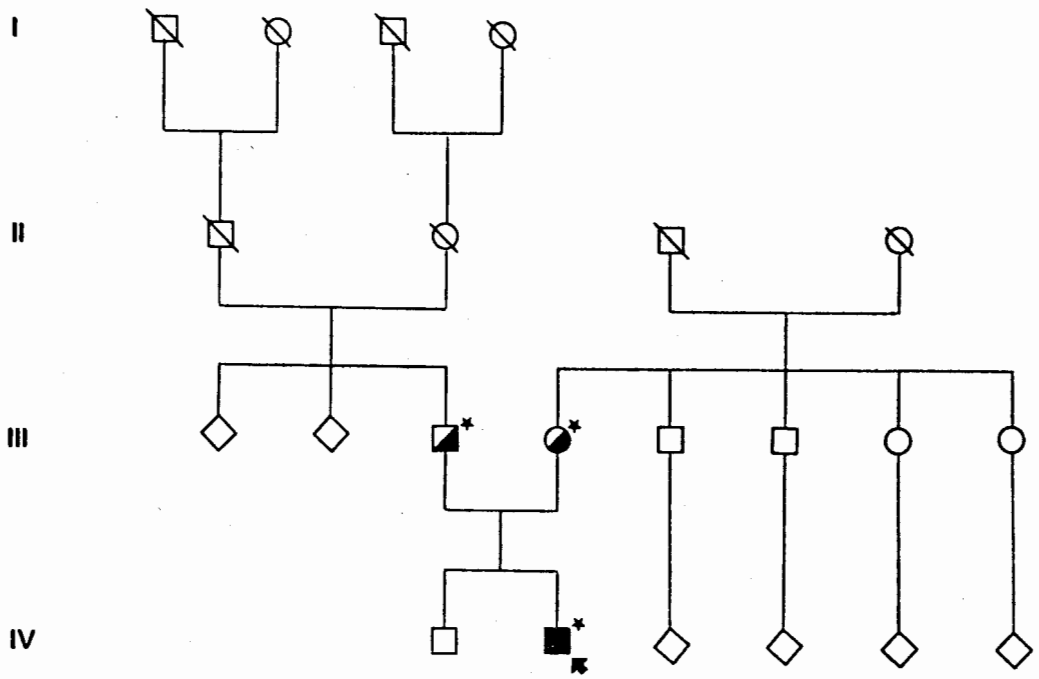


FIGURE 25: PEDIGREE OF PATIENT 21.

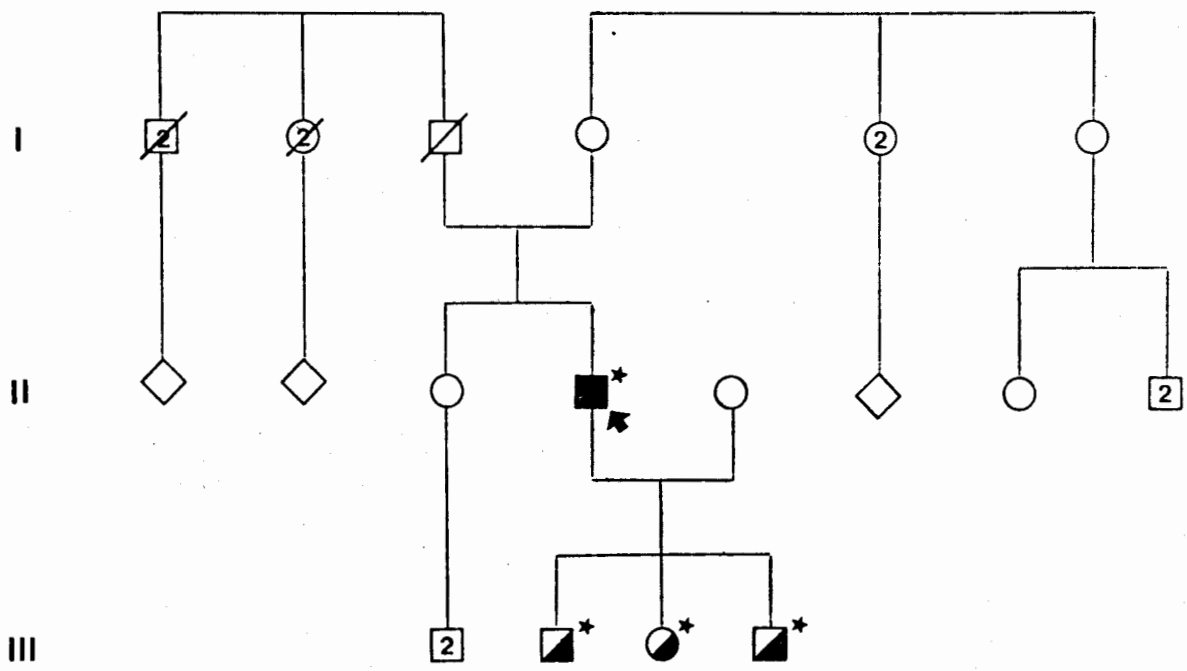


FIGURE 26: PEDIGREE OF PATIENT 15.

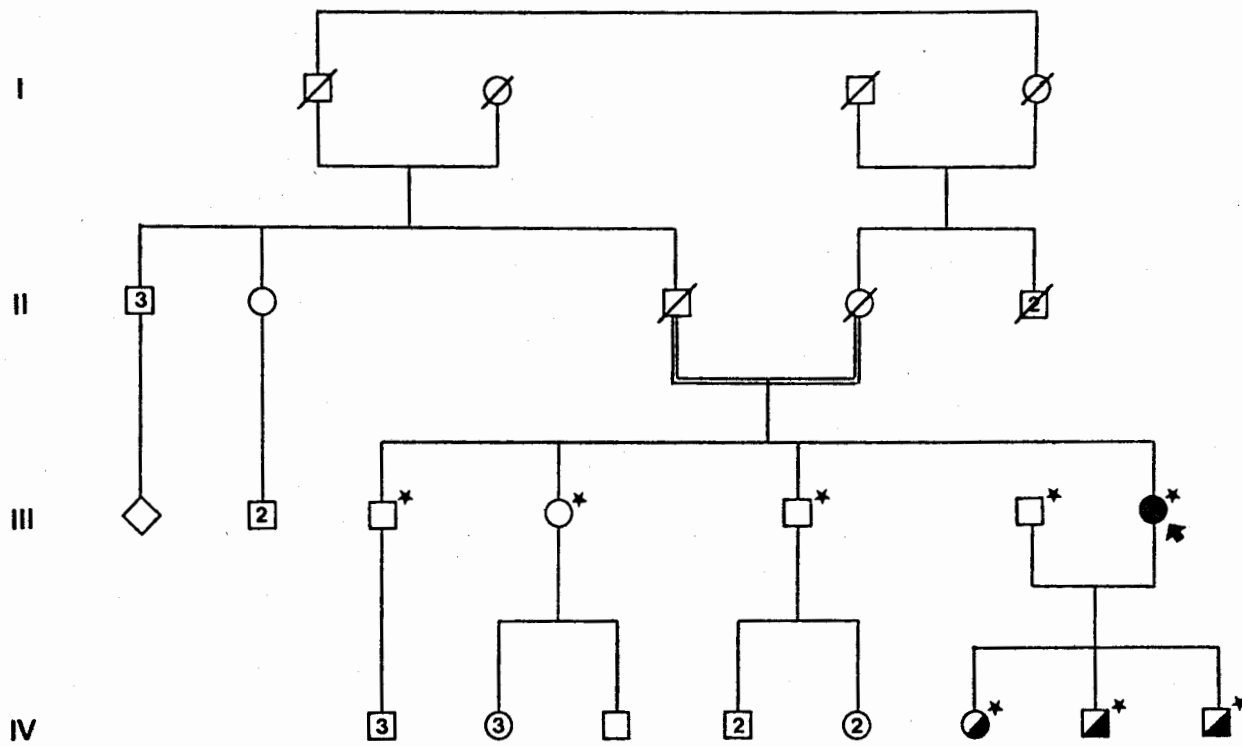


FIGURE 27: PEDIGREE OF PATIENT 16.

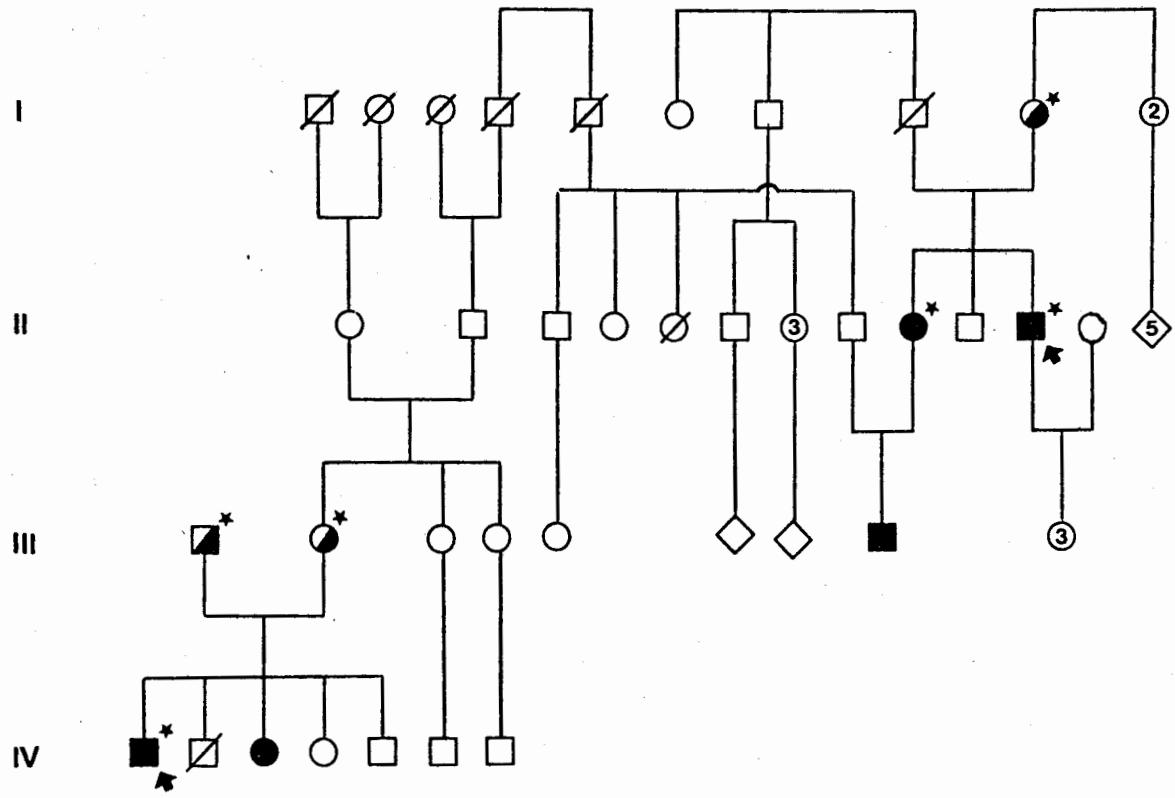


FIGURE 28: PEDIGREE OF PATIENTS 17, 18 and 4.

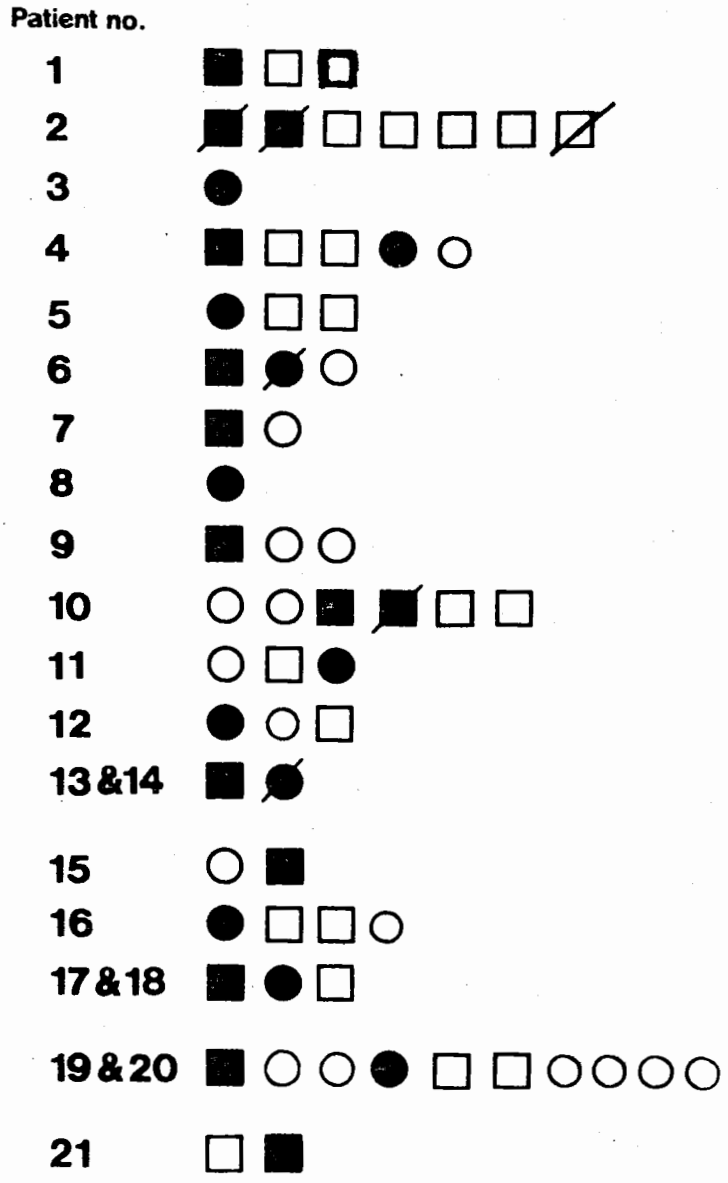


FIGURE 29: ABBREVIATED PEDIGREE DATA FROM EIGHTEEN AFFECTED KINDREDS.

ANALYSIS OF PEDIGREES

Data from 18 kindreds containing 21 patients, 4 known, affected siblings, and 38 healthy sibs have been tabulated. Segregation analyses have been performed, (Tables 19 and 20), by two methods, for the confirmation of an autosomal recessive mode of inheritance. The other eight affected patients are not included in this analysis as their full pedigrees were not available to the author.

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TABLE 19: GAUCHER DISEASE - SEGREGATION ANALYSIS BY THE SIMPLE BY THE SIMPLE SIB METHOD, FISHER (1934), ASSUMING SINGLE INCOMPLETE ASCERTAINMENT

KINDRED (No.)	OBSERVED		AFFECTED AFTER DELETING PROBAND
	NORMAL	AFFECTED	
3	0	1	0
7	1	1	0
19,20	8	2	1
16	3	1	0
5	2	1	0
2	5	2	1
6	1	2	1
1	2	1	0
13,14	0	2	1
15	1	1	0
11	2	1	0
21	1	1	0
10	4	2	1
8	0	1	0
9	2	1	0
4	3	2	1
12	2	1	0
17,18	1	2	1
TOTAL	38	25	7
EXPECTED	33.75		11.25

$\therefore \chi_1^2 = 2.1407$ (Not significant)

$\therefore$ Supports recessive hypothesis.

TABLE 20: GAUCHER DISEASE - SEGREGATION ANALYSIS BY HOGBEN (1946) METHOD ASSUMING COMPLETE ASCERTAINMENT

SIBSHIP SIZE	NO. OF SIBSHIPS	NUMBER AFFECTED		VARIANCE
		OBSERVED	EXPECTED	
1	2	2	2	0
2	4	5	4.572	0.490
3	7	9	9.079	1.841
4	1	1	1.463	0.420
5	1	2	1.639	0.502
6	1	2	1.825	0.776
7	1	2	2.020	0.970
10	1	2	2.649	1.591
TOTALS:	18	25	25.247	6.590

$\therefore$ Standard deviation = 2.567

$\therefore$ Supports recessive hypothesis -

DISCUSSION:

Detailed Pedigrees

In the detailed pedigrees only those individuals whose genotype status has been biochemically confirmed have been designated as heterozygotes. Figures 25 and 26 show two typical kindreds confirming the autosomal recessive nature of Gaucher disease. The parents of Patient 21 were clinically normal, but beta-glucosidase assay confirmed their carrier status. Similarly, the children of Patient 15 had biochemical evidence of heterozygosity, with no clinical stigmata of Gaucher disease.

Kindred 16 represents the only instance of consanguinity encountered in this survey. The parents of this affected individual were first cousins. The kindred in Figure 28 superifically appeared to show autosomal dominant inheritance of Gaucher disease. The family of Patients 17 and 18 revealed their ancestral link with another affected individual, Patient 4. The transmission of Gaucher disease from mother to child was most likely on the basis of her marrying a heterozygote, i.e. the phenomenon of quasidominant inheritance. Unfortunately, this was not biochemically confirmed as the suspected heterozygote was unavailable for testing.

Segregation Analyses

Both the analyses, (Tables 19 and 20), support the concept of autosomal recessive inheritance of Gaucher disease. This has also been confirmed by biochemical determination of genotype status in many of these kindreds. No instance of true dominant transmission was seen during the course of the investigation, and only one example of quasidominant inheritance was encountered, *vide supra.* Biochemical testing of all parents and children of affected individuals confirmed their obligate heterozygosity.

Dominant inheritance has been reported on numerous occasions, (Morgans, 1974; Groen and Garrer, 1948; Farber, 1952; Hsia *et al*, 1959; Sood and Fielding, 1971). In some instances, problems have arisen as a result of the clinical criteria used to establish a diagnosis in relations of the affected proband. Asymptomatic, subclinical presumed carriers of the Gaucher gene have been found to have Gaucher cells in their bone marrow, (Gerken *et al*, 1964; Wiedemann and Gerken, 1964), and this heterozygous manifestation has led to an incorrect diagnosis of Gaucher disease, and the postulation of dominant modes of inheritance.

The other source of discrepancy is most probably the occurrence of quasidominance in certain high-risk population groups. With the high gene frequency occurring in Ashkenazi-Jewish populations, the marriage of homozygous affected individuals to heterozygous carriers is not unlikely. Indeed, this situation occurred in one large kindred in the author's series, (Figure 28). The answer to this problem lies in biochemical determination of specific genotypes. Unfortunately, none of the so-called instances of dominant inheritance reported in the literature have been confirmed by biochemical analysis.

Finally, the fact that the other biochemical genetic defects are all transmitted as autosomal recessive conditions also reinforces this conclusion.

CHAPTER 25

POPULATION GENETICS

INTRODUCTION

Although the condition reaches maximal frequency in Ashkenazi-Jews, there are numerous reports in the literature which indicate widespread distribution of the abnormal gene. Matoth and Fried, (1965), first reported the occurrence of Gaucher disease in a non-Ashkenazi Jewish individual and there are many other reports of affected persons with no apparent Jewish ancestry. These include affected negroes, Choisser and Montgomery, 1949; Herndon and Bender, 1950; Reich *et al*, 1951; Stansbury and Schwartz, 1952; Orientals - Chung *et al*, 1948; Englishman - Hancock, 1971; Italians - Medoff and Bayrd, 1954; Amstutz and Carey, 1966; Indian - Srinivasa *et al*, 1969; Americans, Peruvian, Greek - Medoff and Bayrd, 1954; New Zealander - Berry, 1965; New Zealand Maori - Woodfield and Rouse, 1966.

Although this thesis is primarily concerned with the non-neuropathic form of Gaucher disease in Ashkenazi-Jews, it is worthy of consideration that other patients ascertained in South Africa were of varied ethnic groups:-

33	Ashkenazi-Jews	(62%)
10	Afrikaners	(20%)
4	Mixed Ancestry	(8%)
2	Sephardic Jews	(3%)
2	African Negroes	(3%)
2	English	(3%)

None of the non-Jewish kindreds claimed any Jewish ancestry in preceding generations, nor originated from Eastern Europe. The question of heterogeneity leading to a common abnormality of beta-glucosidase deficiency was discussed in Chapter 4.

RESULTS

A total of thirty-three Ashkenazi-Jewish patients were ascertained during the course of the survey. Five of these affected individuals have demised, three over the last five years. Therefore, gene frequency analyses have been performed using two sets of figures, Page 176. In the first calculation it has been accepted that there are presently a minimum of 28 affected individuals living in South Africa. In the second instance, gene frequencies have been calculated on the total number of affected individuals diagnosed during the last five years, i.e. thirty-one patients.

The last official census in this country was performed in 1970. In this census, 117 990 Jewish persons were known to be living in the Republic. During the nine year period 1970-1979, there has been only minor flux in this population size. It is therefore estimated that the present South African Jewish population numbers approximately 120 000 people.

GAUCHER DISEASE - CALCULATION OF MINIMUM GENE FREQUENCY FOR ASHKENAZI-JEWISH POPULATION OF SOUTH AFRICA

1. Total No. of affected individuals = 28
   Total Jewish population = 120 000

   $\therefore$ Prevalence = $^{28}/_{120\ 000}$

   $\therefore$ Gene Frequency = $\sqrt{^{28}/_{120\ 000}}$

   = 0.015275

   $\therefore$ Carrier Frequency = 0.030551

   $\therefore$ No. of Carriers = 3,666

   Or Carrier Frequency = $^{1}/_{32.7}$ of population.

2. Total No. of affected individuals = 31

   $\therefore$ Prevalence = $^{31}/_{120\ 000}$

   $\therefore$ Gene Frequency = $\sqrt{^{31}/_{120\ 000}}$

   = 0.0161

   $\therefore$ Carrier Frequency = 0.0322

   $\therefore$ No. of Carriers = 3864

   Or Carrier Frequency = $^{1}/_{31.05}$ of population.

DISCUSSION

There can be no doubt that Gaucher disease reaches maximal prevalence in South Africa in individuals of Ashkenazi-Jewish stock, Page 176. The carrier rate in this ethnic group of about 1 in 30 makes this genetic condition a significant disease in this well-defined population. This high local prevalence is explicable by the genetic mechanism of founder effect. The immigrant Lithuanian people brought the gene with them by virtue of its prevalence in their respective Lithuanian communities. They have not inhabited South Africa long enough for any other genetic process or biological pressure to have been operative in this regard.

It is of more particular interest to consider the reasons for the high frequency in their original Lithuanian communities (Chapter 27). Before these theories are discussed, it is necessary to outline the origins of the South African Ashkenazim with special reference to the progenitors in this survey. Historical details of the Ashkenazim are reviewed in Chapters I and 2.

CHAPTER 26

ORIGINS OF PROGENITORS OF GAUCHER DISEASE PATIENTS

RESULTS

The ancestral origins of all the patients ascertained in this survey were investigated and are listed in Table 21. These results were plotted on a map of the Greater Lithuanian region to show their geographical distribution, (Figure 30). The map showing the pattern of immigration of the respondents has then been superimposed on that produced by both Meals, (1971), and Goodman, (1974), for the other genetic diseases of the Ashkenazim, (Figure 31). The exact spelling of Lithuanian towns varies according to different dialects. Therefore the names of towns used in this chapter have been chosen as an acceptable compromise.

TABLE 21: ORIGINS OF ANCESTORS OF PATIENTS

PATIENT	MATERNAL		PATERNAL	
	Country	Town	Country	Town
1	Russia	-	Poland	-
2	Lithuania	-	Russia	Moscow
3	Lithuania	Linkuva	Lithuania	Pampenai, Ponevez
4	Lithunia	Shavel	Lithuania	Vilna, Shavel
5	Lithuania	-	Lithuania	-
6	Lithuania	Sedowa	Lithuania	Sialenai
7	Poland	Zhitomlya	Poland	Kalish
8	Lithuania	Seduva	Poland	Warsaw
9	Holland	-	Lithuania	Zagare, Ponevez
10	Lithuania	Seduva	Poland	Warsaw
11	Poland	Lodz	Lithuania	-
12	Germany	Frankfurt	Germany	Frankfurt
13	Poland	Kalish	Czechoslovakia	Saaz-Karlspad
14	Poland	Kalish	Czechoslovakia	Saaz-Karlspad
15	Lithuania	Shavel	Russia	-
16	Poland	Pinsk	Poland	Cheln
17	Poland	Wloktawek	Lithuania	Krakes
18	Poland	Wloktawek	Lithuania	Krakes
19	Lithuania	Shavel	Lithuania	Shavel
20	*Lithuania*	*Shavel*	*Lithuania*	*Shavel*
21	Poland	Vilna	Latvia	Riga, Karsava, Ludza

FIGURE 30: TOWNS OF ORIGIN OF ANCESTORS OF SOUTH AFRICAN GAUCHER DISEASE PATIENTS.

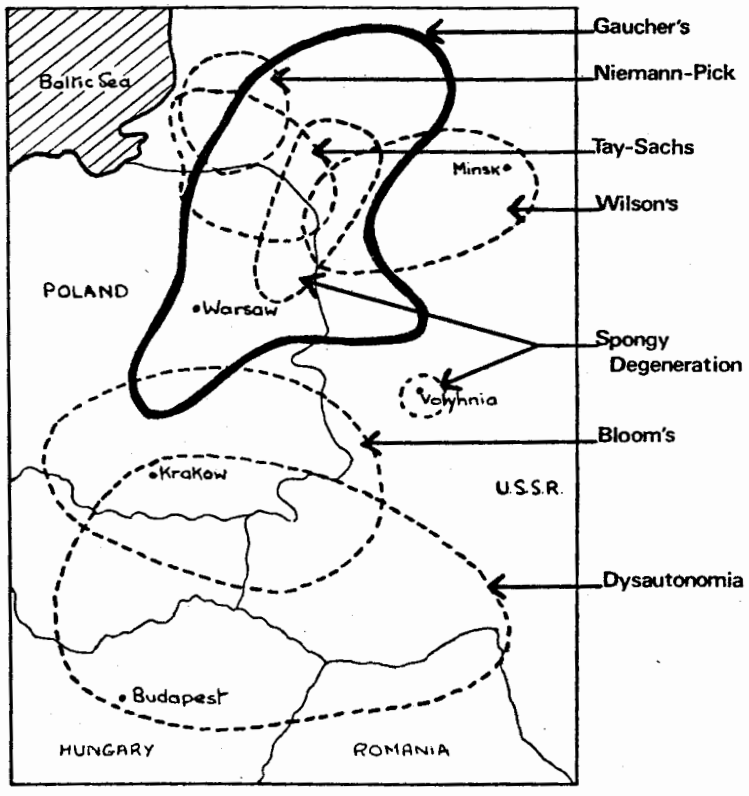

FIGURE 31: THE INITIAL EUROPEAN LOCALISATION OF GAUCHER DISEASE AND OTHER AUTOSOMAL RECESSIVE DISORDERS OF THE ASHKENAZI-JEWS (after MEALS, 1971).

DISCUSSION

These results show a definite aggregation of geographical origins of ancestors of patients in this series. The majority originally immigrated to South Africa from a localised area of Eastern Europe, incorporating Greater Lithuania and parts of the present-day Poland, White Russia and Latvia.

One individual, (Patient 12), was entirely of German Stock with no familial contact with the described area. The paternal family of Patients 13 and 14 had previously lived in Czechoslovakia. Patient 9's maternal kindred were immigrants from Holland. This family had no knowledge of their previous ancestry before settling in Holland a number of generations ago. Some families knew of their origins from the specific Lithuanian region but were unaware of the precise locality. Most of the Eastern European towns had alternative names depending on the language and dialect used for this designation. For example, a town had the Lithuanian name of Seduva, and it was called Shadov in Russian and Shadove in Yiddish. Problems therefore arose with regard to the exact spelling of these towns and their positions on the map.

This Eastern European localisation of places of origin of the majority of South African Gaucher disease patient kindreds corresponds with that found for other predominantly Ashkenazi genetic diseases, (Meals, 1971). The absolute relevance of this can only be gauged in comparison to exact places of origin of 'non-Gaucher disease' Ashkenazi-Jewish families in South Africa. Accurate data of this kind is not available and an extensive search covering immigration documents with The Jewish Board of Deputies, Jewish libraries and The South African Archives, only revealed one significant set of figures.

This was a list of Eastern European towns of origin of 1 237 Jewish residents registered with the Cape authorities in the years 1904 to 1906, cited by L. Hotz, (1963), Figure 32. Whether this microcosm of the South African Ashkenazi community is representative of Jewish immigration as a whole is not known. It is however thought by Hotz, (1963), to be fairly typical of Jewish immigration during the latter period of the 19th Century and this group represented approximately fourteen per cent of the Jewish adult male population of the Cape. A wealth of anecdotal evidence also exists to verify this theory, (Gershater, 1955). The register showed that their places of origin were spread over nearly three hundred towns in Eastern and Central Europe, the most important of which are shown in Figure 32. Eighty per cent of the respondents originated from Lithuania, Poland, Latvia and Estonia.

Towns from which an appreciable number of immigrants originated (number of immigrants in parenthesis) were Kovno (228), Vilna (51), Ponevez (36), Shavel (35), Plungian (26), Wilkomir (20) in Lithuania; Minsk (38), Dwinsk (28) in Russia; Warsaw (27), Grodno (28) in Poland; Riga (18) in Latvia. This general pattern of immigration is compatible with that found for the Gaucher disease kindreds as shown by comparing Figure 32 with Figures 30, 31. The fact that none of the Gaucher disease progenitors originated from Kovno is of interest, as nearly twenty per cent of the group of Cape Ashkenazim, discussed above, immigrated from this town to South Africa.

FIGURE 32: EASTERN EUROPEAN TOWNS OF ORIGIN OF ASHKENAZI-JEWISH COMMUNITY OF THE CAPE, 1904 TO 1906.

CHAPTER 27

MECHANISM OF FREQUENCY AND DISTRIBUTION OF GAUCHER GENE

Multiple theories have been put forward in attempts to explain the differential frequency of genetic conditions in various population groups. However, none of these entirely satisfies the conditions necessary for the production of the high frequency of Gaucher disease in the Ashkenazi-Jews.

It is assumed in this study that the ascertainment process covered all sectors of the population. Although the in-depth analysis was only performed on the Ashkenazi patients, all affected South African individuals with Gaucher disease were sought. It is possible that the better medical care available to the whites in this country would tend to produce an ascertainment bias in their favour. However, the magnitude of the differential frequencies is so gross as to negate this as a significant factor. Ascertainment bias would also not satisfactorily explain the low prevalence found in the non-Jewish white sectors of the community, in whom there are more or less equal diagnostic possibilities with regard to Gaucher disease.

A most attractive exposition on the 'paradoxical frequencies of recessive disorders in Ashkenazi-Jews' has been presented by Meals, (1971). In summary, he reiterates the conclusion that certain autosomal recessive disorders occur with increased frequency in Ashkenazi-Jews and states that "drift (coupled with founder effect) and selection are favoured explanations".

When genetic results in this series are analysed they show a trend concordant with the above views. Evidence of an Eastern European geographical aggregation of birth-places of the ancestors of Gaucher disease patients in South Africa further emphasises the roles of founder effect and random genetic drift in producing this high frequency.

No in-depth search for selective factors was performed on the potential respondents in this series. A survey of this nature suffers from the shortcomings of a paucity of data available from the indigenous pre-immigration regions in Lithuania.

Meals', (1971), theory concerning superior intelligence of heterozygous individuals was borne out by an impression gained from this small series. Although quantitative analysis is not currently feasible, kindreds of affected individuals did possess a large number of persons who achieved great success in scholarly fields. No attempt has been made to accurately assess this phenomenon because of the great difficulty in standardising intelligence, and the lack of comparable data in the non-affected kindreds. The Ashkenazi community in South Africa is on the whole steeped in the tradition of learning and educational advancement.

Livingstone's, (1969), computer simulations with respect to founder effect being responsible for present-day gene frequencies in the Ashkenazi-Jewish population, are also consistent with the findings in this series.

CHAPTER 28

POPULATION SCREENING

BIOCHEMISTRY

The results of the biochemical investigation in this study raise the possibility of population screening for Gaucher disease in the Ashkenazi-Jewish community of South Africa. However, the problems involved in this operation make a full-scale venture, comparable to that which Kaback and O'Brien, (1973), undertook for Tay-Sachs's disease in the Washington-Baltimore area, not feasible at present. When analysing the possibilities for undertaking screening for Gaucher disease according to their criteria, the following conclusions may be drawn:

i The disease must be present in a very high frequency in a defined population group. This criterion is obviously fulfilled and the magnitude of the local frequency was discussed in Chapter 25.

ii Facilities for pre-natal diagnosis must be available. One successful pre-natal diagnosis was performed during this survey and it is eminently possible to test further pregnancies with present laboratory expertise and the established procedure.

iii Carriers must be ascertained by a simple, accurate and inexpensive method. In this regard, problems arise as already discussed in Section VI. A degree of accuracy is possible, but the method of attainment is very laborious, difficult, expensive and totally unsuitable for automation at present.

A technician is totally occupied for a working day, during the course of which she can only process a maximum of six blood specimens. Other screening procedures which have been tried have not proved successful. The serum level of the enzyme is very low and an automated serum test has proved unreliable. The other problem is that the serum enzyme might not necessarily show the same deficit as the tissue enzyme. To determine urine levels of beta-glucosidase requires a difficult chromatographic technique; also the reliability of this procedure remains unproven. (Desnick *et al*, 1971).

Acid phosphatase levels are normal in carriers and have therefore no screening potential. Beta-glucosidase assays on skin fibroblasts have proved accurate for confirmation of genotypes but this method is difficult and requires a laborious procedure which is most unsuitable for mass screening. (Beutler *et al*, 1970, 1971). It was tested during the course of this survey, but only on a small scale, to develop laboratory technique and confidence and for pre-natal screening.

Finally, Kozower *et al*, (1974), described a patient whose lymphocytes hydrolysed the artificial substrate in the normal fashion, but showed a deficiency of beta-glucosidase when incubated with a radioactive labelled natural substrate. They suggested that for this reason the artificial substrate methyl-umbelliferryl beta-D glucopyranoside might have a limited use in screening programmes. Unfortunately the natural substrate is very difficult to manufacture and is, therefore, not available for general experimental purposes.

PSYCHO-SOCIAL ASPECTS

It is also necessary to consider the psycho-social problems involved in such a screening programme. Gaucher disease is not a consistent condition with as predictable a course as, for example, Tay-Sachs disease. In Gaucher disease there is a great variability in clinical manifestations, age of onset, course and prognosis. This leads in most cases to a wide range of opinion of individuals regarding termination of homozygous affected foetuses. The controversy usually occurs in a kindred with a mildly affected relative in whom physical function is only minimally impaired. However, the majority of patients suffer chronic ill health, with episodic pain and physical disability. Their long-standing debility emphasises the necessity to institute appropriate preventative measures.

The other problem in random screening, which will assume great importance when effective therapy is instituted, is the detection of preclinical asymptomatic individuals suffering from Gaucher disease. With no primary therapy available, it is questionable whether it is fair to expose an individual and his kindred to years of tension and expectation. In this series, it has already occurred that an asymptomatic sibling was diagnosed as having Gaucher disease on routine kindred screening following discovery of the condition in her brother. After the diagnosis was confirmed, she began to experience multiple, diffuse, subjective symptoms in relation to her condition.

CONCLUSION

In summary, it is envisaged that through referral of all affected individuals to one investigation centre, screening could be undertaken on a small scale amongst relatives of affected individuals. This screening on a relatively small, high-risk population sub-group, would lead to more effective counselling, some measure of prevention and control, and possible detection of preclinical cases in the future when enzyme therapy becomes feasible. In theory, prevention of later clinical manifestations could be achieved in this manner. This theoretical, future alternative is more desirable than the present method of choice, which is termination of pregnancies involving homozygous Gaucher disease foetuses.

S E C T I O N VIII

NON-ASHKENAZI SOUTH AFRICAN PATIENTS

CHAPTER 29

NON-ASHKENAZI SOUTH AFRICAN CASES

RESULTS

Twenty non-Ashkenazi patients were ascertained during the course of the survey. The features in these individuals have been analysed for comparison and contrast with certain factors determined for the Ashkenazi individuals.

The ethnic breakdown of these patients is shown below:

10	Afrikaners
2	Sephardic Jews
2	English
2	African Negroes
4	Mixed Ancestry

The ten Afrikaners represented a fairly substantial number of affected individuals in a well-defined population group. Although of far rarer occurrence than found in the Ashkenazi-Jews, the condition does appear to be more frequent in the Afrikaners than in other non-Jewish universal population groups. The estimated minimal heterozygote rate in this group is 1 in every 227 of the population, Page 193.

The two Sephardic sisters were of unique interest. The condition has only rarely, previously, been described in Jews of Sephardic origin, (Fried, 1973). The parents of these girls originated from Bulgaria.

The two affected individuals of English stock are fairly representative of the normal great rarity of the condition as described in other non-Jewish groups.

With regard to the other population groups, the disease appears to be extremely rare in African Negroes. Two patients were ascertained in this group of an estimated population of over sixteen million. Gene frequencies have not been estimated in the English and African Negro populations as the small number of affected individuals would result in spurious calculations.

The 'Coloured' population of South Africa is a heterogeneous group derived from the intermarriage of migrant whites and malays and indigenous Khoisans. Further racial admixture has occurred with the white population and more recently individuals of African Negro stock. Four affected individuals of mixed ancestry were ascertained and represent a minimal heterozygote rate of 1 per 357 of population, Page 194.

GAUCHER DISEASE - CALCULATION OF GENE FREQUENCY IN AFRIKANER POPULATION

Total number of Afrikaners affected = 10

Estimated total South African Afrikaner population = 2 million

$\therefore$ Prevalence = $^{10}/_{2\ 000\ 000}$

$\therefore$ Gene Frequency = $\sqrt{^{10}/_{2\ 000\ 000}}$

= 0.0022

$\therefore$ Carrier Frequency (Heterozygote Rate) = 0.0044

$\therefore$ No. of Carriers = 8800

$\therefore$ Carrier Frequency = $^{1}/_{227}$ population

GAUCHER DISEASE - CALCULATION OF GENE FREQUENCY IN SOUTH AFRICAN POPULATION OF MIXED ANCESTRY

Total number of Mixed Ancestry affected = 4

Estimated total South African Mixed Ancestry Population = 2 000 000

∴ Prevalence = $^{4}/_{2\ 000\ 000}$

∴ Gene Frequency = $\sqrt{^{4}/_{2\ 000\ 000}}$

= 0.0014

∴ Carrier Frequency = 0.0028

∴ No. of Carriers = 5 600

∴ Carrier Frequency = $^{1}/_{357}$ of populatior

CASE REPORT

An example of a severely affected Afrikaner individual is Patient W.M.

W.M. was a severely affected Afrikaner girl who died at the age of sixteen years.

She was initially diagnosed as having Gaucher disease when, at the age of 2 years, her asymptomatic, grossly enlarged spleen was palpated. The diagnosis was confirmed on histological examination of the bone marrow. At the age of six years, she underwent a splenectomy in an attempt to correct her worsening hypersplenism and bleeding problems and in the same year she fractured her right wrist following a fall. She also fractured her right humerus on two occasions from minor trauma four and six years later.

She had a limp from the age of ten years and radiographic studies revealed bilateral femoral head aseptic necrosis and collapse. She had also experienced episodes of osteomyelitis in both humeri. She described a tendency to easy tanning and a permanent blue hue of lips and digits.

Her family history was non-contributory except that the patient was adopted at an early age from an Afrikaner kindred. At the age of sixteen years she had not yet begun to menstruate.

Examination revealed a small girl, 153cms in height, and 33kgs in weight. She exhibited no secondary sexual characteristics. She was centrally and peripherally cyanosed and had gross digital clubbing. There were multiple

telangiectasia over the arms and chest, non-specific red macules over her back and multiple, diffuse ecchymoses.

Examination of the respiratory system revealed no clinical abnormality to explain the cyanosis. The circulation was hyperdynamic, but otherwise normal.

Her abdomen was filled by a grossly enlarged liver extending down to the right iliac fossa. The surface of the liver was smooth and non-tender.

The right humerus and femur were deformed with marked anterior bowing and movements of the right shoulder were limited because of the humeral deformity. She had a mild gibbus at the level of the tenth thoracic vertebra.

Special investigations

Haematological studies revealed a Hb of 12.7gms %, a platelet count of 63 x $10^9/\ell$. The routine 12/60 biochemical analysis was normal.

Radiographic studies showed the long bone deformity caused by the pathological fractures, the mild gibbus at the tenth thoracic vertebra and collapse of the femoral heads.

Respiratory function tests confirmed a severe hypoxia by blood gas analysis (po_2= 6.6KPa pCO_2 = 4.2KPa). The lung volume wa relatively normal. Diffusing capacity for carbon monoxide was reduced to 6 (normal = about 20). Despite the relatively normal lung volume she had severe lung disease with the accent being on the problem of the diffusion, accounting for the gross hypoxia.

She was admitted to Groote Schuur Hospital at the age of sixteen years with a terminal attack of haematemesis and meleana and she died despite attempted resuscitation and transfusion.

Autopsy showed massive Gaucher cell infiltration of the liver, fémora which were flask-shaped, lungs, lymphnodes diffusely, (i.e. coeliac axis, mesenteric, para-aortic, lingual tonsils), and an infantile uterus and genital organs. A massive intragastric haemorrhage from associated oesophageal varices appeared to have resulted in her demise.

Conclusion

This severely affected girl had widespread, massive systemic infiltration with Gaucher cells. The unusual gross respiratory infiltrations caused a diffusion defect with consequent marked hypoxia. The oesophageal varices on the basis of Gaucher cell infiltration of the liver are a rare feature and were not found in the Ashkenazi patients. Multiple bony problems were experienced with pathological fractures sustained on three occasions. The marked bony infiltration with Gaucher cells probably contributed to the post-splenectomy thrombocytopaenia.

DISCUSSION

Although this is a small series of affected individuals with Gaucher disease, certain impressions were gained of the heterogeneity of this condition presented biochemically in every instance as a deficiency of the beta-glucosidase enzyme. In this context, it must be mentioned that none of the patients was aware of any Jewish ancestry nor any consanguinity in their kindreds.

It is well documented that small numbers of Ashkenazi-Jews were amongst the early permanent settlers in the Cape in the 17th and 18th centuries, (Jenkins *et al*, 1977). They were forbidden to practise their Judaism by the Dutch East Indies Company policy. It is highly likely that in this manner certain autosomal recessive, peculiarly Ashkenazi genes were introduced into the Afrikaner population. However, there has been insufficient time since the major waves of Jewish immigration in the past one hundred years for gene flow to account for the present relatively high gene frequency in the Afrikaner population.

Another explanation arises via the theory of genetic heterogeneity for this condition. The great clinical variability found in these diverse population groups would certainly suggest the presence of multiple mutant genes being able to produce a similar clinical picture. It is highly possible that the condition in the Afrikaner differs from that of the Ashkenazi by virtue of an alternate basic point mutation which must have arisen independently in their Dutch progenitors. In either event, the operation of the 'founder effect' in the small but rapidly expanding white South African population of those times could account for the current high gene frequency in this group. The answer to this problem might well lie in the differentiation of beta-glucosidase iso-enzymes through cellular cross-over culture or biochemical techniques.

Clinically, Gaucher disease is a precocious and more severe condition when encountered in an individual of Afrikaner stock. Two of the ten patients demised during the course of the survey, one aged thirty-seven years and the other only sixteen years old. The other surviving patients are all severely affected. Apart from the differences in severity and variability in course and prognosis, the clinical condition encountered in these patients was the same as that described for the Ashkenazi patients in this series.

S E C T I O N IX

PRACTICAL IMPLICATIONS

CHAPTER 30

PRACTICAL IMPLICATIONS

CONCLUSION

This work presented an opportunity for the study of the clinical, genetic, radiographic and biochemical characteristics of a substantial number of patients with Gaucher disease. The majority of these patients were Ashkenazi-Jews with ancestral origins in Eastern Europe. The autosomal recessive nature of the condition was confirmed and this presents a theoretical opportunity for carrier screening.

The importance of considering the diagnosis of Gaucher disease when faced with a problem of splenomegaly in an Ashkenazi-Jew is emphasised. Also the frequency of severe bone and joint complications merits the inclusion of Gaucher disease in the differential diagnosis of orthopaedic and arthritic problems. In the majority of patients, the diagnosis was not initially made and often resulted in protracted unnecessary management for other conditions.

Practitioners need also to be aware of the relative safety of pregnancy in a patient with Gaucher disease. With appropriate assessments during pregnancy, the potential haematological complications were easily managed with successful outcome for mother and foetus.

The index of all affected patients in this country, which the author has established, will allow these individuals to efficiently receive therapy when this becomes feasible. Furthermore, biochemical screening would detect asymptomatic, affected individuals at an early age where therapy would be of most benefit.

Therapy

Exciting advances have occurred in the modes of therapy of Gaucher disease. Splenectomy has proved to be a safe procedure with excellent, sustained post-operative haematological response. The subsequent accumulation of cerebrosides in the residual reticulo-endothelial system results in no detectable organ dysfunction and no deterioration in orthopaedic complications.

The early diagnosis of the orthopaedic manifestations of Gaucher disease is important because of the availability of specific therapeutic procedures and for the avoidance of unnecessary, potentially harmful, invasive management on the basis of an incorrect diagnosis. Prosthetic replacement of affected hip joints has produced gratifying results in this condition. The patients tolerated the operation well and have excellent, long-term post-operative mobility.

All these therapeutic modalities are symptomatic and aimed at the secondary effects of the abnormal lipid accumulation on the affected organ and it is clear that the future lies in directing therapy at the underlying defect.

Enzyme replacement.

Therapy for the genetically determined enzymopathies is currently undergoing vast research. The beta-glucosidase enzyme has been isolated from human placentae, (Pentchev *et al*, 1973), and infused into Gaucher patients as a therapeutic trial, (Brady *et al*, 1974). Preliminary results are most encouraging and show the potential for reversing the quantity of abnormal lipid accumulation to a measurable extent. With the future availability of this specific therapy, awareness of this condition is even more necessary to identify affected individuals at an early age before the development of the destructive secondary effects of Gaucher disease.

The early diagnosis and therapeutic intervention should theoretically produce a sufficiently normalised metabolic state *in vivo* to prevent the future accumulation of abnormal metabolites. Further administration would then be necessary to maintain this metabolic correction as, for example, with insulin therapy in diabetics. The potential, therefore, exists to effectively treat Gaucher disease patients as a feasible alternative to large-scale carrier screening in an attempt to prevent the birth of affected individuals.

Biochemistry

The beta-glucosidase enzyme assay was a hundred per cent accurate for confirmation of homozygous Gaucher disease status. In addition, the biochemical assay detected carriers with an intermediate level of beta-glucosidase enzyme but was unfortunately not entirely accurate in distinguishing homozygous normals from heterozygous carriers. The problem appears to lie in the method of biochemical analysis and experimentation is therefore continuing on assaying the enzyme level in a protein concentration of lysed cells rather than relating this to an intact cell count. Preliminary results show greater accuracy with the latter method.

Although the present biochemical method is laborious and not amenable to mass screening, it allows limited screening of a well-defined high-Gaucher-disease-prevalent population group. This situation clearly exists in the Ashkenazi community in South Africa and through referral of all presently affected individuals to one centre a more specific sub-group consisting of first and second degree relatives of affected individuals could be defined.

Amniocentesis and enzyme assay on shed foetal cells has resulted in the possibility for diagnosing Gaucher disease *in utero*, early in pregnancy. Termination of affected foetuses remains ethically and morally a controversial method of controlling the birth of affected cases and preventative measures via carrier screening offer an acceptable alternative.

Historical aspects

The exact historical background and definitive genetic origins of the present-day Jewish people remains a controversial and scientifically puzzling subject. The occurrence of high-prevalence, group-specific genetic diseases in the various Jewish ethnic groups is of great interest. Superficially, it would appear possible to use these genetic markers to further delineate the major Jewish sub-divisions. Furthermore, through this mechanism their history could be mapped out by comparative studies on the indigent populations encountered during the course of the diaspora. The identification of a geographical aggregation of the origins of the ancestors of the South African Gaucher disease patients is therefore important. Unfortunately, current political considerations prevent further studies on the non-Jewish inhabitants of this particular region in Eastern Europe.

Afrikaner population

The relatively high frequency of the Gaucher gene in the Afrikaner population was of interest. Here the disease appeared to be more aggressive in nature, with patients being severely affected at a younger age. Further biochemical research is necessary to delineate possible differences in the enzyme deficiency which results in this spectrum of clinical manifestations.

Classification

The present clinical classification into three sub-types needs clarification on the basis of this clinical variability and overlap, *vide supra*. The young, severely affected non-Ashkenazi patients fall into a fourth sub-type which shows features of both the infantile neuropathic and adult, chronic non-neuropathic varieties. This would be preferable to them being included at the severe end of the spectrum of the latter, non-neuropathic type.

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SECTION XI

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APPENDIX

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CASE REPORTS

PEDIGREES

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CASE SUMMARIES

INTRODUCTION

The case histories of the other eighteen Ashkenazi-Jewish, affected individuals have been summarised in this section. Clinical and laboratory findings which were shared by the majority of these patients have already been mentioned in Chapter 9, and are, therefore, not described with each case summary.

The majority of the patients have their ancestral origins in Eastern Europe and only the exceptional finding of progenitor origins outside this area will be mentioned.

As the Gaucher disease did not affect the patient's growth, (Chapter 13), respective heights and weights have not been detailed.

The majority of the patients had pingueculae and diffuse dermal hyperpigmentation of varying degree, and dermal and ocular signs have, therefore, only been mentioned when they differed from the classical findings described in Chapters 14 and 15.

The results of beta-glucosidase assays performed on serum from the patients and their relatives are not shown in this section, but are discussed in Section VI.

Results obtained from the radiographic, haematological and biochemical investigations have also been omitted. These summaries, therefore, describe the spectrum of the course and clinical manifestations in each individual patient. The repetitive clinical features and results of special investigations have not been included here, but are preferentially discussed in other relevant chapters.

CASE 4

History

This patient is an 18 year old unmarried, male student. He was found to have an enlarged spleen at the age of 11 years but no investigations were performed at that stage and the condition remained undiagnosed. He remained well until the age of fifteen years, when he had a severe pain in the left hypochondrium which was especially aggravated by exercise. Simultaneously, he began to experience malaise and tired easily. His exercise tolerance had also markedly decreased over the preceding few years. His only other complaints were of multiple episodes of epistaxis and vague abdominal pains associated with recurrent attacks of diarrhoea of unknown cause.

The diagnosis of Gaucher disease was eventually reached when the patient was 17 years of age, following histological examination of the bone marrow and the demonstration of a raised serum acid phosphatase level.

His younger sister has splenomegaly and it is likely that she is also suffering from the condition, although she has not yet been fully investigated.

This youth and two other patients (Cases 17 and 18) in this study were found to share a common great-great-grandparent. No other members of the immediate family had Gaucher disease. A maternal aunt, maternal grandfather, two maternal uncles and a maternal grandmother are all diabetics. His father and a maternal aunt suffer from cholelithiasis.

Examination

Examination revealed a fit-looking youth. He had multiple telangiectasia over the anterior region of the neck, and the only other clinical feature of note was a 4cm firm, non-tender splenomegaly.

Comment

This youth, aged 18 years, presented with predominantly haematological complications. He is mildly affected at present, but the progressively enlarging spleen is an adverse prognostic sign. The associated family history of diabetes and cholelithiasis is of interest. (Chapter 19).

CASE 5

History

This eighteen year old scholar initially presented with asymptomatic splenomegaly at the age of four years and the diagnosis was immediately confirmed as Gaucher disease on histological examination of the bone marrow and liver. She remained well until aged ten years, when nodules were palpated on the spleen and a splenectomy was performed. In the same year, the patient suffered an attack of severe pain in the right femur and knee joint. She was pyrexial and the knee was warm, red and swollen. This attack of Gaucher arthritis was treated for two months with bed rest, traction, analgesia and antibiotics. No surgical procedures were undertaken during the course of this illness, the arthritic symptoms subsided and the patient resumed full, normal activity.

At the age of twelve years, she experienced an acute arthritic attack in the right hip joint. The symptoms remitted after two weeks of traction, but residual damage remained and radiographic studies showed aseptic necrosis of the right femoral head. She then experienced a similar episode in the left hip and the left femoral head became fragmented. Thereafter, she was only able to walk with the aid of a stick and two years later she underwent a prosthetic replacement of the right hip joint.

Her main complaints at present are a limp, due to shortening of the left leg, and episodic, non-specific left hip pain which is especially aggravated by exercise. She also suffers from a marked bleeding tendency, which manifests with easy bruising, menorrhagia and occasional purpuric spots on her arms.

Examination

On examination, she appeared generally fit apart from a marked left-sided limp. There was no abnormal hyperpigmentation of the skin but numerous white macules, 1cm in diameter, were scattered over her legs. Abdominal examination revealed a 15cm, non-tender, firm hepatomegaly.

She had full, painless movement of all joints and her left leg was 2cm shorter than the right. There was no other clinical evidence of Gaucher disease infiltration.

Comment

This young girl was initially diagnosed as having Gaucher disease at a very early age and subsequently developed severe osseous involvement and haematological complications. The excellent response to prosthetic hip replacement is demonstrated in this patient.

CASE 6

History

This medical practitioner, aged forty-nine years, initially suffered recurrent non-specific bone pain at the age of ten years. These attacks, which were episodic over the next three years, always occurred bilaterally in the region of the lower femora and necessitated hospitalisation on numerous occasions. No diagnosis was made and they subsided spontaneously without operative intervention. At no stage were there any associated focal inflammatory signs.

He then remained well until he was twenty-six years of age when he suffered a severe attack of pain in the right shoulder and upper arm. The pain was aggravated by movement and subsided after three weeks of physiotherapy and simple analgesics. Radiographic studies at that stage were normal and a diagnosis of "fibrositis" was made.

Two years later, he experienced an attack of acute abdominal pain and an enlarged spleen was palpated. Simultaneously, he suffered severe pain in the left sacro-iliac, hip, femoral, knee and fibular regions. The diagnosis of Gaucher disease was confirmed on histological examination of a bone marrow biopsy specimen.

Subsequently he suffered occasional episodes of incapacitating pain in both hips and shoulders. These attacks would occur spontaneously, but the symptoms were aggravated by exercise. By the age of thirty-eight, in addition to destruction of femoral and humeral heads by Gaucher disease, he had developed secondary osteoarthritis in the hip joints. Despite the increasing severity and incapacitating effect of his symptoms, he continued his medical practice, married and raised four children.

The severity of the left hip joint involvement eventually necessitated the insertion of a McKee-Farrar prosthesis in 1972. The operation was uncomplicated and the patient progressed from crutches to a stick, walking unaided after three months.

He has had few symptoms over the last five years. These have mainly been of mild discomfort in the shoulders and associated stiffness and pain on moderate exertion. He has never shown any evidence of a bleeding diathesis. He tans exceptionally easily and even after only a few hours of exposure to the winter sun his complexion darkens noticeably.

The patient's sister had Gaucher disease, but died at the age of 55 years from a carcinoma of the ovary. There was no other significant family history.

Examination

Examination revealed a well-tanned, fit-looking man who walked with a slight limp. The spleen was 7cm enlarged and was firm and non-tender. There was a right subcostal fullness, but no liver edge was palpable. He had full movement of all joints, with no bony tenderness. The systematic examination revealed no other clinical features of Gaucher disease.

Comment

This patient has severe osseous involvement with minimal haematologic complications. He has coped extremely well with his illness and managed throughout to continue his medical practice. The co-incidental association of carcinoma and Gaucher disease in his sister is of doubtful significance. The excellent response to prosthetic hip replacement is of considerable importance.

CASE 7

History

This fifty-three year old businessman was found to have an enlarged spleen at the age of six years, but at this time his mother refused to allow any further investigations. He suffered two attacks of pleurisy as a child and when aged twelve years experienced a severe arthritis of the left hip. This was misdiagnosed as tuberculosis and he was immobilised in hospital for six months on anti-tuberculous therapy. During the course of this illness the hip-joint collapsed and subsequently formed a stable ankylosis. The diagnosis of tuberculosis was eventually retracted but no alternative was offered.

He walked with a limp, but otherwise was well until thirty-six years of age. He then suffered another bout of severe left hip pain in the absence of any local inflammatory signs. He was treated for two weeks on antibiotics and the pain resolved. He suffered recurrent attacks of bilateral, severe arthritis over the next two years but was never confined to bed. The diagnosis of Gaucher disease was finally confirmed after histological examination of the bone marrow, a skeletal survey and a demonstration of a raised serum acid phosphatase level.

He remained reasonably well for the next eight years. He then developed a painful right hip which was initially diagnosed as bursitis. This was subsequently found to be due to an osteitis of the femoral neck and resolved on antibiotic therapy. Radiographic studies revealed collapse of the right femoral head due to avascular necrosis and he was subsequently incapacitated with a painful, unstable hip joint. His only medication was regular administration of analgesic tablets.

At this stage he was considered for prosthetic hip replacement but controversy arose as to the safety of orthopaedic surgery in the presence of the thrombocytopaenia. In the meantime, the symptoms had abated and the patient was able to walk comfortably with the aid of a stick. The pain has been mild ever since and the operation was never performed.

His only complaints at present are of occasional episodes of mild, bilateral hip pain which is aggravated by exercise, and is easily controlled by simple analgesics. He discarded his walking stick three years ago but still has decreased mobility due to severe limitation of hip movements.

He has a tendency to bleed easily and occasionally notices crops of dermal purpura. He also tans very easily. There are no other known patients with Gaucher disease in the family and he has three healthy children. His mother has maturity-onset diabetes.

Examination

Examination revealed a fit-looking man with a grossly abnormal gait due to limited hip mobility. There was shortening of the left leg and a few discrete lymph nodes could be palpated in the left groin. The spleen was firm, non-tender and 10cms enlarged, and the liver was 6cms enlarged.

He had bilateral gross limitation of active hip movement, and mobility of the left hip was diminished in all directions while the right hip flexed to a maximum of 90 degrees. Movements of the other joints were full and painless.

Comment

Severe osseous involvement with Gaucher disease has inflicted marked limitation of mobility on this patient. Progressive haematological involvement is also shown by the enlarging spleen and increasing thrombocytopaenia. The spleen has, in fact, enlarged from 6cms in 1972 to 15cms in 1976.

The incorrect diagnosis of tuberculous arthritis and the consequent inappropriate long-term medication is of importance.

CASE 8

History

This female schoolteacher, aged thirty-three years, was ten years old when hospitalised for two months with a diagnosis of osteomyelitis of the left femur. The limb was extremely painful and tender, but there was no associated redness or swelling. She was treated with bed-rest, antibiotics and analgesics and no operation was undertaken. She suffered persistent pain after discharge from hospital and was unable to walk for a further six months. Since then she has suffered intermittent episodes of dull pain in both legs. There are no specific areas of localisation of this pain and it usually subsides spontaneously after about two days. There are no apparent precipitating or aggravating factors.

At the age of twenty-one years, she suffered a protracted episode of jaundice which was due to infective hepatitis. During the course of investigations, histological examination of the bone marrow was performed and Gaucher disease was diagnosed.

She presently suffers from episodic flitting pains involving the groin, hips, knees and ankles. She also experiences generalised pains in the arms following moderate exertion. She has a bleeding tendency as shown by long-standing menorrhagia, multiple expistaxes, episodes of dermal purpura and a prolonged bleeding time.

She has had four full-term pregnancies and these were all uncomplicated, but induction of labour was required in each instance. She had normal deliveries, except the first, which required instrumentation because of inadequate uterine contractions. The other three labours were of normal duration.

CASE 8

History

This female schoolteacher, aged thirty-three years, was ten years old when hospitalised for two months with a diagnosis of osteomyelitis of the left femur. The limb was extremely painful and tender, but there was no associated redness or swelling. She was treated with bed-rest, antibiotics and analgesics and no operation was undertaken. She suffered persistent pain after discharge from hospital and was unable to walk for a further six months. Since then she has suffered intermittent episodes of dull pain in both legs. There are no specific areas of localisation of this pain and it usually subsides spontaneously after about two days. There are no apparent precipitating or aggravating factors.

At the age of twenty-one years, she suffered a protracted episode of jaundice which was due to infective hepatitis. During the course of investigations, histological examination of the bone marrow was performed and Gaucher disease was diagnosed.

She presently suffers from episodic flitting pains involving the groin, hips, knees and ankles. She also experiences generalised pains in the arms following moderate exertion. She has a bleeding tendency as shown by long-standing menorrhagia, multiple expistaxes, episodes of dermal purpura and a prolonged bleeding time.

She has had four full-term pregnancies and these were all uncomplicated, but induction of labour was required in each instance. She had normal deliveries, except the first, which required instrumentation because of inadequate uterine contractions. The other three labours were of normal duration.

Abnormal mild post-partum haemorrhages which followed all four deliveries, responded to routine conservative measures and only after the second delivery was transfusion of a single unit of blood necessary. The only medication administered during the pregnancies was iron tablets for the mild anaemia.

Two of this patient's offspring suffer from Hurler's syndrome, but her other two children are entirely normal. There is no family history of Gaucher disease.

Examination

Examination revealed a fit-looking woman with scattered crops of purpura over the arms and numerous telangiectasia over the arms and face.

A 1cm enlarged, tender spleen and a 5cm non-tender, smooth-surfaced, enlarged liver were palpated. She had full, painless movement of all joints. There was no other clinical evidence of Gaucher disease.

Comment

This patient complains of mild symptoms at present, with minimal clinical evidence of Gaucher disease complications. Few problems arose during her four pregnancies, which she tolerated extremely well. The familial association of Gaucher disease and Hurler's syndrome is of interest. Both are autosomal recessive conditions due to a genetically determined biochemical abnormality, but their existence in this family is probably co-incidental.

CASE 9

History

This schoolboy, aged sixteen years, was initially noted to have splenic enlargement at the age of fifteen years, when he presented with acute abdominal pain. No operation was undertaken and the symptoms resolved on conservative analgesic management. Four months later, he experienced acute excruciating pain in the right lower femur. There were no focal or generalised inflammatory signs and he remained apyrexial throughout. The skin over the affected area took on a brown, macular, mottled appearance. Analgesics were administered and the condition resolved spontaneously. Radiographs at that stage showed an area of rarefaction in the lower femur and histological examination of the bone marrow and beta-glucosidase enzyme assay confirmed the diagnosis of Gaucher disease.

He has since had no further episodes of bone or joint pains and he has never experienced any bleeding problems. His only other complaint is one of chronic, non-specific diarrhoea, with no associated, aggravating or precipitating factors.

There is no family history of Gaucher disease. His father's parents were immigrants from Eastern Europe and his maternal grandparents are Dutch Ashkenazi-Jews.

Examination

Examination revealed a generally fit-looking youth. He had an area of brown macular pigmentation over the anterior aspect of the right upper thorax and the only other clinical finding of note was a 2cm splenic enlargement.

Comment

This patient is very mildly affected with Gaucher disease and his only past problem was a single attack of femoral pain. The aetiology of his diarrhoea is not known but theoretically may be due to Gaucher cell infiltrates in the bowel submucosa.

CASE 10

History

This businessman, aged fifty-eight years, initially experienced severe pain in the finger tips of both hands when forty-nine years of age. The pain was of a non-specific nature with neither precipitating nor aggravating factors and no features to suggest Raynaud's disease. Splenic enlargement was noted during the course of this illness and Gaucher disease was diagnosed after histological examination of a bone marrow biopsy but no specific diagnosis was established for the peripheral symptoms in his fingers. The patient was advised to give up smoking. His symptoms resolved after two weeks and he has subsequently had no recurrence.

A year later he suffered episodes of severe pain in the left ankle and the toes of both feet and a diagnosis of gout was made after hyperuricaemia was recognised. This condition responded well to therapy with analgesics and uricosuric drugs.

At present he is well, complaining only of pain in the left shoulder following exertion and early morning stiffness in his hips and knees. For the last ten years he has noticed a tendency to protracted bleeding following dermal trauma but has never experienced purpura or spontaneous bruising.

The patient is a widower with two healthy children. His brother was diagnosed as having Gaucher disease following splenectomy at the age of twenty-seven years and he died a year and a half later of disseminated metastases from an undetected primary carcinoma. There is no other family history of Gaucher disease.

Examination

Examination revealed a fit-looking man. There were numerous scattered telangiectasia over his upper arms, face and chest. Abdominal examination revealed a 3cm firm, non-tender splenomegaly and a 2cm enlarged liver. There was painful limitation on attempted full movement of the left shoulder joint. Otherwise the clinical examination showed no further evidence of Gaucher disease.

Comment

This individual is mildly affected with a late onset of symptoms. The co-existence of Gaucher disease and carcinoma in his deceased brother and Gaucher disease and hyperuricaemia in the patient is of interest. However, these associations are of doubtful clinical significance.

Although his initial complaint appeared to be related to cigarette smoking, the possibility of Gaucher cell infiltration of peripheral vessels as a causative factor cannot be entirely dismissed.

CASE 11

History

This librarian, aged thirty-seven years, initially experienced severe right hip pain following a minor fall at the age of twenty. She was apyrexial and although there were no local or generalised inflammatory signs, the throbbing pain worsened over the ensuing two weeks and eventually she required hospitalisation. There she was found to be severely anaemic, an enlarged spleen was palpated and the diagnosis of Gaucher disease was made following histological examination of the bone marrow. She received multiple transfusions to correct the anaemia and a splenectomy was then undertaken. She did very well post-operatively, remaining asymptomatic except for slight limitation of hip movement.

She remained well until six years later, when at the seventh month of pregnancy she suffered from severe left hip pain. She also became very anaemic and required multiple blood transfusions throughout the pregnancy. The pain and the anaemia persisted till the early post-partum period and then rapidly abated. She had an uncomplicated labour resulting in a vaginal delivery of a normal infant. The patient was advised by her practitioner to have no further pregnancies because of her "inadequate bone marrow".

The left hip function continued to deteriorate over the next two years and she eventually had the joint replaced with a McKee-Farrar prosthesis. She used crutches for only six months post-operatively and subsequently walked unaided with no further problems in the prosthetic joint.

Four years ago, she started experiencing attacks of severe pain in the right hip. These initial episodes, which lasted for about two weeks, resulted in impaired mobility for at least two months. They have, however, become less frequent and far less severe over the last few years.

Her complaints at present are of a mild, dull, non-specific throbbing pain in the legs and discomfort in the right hip on walking. She has also been diagnosed as suffering from cholelithiasis. She has no symptoms of a bleeding tendency. An enlarged lymph node excised from the region of the parotid gland in 1976 was found to be heavily infiltrated with Gaucher cells.

Examination

Examination revealed a fit-looking woman and the only significant clinical finding was a 7cm enlarged, firm, non-tender liver.

Comment

Her disease appears to be running a milder course with advancing age. She has shown excellent haematological response to splenectomy, only relapsing during her single pregnancy. She suffered severe bony complications before and after splenectomy. The association of Gaucher disease and cholelithiasis in this patient is of interest.

CASE 12

History

This housewife, aged sixty-five years, had a medically uneventful childhood except for a marked bleeding tendency. This manifested itself with menorrhagia, multiple epistaxes, recurrent bleeding of the gums and a persistent mild anaemia.

She was found to have splenomegaly on routine examination at the age of thirty years. A splenectomy was performed and histological examination revealed the spleen to be packed with Gaucher cells. Following splenectomy, she had no symptoms from her Gaucher disease for the ensuing 35 years. She has had arthritic problems in her right knee over the last two years but the clinical features were consistent with a diagnosis of osteoarthritis rather than infiltration by Gaucher disease. Six years ago, she underwent a cholecystectomy for cholelithiasis and her mother had also suffered from cholelithiasis.

Her obstetrical history is of a spontaneous abortion at three months, followed by two normal pregnancies with full-term, normal vaginal deliveries. There were no problems with the labours or in the post-partum periods.

The family originates from Germany and they have no family history of Gaucher disease.

Examination

Examination revealed an overweight woman. Her liver was firm, non-tender and 2cms enlarged. Her right knee had very limited movement, but mobility of all other joints was full and painless.

Comment

This patient had severe haematological complications of Gaucher disease until her splenectomy was performed. She has since remained asymptomatic for thirty-five years. The finding of cholelithiasis in the patient and her mother is of interest.

CASE 13

History

This school teacher presented at the age of eighteen years with a distended abdomen due to gross splenomegaly. The following year she underwent splenectomy for the relief of severe abdominal discomfort. She did well post-operatively, apart from episodes of frequent bruising. However, two years later she experienced a severe pain in the right hip following a minor fall and had almost constant pain which radiated down the leg and into the ankle. The pain tended to persist as a dull ache, with fluctuating severity, and was aggravated by exertion.

At the age of twenty-eight years, she started to feel very unwell. She began to lose weight, suffered from progressive abdominal distension and discomfort and also had persistent anaemia and malaise. Her general physical state progressively deteriorated and she never regained full health over the ensuing seven years.

The patient herself was a spinster, with one brother who has proven Gaucher disease and is included in this survey. There is no other family history of Gaucher disease.

Examination

When originally examined, the patient appeared debilitated by her condition and she had a wasted appearance with a markedly distended abdomen. She was mildly dyspnoeic and exhibited peripheral cyanosis. She was generally pale and had telangiectasia over the arms and neck, with a few bruises on the arms and scattered purpura over her back.

There were no abnormal, clinical, cardiovascular or respiratory signs to explain her dyspnoea or cyanosis. The abdomen was filled and distended by the enlarged liver which extended from the costal margin to the iliac fossa. Flexion of the right hip was limited to 90 degrees but movements of all the other joints were full and painless.

Course

Shortly after this examination, the patient became severely ill with tuberculous meningitis, which progressed to form a cerebral abscess. The abscess was drained and the patient made good progress post-operatively. She suffered some adverse reactions to the anti-tuberculotic drugs but her general health continued to improve over the next year. However, she then suddenly deteriorated and died at the age of thirty-five years.

Comment

This patient was severely affected by Gaucher disease and suffered ill-health for the last eight years of her life. The tuberculosis was possibly related to her general debility and immune incompetence from severe, diffuse organ infiltration by the Gaucher disease process.

CASE 14

History

This medical practitioner, aged thirty-nine years, was seven years old when he presented with acutely swollen and painful knee joints. This illness, which was diagnosed as rheumatic fever, remitted spontaneously on bed-rest and analgesia. Three years later, he suffered a similar recurrence and an enlarged spleen was palpated. Gaucher disease was then diagnosed on histological examination of the bone marrow. The spleen enlarged markedly over the following two years and he suffered from multiple epistaxes and persistent anaemia.

Splenectomy was undertaken at the age of twelve years to relieve his abdominal discomfort and to attempt to reverse the hypersplenism. He did very well post-operatively, suffering no further haematologic problems. He did, however, begin to experience recurrent attacks of acute, severe arthritis in the shoulders, hips and knees. These attacks occurred at approximately six-monthly intervals and remitted spontaneously after a few weeks. The affected joints were extremely painful and exhibited signs of an acute inflammatory process. These attacks decreased in severity and occurred less often over the following years. Slowly, progressive destruction of the right femoral head has resulted in secondary osteoarthritis in that hip. However, he suffers minimal pain from this severely affected right hip joint, which has limited movement.

At the age of thirty-one years, he was diagnosed as having cholelithiasis. His problems, at present, are a mild degree of abdominal discomfort due to his enlarged liver and the previously mentioned orthopaedic complications.

He is a widower with three healthy children. His sister, Patient 13, is the only other person in this family known to have Gaucher disease.

Examination

Examination revealed a fit-looking man who walked with a right-sided limp. He had a 20cm firm, non-tender enlarged liver. Movements of the right hip joint were severely restricted, being limited to a twenty degree arc. The systematic clinical examination otherwise showed no further evidence of Gaucher disease.

Comment

This patient emphasises the diagnostic problem which arises when Gaucher disease initially presents with an acute arthritis. His orthopaedic problems pre-dated the haematologic complications and it is therefore unlikely that the splenectomy was responsible for a worsening of orthopaedic problems. This patient did very well after splenectomy and the clinical effects of his disease appear to be lessening with advancing age. The association of Gaucher disease and cholelithiasis is of interest.

CASE 15

History

This businessman, aged forty-four years, initially presented with acute pain in the left hip at the age of thirty-eight years. The condition was undiagnosed and resolved spontaneously after one week's bed rest. However, over the next six months he began to experience progressively increasing stiffness in the left hip joint and radiographs revealed aseptic necrosis of the left femoral head. The diagnosis was not confirmed until two years later when he again presented with acute, severe left hip pain. At this time, the typical histological appearances of Gaucher disease were recognised in a specimen of bone marrow.

Following this acute attack, a cup arthroplasty was performed on the left hip joint. He remained well post-operatively and has been asymptomatic ever since, although radiographs show progressive deterioration of the right femoral head. He has never suffered any haematological problems.

He is married with three healthy children. There is no known family history of Gaucher disease.

Examination

Examination revealed a fit-looking man who walked with a left-sided limp. The spleen was 1cm enlarged and the liver edge was not palpable. Left hip movement was grossly restricted to only sixty-five degrees of flexion and abduction-adduction was limited to ten degrees.

Comment

This individual is mildly affected with Gaucher disease, and presented initially with orthopaedic problems at the age of thirty-eight years. Although there was no clinical evidence of haematological involvement, laboratory studies revealed a mild pancytopaenia, especially involving the platelets.

CASE 16

History

This housewife, aged thirty-seven years, presented to her practitioner at the age of thirty-two years with mild, spontaneous bleeding. The patient was found to have hepato-splenomegaly and subsequent histological examination of the bone marrow confirmed the diagnosis of Gaucher disease.

She had previously suffered from malaria and menorrhagia, but had otherwise been well. Over the last two years she had experienced a recurrent, non-specific mild pain in her knees and pelvis. These pains were of short duration and resolved spontaneously with no residual symptoms.

She has three healthy children and her pregnancies and deliveries were all normal, except for a mild anaemia which was treated with haematinics. She suffered a mild post-partum haemorrhage with the third pregnancy, which was easily controlled and did not require a blood transfusion.

Her parents, who are of Eastern European origin, are first cousins. There is no other known family history of Gaucher disease.

Examination

Examination revealed a fit-looking woman and the only abnormal dermal changes were bruising over the lower legs. She wore glasses for her astigmatism. A 3cm, non-tender, enlarged spleen and a 2cm non-tender, enlarged liver were

palpated. All joint movements were full and painless and clinical examination was otherwise entirely normal.

Comment

This individual is mildly affected with Gaucher disease. The fact that her parents were first cousins is of interest as this is the only instance of a consanguinous marriage in this series. Although laboratory data revealed a mild pancytopaenia, there were no haematological complications in her three pregnancies.

CASE 17

History

This businessman, aged thirty-five years, initially presented to his practitioner at thirty-one years of age with pain in the left upper quadrant of his abdomen. He suffered multiple attacks of a continuous, dull ache, which became sharp and spasmodic on movement. He was found to have splenomegaly and subsequent histological examination of the bone marrow confirmed the diagnosis of Gaucher disease. The pain abated spontaneously and he has since had only mild recurrences.

His only complaint, at present, is of pain in the region of the right lower femur and knee joint. This pain is experienced as an episodic, dull ache, which resolves spontaneously without any therapy. The only evidence of a bleeding diathesis is his subjective observation of easy bruising.

He has three daughters, who are all healthy. His sister has proven Gaucher disease and is also included in this series. The patient suffers from maturity-onset diabetes.

Examination

Examination revealed a thin, fit-looking man. The only significant clinical feature was the 7cm firm, non-tender, enlarged spleen.

Comment

This individual is mildly affected with Gaucher disease. The association of Gaucher disease and diabetes in this patient is of interest.

CASE 18

History

This housewife, aged thirty-two years, was diagnosed as having Gaucher disease following routine family screening after confirmation of the diagnosis in her brother, Patient 17. She was found to have an enlarged spleen and Gaucher disease was diagnosed on histological examination of her bone marrow. She had previously been entirely asymptomatic.

Over the last two years, she has experienced a dull, non-specific pain in the left upper quadrant of her abdomen. She also complains of pain in the left shoulder following exertion and a progressively worsening feeling of malaise. She has always bruised easily and occasionally notices crops of dermal purpura. During her pregnancy, seven years ago, she suffered her only anaemic episode which was of a mild degree and responded to haematinic therapy. The pregnancy was also complicated by pre-eclamptic toxaemia which necessitated caesarian section for delivery of a healthy infant. She experienced no post-partum problems.

This patient is a divorcee who lives with her seven year old son, in whom the diagnosis of Gaucher disease has recently been confirmed. Her ex-husband shares a common great-gandfather with another Gaucher disease patient in this series, (Case 4). Her brother, (Case 17), also has Gaucher disease, as described above.

Examination

Examination revealed a generally fit-looking woman who showed no abnormal dermal signs. The only significant clinical finding was a 3cm firm, non-tender enlarged spleen.

Comment

This patient is mildly affected with Gaucher disease. The fact that her symptoms only occurred following positive diagnosis raises the possibility of a psychosomatic overlay. The observation of apparent dominant transmission from mother to son is of interest. The pedigree revealed, however, the presence of Gaucher disease in her ex-husband's family. Unfortunately, he was not available for testing, but it seems likely that this is an example of quasi-dominant or pseudo-dominant inheritance.

CASE 19

History

This housewife, aged seventy-two years, suffered from severe menorrhagia thirty years ago and was simultaneously found to have a moderate pancytopaenia and an enlarged spleen. Her condition went undiagnosed and the severity of the menorrhagia eventually necessitated a hysterectomy. She did very well post-operatively and has remained in good health ever since.

She recently had a minor stroke but made a full recovery and is now fit and well. Her brother is a known patient with Gaucher disease and she was therefore tested as part of the family screening programme. The beta-glucosidase enzym assay confirmed the diagnosis of Gaucher disease. She has never suffered any bone or joint problems.

She has had two normal pregnancies, labours and deliveries. There were no post-partum problems. Her son and daughter are both healthy.

Examination

Examination revealed a fit-looking, elderly lady who had a few telangiectasia on her face but otherwise showed no abnormal dermal signs. The liver and spleen were not clinically enlarged. There was evidence of osteoarthritis in her hips, wrists and knees.

Comment

This patient is very mildly affected with Gaucher disease. The condition was only recognised following confirmation of the diagnosis in her brother.

CASE 20

History

This retired businessman, aged sixty-three years, is the brother of Case 19. His enlarged spleen was initially discovered during an attack of viral neuronitis approximately twenty years ago. No diagnosis was made at the time. Six years ago he presented with a bleeding diathesis and was admitted to hospital for investigation. The enlarged spleen was again palpated and laboratory investigations showed the presence of hypersplenism. The diagnosis of Gaucher disease was confirmed by the presence of a raised serum acid phosphatase level and characteristic Gaucher cells in his bone marrow. He subsequently underwent a splenectomy with very good post-operative haematologic response. The spleen was found to be packed with Gaucher cells as was the liver biopsy specimen. He still suffers from exacerbations of dermal purpura, especially on the dorsum of the hands and shins, and spontaneous, easy bruising on mild trauma. He has never had any bone or joint problems.

The patient was born in Lithuania and then immigrated to South Africa. He has three normal, healthy children, but one of his sisters, a nephew and two grand-nieces all suffer from diabetes mellitus.

Examination

Examination revealed a generally fit-looking man. The only abnormal clinical feature was a 3cm non-tender, firm, enlarged liver.

Comment

This patient is very mildly affected and has shown good haematologic response to splenectomy. The associated family history of Gaucher disease and diabetes mellitus is of interest.

CASE 21

History

This accountant, aged twenty-four years, presented at the age of eleven years with epigastric pain. Despite the finding of hepato-splenomegaly at this initial examination, a diagnosis of an uncomplicated duodenal ulcer was made and the pain resolved on antacid therapy.

He remained well until he experienced an acute onset of pain in the left hip five years later. This condition was undiagnosed and treated with intra-articular cortisone. The pain settled after a few weeks but he was left with a left-sided limp. Subsequently, his condition deteriorated and he was confined to bed for the following one and a half years. During this illness, a bone marrow biopsy was performed and the histologic findings confirmed the diagnosis of Gaucher disease.

Over this period, he developed a septic osteomyelitis in the left hip which was treated with incision and drainage and intravenous antibiotics. After the infective process settled, a Girdlestone operation was performed on the left hip. He made good progress post-operatively but required long immobilisation. After six months, he began to walk with calipers and then crutches. Nine months later, he was fully mobile with the aid of a stick.

He has had no further bone or joint problems. His only complaint at present is stiffness and mild pain in his shoulders and hips following moderate exertion.

He is unmarried and there is no known family history of Gaucher disease.

PEDIGREES OF AFFECTED KINDREDS

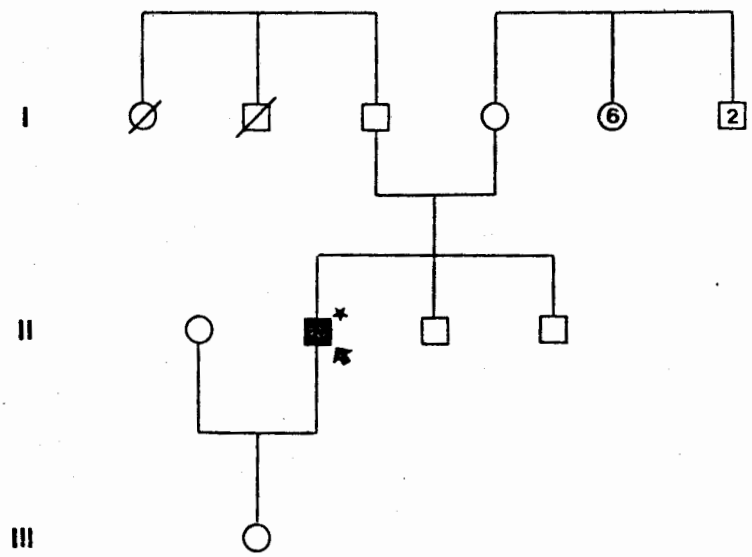

FIGURE 33: CASE 1.

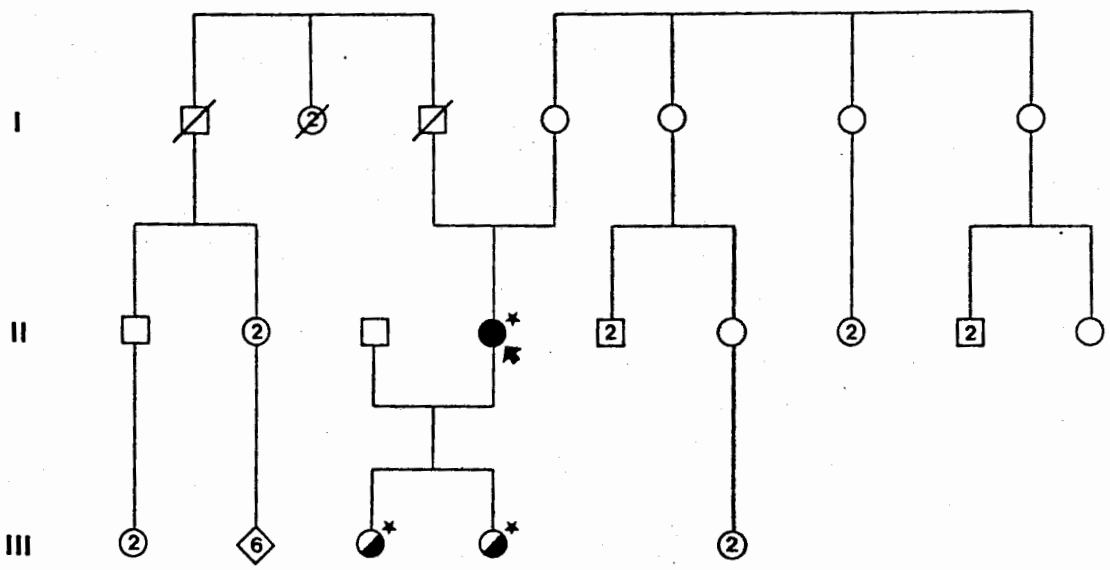

FIGURE 35: CASE 3.

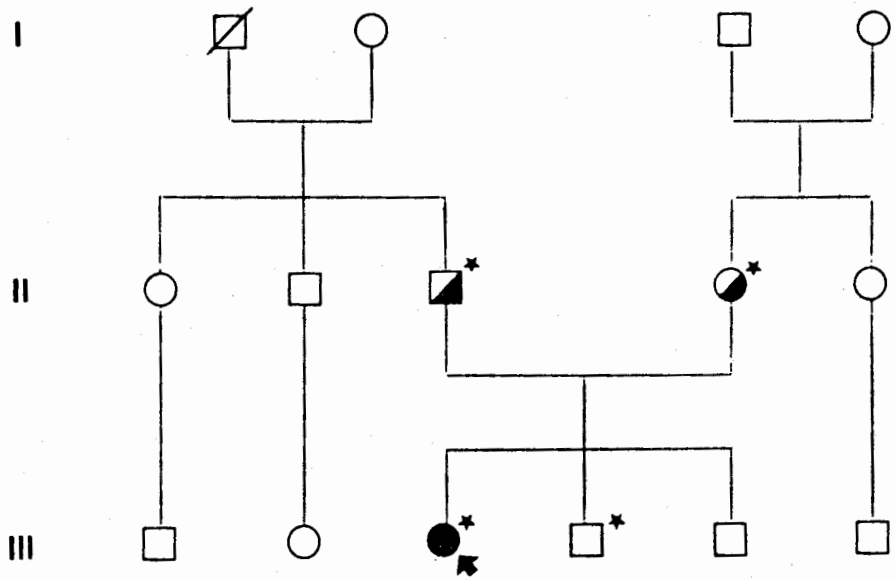

FIGURE 36: CASE 5.

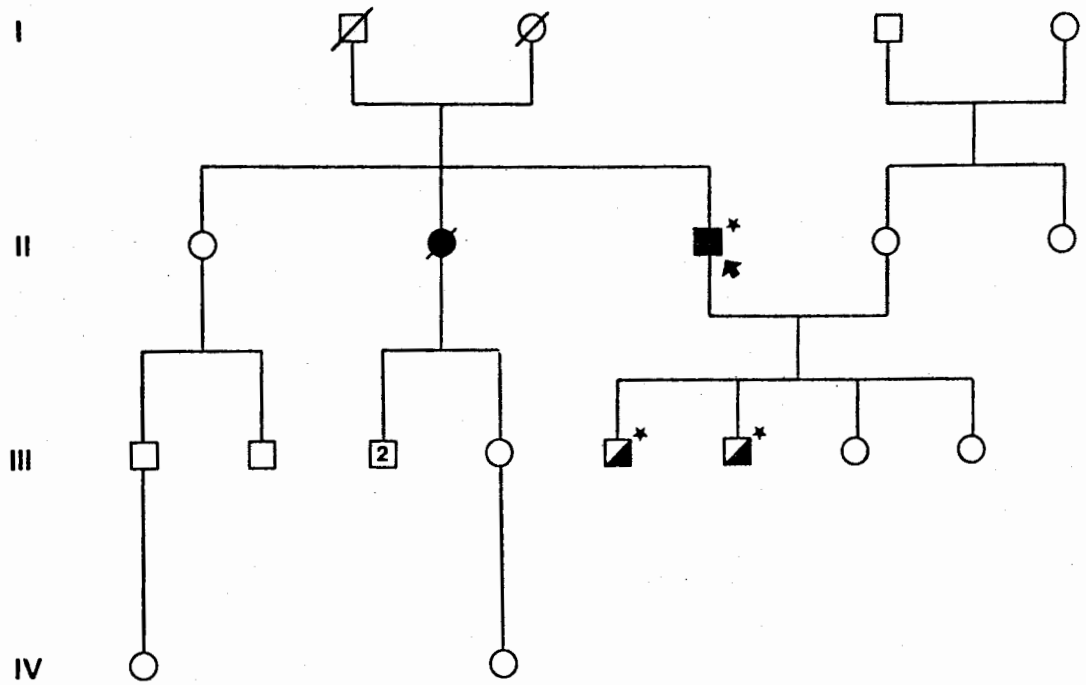

FIGURE 37: CASE 6.

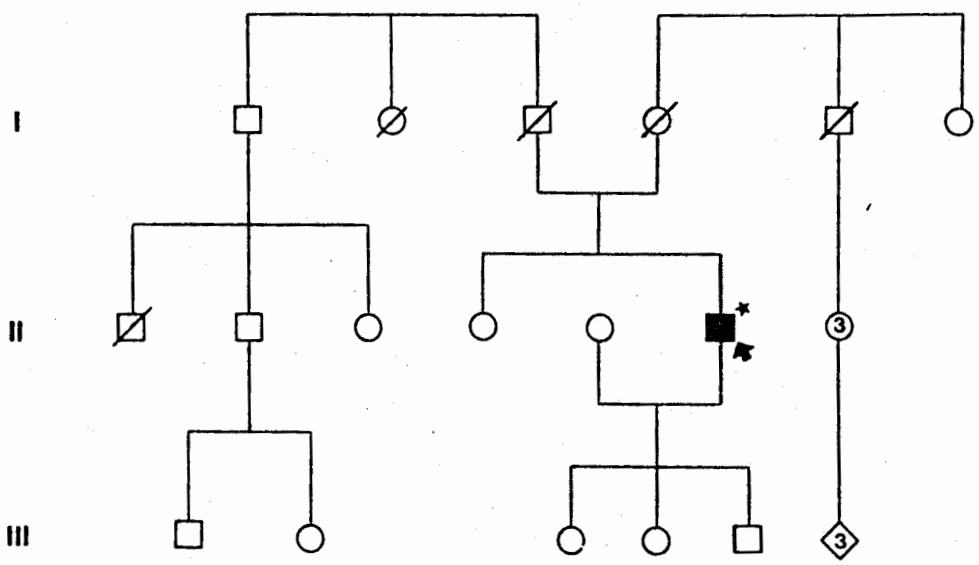

FIGURE 38: CASE 7.

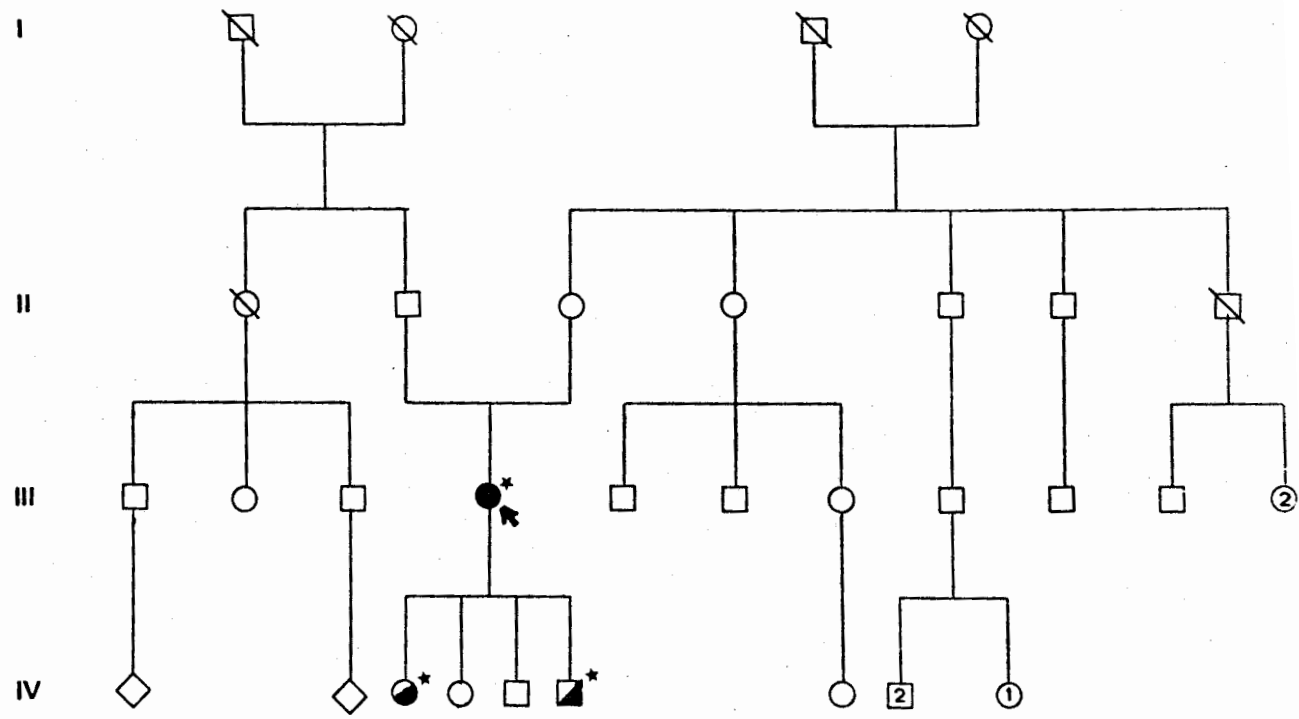

FIGURE 39: CASE 8.

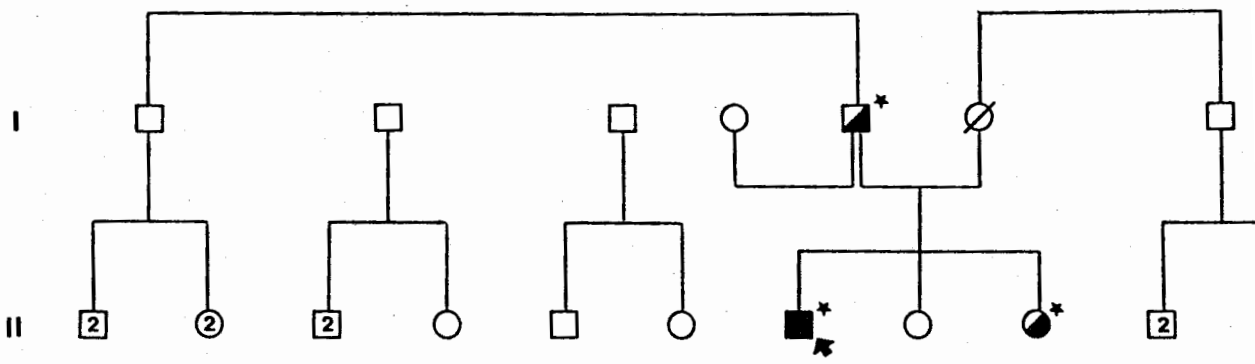

FIGURE 40: CASE 9.

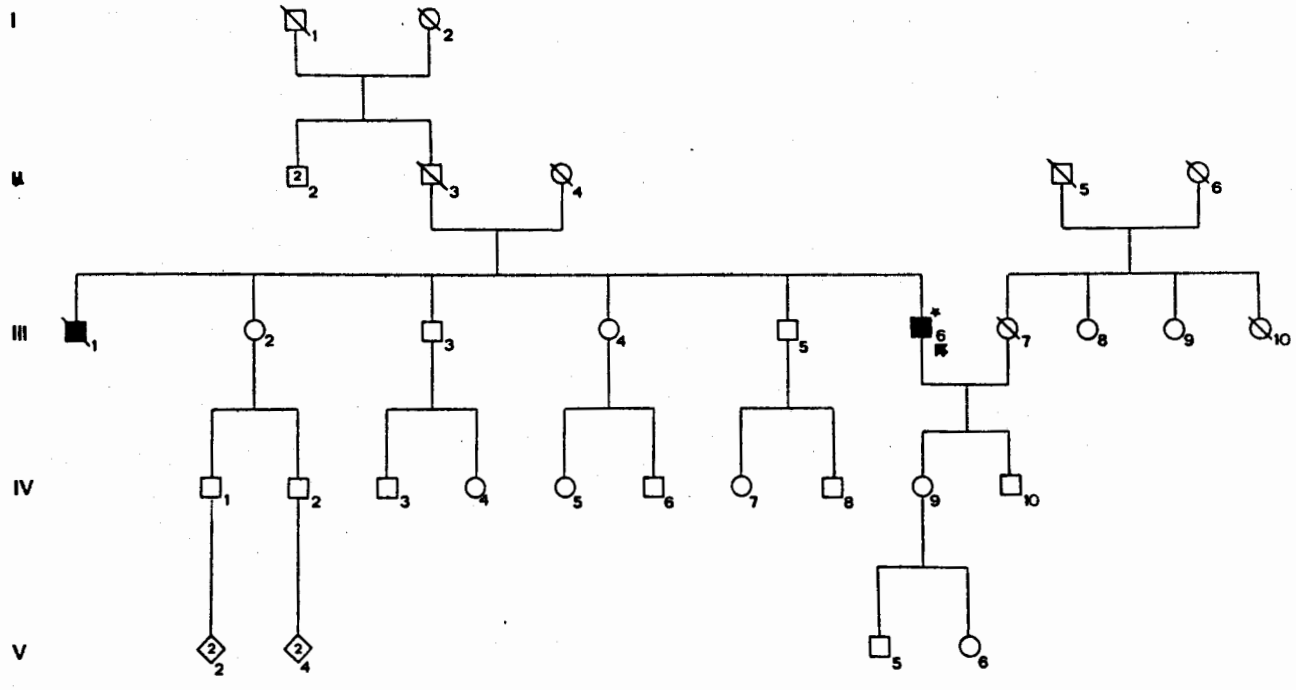

FIGURE 41: CASE 10.

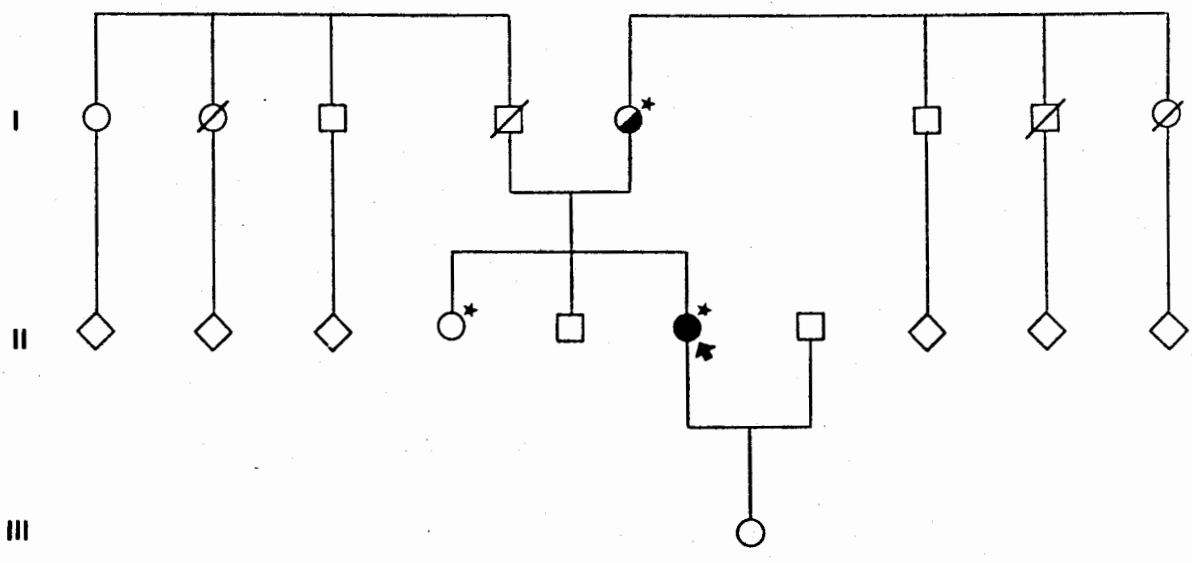

FIGURE 42: CASE 11.

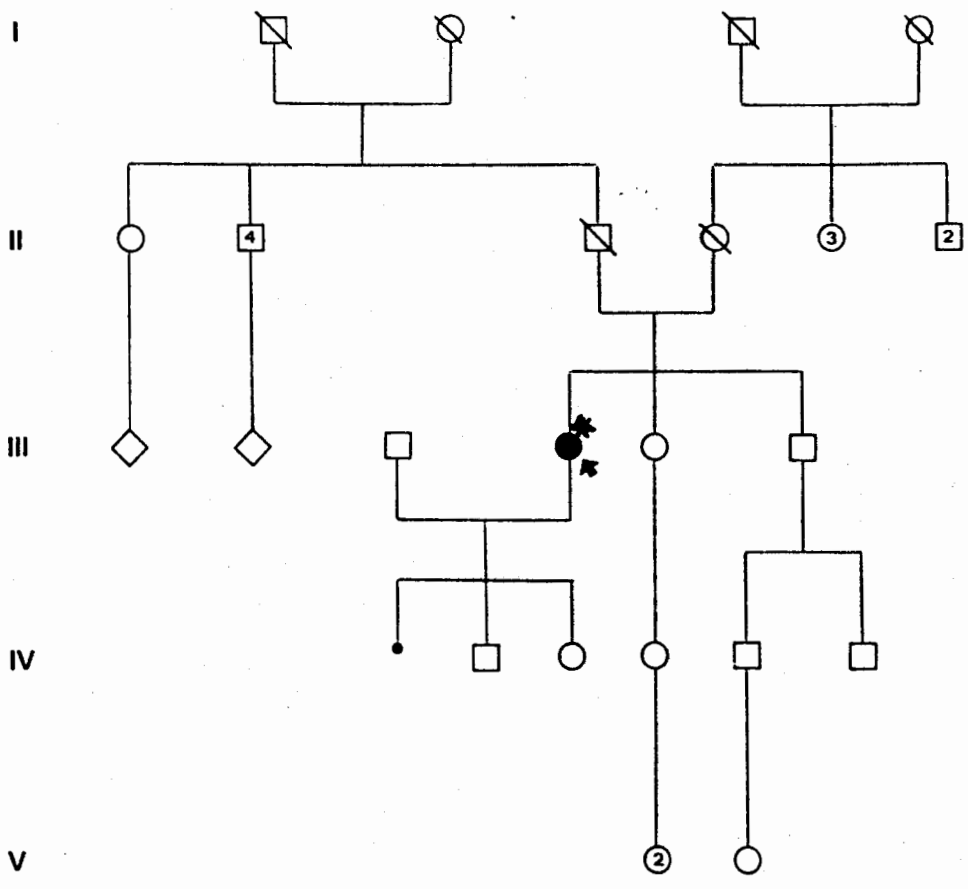

FIGURE 43: CASE 12.

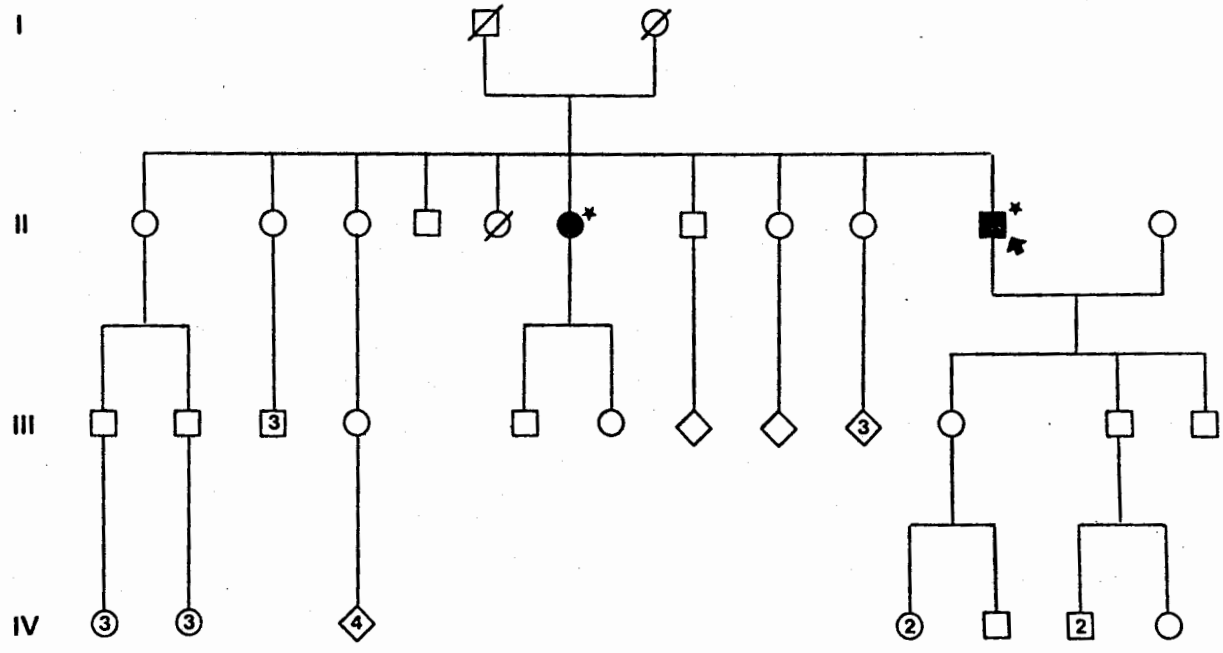

FIGURE 45: CASES 19 AND 20.

PROFORMAT

(1) Patient Clerking Notes

(2) Beta-Glucosidase Assay

GAUCHER'S DISEASE

Name:

Age:

Sex:

Ethnic Group:

Occupation:

Marital Status:

Age of positive diagnosis:

Age of onset of symptoms:

Present symptoms:

Past History:

Previous Operations:

Therapy:

Family history and Pedigree:

Associated family disease: - cholelithiasis, diabetes mellitus, stunted growth, mental retardation, hyperinsulinism.

Personal History:

Systemic Interrogation:

Respiration:

C.V.S.:

C.N.S.:

Abdominal:

Genito-urinary:

Skeletal and Joints:

Skin:

Examination: (General)

Height:

Weight:

Skin changes:

Bleeding Diathesis:

Lymphadenopathy:

Liver dysfunction:

Clubbing:

Eyes:

Hyperlipidaemia:

Examination: (cont.)

C.V.S.

Respiratory:

Abdominal:

C.N.S.

Skeletal:

Special Investigations:

P U B L I C A T I O N S

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The Orthopedic Aspects of Gaucher Disease

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Orthopedic complications predominate in the adult, chronic or nonneuropathic form of Gaucher disease. This condition, which is inherited as an autosomal recessive, is present in particularly high prevalence in the Ashkenazi Jewish community of South Africa, and it also occurs less frequently in other ethnic groups.

During the past 7 years we have studied 35 affected individuals. Their orthorpedic problems are presented and discussed in this paper.

CLASSIFICATION

Infantile, juvenile and adult forms of Gaucher disease are recognized. Progressive neurological involvement is a feature of the infantile and juvenile types, which are usually lethal. The adult or nonneuropathic variety, which is the subject of this paper, follows a more benign course and neurological complications do not develop.

Since the 'adult' form frequently presents in childhood as splenomegaly of uncertain etiology, the designation "nonneuropathic" is preferable for this disorder. It was originally thought that there were 2 types of adult Gaucher disease, a purely osseous type and a predominantly splenomegalic type.[5] It is now known that the orthopedic complications are a reflection of the underlying involvement of the reticuloendothelial system and therefore this subdivision is unnecessary. However, there may well be heterogeneity, as evidenced by the greater severity and more rapid course of the condition in Afrikaner patients, as compared with the Jewish group.

INVESTIGATION SUBJECTS

The patients in this series were found following a nationwide survey of Gaucher disease in South Africa. Many were attending orthopedic clinics in Johannesburg and Cape Town, while others were referred to us for study by their private practitioners. A full clinical and genetic evaluation was carried out in each instance and the diagnosis was confirmed by the recognition of the characteristic foamy Gaucher cells in the bone marrow and the demonstration of deficient activity of beta-glucosidase in cultured leucocytes.

As there are considerable discrepancies in the geographic and racial distribution of Gaucher disease, information was obtained concerning the ethnic origins of the patients.

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Twenty-eight were Ashkenazi Jews, 3 were Afrikaners, 2 were African Negroes and 2 were British. The progenitors of the Jewish population had immigrated from Lithuania at the turn of the century, while the Afrikaners were of Dutch stock. The African Negroes were members of the Zulu and Tswana groups, while the British patients had their antecedents in England and Scotland. The age, sex, ethnic group, orthopedic complications and mode of presentation of the condition in the 35 patients are shown in Table 1.

GENERAL COURSE AND PROGNOSIS

The course of the disease was very variable, the majority of patients experiencing fluctuating but slowly progressive ill-health. Splenomegaly was the most common mode of presentation and the condition was usually recognized in early adulthood. Anemia or abnormal bleeding drew attention to an enlarged spleen in several patients, while in others it was palpated during routine examination. Orthopedic problems such as aseptic necrosis of the femoral head or bone pain were other frequent presenting features.

Two of the Afrikaners and 3 Jewish patients died during the course of the study. The health of the others ranged between severe incapacity and relative normality. The age of onset was earlier and the clinical course and rate of progression was much more severe in the Afrikaners than in individuals of other population groups.

ORTHOPAEDIC COMPLICATIONS

Twenty-nine of the 35 patients had significant orthopedic problems. In general, these were age related, and usually appeared in the second or third decade.

Nonspecific Bone Pain

Twenty-one patients experienced nonspecific bone pain. They described this as a deep seated, persistent, dull ache in both thighs. Episodes lasted for 1–2 days and recurred at irregular intervals. They were rarely of sufficient severity to cause incapacity and resolved spontaneously or following treatment with simple analgesics.

Pseudo-osteomyelitis

Fourteen patients experienced attacks of pseudo-osteomyelitis. The clinical picture was variable, but localized tenderness, redness, swelling and warmth were usually present. The femur was most commonly affected. The patient was often pyrexial, with a raised erythrocyte sedimentation rate and a polymorph leucocytosis. These episodes resembled acute pyogenic osteomyelitis and differentiation was sometimes very difficult. The main distinguishing features of pseudo-osteomyelitis were the absence of severe toxemia and a consistently negative blood culture. The acute attacks usually settled after a few days but occasionally lasted for some weeks.

Pyogenic Osteomyelitis

One young male had an acute hematogenous infective osteomyelitis of the femur and sinuses formed following curettage and drainage. These persisted with intermittent discharge of sterile necrotic material.

An adolescent girl had acute osteomyelitis of the femoral neck. Blood culture revealed bacillus coli and she was treated with antibiotics, steroids, blood transfusion and drainage of a large subperiosteal abscess. She eventually recovered after a prolonged illness.

Joint Pain

Twenty-one patients had chronic pain and stiffness of the large joints with periodic acute exacerbations. These symptoms, which were of variable severity, were precipitated and aggravated by cold and exertion and ameliorated by rest and analgesics.

In one young woman prolonged bed rest was required for the relief of pain. Soft tissue contractures developed and she was subsequently confined to a wheelchair for 5

TABLE 1. Presenting Features and Orthopedic Complications

Patient	Age in 1976	Sex	Ethnic Group	Mode of Presentation	Orthopedic Complications					Hip Joint Prosthesis
					Nonspecific Bone Pain	Pseudo-Osteo-myelitis	Acute Arth-ritis	Collapse of Femoral Heads	Others	
1	33	M	J	Splenomegaly	+	−	+	−	−	
2	31	F	J	Asymptomatic splenomegaly	−	−	+	−	−	
3	14	F	J	Abdominal pain Splenomegaly	+	+	+	+	−	Thompson
4	32	F	J	Pseudo-osteomyelitis	+	+	+	−	−	
5	28	F	B	Acute arthritis	+	+	+	+	Pathological fractures	
6	45	M	J	Asymptomatic splenomegaly	+	+	+	+	Pathological fracture Kyphoscoliosis	
7	33	M	J	Pseudo-osteomyelitis	+	+	+	+	−	
8	63	F	J	Asymptomatic splenomegaly	−	−	+	−	−	
9	35	F	J	Splenomegaly	+	+	+	+	−	
10	38	M	J	Acute arthritis	−	−	+	+	−	
11	51	M	J	Splenomegaly	−	−	+	−	−	
12	43	M	J	Acute arthritis	−	−	+	+	−	Cup Arthroplasty
13	16	M	J	Abdominal pain Splenomegaly	+	+	−	−	−	
14	23	M	J	Acute arthritis Splenomegaly	+	+	+	+	−	
15	18	M	J	Asymptomatic splenomegaly	−	−	−	−	−	
16	36	F	J	Acute arthritis Splenomegaly	+	−	+	+	−	McKee-Farrar
17	36	F	J	Thrombocytopenic purpura Splenomegaly	+	−	−	−	−	

18	48	M	J	Pseudo-osteomyelitis Splenomegaly	+	+	+	+	–	McKee-Farrar
19	42	M	J	Splenomegaly	–	–	–	+	Kyphoscoliosis	
20	72	F	J	Asymptomatic splenomegaly	–	–	–	–	–	
21	61	M	J	Thrombocytopenic purpura Splenomegaly	–	–	–	–	–	
22	38	F	J	Anaemia in pregnancy Splenomegaly	+	–	+	+	–	
23	16	F	A	Asymptomatic splenomegaly	+	+	+	+	Pathological fracture	
24	26	F	A	Asymptomatic splenomegaly	+	+	+	+	–	Muller
25	40	F	J	Chronic malaise Splenomegaly	+	–	–	–	–	
26	49	M	B	Asymptomatic splenomegaly	–	–	–	–	–	
27	40	F	N	Splenomegaly	–	–	+	+	Kyphoscoliosis	Charnley
28	51	M	J	Femoral head collapse Splenomegaly	+	+	+	+	–	Charnley
29	41	M	J	Splenomegaly	+	–	+	+	Kyphoscoliosis	Cup arthroplasty
30	24	M	N	Abdominal pain	–	–	–	+		
31	49	M	J	Splenomegaly	–	+	–	+	–	
32	17	F	J	Splenomegaly	–	–	–	+	–	Charnley
33	37	F	A	Asymptomatic splenomegaly	+	–	–	–	–	
34	23	F	J	Asymptomatic splenomegaly	–	–	–	–	–	
35	17	F	J	Acute osteomyelitis	–	–	–	+	–	

Key: J = Jewish, A = Afrikaner, N = Negro, B = British.

FIG. 1. Anteroposterior radiograph of the pelvis of a 45-year-old woman, showing collapse of both femoral heads.

years. However, following intensive physiotherapy, she ultimately regained a reasonable degree of mobility.

ASEPTIC NECROSIS OF THE FEMORAL HEADS

Twenty patients had aseptic necrosis of the femoral heads. This complication presented with pain and limitation of movement of the affected hip and caused considerable disability. However, in the early stages, radiographic changes were minimal. Progressive joint degeneration occurred with collapse of the femoral heads and destruction of cartilage (Fig. 1).

Nine of these patients had prostheses inserted into their hip joints. They have all done exceptionally well following the operations, without sepsis and with relief of pain and increased mobility.

PATHOLOGICAL FRACTURES

Three patients, all of Afrikaner stock, experienced pathological fracture following minor trauma. Of these, 2 sustained fractures of the humerus while one had a fractured fibula.

SPINAL MALALIGNMENT

In 3 Jewish patients collapse of vertebral bodies led to the development of kyphoscoliosis. In one, lung function was compromised by spinal deformity but in the other 2 there were no untoward sequelae. None had spinal cord compression. A Zulu woman had paraplegia due to a gibbus in the thoracolumbar region. This complication was of recent onset and she is still under treatment.

BONE DEFORMITY

Anteroposterior radiographs of the knees of several patients revealed expansion of the lower thirds of the femora. This "Erlenmeyer flask" deformity was accompanied by thinning of the cortex and patchy sclerosis. No patients had symptoms which could be attributed to bone involvement at this site.

GROWTH AND STATURE

Generalized stunting of skeletal growth was not observed and in general the average heights of the affected adults did not appear to be reduced. However, 3 Jewish patients had lost height due to their spinal deformity and one Afrikaner girl had small stature due to pituitary infantilism.

MANAGEMENT

Marrow infiltration and hypersplenism may lead to thrombocytopenia and abnormal bleeding and regular blood cell and platelet counts are indicated. Splenectomy is of value in the restoration of normal clotting activity but the timing of this operation is dependent upon critical assessment of hematological status. Schein and Arkin[8] stated that orthopedic complications in Gaucher disease may worsen after splenectomy. However, 17 of our patients had splenectomy without any exacerbation of their skeletal problems and we believe this supposition to be erroneous.

In the majority of patients, the aching, nonspecific bone and joint pains responded to simple analgesics. Bed rest and immobilization were occasionally necessary for pain relief and in a few patients traction was

employed to prevent soft tissue contractures. Attacks of pseudo-osteomyelitis were treated by bed rest, analgesics and antibiotics which were given as a precautionary measure against infection. Yossipovitch, Herman and Makin[9] have drawn attention to the resemblance of "pseudo" or "aseptic" osteomyelitis to acute hematogenous osteomyelitis. The accurate diagnosis of noninfective pseudo-osteomyelitis is critical because of the serious sequelae which may result from injudicious operation 4.

Pain and disablement consequent upon femoral head collapse was the most common and important orthopedic problem in our patients. Analgesics and walking aids were of value in the early stages but incapacity steadily increased. Prosthetic joint insertion has proved to be of great value in management. Nine patients had operations of this type: (Cup arthroplasty, one unilateral, one bilateral; Charnley prostheses, 2 unilateral, one bilateral; McKee-Farrar, 2 unilateral; Thompson femoral prosthesis, one unilateral; Müller prosthesis, one unilateral.) The results of these procedures have been uniformly excellent and none of the patients has experienced untoward postoperative problems. The youngest patient to have a prosthesis inserted was 14 years of age. A 42-year-old man had bilateral cup arthroplasties 12 years ago. These have functioned well until recently but he is now experiencing hip pain and replacement arthroplasty is being considered.

In the late stages of the disease, respiratory function may be compromised by pulmonary infiltration and by diaphragmatic elevation due to hepatosplenomegaly. Vertebral collapse leading to thoracolumbar kyphoscoliosis can exacerbate an already critical situation. Management of this complication is difficult and essentially conservative.

Currently there is no specific therapy for Gaucher disease and complications are treated on their own merits. Nevertheless, it can be foreseen that replacement of the defective enzyme may eventually be possible.

DISCUSSION

The fundamental abnormality in the condition is defective activity of the enzyme beta-glucosidase and the consequent accumulation of cerebroside-laden cells in the bone marrow. The clinical features result from pressure of the expanding abnormal cell mass and mechanical interference with normal vascular supply to the affected bone. The vascular insufficiency results in bone necrosis, pseudo-osteomyelitis and collapse of the femoral heads.[7]

In a clinical study of 34 Israeli patients with chronic Gaucher disease, Matoth and Fried[2] pointed out that diagnostic confusion often arises if an affected patient presents with joint involvement. Reported misdiagnoses include acute infective arthritis, Perthe's disease, idiopathic avascular necrosis, sickle-cell anemia, leukemia, Hodgkins disease, syphilis, growing pains, tuberculosis and rheumatic fever.[6] Similarly, it should be emphasized that the "Erlenmeyer flask" configuration of the distal femora occurs in a number of conditions other than Gaucher disease.[3]

The Jewish population of South Africa totals approximately 120,000 and as 28 patients have been identified in this group, the minimum prevalence of Gaucher disease is about one in 4,300. There must be a number of affected individuals who are as yet undiagnosed and others who are not known to us. Thus this figure is necessarily an under estimate and the true prevalence is probably of the order of one in 2,500.[1] Gaucher disease is also comparatively common in Israel[2] and in certain parts in North America where there are large numbers of Jewish immigrants of Eastern–European ancestry. In these regions joint problems associated with splenomegaly in an Ashkenazi Jewish patient should immediately raise the possibility of a diagnosis of Gaucher disease.

SUMMARY

Orthopedic problems are an important feature of the adult, chronic or non-neuropathic form of Gaucher disease. Thirty-five South African patients have been investigated and of these 29 had significant skeletal complications. Twenty-one had nonspecific bone pains, 14 had episodes of pseudoosteomyelitis and 2 had acute hematogenous osteomyelitis. Twenty experienced collapse of femoral heads and in 9, prosthetic joint replacement had been successfully undertaken. Four had kyphoscoliosis due to wedging of vertebral bodies and three had pathological fractures of tubular bones. Twenty-eight of the patients were of Askhenazi Jewish stock and the minimum prevalence of the disorder in this group in South Africa is one in 4,300. If skeletal problems and splenomegally coexist in a Jewish patient, the diagnosis of Gaucher disease warrants serious consideration.

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Gaucher Disease in the Afrikaner Population of South Africa

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SUMMARY

The chronic non-neuropathic form of Gaucher disease has been encountered in 10 individuals in the Afrikaner population of South Africa. The minimum prevalence in this community is 1 in 200 000 with a gene frequency of 0,0022, a heterozygote rate of 0,0044 and at least 9 000 clinically asymptomatic carriers of the abnormal gene. This gene must be present in about 1 in every 220 Afrikaners.

The majority of previously reported patients have been Ashkenazi Jews, in whom the condition is relatively benign. By contrast, the disorder in the Afrikaners is precocious in onset, with serious complications and rapid progression. The occurrence of Gaucher disease in a relatively high frequency in the Afrikaner population is important in terms of differential diagnosis, genetic counselling and prevention.

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The adult, chronic or non-neuropathic form of Gaucher disease is an uncommon disorder in which a genetically determined defect of the enzyme β-glucosidase leads to the accumulation of cerebrosides in the reticulo-endothelial system. Splenomegaly is often the presenting feature and other important complications include dyshaemopoiesis, collapse of the femoral heads and osteomyelitis. The clinical manifestations usually become apparent in early adulthood and the condition follows a fluctuant but progressive course.

This type of Gaucher disease is found most frequently in Ashkenazi Jews.[1] It has been reported in this ethnic group in South Africa[2,3] but in non-Jewish populations it is regarded as a rarity.

In a survey of Gaucher disease in all communities in South Africa, which commenced in 1971, we have encountered 46 affected individuals. Although the majority of patients were Jewish, no less than 10 were Afrikaners. In this particular group, the condition has a precocious onset, with severe complications and a poor prognosis. The purpose of this paper is to document the course and manifestations in these patients and to draw attention to the presence of this inherited disorder in the Afrikaner population.

PATIENTS AND METHODS

The patients in this series were encountered in the course of a nation-wide survey which we have undertaken during the past 7 years. A full clinical examination has been carried out on each patient and, in every instance, the diagnosis has been confirmed histologically or by biochemical demonstration of defective activity of β-glucosidase in leucocytes or cultured skin fibroblasts.

The ethnic origins of the 46 investigation subjects were: Ashkenazi Jews 28, African Negroes 2, mixed ancestry 3, British 3 and Afrikaners 10. The Afrikaner patients form the subject of this paper.

RESULTS

Details of the family background, mode of presentation, manifestations and complications are given in Table I.

As the Afrikaner population numbers approximately 2 million, 10 affected individuals in this group (including the 2 recently deceased patients) give a minimum prevalence for Gaucher disease of 1 in 200 000. On this basis, the minimum gene frequency is 0,0022, with a heterozygote or carrier rate of 0,0044. About 1 in every 220 Afrikaners has the faulty gene and there must be at least 9 000 of these clinically asymptomatic carriers in this community.

It is probable that there are other affected individuals who are not known to us, or in whom the diagnosis has not yet been reached. For these reasons, the prevalence rates and gene frequencies which we have been able to calculate may well underestimate the true situation.

DISCUSSION

Gaucher disease is conventionally classified into infantile and juvenile neuropathic types, and the adult chronic or non-neuropathic form. Although they share the same enzymatic defect, these three conditions are clinically distinct. In particular, involvement of the central nervous system is the predominant feature of the infantile and juvenile types, while this complication is absent in the adult or chronic type. This latter form of Gaucher disease is regarded as a disorder of the Ashkenazi Jews and it occurs in a prevalence of about 1 in 4 000 of this group in South Africa.[4]

Gaucher disease in the Afrikaners is much more severe than in the Jews, with earlier onset, serious complications and an accelerated course. As shown in Table I, symptoms developed in childhood in 6 of our 10 Afrikaner patients, while 2 died during the course of the survey. In the majority of the survivors, hepatosplenomegaly, bleeding problems and orthopaedic complications have caused considerable disability.

There is no specific therapy for Gaucher disease, but well-timed splenectomy and prosthetic hip joint replacement have proved to be of value in several Jewish

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TABLE I. CLINICAL AND GENETIC FEATURES IN 10 AFRIKANER PATIENTS WITH GAUCHER DISEASE

Patient	Sex	Year of birth	Age of diagnosis (yrs)	Presenting features	Course and complications	Splenectomy	Affected kin
1	F	1968	1½	Splenomegaly	Hypersplenism	+	—
2	F	1972	3½	Splenomegaly	Pseudo-osteomyelitis Thrombocytopenia	+	Brother (patient 3)
3	M	1974	3½	Splenomegaly Epistaxis	Bone pain Thrombocytopenia	+	Sister (patient 2)
4	F	1958	2	Splenomegaly	Pseudo-osteomyelitis Pathological fractures Thrombocytopenia Pulmonary infiltration Sexual infantilism Died aged 16	—	—
5	M	1974	6½	Hepatosplenomegaly	Hypersplenism Recurrent respiratory infections	—	Sister ?
6	F	1977	1	Hepatosplenomegaly	—	—	Aunt (patient 7) Uncle (patient 8)
7	F	1950	21	Splenomegaly	Bone pain Acute arthritis Collapse of femoral heads	+	Niece (patient 6)
8	M	1935	17	Splenomegaly	Collapse of femoral heads Anaemia Thrombocytopenia	+	Niece (patient 6)
9	F	1957	2	Splenomegaly Intermittent pyrexia	Thrombocytopenic purpura Anaemia	+	—
10	F	1938	30	Splenomegaly	Bone pain Anaemia Thrombocytopenic purpura Died aged 37		—

patients.[5] The same measures are applicable to the Afrikaner patients but, although the quality of life may be improved, it is unlikely that the ultimate poor prognosis is influenced to any extent. However, initial reports on enzymatic replacement have been encouraging and this form of therapy may be of value in the future.[6]

To the best of our knowledge, our findings indicate that the prevalence of the non-neuropathic form of Gaucher disease in the Afrikaner population is higher than that in any other group in the world, with the exception of the Ashkenazi Jews. As the same enzyme is defective in these two groups, it is possible but by no means certain that the same abnormal gene is involved. There is no known Jewish ancestry in any of the affected Afrikaner kindreds and the source of the faulty gene in this population is uncertain. There has been insufficient time since the major waves of Jewish emigration in the past one hundred years for gene flow to account for the present relatively high gene frequency in the Afrikaner population. The abnormal gene could have been derived from Jewish sources at the time of the emigration of the first burghers to South Africa three centuries ago. Equally, the gene might have arisen independently by mutation in the Dutch progenitors of the Afrikaner community. In either event, the operation of the 'founder effect' in the small but rapidly expanding White South African population of those times could account for the present-day high gene frequency in this group.

As Gaucher disease is inherited as an autosomal recessive gene, there is a 1 in 4 chance of recurrence in any further progeny of the parents of an affected child. In view of the severity of the condition in the Afrikaner population this genetic situation has important implications. The condition can be recognized in the fetus by estimation of enzymatic activity in cultured amniotic fluid cells and antenatal diagnosis is possible.[7] This procedure, together with selective termination, is an option which warrants consideration by any Afrikaner couple who have declared themselves to be 'at risk' by having produced an affected child.

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GAUCHER'S DISEASE IN SOUTH AFRICA

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Gaucher's disease in South Africa

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SUMMARY The adult non-neuropathic form of Gaucher's disease has been identified in 32 patients in 25 Ashkenazi Jewish kindreds in South Africa. The minimum prevalence in this population is 1 in 5000, with a gene frequency of 0·014 and a carrier rate of 1 in 36. On correction for bias resulting from possible under-ascertainment, these minimum figures become 1 in 4000, 0·0166, and 1 in 30, respectively.

Confirmation of autosomal recessive inheritance was obtained by segregation analysis by the 'a priori' and 'simple sib' methods.

The Ashkenazim of South Africa have their origins in Lithuania and it is evident that the high gene frequency in South Africa is a reflection of the genetic constitution of the immigrant population. The localisation of the Gaucher gene to Lithuania represents a further step in the determination of the early geographic distribution of the genetic disorders of the Jewish race.

The adult chronic or non-neuropathic form of Gaucher's disease is an autosomal recessive disorder in which activity of the enzyme β-glucosidase is defective. The condition runs a fluctuant but progressive course and the main clinical problems are splenomegaly, dyshaemopoeisis, osteitis, and collapse of weight-bearing joints (Matoth and Fried, 1965).

This type of Gaucher's disease is relatively common in the Ashkenazi Jewish population of South Africa (Beighton and Sacks, 1974). During the course of a nationwide survey we have attempted to ascertain and investigate every affected person, and in a 5-year period we have studied 32 patients in 25 Jewish kindreds. Our findings concerning the prevalence of the condition, the frequency of the abnormal gene, and the historical and geographic origins of the disorder are presented and discussed in this paper.

Classification

Gaucher's disease is conventionally classified into infantile, juvenile, and adult forms, which have also been given numerical designations. These conditions differ in the chronology of their clinical presentation and in their manifestations, course, and prognosis.

In the infantile form, death usually occurs in early childhood after infiltration of the central nervous system, spleen, and bone marrow with cerebrosides. Affected subjects have been encountered in many different ethnic groups.

The juvenile form is characterised by progressive dementia, cerebellar ataxia, and extrapyramidal dysfunction. The majority of patients have been reported from Sweden.

The adult chronic or non-neuropathic type, which forms the subject of this paper, usually presents in early adulthood. Lack of involvement of the central nervous system and a predominance in people of Ashkenazi Jewish stock are the main distinguishing features (Fried *et al.*, 1963). The fact that this type of Gaucher's disease is sometimes diagnosed in childhood has been the source of considerable semantic and nosological confusion. However, the situation may be clarified by the use of the term 'non-neuropathic' and the avoidance of the designation 'adult'.

The Jewish population of South Africa

The immigration patterns of South Africa's Jewish community fall into a number of distinct periods. Before 1800 a few Jewish settlers, who were rapidly assimilated into the Christian community, came with the ships of the Dutch East India company. Between 1800 and 1880 several thousand Jews arrived from Germany, Holland, and England. They were more communally orientated than the original settlers and organised religious congregations. However, they also were assimilated into the Christian majority so

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that few, if any, practising Jewish descendants of these families remain today.

The Jewish community of South Africa was largely fashioned by the mass immigration of Eastern European Jews between 1881 and 1910, who left their countries of origin, especially Lithuania, because of pogroms and persecution. Whole communities came in this way, bringing their distinctive traditions and culture.

In the 1930s, further immigration of Jews from Germany and other Nazi occupied countries took place, but the arrival of individual Jews since this period has been a very insignificant factor in population growth of the Jewish community. It has been estimated that between 1880 and 1940 about 40 000 Ashkenazi Jews entered this country from Eastern Europe. This movement ceased in 1937 after the passing of the Aliens Act.

The present day South African Jewish community of approximately 120 000 is largely derived from Eastern European ancestors. In a survey of Johannesburg Jews (50% of South Africa's Jewish population), it was found that 70% were descendants of parents or grandparents born in Eastern Europe, or were themselves born there.

Methodology

A circular letter requesting patient referrals was sent to every medical colleague in South Africa who was likely to care for patients with Gaucher's disease. These included orthopaedic surgeons, physicians, and general practitioners who served the Jewish community. The investigation was publicised in a national medical newsletter, in an article in the South African Medical Journal, and at national congresses. The Jewish community have an active interest in genetic problems and the condition was discussed at meetings of various cultural groups, in lay magazines, and in radio broadcasts. Hospital records and pathology and radiology museums provided further information.

The authors travelled throughout South Africa in order to investigate affected subjects, and clinical, radiographic, and laboratory studies were undertaken in most instances. A detailed family history was obtained, with particular reference to the geographic origin and ethnic background of the patient's progenitors.

Fresh samples of venous blood were obtained and transported by air, if necessary, to the genetic biochemical laboratory of the Medical School, Cape Town. β-glucosidase activity was determined in the white cells of the respondents and their sibs by the method of Beutler and Kuhl (1970). Before these special studies, the diagnosis had already been confirmed in the majority of patients by demonstration of the typical foamy Gaucher cells in bone marrow biopsy specimens.

Results

Thirty-two Ashkenazi Jewish patients in 25 kindreds were ascertained. Of these, 24 in 21 families were examined and investigated, while firm medical evidence permitted a positive diagnosis in 4 sibs of these subjects who were abroad or deceased. Medical data were also available concerning 4 other affected Jews in South Africa, who were not available for examination in the survey.

PREVALENCE

On a basis of the 24 living patients with Gaucher's disease in a total Jewish population of 120 000, the minimum prevalence of the disorder in this group is about 1:5000. This figure rises to approximately 1:4000 if the 4 patients who were not examined are included in the calculation.

GENE FREQUENCY

Taking the figures of 24 homozygotes in a population of 120 000, with a prevalence of 1:5000, the gene frequency (q) is 0·014. Therefore, the frequency of heterozygotes (2pq) is 0·028 (1/36) and the number of heterozygotes in the population of 120 000 is 3346.

If these figures are recalculated with the inclusion of the 4 patients who were not examined, together with an estimate of existing undiagnosed cases, based upon average age of presentation, birth rate, and population size, the minimum prevalence becomes 1:4000, with a gene frequency of 0·0166, and a carrier rate of 1 in 30 or 0·332.

GEOGRAPHIC ORIGINS

Information concerning the geographic origins of immigrant progenitors was available from 20 kindreds. In 13, both paternal and maternal families had lived in Greater Lithuania during the 19th century. In 6, only one side of the kindred came from this area, the others originating in Russia (4), Holland (1), and Czechoslovakia (1). In one family, both parents had emigrated to South Africa from Germany and had no known ancestral connections with Lithuania. The area of origin of the Gaucher's disease gene in Europe is shown in Fig. 1, in relationship to the distribution of other genetic disorders which reach their highest prevalence in the Ashkenazim, as determined by Meals (1970).

PEDIGREE DATA

Abbreviated pedigree data concerning the 21

kindreds are shown in Fig. 2. There were 15 male and 13 female patients.

There was no generation to generation transmission. Known consanguinity was present in one kindred.

The results of segregation analysis on 21 informative kindreds by the 'a priori' or Apert method were in accordance with autosomal recessive inheritance (21 sibships, 71 sibs, 28 affected, 28·98 expected, SE 2·69). Analysis by the simple sib method, after deletion of the proband, gave 7 observed, 12·5 expected, with a variance of 6 (limits 6·5 to 18·5), thus confirming the autosomal recessive mode of inheritance.

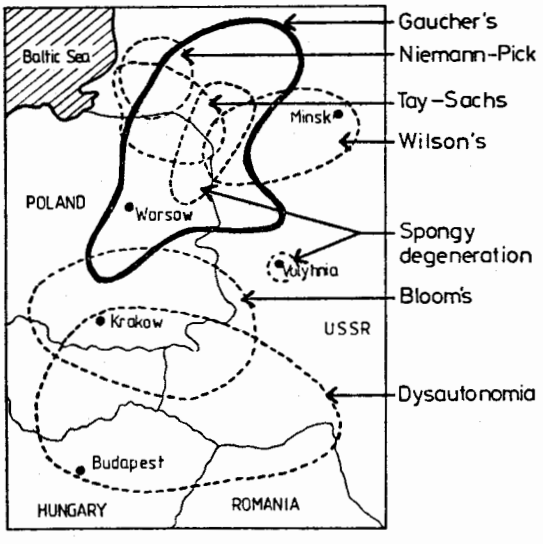

Fig. 1 *Initial European localisation of Gaucher's disease and other autosomal recessive disorders of the Ashkenazi Jews (Meals, 1970).*

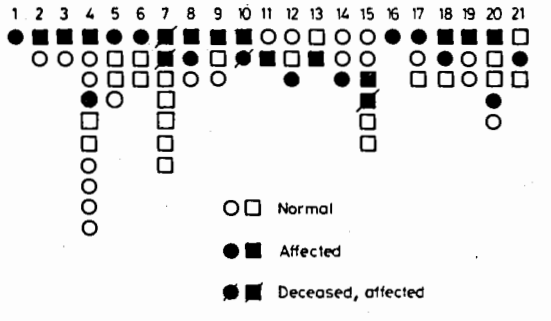

Fig. 2 *Abbreviated pedigree data from 21 kindreds with Gaucher's disease.*

GAUCHER'S DISEASE IN OTHER POPULATIONS IN SOUTH AFRICA

Information was available on a few subjects of non-Jewish stock, all with the non-neuropathic form of Gaucher's disease: 11 Afrikaners, 2 African Negroes, 2 British, and 2 sibs of mixed ancestry. Though no attempt was made at complete ascertainment in these populations, it is probable that a significant proportion of diagnosed cases would have come to our notice. The prevalence of the disorder in the British community (2 in 1·5 million) and the African Negro group (2 in 16 million) was very low. In the Afrikaners, the minimum prevalence was 1 in 200 000, with a gene frequency of 0·0022 and a carrier rate of 1 in 220. Approximately 9000 heterozygotes are present in this community (Goldblatt and Beighton, 1979).

Discussion

The progenitors of the Jewish population of South Africa had their origins in Lithuania and the prevalence of Gaucher's disease in this group reflects the genetic status of the early immigrants. The reason for the high frequency of the Gaucher gene in Lithuania is unknown and, superficially at least, heterozygotes do not seem to possess any biological advantage.

The recognition of Gaucher's disease in the Negro and British population of South Africa is not unexpected, as the condition occurs with low frequency in many non-Jewish groups. The comparatively high prevalence in the Afrikaner population is probably explicable on the basis of the founder effect, as this community is descended from a relatively small number of immigrants of Dutch stock.

Though activity of the enzyme β-glucosidase is defective in affected subjects in all populations the manifestations of the disease develop earlier and are more severe in the Afrikaners. At a fundamental level, it is not known whether the abnormal genes in the different communities are identical, allelic, or situated at different loci.

The high frequency of the Gaucher disease gene in the Jewish population of South Africa is of potential importance from the point of view of screening and prevention. However, laboratory procedures for detection of heterozygotes are complex, and at present population screening is not feasible.

From the clinical point of view, the high prevalence of Gaucher's disease in this community is important in terms of differential diagnosis. Indeed, unexplained splenomegaly or orthopaedic problems in a young adult of South African Jewish stock immediately raise the possibility of Gaucher's disease (Goldblatt *et al.*, 1979).

There have been numerous reports concerning the geographic origins of autosomal recessive disorders of the Ashkenazi Jews (Bearn, 1960; Barker *et al.*, 1964; Myrianthropoulos and Aronson, 1967; Meals, 1970). The localisation of Gaucher's disease to Lithuania represents a further step in the elucidation of this complex pattern.

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NON-NEUROPATHIC GAUCHER DISEASE PRESENTING IN INFANCY

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Non-neuropathic Gaucher disease presenting in infancy

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SUMMARY The non-neuropathic form of Gaucher disease was diagnosed in 11 children of non-Jewish ancestry in South Africa; all were under the age of 4. None had any neurological involvement and, apart from the precocious presentation and rapid course, the features in each resembled those of the classical 'adult' or chronic non-neuropathic form of Gaucher disease. By contrast, the condition presented after puberty in 24 out of 28 Ashkenazi Jews who were studied during the same investigation. Activity of β-glucosidase was defective in both groups of patients and they could not be distinguished by histological criteria. Only one child with the infantile neuropathic form of Gaucher disease was identified during the survey. The preponderance of the atypical non-neuropathic form of the disorder in young children is of practical importance from the point of view of differential diagnosis in any child with hepatosplenomegaly.

Gaucher disease is conventionally classified into three types: the adult or chronic non-neuropathic, the acute neuropathic infantile, and the subacute neuropathic juvenile (Fredrickson and Sloan, 1972).

The adult or chronic non-neuropathic form is characterised by splenomegaly, dyshaemopoeisis, and orthopaedic complications, in the absence of any neurological involvement. This entity has an overwhelming predilection for Ashkenazi Jews and is by far the most common form of Gaucher disease (Matoth and Fried, 1965). In the infantile type cerebrosides accumulate in the brain and death occurs before age 2. The rare, poorly defined juvenile type has onset in later childhood, involvement of the central nervous system, and a subacute course.

In a survey of all forms of Gaucher disease in South Africa in which 46 patients were investigated we found 13 young children with non-neuropathic Gaucher disease. In 11 of these, the disorder was diagnosed by age 4. As this condition usually presents in adulthood, this precocious onset is a matter of considerable clinical importance. A typical case is reported and details of the manifestations in the other affected children are tabulated and discussed in order to arouse diagnostic awareness and to emphasise that the non-neuropathic form of Gaucher disease can occur in infancy.

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Patients and methods

Since 1971, attempts have been made to examine and investigate every patient with Gaucher disease in South Africa. So far 46 with the chronic non-neuropathic form have been studied and in each the diagnosis was confirmed histologically or by demonstration of defective leucocyte β-glucosidase activity. Of these patients 28 were Ashkenazi Jews, 10 were Afrikaners, 3 were of mixed ancestry, 2 were African Negroes, and 3 were British. The survey methodology and the findings in the Ashkenazim have been reported elsewhere (Beighton and Sacks, 1974; Myers *et al.*, 1975; Goldblatt *et al.*, 1978). The genetic implications of Gaucher disease in the Afrikaners, including 7 of the patients in the present series, have also been reported (Goldblatt and Beighton, 1979b).

Surprisingly, the so-called 'adult' non-neuropathic form of Gaucher disease was diagnosed before age 4 in 11 patients, and at 6 and 8 years in 2 others. Apart from a pair of siblings in a Sephardic-Ashkenazi family, all these children were Afrikaners or of mixed ancestry. By contrast, the condition was clinically apparent in only 4 of the 28 Ashkenazi Jews before puberty and their symptoms were slight.

The classical infantile neuropathic form of Gaucher disease was found in only one patient, a baby born to a consanguineous Indian couple.

Personal and clinical data on the children with non-neuropathic Gaucher disease are shown in the Table, and a brief case report is given below.

Case report. Case 9, the only child of nonconsanguineous parents of mixed ancestry was born in 1974. He weighed 2·6 kg at birth and his neonatal course was complicated by jaundice, for which he received phototherapy.

He had several episodes of croup and bronchospasm during infancy and, at age 2, hepatosplenomegaly was detected during routine examination. Histological studies of bone marrow were undertaken and the diagnosis of Gaucher disease was established. Up to this point, his developmental milestones had been normal.

He was then lost to follow-up until, at age 3½, he again presented with shortness of breath and pyrexia. At this stage his abdomen was distended by a huge spleen which extended into the right iliac fossa, and the liver projected 10 cm below the inferior costal border (Figure). No abnormality could be detected in his central nervous system.

Figure *3-year-old child (Case 9) with Gaucher disease. Massive hepatosplenomegaly is evident.*

At this time he was pancytopenic with Hb 6·3 g/dl, a platelet count of 35·0 × 10^9/l and total WBC of 3·4 × 10^9/l, of which 8% were polymorphs.

During his stay in hospital he had several episodes of massive epistaxis which were attributed to his

Table *Clinical manifestations of children with non-neuropathic Gaucher disease*

Case	*Sex*	*Ethnic group*	*Age at diagnosis (years)*	*Presenting feature*	*Complications*			*Management*	*Family history*
					Skeletal	*Haematolcgical*	*Other*		
1	F	Afrikaner	1½	Splenomegaly	—	Hypersplenism	—	Splenectomy	—
2	F	Afrikaner	3½	Splenomegaly	Pseudo-osteomyelitis	Thrombocytopenia	—	Splenectomy	Brother (Case 3)
3	M	Afrikaner	3½	Splenomegaly. Epistaxis	Bone pain	Thrombocytopenia	—	Splenectomy	Sister (Case 2)
4	F	Afrikaner	2	Splenomegaly	Pseudo-osteomyelitis. Pathological fractures	Hypersplenism	Pulmonary infiltration. Sexual infantilism. Died age 16	—	—
5	M	Afrikaner	6	Hepatosplenomegaly	—	Hypersplenism	Recurrent respiratory infections	—	Affected sister?
6	F	Afrikaner	1	Hepatosplenomegaly	—	—	—	—	2 adult relatives affected
7	F	Mixed ancestry	8	Hepatosplenomegaly	—	Thrombocytopenia	—	—	Brother (Case 8)
8	M	Mixed ancestry	3½	Respiratory infections. Anaemia	—	Thrombocytopenia	Recurrent respiratory infections	—	Sister (Case 7) 3rd sibling probably affected
9	M	Mixed ancestry	2	Hepatosplenomegaly	Rib and clavicle involvement	Hypersplenism	Recurrent respiratory infections	—	—
10	M	Afrikaner-Hungarian	1½	Hepatomegaly	Arthritis. Fractured femoral neck	—	—	Splenectomy	—
11	F	Ashkenazi-Sephardic	4	Malaise. Splenomegaly	—	Hypersplenism	—	—	Sister (Case 12)
12	F	Ashkenazi-Sephardic	3	Croup. Splenomegaly	—	Hypersplenism	—	—	Sister (Case 11)

thrombocytopenia. Cardiac failure developed after numerous blood transfusions, and treatment with digitalis was eventually needed.

β-Glucosidase activity in cultured fibroblasts obtained after skin biopsy was markedly diminished. His mother had intermediate levels of activity in her own cultured fibroblasts, and this was taken to be indicative of her status as a heterozygote for the Gaucher disease gene. The father was not available for investigation.

The patient is now aged 3½ years. He experiences considerable malaise and his activity is impaired by the gross distension of his abdomen. He has severe hypersplenism and chronic anaemia with a large heart and borderline cardiac failure. His prognosis is considered to be poor.

Discussion

Although they share a common autosomal recessively inherited defect of the enzyme β-glucosidase (Brady, 1978), it is generally accepted that the infantile, juvenile, and adult or non-neuropathic forms of Gaucher disease are separate conditions. At a clinical level death from central nervous system involvement in the infantile and juvenile types, and the prolonged course and absence of neurological complications in the adult form, represent obvious distinctions between these entities.

The ethnic predilection of the adult form of Gaucher disease for the Ashkenazim is well known and in the Jewish community of South Africa this condition is present in about one in 4000 (Goldblatt and Beighton, 1979a). None of our Ashkenazi Jewish patients with this type of the disorder had any neurological involvement and only 4 experienced symptoms before puberty, and these were slight. By contrast, with the exception of the pair of siblings with an Ashkenazi father and a Sephardic mother, none of the 11 children who developed symptoms before age 4 was Jewish. In these children there were no changes in the central nervous system and, apart from the precocious onset and rapid progression, the disease followed the same general course as in the Jewish patients.

The reason for this temporal discrepancy in the development of the disorder is unknown although at a fundamental genetic level allelism or epistasis could be invoked as possible explanations. In view of the nature of our survey methodology, it is unlikely that ascertainment bias or inadequate case investigation could be responsible for this paradox. It is interesting that there was no correlation between the magnitude of the enzymatic defect and the severity of clinical manifestations in any patient.

The occurrence of non-neuropathic Gaucher disease in infancy was noted 40 years ago (Aballi and Kato, 1938), but this form of the condition has been ignored in conventional classifications. However, in a report of these infants with hepatosplenomegaly, Schneider *et al.* (1977) drew attention to early onset and rapid progression in certain non-neuropathic cases.

The magnitude of the problem of early presentation is highlighted by the fact that we found only one patient with the classical infantile neuropathic type of Gaucher disease, in contrast with the 13 children who had the atypical non-neuropathic form. This 13-fold preponderance is of considerable importance from the point of view of differential diagnosis in any child with unexplained hepatosplenomegaly.

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