Departments of Medical Genetics (Franz J. Kallmann, M. D.) and Neuropathology (Armando Ferraro, M. D.) of the New York State Psychiatric Institute, Columbia University, New York 32, N. Y. (U. S. A.)

A GENETIC STUDY OF PAGET'S DISEASE (OSTEITIS DEFORMANS) IN MONOZYGOTIC TWIN BROTHERS

by

Bertha M. Aschner, M. D., Lewis A. Hurst, M. D. and Leon Roizin, M. D.

Since the various applications of the twin study method are certain to play an essential part in the study of many disease entities of still unknown etiology, Prof. Gedda's project of an archive devoted exclusively to observations on twins appears to be an admirable idea. Statistical research data and casuistic reports dealing with the histories of twins have rapidly increased in recent years, both in volume and in the number of publications, in which they may be found. How long this increase will continue, and how far it will advance our knowledge of genetic background factors, is still difficult to foresee at this point. It is quite evident, however, that as a supplement to Gedda's recent book on twins (8), a scientific journal continuing his encyclopaedic work will serve a very useful purpose.

Without such an archive, many casuistic reports on twin pairs either will be lost entirely or would be very limited in value. This statement refers especially to rare disorders or to very unusual complications of more common conditions assumed to be determined genetically. With respect to uncommon pathological traits, individual investigators or research organizations will often find it difficult to make definitive contributions to an understanding of the given etiological problems, since they may not be able to collect data on a sufficiently representative series of cases within a reasonable period of time. The best that can be done in these instances is a recording of isolated observations in a special archive, in the hope that the given problem will lend itself to statistical analysis at some future date.

With this idea in mind, we feel justified in presenting a report on a pair of one-egg twins incompletely concordant as to Paget's disease (osteitis deformans), although this condition can no longer be classified as rare in the literal sense of the term. In fact, medical interest in this disorder has considerably increased in recent years, because its occurrence appears to be less infrequent than was assumed originally. Much of the current interest is directed toward the etiological aspects of the disease, since the clinical, anatomical and diagnostic features have

Ricevuto il 20. XI. 1951

been sufficiently explored and the ineffectiveness of the known methods of treatment is rather generally accepted.

As to the etiology of Paget's disease, it may be noted that many investigators have been satisfied with theories explaining the disorder on an endocrinological basis. This suggestion was originally made by analogy with generalized cystic osteitis (Recklinghausen), which at that time was not clearly distinguished from Paget's disease. Later it was recognized that the two syndromes were different nosological entities, and it also became obvious that there was no endocrine dysfunction that would produce Paget's disease. The theory of an endocrine origin was rejected especially by Kay and his collaborators (16) as well as by Hanke (12).

Similarly, the notion of a possibly syphilitic nature of the condition as expressed by older French authors (6) was abandoned very soon. In the vast majority of cases, the Wassermann reaction was found to be negative, and no other evidence of syphilis was ever elicited.

According to Hurwitz (13), Paget's disease was to be regarded as a metabolic disorder, but increased phosphatase in the blood was the only disturbance in the mineral metabolism known to be associated with the disease. Similar doubts appeared to be warranted with respect to a disturbed carbohydrate metabolism, evidence of which was described by Moehlig and Adler (22). They observed a " diabetic " type of alimentary hyperglycaemia in some of their cases, and a familial form of diabetes mellitus in 30 per cent of their total material. The observation of diabetes mellitus in the families of Paget cases was also reported by Newman (27) and some other investigators, although it should be borne in mind that the vast majority of diabetics remain unaffected by osteitis deformans.

In the opinion of Sabatini (29), an infective agent in association with a certain degree of hypovitaminosis was to be considered as an important etiological factor. This theory was based on his own observation of two similar cases of osteitis deformans in husband and wife, and on hearsay knowledge of another conjugal case. However, such cases are extremely rare, and most probably coincidental. Both Lereboulet (1922) and Faugeron (6) saw only one case each in consorts, and Sear (32) described the occurrence of the disease in two brothers-in-law who did not live in the same household.

By contrast, the tendency of Paget's disease to occur in several members of the same kinship (blood relatives) is far more striking than its rare occurrence in two marriage partners. In 1923, Faugeron (6) was able to collect 14 families with 29 afflicted members from the older literature, and 23 years later, a total of 27 families were reported by Koller (18), including two families which he had observed. In Koller's series, there were three families with four affected members, seven families with three, and seventeen families with two. In 1948, over 30 families with at least two affected members were recorded by Montagu (25). According to Lasserre and Faugeron (6), familial occurrence was demonstrable in seven per cent of the Paget cases reported in earlier publications.

Since the familial cases included in Koller's series were extensively reviewed

by him, it may suffice here to specify those cases which were not available to him. Thus it may be noted that Richard (1887) saw the disease in father and son, Cockayne (28) in father and daughter, Thalmann (37) in mother and daughter, and Robinson (1887) as well as Dubreuilh and Laubie (1924) in two brothers. In addition, familial occurrence was observed by Da Costa (19) in two sisters, by Walter (19) in brother and sister, by Schwartz (31) in three brothers, and by Newman (27) in two siblings of unspecified sex. Boyd (3) mentioned two families with three cases in each, while a total of 16 familial cases were found by Dickson, Camp and Ghormley (4) among 367 cases of the Mayo Clinic (4.4 percent with a positive family history). In 14 families of the latter series, there was only one secondary case in the family. In another family, three siblings were affected, and especially interesting was a family unit, in which the disease was traceable through four generations (the index case and a brother, their mother and a maternal aunt, the maternal grandmother and the maternal great-grandmother). The last family should be given as much emphasis as was placed by Koller upon the interesting pedigree followed by Bogaert and his father through five generations. In the Belgian family, seven cases of Paget's disease occurred in three generations, either alone or in combination with retinitis pigmentosa, but the youngest available generation had not reached the age of manifestation of the disease. It was observed by Sear too, that osteitis deformans tended to run in families.

In investigating the basis of this statement, one finds reference to a total of 55 familial cases in the literature. Irrespective of the fact that 16 of these family units included more than two affected members (actually, in two families the disease ran through three or four generations), an explanation in terms of pure coincidence would seem to be rather improbable in view of the relative infrequency of the disease. According to Koller, the observed incidence of Paget's disease in the Swiss population is only .013 per cent, and this figure is in agreement with the rate given by Gutman and Kasabach (11) as well as by Newman (27) for the American population. In fact, the occurrence by chance of three cases of Paget's disease in a family comprising eleven persons was estimated by Koller at 1 : 3,500,000,000. There is little doubt, therefore, that the tendency of Paget's disease to recur in certain families definitely exceeds random expectation. In other words, the genetic theory offered by a number of investigators appears to have been justified (Aschner, Bogaert, Moehlig and Murphy, Rast and Parkes Weber, Koller, Montagu and others).

The genetic hypothesis is strengthened by the observation of an equally unusual localization of the disease in some families. For instance, in the two siblings described by Kay, Simpson and Riddoch (16) it was mainly the radius which revealed osteitic deformities.

Unfortunately, the evidence regarding the mode of inheritance involved is still rather obscure. One complicating feature is that a diagnosis of Paget's disease cannot be excluded without roentgenographic verification. There are numerous asymptomatic cases which can be identified only by X-ray. For instance, in the

sample of 116 cases of Paget's disease recorded by Gutman and Kasabach (11), 27 cases were discovered accidentally when a skull X-ray was taken. In fact, there is reason to believe that no more than one-third of Paget cases can be diagnosed clinically with any degree of certainty. According to Dickson and his collaborators (4), a series of 367 cases included 75 patients who had been clinically asymptomatic and were accidentally discovered by X-ray.

Another difficulty stems from the tendency of Paget's disease to manifest itself comparatively late in life, and even then sometimes only in a mild form. It is quite certain, therefore, that the number of affected individuals in the family units recorded in the literature would have been considerably higher if all the persons in question would have been beyond the age of 60 and would have been examined by X-ray. In view of these facts, Montagu may have been correct in suggesting an incompletely dominant type of inheritance in Paget's disease.

In order to prove or disprove the theory of incomplete dominance, it would be desirable to have a representative series of observations on the rate of concordance in monozygotic twins. Unfortunately, the only pair on record seems to be that of identical twin brothers reported by Martin (20). One of the twins had a generalized type of the disease, while the other had a clinically asymptomatic type of osteitis deformans of the spine, which was discovered only by autopsy.

Since the available literature on the occurrence of Paget's disease in twins is rather inadequate, it is essential to record every new case. The present total number of 5865 adult twin index cases, kept under observation at this Institute (Dr. Kallmann) either for psychiatric or for geriatric reasons, includes an unselected series of over 2,500 senescent twin index pairs over age 60 (14). However, a thorough investigation of this series yielded only two pairs, in whom evidence of Paget's disease had been observed. One pair was dizygotic and to be classified as discordant as to the disease. The other pair (Figures 1 and 2) was monozygotic and displayed an incomplete degree of concordance. The histories of this pair were sufficiently interesting, both clinically and histopathologically, to be reported here in some detail.

William and Charles K. were born in 1877, of Irish descent. They always looked so much alike that neither their own relatives nor their wives could tell them apart. They grew up together, were extremely similar in their personalities, and progressed equally well in school. They chose similar occupations and worked themselves up to the status of foremen, William in a mill, and Charles in a factory. Although they were separated through Charles' marriage at the age of 19, they continued to live in the same small town, remained very close to each other, and attained a similar degree of respectability. The marriages of both twins were happy. William had one son, while Charles had a son and a daughter. The latter developed an unusual neurological disorder with anemia, diagnosed as a sprue-like vitamine deficiency disease with a localized lesion in the spinal cord, and died at the age of 38.

Family History: The father of the twins drank excessively and died of Bright's

disease. The mother and one of her sisters succumbed to a stroke at a rather young age. Another sister died of pulmonary tuberculosis and a third one of an acute infective condition, possibly influenza or poliomyelitis. A half-sister of the twins' father developed a paranoid type of schizophrenia in her thirties.

William's Clinical History: Apart from two attacks of pneumonia and frequent headaches, William's state of health was satisfactory until he reached the age of 55 (1932). At that time, apparently following a brief illness (tonsillitis), an impairment in his hearing became noticeable, which soon led to almost complete deafness and the loss of his job. Concomitantly, he showed evidence of unsteady gait, a gradual increase in the size of his head (1935), and general emotional instability with marked anxiety and temporary hallucinatory episodes (visual hallucinations). In 1937, his psychotic behavior required admission to a mental hospital.

Upon admission, the internal organs and the neurological status were recorded as normal, except for almost complete deafness and a systolic murmur over the apex of the heart. Laboratory findings including blood chemistry were negative. The circumference of the skull was 24 inches, and roentgenographically there was definite mottling of the bones of the skull, compatible with the clinical diagnosis of Paget's disease. Some of the ribs showed similar changes, but the long bones were essentially normal. Psychiatrically, William was found to be slightly disoriented and quite uncooperative. He complained of visual hallucinations and had a tendency to grind his teeth.

Subsequently, the head continued to grow in size. In 1939, X-rays revealed a considerable progression of the disease and its extension to the tibiae. Hallucinations disappeared in 1938, but recurred toward the end, together with advancing mental deterioration. Death occurred on October 24, 1940, and was ascribed to pulmonary congestion in a 63 year-old psychotic patient affected by Paget's disease.

The autopsy revealed that all of the bones of the skull were markedly thickened, especially in the frontal region where the bone measured about seven-eighths of an inch in thickness. The bone structure of the skull was soft, while the ribs and tibiae showed deformations characteristic of Paget's disease. Sella turcica and pituitary were free of gross pathological changes. The same was true for lungs and heart. The circumference of the aorta 10 mm. above the aortic cusps was 68 mm. Its elasticity was diminished, and there were many atheromatous patches throughout the thoracic and abdominal portions. While the common iliac arteries showed similar well-defined atheromatous changes, the abdominal organs were free of gross pathological lesions.

Neuropathologic observations

Macroscopic Findings: The brain weight was 1212 gm. The dura was thin and moderately adherent posteriorly along the longitudinal fissure, but was free elsewhere. The pia was thin and clear. The vessels of the base were thickened and showed slight atheromatous changes. Those of the convexity were thin and free

of gross changes. The convolutions were regular in their arrangement and pattern, although somewhat broad and definitely flattened throughout, with slight widening of the sulci. There was a moderate increase of the cerebrospinal fluid.

The whole brain was fixed in 10 % formalin. Frontal section through the brain disclosed marked dilatation of the lateral ventricles and thinning of the sur-

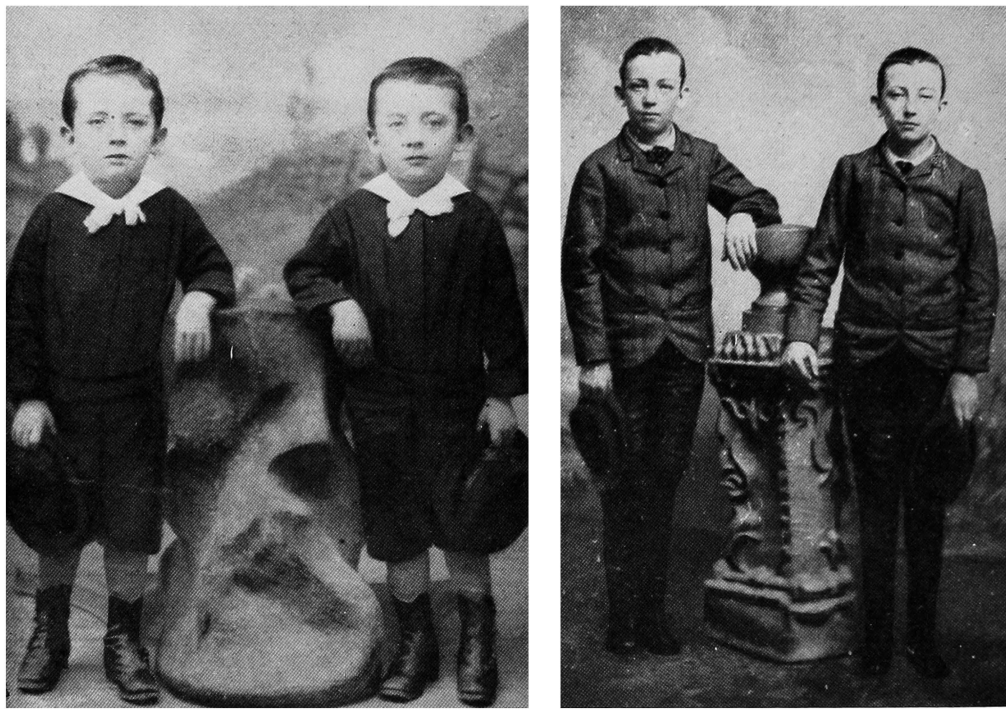


Fig. 1. The K. twins in childhood

rounding white matter. There were neither any notable signs of obstruction of the communicating interventricular openings nor any gross changes in the choroid plexus. The walls and the floor of the third and fourth ventricles appeared smooth.

Blocks were taken from the frontal, parietal, temporal and occipital lobes; also from the basal ganglia, mesencephalon, pons, cerebellum and medulla oblongata.

Microscopic Findings: By means of various laboratory techniques for the study of nerve cells, glia elements, blood vessels, myelin sheaths, various degenerative products, nerve fibers and senile plaques, the following histological observations were made:

1. *Vascular Alterations:* The main features consisted of mild arteriosclerotic changes of the intima, associated with some atrophy and hyalin degeneration of the muscularis. Occasionally, thickening of the adventitia was observed, in addition to dilatation of the perivascular spaces, which sporadically were filled with glia nuclei and more frequently with compound granular corpuscles. In Nissl

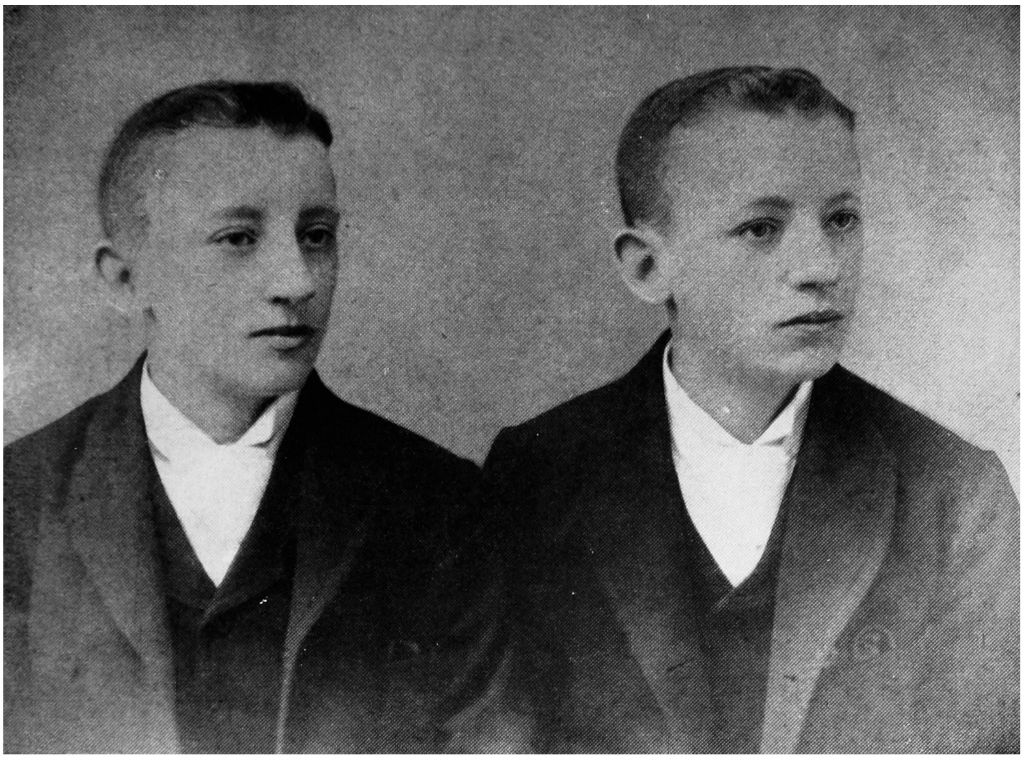


Fig. 2. The K. twins at the age of 16

preparations and in those made with Hematoxylin and Eosin, most of the phagocytic material of the compound granular corpuscles assumed a bluish coloring. The fat staining methods disclosed fatty products of degeneration, especially in the intima and media. In other instances, the fatty material of degeneration was incorporated in the compound granular corpuscles. Around the blood vessels and, as stated previously, in the perivascular spaces, some of the compound granular corpuscles were mixed with metachromatic and amyloid bodies.

The Van Gieson method revealed spotty but definite proliferation of the connective tissue, involving mostly the adventitia and occasionally the surrounding

tissue. The Weigert method for elastic tissue disclosed some degeneration as well as splitting and thickening of the elastic membranes.

2. *Degenerative Changes of the Nerve Cells:* The neurons of the various layers of the gray matter of the cortex (Figures 3a and 3b) as well as a large number of those of the nuclear formations of the basal ganglia, hypothalamus, mesencephalon, pons, cerebellum and medulla showed various degrees of degeneration. In the brain cortex, some small acellular areas were seen. Rarefaction of the neurons appeared to be scattered in various regions of the central nervous system, and was somewhat more pronounced in the Purkinje layer of the cerebellum. In several folia of the cerebellum " conglutination " of the granular cells was prominent.

Fat staining methods disclosed a large number of nerve cells, which were undergoing fatty degeneration (Figs. 3c and 3d) with no predilection for any area or layer of the cortex. Ganglion cells of the different nuclear formations of the basal ganglia, thalamus, brain stem, pons, cerebellum and medulla showed a similar process of fatty degeneration, but to a lesser degree than was seen in the neurons of the gray matter of the cerebral cortex.

3. *Demyelination:* Slight demyelination was noticed particularly in the periventricular regions of the lateral ventricles and extended into a part of the centrum semiovale, where Roizin's combined method for myelin sheaths and lipid products of disintegration showed rarefaction and moderate degenerative changes of the myelin sheaths. Products of myelin disintegration and lipid material of degeneration in the given areas were seen only sporadically, but were more pronounced in some perivascular spaces or in the surrounding tissues. The silver impregnation of nerve fibres revealed no marked involvement of the axon cylinders in these areas, although slight rarefaction of axon cylinders was encountered in a few instances.

4. *Metabolic Degenerative Products:* Metachromatic or amyloid bodies were noticed in Nissl, Hematoxylin and Silver impregnation. These structures appeared especially in the subependymal and surrounding regions of the lateral and third ventricles, in some subpial areas of the brain cortex and in certain perivascular spaces (mostly in the white matter). Fibrosis of the choroid plexuses was observed in Hematoxylin and Eosin, and in Van Gieson preparations. In addition, there were psamoma bodies or concentric-like calcifications in certain areas around blood vessels (Fig. 3e) and within the stroma of the choroid plexuses (Fig. 3f). No calcifications of this kind nor any other types of calcium deposit were found in the nervous tissue studied.

The Braunmühl Silver method revealed no evidence of senile plaques.

5. *Glia Reaction:* There were signs of a slight gliosis, particularly in the periventricular regions of the lateral ventricles and in the areas of mild demyelination.

In general, the histopathological impression was that the available material did not suffice to clarify the basic etiological problems posed by Paget's disease. In particular, it remained for future investigations to determine whether and to

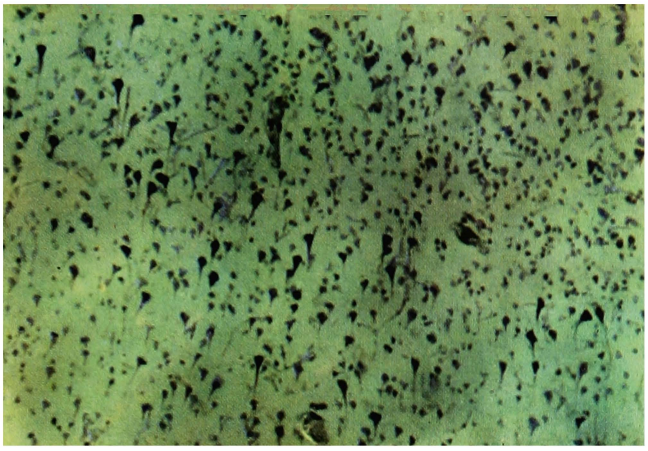


Fig. 3a
Cerebral cortex, frontal lobe. Nissl stain.
Low power magnification.

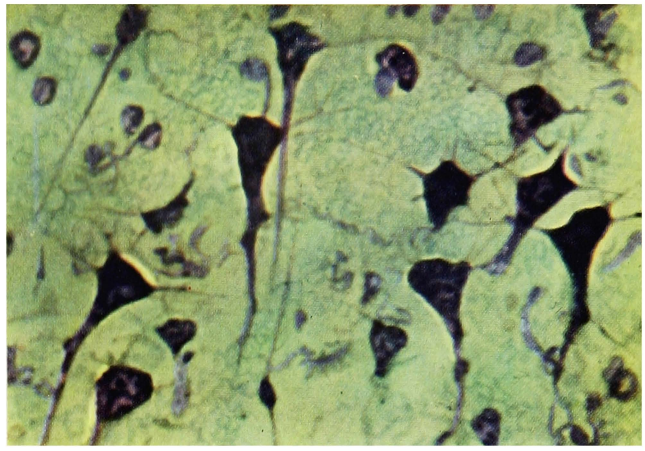
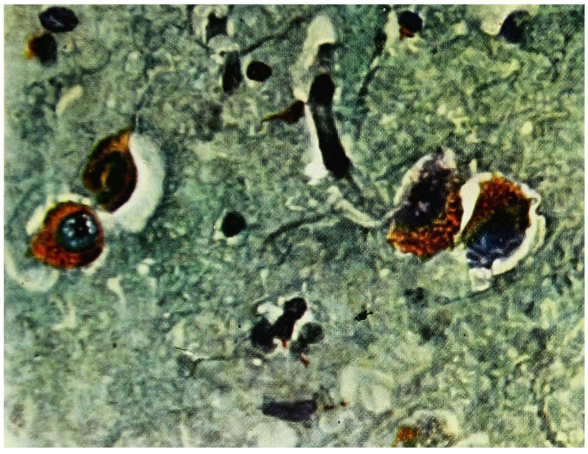
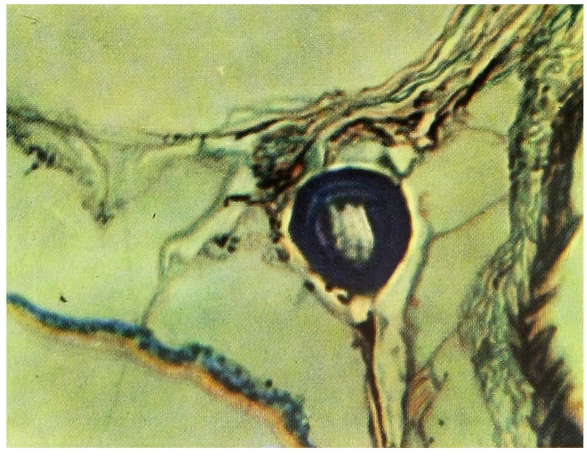


Fig. 3b
Cerebral cortex, temporal lobe. Nissl stain.
High power magnification.



Figg. 3c and 3d
Various areas from cerebral cortex. Sudan III stain.
High power magnification.



Figg. 3e and 3f
Calcifications in choroid plexuses. Nissl stain.
Low power magnification.

https://doi.org/10.1017/S1120962300042384 Published online by Cambridge University Press

what extent the observed histological changes were an expression of a specific structural or generalized metabolic disturbance on the basis of some genically controlled endocrine disorder or a nutritional imbalance of an organic or inorganic nature.

Charles' Medical History: At the time when William's condition became so pronounced that it required hospitalization, Charles was reported by his family physician to have complained of " rheumatic pains " in the arms and legs for several years. He also showed evidence of a moderate hearing defect and of an increasing emotional instability with marked anxiety and suspiciousness. His illness was diagnosed as " rheumatoid arthritis ", if only because the patient refused to undergo a thorough physical examination in the local hospital. He became more and more seclusive and failed to cooperate with any diagnostic or therapeutic scheme suggested to him. In 1945, his head was described as " large ", but no measurements were taken. A few months later, he developed an apparently acute confusional state, which was followed by stuporous apathy and, in March 1946, necessitated his admission to a mental hospital. Upon the insistence of his family, he was not brought to the nearest hospital where his twin brother had died, but to another institution. There he was found to be agitated, confused and entirely disoriented. His physical condition was so poor that a complete examination could not be undertaken. There was a systolic murmur over the apex of the heart, but the blood pressure was within normal limits. The urine contained a moderate amount of albumen, while NPN was 66.6 mg%, uric acid in the blood was 6 mg%, and blood creatinine was 2.2 mg%. Death occurred on the twelveth day after admission, but permission for an autopsy could not be obtained.

In the absence of a complete medical history and especially without roentgenographic and histopathological findings, it was impossible with respect to Charles' condition either to preclude a diagnosis of Paget's disease or to ascertain it with the same degree of certainty as in William's case. It was definite only that the twins were monozygotic, that William died of Paget's disease at age 63 after an illness of approximately seven years' duration, and that Charles died in a stuporous condition six years later after he had had severe " rheumatic " pains in both arms and legs for many years. In addition, both twins developed hearing deficiencies, diffuse mental changes and enlargement of the size of the skull in their late fifties, but William's symptomatology was unquestionably more severe in every respect. It can only be stated, therefore, that Charles may have had an unusually mild and clinically almost asymptomatic form of Paget's disease. If one accepts this classification, there were striking dissimilarities in the symptomatology, course and severity of the disease, although the twins were monozygotic, that is, genotypically alike.

It is of interest to note that the only other pair of one-egg twins with Paget's disease, recorded in the literature (20), showed the same degree of dissimilarity in the manifestation of the disease. In Martin's case, one twin had a severe, generalized form of the disorder, while the other twin was more or less asymptomatic

from a clinical standpoint and was found only anatomically to have typical bone changes in the spine.

It is reasonable to conclude, therefore, that the mutant gene or genes, which appear to be responsible for the underlying metabolic dysfunction resulting in Paget's disease, must be expected to display varying degrees of penetrance and phenotypical expressivity. Evidently, this conclusion is compatible with Montagu's theory of an incompletely dominant mode of inheritance.

In relation to the apparent variability of expression of the given genotype, it is essential to bear in mind that Paget's disease tends to occur more frequently in males than in females. According to Sugarbaker (36) and other investigators, the observed sex distribution favors the female sex, as there is a definite excess of affected males over affected females, the ratio approximating 3 : 2. It is obvious that this type of sex distribution precludes the ordinary forms of sex-linked inheritance. If a sex-linked gene is dominant, an excess of affected females is to be expected, while recessive sex linkage usually leads to a more unequal distribution of the sexes in the opposite direction.

Another point of interest is the tendency of Paget's disease to occur in association with other severe disturbances. According to Newman (27), Snapper (34), Moehlig and Adler (22), Sear (32) and others, the list of concurrent diseases observed includes benign and malignant tumors, diabetes mellitus, obesity, goiter, renal calculi, gallbladder stones, and retinitis pigmentosa. Unfortunately, most of these observations of concurrence with Paget's disease have been in reference to single family units. It is apparent, therefore, that statistically more adequate investigations will be required for establishing the general validity of these casuistic findings. This statement holds true especially for the very interesting combination of Paget's disease with sarcomatous or carcinomatous (metastatic) growth in affected bones or in other parts of the skeletal system as reported by Sugarbaker (36), Sear (32), Martin (20) and others.

From a neuropsychiatric standpoint, the frequent association of Paget's disease of the skull with neurological symptoms or various mental changes is of particular significance. Apart from such general symptoms as headache and dizziness, the most common clinical complications are those referable to an impaired function of the cranial nerves. Although the auditory nerve seems to be the most vulnerable one in this syndrome, one also finds cases with optic atrophy and with various disturbances of the other nerves. In Newman's series, about one-quarter of patients afflicted with osteitis deformans showed cranial nerve complications, and of this total of 22 cases, twenty had auditory and two had visual disturbances. In fact, Gutman and Kasabach (11) observed deafness in 26 out of 116 cases of Paget's disease, while Fowler (7) saw this symptom in as many as 41 out of 99 cases.

One of the earliest explanations of this tendency to cranial nerve involvement- and apparently the correct one- was offered by Schüller (1911) in terms of organic changes distinguished by a deformation of the basis of the skull with narrowing

of the foramina of the cranial nerves and with a corresponding stenosis of the foramen magnum. This stenosis has been assumed to cause pressure on the medulla and to press the cerebellum against the tentorium. Anatomical observations in support of this theory have been described by Grünthal (10) and Stauder (35) in the form of hydrocephalus and various destructive changes in the cerebellum, pons and medulla. The given findings have also been held responsible for those mental changes observed in connection with osteitis deformans of the skull.

The psychiatric concomitants described range from diffuse personality changes and convulsive, depressive or paranoid symptoms to severe intellectual defects (dementia) and to gross disturbances in memory and orientation, that is, to Korsakoff-like syndromes. In certain instances, a more or less coincidental association with arteriosclerotic or senile changes is to be expected. It is beyond question, however, that Paget's disease occurs in the absence of cerebral arteriosclerosis, and it is also true that convulsive or clearly psychotic phenomena (delusions, hallucinations) are relatively rare concomitant symptoms. It is possible, therefore, that such rather unusual forms of psychotic symptomatology are best explained by an association of the osteitic genotype with other genetically controlled vulnerabilities (schizoid personality, convulsive tendency etc.). In the present case (especially in William), this explanation would seem to be the most plausible one, since the twins' father had a half-sister who was schizophrenic.

In conclusion, it may be stated that the observation of incompletely concordant behavior of one-egg twins with respect to Paget's disease is consistent with the current genetic theory, according to which it is implied that the condition is based on the effect of an incompletely dominant, autosomal gene with variable degrees of penetrance and expressivity. Apparently, the expression of the genotype may vary from a fairly generalized type of osteitis deformans with cranial nerve involvement (deafness, disequilibrium) and pronounced psychotic phenomena (paranoid delusions, visual hallucinations) as observed in one member of the monozygotic pair recorded (William), to a very mild and clinically almost asymptomatic form of the disease (moderate hearing defect, slight disorientation and general personality change, rheumatic pains diagnosed as rheumatoid arthritis) as reported with regard to the other member of the pair (Charles). Unfortunately, a prolonged lack of cooperation on the part of the latter, intensified by the fatal outcome of William's disease, made it virtually impossible not only to ascertain the diagnosis roentgenographically and beyond a shadow of doubt, but also to obtain a complete medical and psychiatric history. For the same reason, histopathological data are available only for the more seriously affected twin partner.

There is reason to believe that the deforming changes in the skull as characteristic of Paget's disease are insufficient as such to explain the occurrence of convulsive or psychotic phenomena in some of the patients. It is probable that these organic changes (apparently through pressure exerted by the compressed skull) represent only a precipitating trigger mechanism, by which certain endogenous personality trends are released.

In addition to the two pairs of one-egg twins recorded in the literature (that of Martin and the present set), the current number of families, in which Paget's disease is known to have occurred in more than one member, has reached a total of 57 units.

References

1. Aschner, B. and Engelmann, G., *Konstitutionspathologie in der Orthopädie. Berlin,* J. Springer (1928).
2. Bogaert, L. v., *Ueber eine hereditäre und familiäre Form der Pagetschen Osteitis deformans mit Chorioretinitis pigmentosa. Z.* ges. Neur. Psychiat. 147: 327 (1933).
3. Boyd, W., *A Textbook of Pathology.* Philadelphia, Lea and Febiger (1947).
4. Dickson, D. D., Camp. J. D. and Ghormley, R. K., *Osteitis deformans: Paget's disease of the bones.* Radiology 44: 449 (1945).
5. Eeden, J. H. v., *Isolierte Pagetsche Krankheit des Schädels mit Stirnhirnerscheinungen und Korsakoffschem Symptomenkomplex.* Jahrb. Psychiat. 46: 53 (1928).
6. Faugeron, R., *Essai sur les Rapports de la Syphilis et de la Maladie Osseuse de Paget.* Thèse de Paris (1923).
7. Fowler, E. P. Jr., *Paget's disease.* Laryngoscope 47: 586 (1937).
8. Gedda, L., *Studio dei Gemelli.* Rome, Orizzonte Medico (1951).
9. Grosz, K., *Zur Klinik der Osteitis deformans (Paget) des Schädels.* Z. ges. Neur. Psychiat. 73: 464 (1921).
10. Gruenthal, E., *Ueber den Hirnbefund bei Pagetscher Krankheit des Schädels.* Z. ges. Neur. Psychiat. 136: 656 (1931).
11. Gutman, A. B. and Kasabach, H., *Paget's disease (osteitis deformans).* Am. J. Med. Sci. 191: 361 (1936).
12. Hanke, H., *Osteodystrophische Erkrankungen und ihre Begrenzung.* Deutsch. Z. Chir. 245: 641 (1935).
13. Hurwitz, S. H., *Osteitis deformans, Paget's disease.* J. Hopkins Hosp. Bull. 24: 265 (1913).
14. Kallmann, F. J., Feingold, L. and Bondy, E., *Comparative adaptational, social, and psychometric data on the life histories of senescent twin pairs.* Am. J. Human Genet. 3: 65 (1951).
15. Kaufmann, M. R., *Psychosis in Paget's disease (osteitis deformans).* Arch. Neur. Psychiat. 21: 828 (1929).
16. Kay, H. D., Simpson, S. L. and Riddoch, G., *Osteitis deformans.* Arch. Int. Med. 53: 208 (1934).
17. Knab, R., *Myelogenes Plasmocytom bei Osteitis deformans Paget.* Chirurg 17-18: 408 (1946-47).
18. Koller, F., *Ueber die Heredität der Osteitis deformans Paget.* Helvet. Acta Med. 13: 389 (1946).
19. Lasserre, Ch., *Les ostéopathies hypertrophiantes.* Rev. d'Orthop. 18: 457 (1931).
20. Martin, E., *Considérations sur la maladie de Paget.* Helvet. Acta Med. 14: 319 (1947).
21. Mifka, P., *Ueber einen Fall von organischem Psychosyndrom bei Osteitis deformans des Schädels.* Wien. Medizin. Wochenschr. 98: 120 (1948).
22. Moehlig, R. C. and Adler, S., *Carbohydrate metabolism disturbances in osteoporosis and Paget's disease.* Surg. Gyn. Obstetr. 64: 747 (1937).
23. —, and Murphy, J. M., *Paget's Disease (osteitis deformans).* Endocrinol. 19: 515 (1935).
24. —, —, and Reynolds, L., *Attempt to produce Paget's disease by the use of anterior pituitary growth extract and parathyroid extract.* Am. J. Roentgenol. 34: 465 (1935).
25. Montagu, M. F. A., *Paget's disease (osteitis deformans) and heredity.* Am. J. Hum. Genet. 1: 94 (1949).
26. Mufson, J. A. and Chodoff, P., *Convulsions in Paget's disease; electroencephalographic obser- vations.* Ann. Int. Med. 16: 762 (1942).
27. Newman, F. W., *Paget's disease.* J. Bone Joint Surg. 28: 798 (1946).
28. Rast, H. and Weber, P. F., *Paget's bone disease in three sisters.* Brit. Med. J. 918 (1937).

29. SABATINI, G., "*Osteitis fibrosa*" *di Paget in due coppie di coniugi.* Min. Med. Scient. 607 (1948).
30. SCHUELLER, A., *Zur Roentgendiagnose der basalen Impression des Schädels.* Wien. med. Wochenschr. 2593 (1911).
31. SCHWARTZ, L. A., *Paget's disease in three male siblings.* J. Mich. Med. Soc. 47: 1244 (1948).
32. SEAR, H. R., *Osteogenic sarcoma as a complication of osteitis deformans.* Brit. J. Radiol. 22: 580 (1949).
33. SMITH, L. H., *Two cases of Paget's disease (osteitis deformans) associated with mental symptoms.* J. Nerv. Ment. Dis. 68: 578 (1928).
34. SNAPPER, I., *Medical Clinics on Bone Diseases.* New York, Interscience Publishers (1949).
35. STAUDER, K. H., *Psychische Störungen bei Osteitis deformans (Paget) des Schädels.* Arch. Psychiat. 98: 546 (1932-33).
36. SUGARBAKER, E. D., *Osteitis deformans (Paget's disease of bones).* Am. J. Surg. 48: 414 (1940).
37. THALMANN, W., *Ueber die Beziehungen zwischen generalisierter Osteitis deformans Paget und Neurofibromatosis Recklinghausen.* Virch. Arch. 283: 148 (1932).
38. WYCIS, H. T., *Basilar impression (platybasia).* J. Neur. Surg. 1: 299 (1944).

SUMMARY

Observation of the behaviour of a pair of one-egg twins, incompletely concordant with respect to Paget's disease, is consistent with the current theory (based on 57 families in which the disease has occurred in more than one member of the family, and one other pair of one-egg twins), that the condition is of genetic origin, the gene responsible being an incompletely dominant autosomal gene with variable degrees of penetrance and expressivity.

RIASSUNTO

Viene riferita l'osservazione di una coppia MZ maschile di anni 63-69 nella quale i due membri presentavano l'*osteitis deformans* di Paget, in forma parzialmente concordante. Tale osservazione conferma la teoria corrente dell'origine ereditaria della malattia basata su 57 alberi genealogici nei quali la malattia è presente in più di un membro della famiglia e sopra un altro caso di coppia MZ concordante. Il gene responsabile della malattia è incompletamente dominante, autosomico e presenta diversi gradi di penetranza e di espressività.

RESUMÉ

On rend compte de l'examen d'un couple de jumeaux monozygotiques, présentant l'*Osteitis deformans* sous une forme partiellement concordante. Cet examen confirme la théorie courante sur l'origine héréditaire de la maladie en se basant sur 57 arbres généalogiques dans lesquels la maladie atteint plus d'un membre de la famille, et sur un autre cas de couple de jumeaux monozygotiques. Le gène responsable de la maladie est incomplètement dominant, autosome, et présente divers degrés de force de pénétration et d'expressivité.

ZUSAMMENFASSUNG

Beobachtung des nicht völlig konkordanten Verhaltens eines eineiigen Zwillingspaares zu der Pagetschen *Osteitis deformans* scheint die herrschende Theorie zu bestätigen (letztere ist auf eine Untersuchung von 57 Familien, in welchen diese Krankheit in mehr als einem Familienmitglied vorkam, sowie von einem anderen eineiigen Zwillingspaar gestützt), dass dieses Krankheitsbild genetischen Ursprungs ist. Das dafür verantwortliche Gen ist ein nicht ganz dominantes, autosomales Gen mit verschiedenen Graden der Ausdrucksmöglichkeiten und Penetranz.