Departments of Medical Genetics and Neuropathology of the New York State Psychiatric Institute
Columbia University, New York 32, N. Y.

# CONCURRENCE OF MORGAGNI'S SYNDROME, SCHIZOPHRENIA AND ADENOMATOUS GOITER IN MONOZYGOTIC TWINS [1]

by
*Bertha M. Aschner, Franz J. Kallmann* and *Leo Roizin*

The tendency of apparently unconnected pathological traits to occur together under certain circumstances and thus to form a specific syndrome has long been of clinical and genetic interest. One of the earliest syndromes described (1765) was that defined by Morgagni as a combination of obesity, hirsutism and hyperostosis frontalis interna. More recently, this triad has usually been referred to as Morgagni-Stewart-Morel's syndrome (abbreviated as M.S.M. in this report), since Stewart (1928) and Morel (1930) observed many years later, at about the same time but independently, that obesity and hyperostosis frontalis interna tended to associate themselves syndromically with a variety of " neuropsychiatric disturbances ". The typical symptomatology of the skeletal anomaly in both symptom complexes consists of symmetrical bone appositions of high density on the inner side of the frontal bone.

Etiologically, it may be noted that M.S.M.'s syndrome is rare and still very much in dispute as to its basic origin, although there have been numerous reports on the clinical and histopathological aspects (Schneeberg, et al., 1947). Careful review of the literature fails to disclose any indication that the condition has been seen in twins. Hence, the observation of concordance in monozygotic twin sisters is worth being recorded, especially since the syndrome was displayed by them in association with schizophrenia and adenomatous goiter and was verified by autopsy, following prolonged hospitalization [2] necessitated by the psychotic histories of the twins. One of the main shortcomings of twin studies is that they rarely extend to post-mortem examinations.

## Clinical Histories of the T. Twins

Elizabeth and Jean were reared for years in the homes of different relatives, since their father was shiftless and emotionally unstable and their mother had a history of both acute schizophrenic episodes and chronic pulmonary tuberculosis. They were described as having always looked so much alike that they could not even be distinguished by close

[1] Presented at the fifth annual meeting of the American Society of Human Genetics at Cornell University, Ithaca, New York, September 9, 1952.

[2] We are indebted to Dr. Hugh S. Gregory, former director of Binghamton State Hospital, for his generous assistance in procuring the clinical and histopathological data on this interesting case.

Ricevuto il 16.V.1953



https://doi.org/10.1017/S1120962300027153 Published online by Cambridge University Press


Fig. 1. The T. Twins at age 33

relatives and friends, but no photographs were taken of them prior to the one showing them at the age of 33 years (fig. 1). They were classified as monozygotic in accordance with the principles of the similarity method including fingerprint analysis.

Neither twin was married, and both continued to support themselves for several years following the onset of schizophrenic personality changes around the age of 19.



https://doi.org/10.1017/S1120962300027153 Published online by Cambridge University Press


Fig. 2. The T. Twins at age 57



https://doi.org/10.1017/S1120962300027153 Published online by Cambridge University Press

Their psychiatric histories were very similar and were characterized by slowly disintegrating and predominantly paranoid psychoses, which required continuous hospitalization when the twins were in their middle thirties. Their final commitments took place at the ages of 34 and 38, respectively.

The twins were 45 years old when *Elizabeth*, the slightly taller and heavier of the two, was found to have a sizable, partly intrathoracic, multiple-nodular goiter with tre-

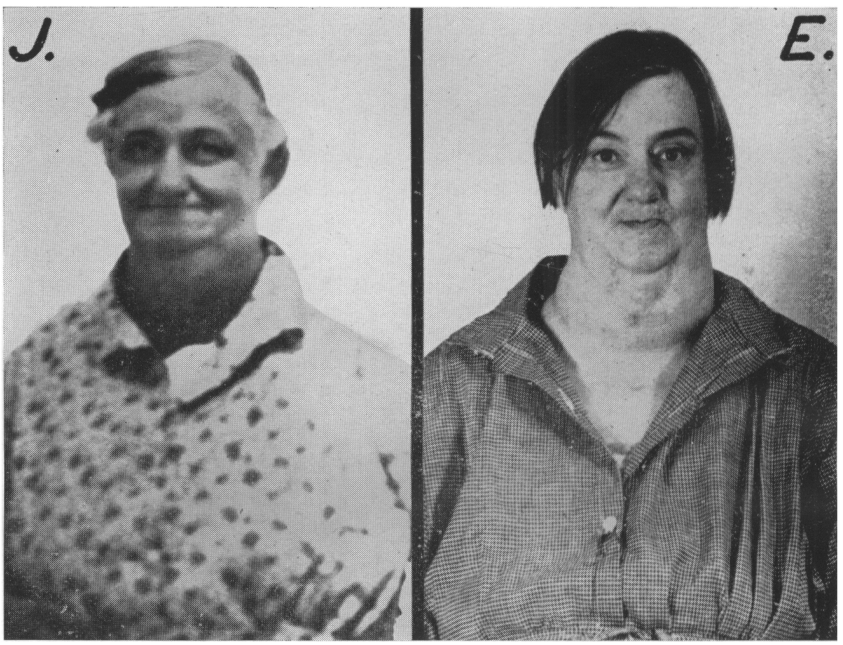


Fig. 3. The T. Twins shortly before their deaths at 69 and 60, respectively

mor, tachycardia, and slight exophthalmos. Surgery was refused, despite definite pressure phenomena. Hence, the circumference of her neck continued to grow until it reached 17 $\frac{3}{4}$ inches at the age of 57 (figures 2 and 3). In addition, Elizabeth showed moderate hypertension, with her blood pressure varying from 170 to 180 over 90, as well as increasing symptoms of obesity. The latter condition began in the early forties, was followed by pronounced hirsutism a few years later, and stabilized itself around a weight of 270 pounds at age 50.

Sudden heart failure caused the patient's death at age 60, following the development of a diffuse abscess of the neck which required surgical drainage.

*Jean's* history duplicated that of her twin sister in all essential details, except for certain differences in the chronology and comparative severity of some of her symptoms. The development of her hard, partly substernal, multiple-nodular goiter was observed



https://doi.org/10.1017/S1120962300027153 Published online by Cambridge University Press

only at the age of 47. The circumference of her neck measured 15 inches at age 57 (fig. 2) and 18¼ inches at age 64 (fig. 3). Her obesity progressed so slowly that the body weight remained slightly below 200 pounds for a considerable period of time and increased to 205 pounds only at age 64. At that time, her symptoms of hirsutism became more and more noticeable, reaching the proportions of a rather excessive beard. She died at age 69, four weeks after a thyroidectomy had been performed on an emergency basis. The operation was necessitated by severe pressure phenomena caused by the goiter, and was followed by auricular fibrillation with increasing signs of heart failure. The immediate cause of death was ascribed to pulmonary infarction.

### Anatomical and Histopathological Findings

*Macroscopic examination in Elizabeth* revealed evidence of marked obesity and a superficial, subcutaneous abscess on the right side of the neck, in addition to diffuse thickening of the skull with bone appositions on the inner side of the occipital and temporal bones and a colloid goiter. Other pathological conditions recorded included a small infarction of the heart; some fatty degeneration of the myocardium and atheromas

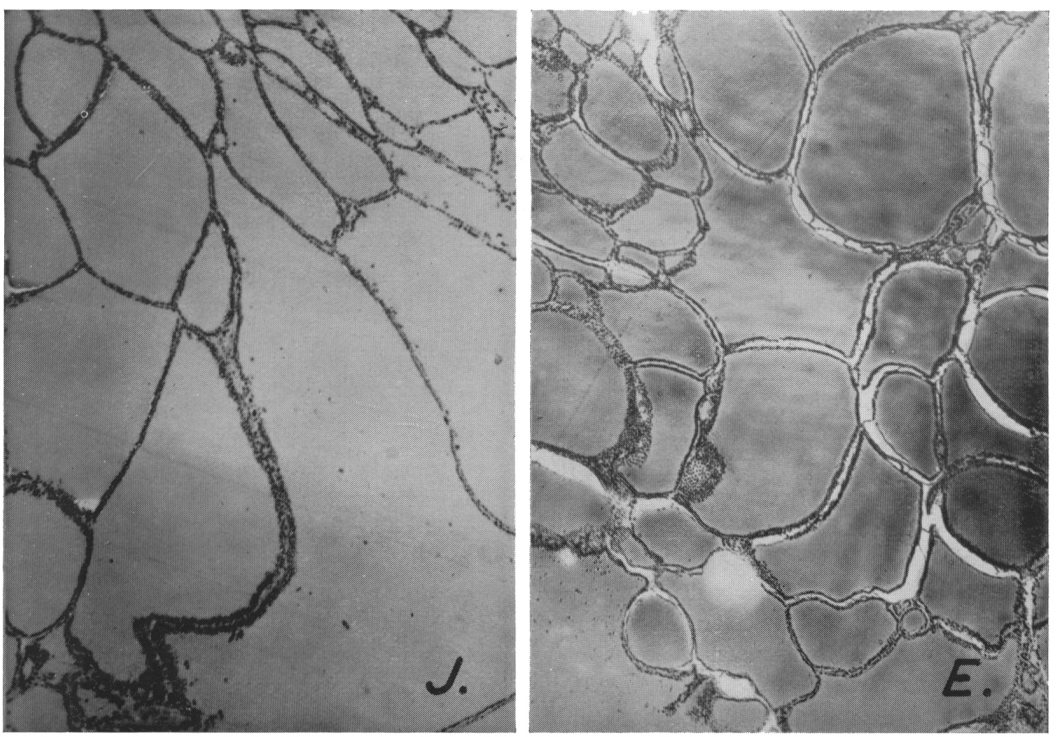


Fig. 4. Colloid nodules of the thyroid



https://doi.org/10.1017/S1120962300027153 Published online by Cambridge University Press

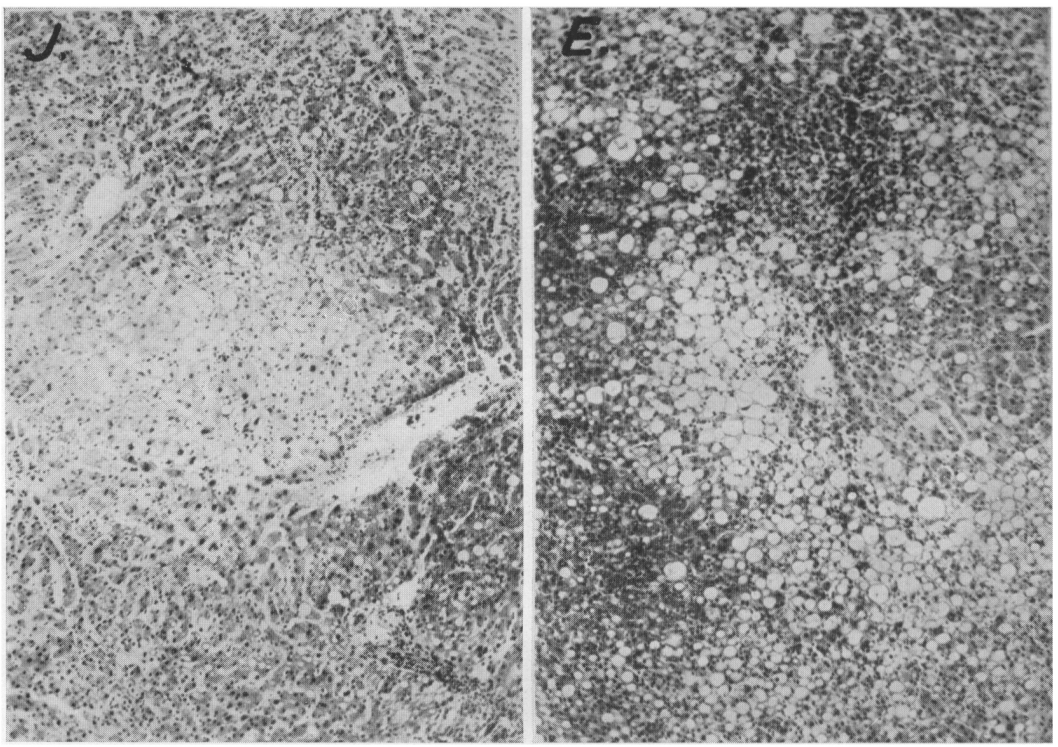


Fig. 5. Fatty degeneration of the liver

of the aorta; passive congestion of lungs, spleen and kidneys; and fatty degeneration of the liver. The weight of the slightly congested brain was 1220 gm.; while the body weight on record was 261 pounds.

*Microscopically*, in the apparent order of their prominence, the following findings were observed:

(1) Adenomatous goiter with vastly dilated, irregular acini which were filled with colloid material and flattened glandular epithelium (right side of fig. 4);

(2) Marked fatty degeneration of the liver with a great number of fat globules of variable size and irregular distribution, almost complete extinction of the normal liver architecture in certain areas, and with portal veins, the walls of which were thickened and replete with round cell infiltration (right side of figure 5);

(3) Marked increase in the subepicardial fat tissue as well as old healed infarctions (fig. 6) and areas of fat degeneration extending within the interstitial tissue of the heart.

The rest of the viscera and body tissues showed some early post-mortem changes and mild arteriosclerotic alterations. The brain was not available for histologic studies.

*Macroscopic post-mortem findings in Jean* (left side of figures 1-6) disclosed general-



https://doi.org/10.1017/S1120962300027153 Published online by Cambridge University Press

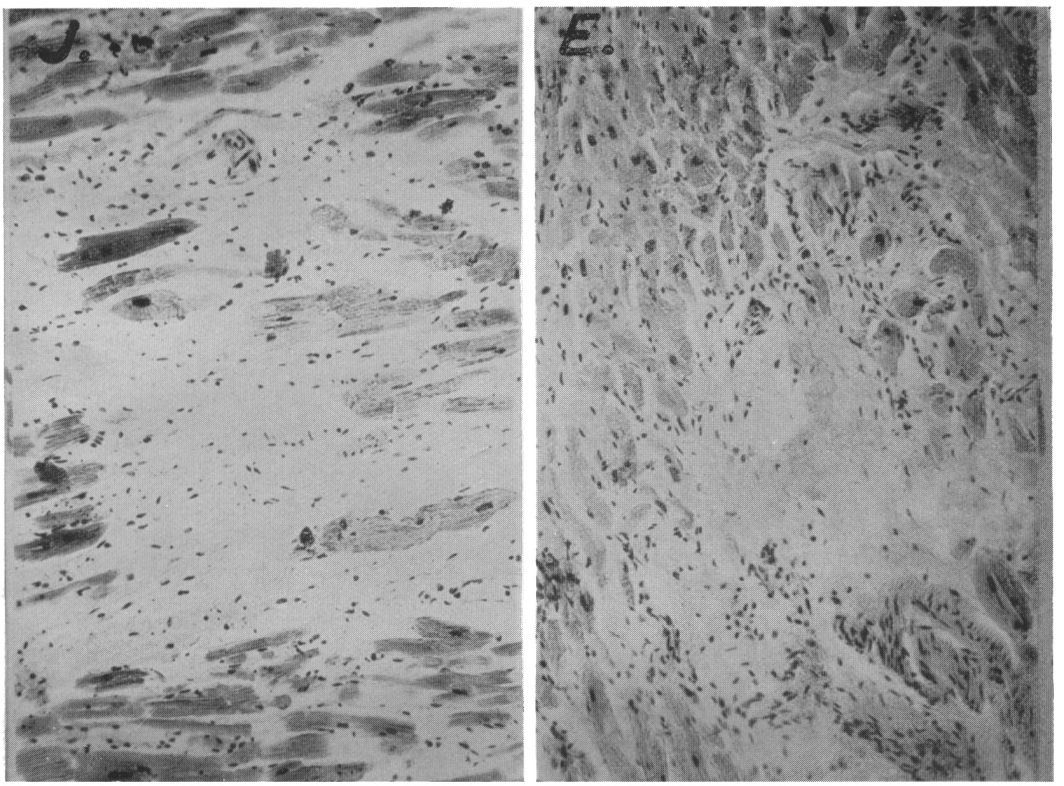

Fig. 6. Myocardial fibrosis

ized obesity (weight 200 lbs.), marked hyperostosis frontalis with osteophytic excrescences in the falx cerebri, and moderate myocardial scarring with some calcifications in the aortic valves. In addition, there were hemorrhagic infarctions and multiple abscesses in the middle and lower parts of the left lung; extensive evidence of fatty infiltration in the liver and of an old, healed perforation in the duodenum; and a large, partly retrosternally situated goiter on the right side of the neck while the left lobe of the thyroid had been removed by surgery.

*Microscopically*, the most significant findings consisted of the following:

(1) Multiple, acute bronchopneumonic foci with hemorrhagic suffusions of irregular size and a few old granulomatous formations in the lungs, apparently tuberculous in origin;

(2) Benign thyroid adenoma with irregular enlargement of the acini, which were lined with cuboid or flat epithelial cells and in their extended lumina were filled with acidophilic colloid material (fig. 4);



https://doi.org/10.1017/S1120962300027153 Published online by Cambridge University Press

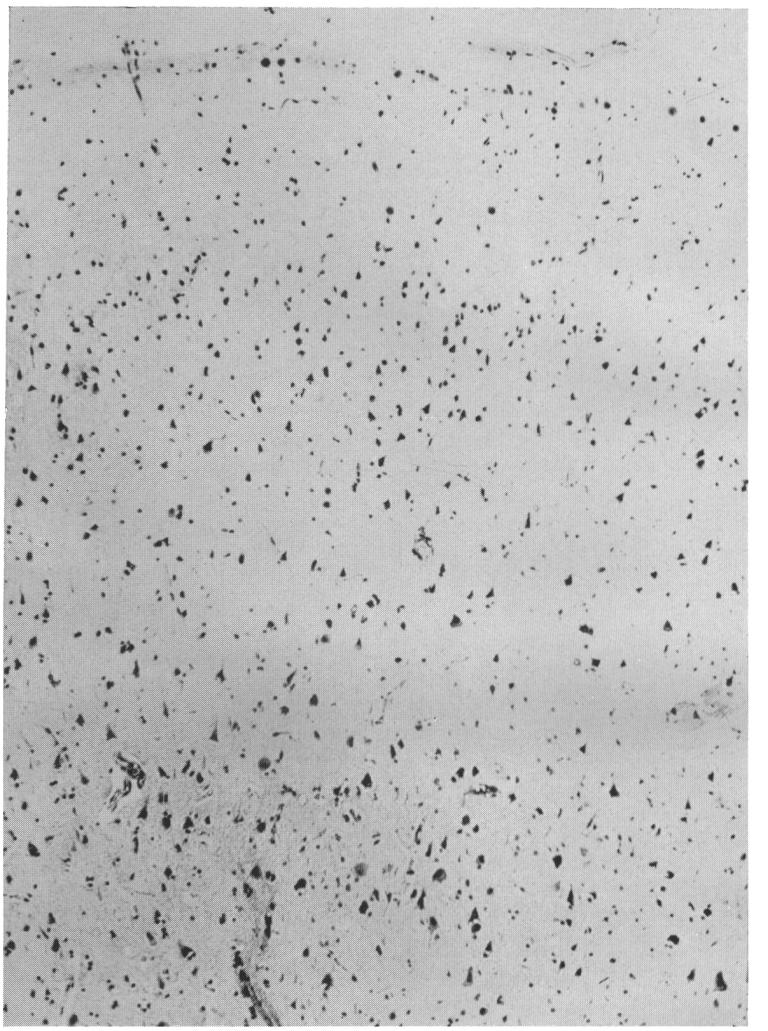

Fig. 7. Cytoarchitectural disorganization with rarefaction of nerve cells (H. & E. stain; medium power mag.)

(3) Fatty liver degeneration and old myocardial infarcts, similar to the changes observed in the other twin (figures 5 and 6);

(4) Abiotrophic alterations in the spleen and ovaries, characterized by atrophy, degeneration and a tendency to fibrosis;

(5) In the available brain sections (stained exclusively with Hematoxylin and Eosin), neuronal scantiness and variable irregularities in the cortical cytoarchitecture



https://doi.org/10.1017/S1120962300027153 Published online by Cambridge University Press

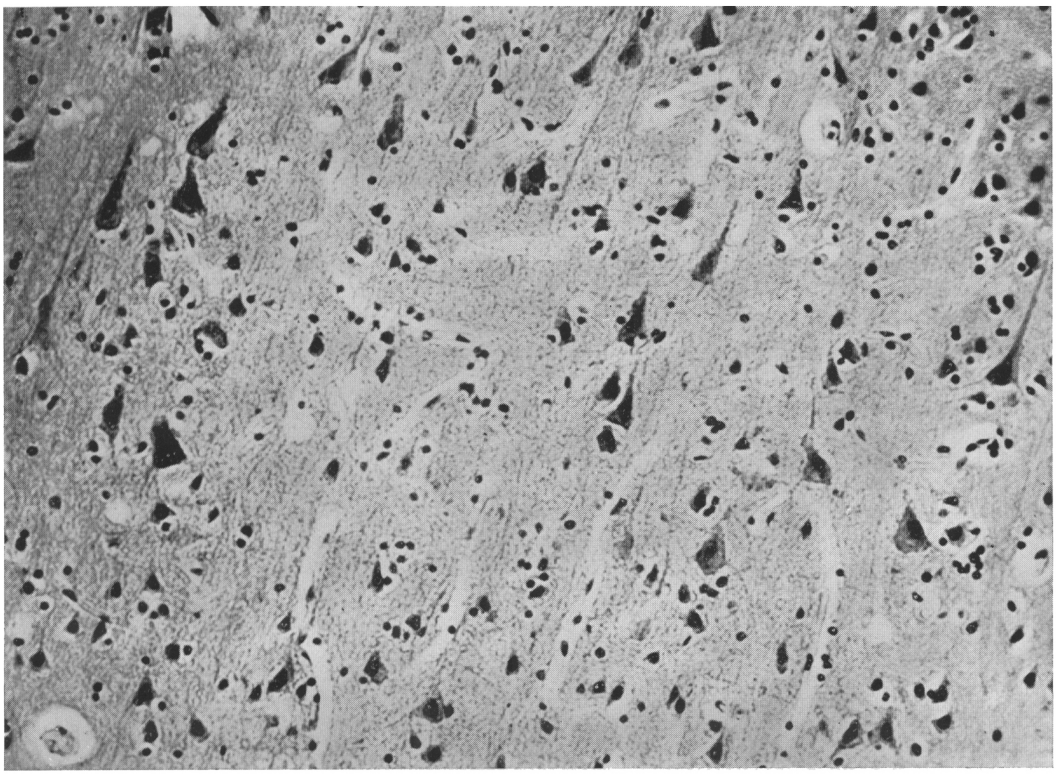

Fig. 8. Neuronal degeneration and pyknosis surrounding a small acellular area (H. & E. stain; high power mag.)

in some areas (figures 7) were often found associated with varying degrees of structural degeneration and pyknosis in the nerve cells of the middle layers, especially around some of the small acellular areas (figures 8 and 9). In addition, there were neuronophagic nerve cell changes in the middle and deeper layers, and mild degenerative changes combined with yellow pigment deposits in the nerve cells of the basal ganglia and the various nuclear formations of the brain stem. The perivascular spaces of some blood vessels, most of which were free of definite structural alterations, appeared enlarged and, here and there, were filled with calcified and amyloid material. These amyloid bodies were also seen in some subpial and subependymal spaces, quite abundantly in the intergyral segments of the cortex, and spreading into the deeper cortical layers and the white matter (fig. 10). The glial elements were free of significant histopathological changes as far as could be established by means of Hematoxylin and Eosin preparations, whereas the previously described findings in the brain appeared to be consistent with a relatively mild but longstanding degenerative process in certain selected segments of the central nervous system.



https://doi.org/10.1017/S1120962300027153 Published online by Cambridge University Press

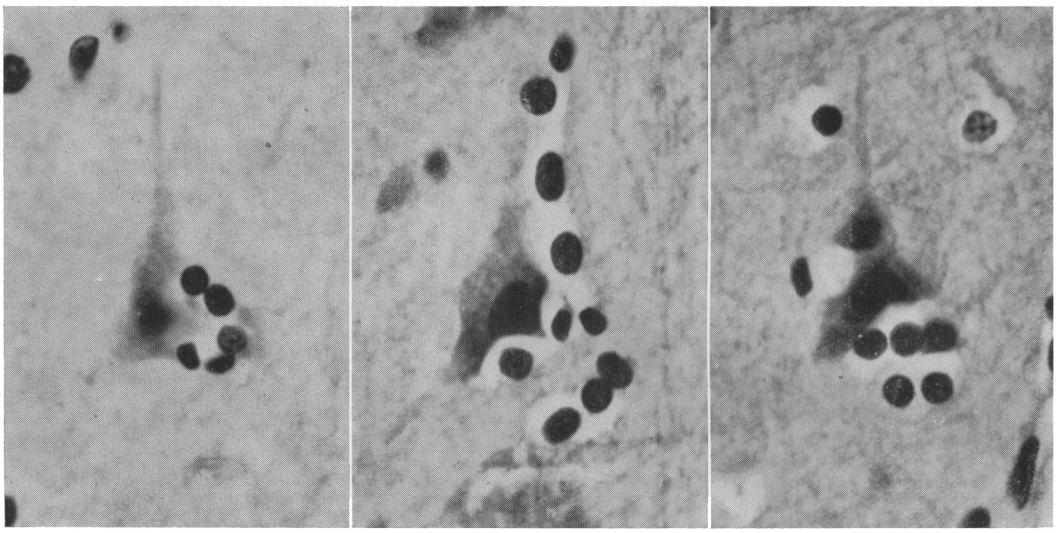

Fig. 9. Neuronophagia of pyramidal cells (H. & E. stain; high power mag.)

## Discussion of the Clinical and Pathological Findings

In a monozygotic pair of schizophrenic twin sisters whose psychoses required continuous hospitalization until their deaths at the ages of 60 and 69 years, respectively, similarity of the clinical records extended to an association with adenomatous goiter and the complete triad of Morgagni.

Although the twins were concordant as to M.S.M.'s syndrome, they showed some symptomatological differences as to age of onset and in the type and extent of the hyperostotic process. In the later-diseased twin (J.T.), the bone anomaly was the typical form of hyperostosis frontalis interna and corresponded to the first group of Moore's classification (1936). Elizabeth's anomaly consisted of a generalized increase in the thickness and density of the skull, as is characteristic of Moore's third group, and of atypical bone appositions on the tabula interna of the occipital bone as well as the petrous portions of the temporal bones.

In an attempt to find possible causal connections among the three pathological traits involved (schizophrenia, adenomatous goiter, and M.S.M.'s syndrome), it is essential to bear in mind that each of them tends to occur more frequently alone than in combination with one or the other, or both, of the remaining syndromes. Schizophrenia is a rather common mental disorder, which is rarely found to be associated with either of the other two conditions and apparently is due to the effect of a specific, single-recessive factor (Kallmann, 1938 and 1953). Nonendemic goiter is equally prevalent as a solitary trait and has been shown by some twin and family studies to be determined by heredity under certain circumstances.



https://doi.org/10.1017/S1120962300027153 Published online by Cambridge University Press

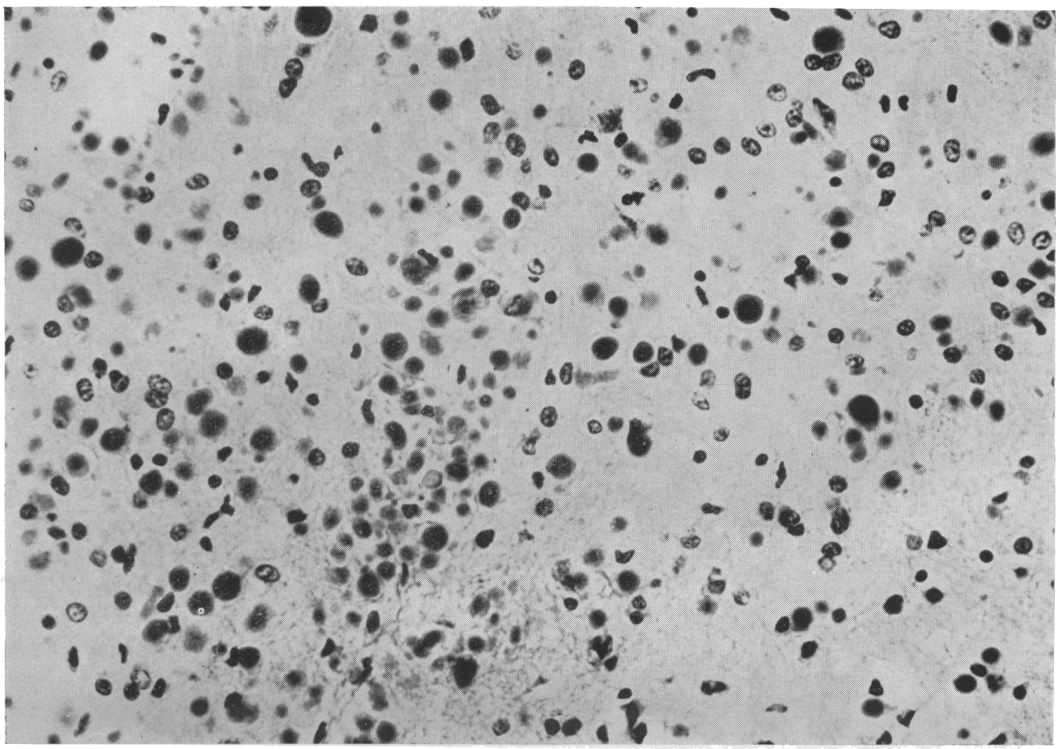

Fig. 10. Amyloid bodies in the white brain matter (H. & E. stain; high power mag.)

The genetic theory of M.S.M.'s syndrome is still insufficiently substantiated, although concordance of such a rare condition in one-egg twins points to the operation of some genetic element. A genetic factor in the etiology of the syndrome has been assumed by various authors, especially by Bauer, Brunner and Buky, Campos, Knies and Le Fever, Montmollin, and Mussio-Fournier's group. Altogether, the histories of 13 families with more than one affected member have been recorded in the literature and are summarized in table 1. In addition, general statements have been made by Grollman and Rousseau as well as by Selye to the effect that a familial incidence of the syndrome is relatively frequent.

The family distribution of hyperostosis frontalis interna alone has been studied by Appel. In a series of 18 patients, he found secondary cases in the families of 12 patients. One of the families included 8 cases in three consecutive generations. Actually, familial occurrence of the bone anomaly — either as an only symptom or as part of M.S.M.'s syndrome — is probably much more common than is demonstrable without careful roentgenographic family studies such as those of Appel.



https://doi.org/10.1017/S1120962300027153 Published online by Cambridge University Press

In any case, the balance of the available family data in a condition as rare as M.S.M.'s syndrome would seem to indicate that a genetic factor is at work in its etiology. The mode of inheritance involved is still unclear, but the limited evidence on record favors either autosomal dominance with irregular penetrance and especially low manifestation in the male or a more complicated type of transmission. The triadic composition of the full syndrome may either be due to the pleiotropic effect of one single gene or to the interaction of several genes located on the same chromosome. The preponderance of the syndrome in the female is fairly well established and apparently the result of specific sex-limiting influences. However, it has been shown by recent investigations that the condition is not as rare in the male as had been believed originally.

The possibility that the observed concurrence of, and striking concordance as to, M.S.M.'s syndrome, goiter and schizophrenia in one pair of monozygotic twins may have been purely coincidental cannot be precluded, of course. On the other hand, it is of interest to note that both M.S.M.'s syndrome and chronic schizophrenic processes tend to be associated with minor endocrine disorders, and that the former has often been observed in conjunction with a variety of mental disturbances (usually non-schizophrenic in nature). It is possible, therefore, that the three pathological conditions combined in the T. twins had a common denominator which may have been genetic in origin. However, that this common denominative cause may have consisted of a new mutation is rather improbable, if only because the twins' mother was schizophrenic but apparently not afflicted with the other two conditions. One might speculate on the possibility that a biochemical disturbance in the enzymatic range, caused by the schizophrenic genotype, in some way precipitated, or contributed to, the manifestation of two latent gene-specific predispositions, those for goiter and M.S.M.'s syndrome.

*In conclusion*, it may again be emphasized that the observed concordant concurrence of schizophrenia, goiter and M.S.M.'s syndrome in monozygotic twin sisters may have been entirely accidental. This possibility cannot be excluded, especially since each of the three traits seems in most instances to depend on the effect of specific genetic factors transmitted by different modes of inheritance, and two of them (schizophrenia and goiter) have a comparatively high incidence rate in modern populations. There is reason to believe, however, that the association of the three traits in the given pair of twins may have had some common denominator, either in terms of a common genetic cause or in those of interdependent precipitation and manifestation mechanisms. The main support for this assumption comes from the observed concordance of each of the three traits in monozygotic twin sisters.

Apart from presenting this complex genetic problem, one of the objectives of the present report has been that of recording the first observation of Morgagni's triad in one-egg twins concordant as to this rare syndrome, usually referred to as Morgagni-Stewart-Morel's syndrome. Another objective has been to call attention to the need of extending comparative long-term observations on twin pairs, concordant or discordant as to etiologically unclear and apparently unconnected pathological traits, to a comparison of verifying histopathological data.



https://doi.org/10.1017/S1120962300027153 Published online by Cambridge University Press

Table 1

| | Author | Index Case[1] | Other Affected Members | Clinical Specifications Recorded |
|---|---|---|---|---|
| 1. | Hemphill and Stengel, 1940 | F., o., h. f., m. | 1 dau. and 1 granddau. (age 10) | Full MSM syndrome in dau., absence of obesity in granddau. |
| 2. | Knies and Le Fever, 1941 | F., o., h. f., h. | 1 dau. and 2 sons (13, 16, 19 years) | All 3 children mentally retarded but not obese, |
| 3. | Samson, Caron and Martin, 1942 | F., o., h. f. | 1 dau. and 2 sons | 1 son had o. and h. f., while the other sibs were not obese. |
| 4. | Campos (1), 1943 | F., o., h. f., h. | 2 dau. | Younger dau. hypertensive like the patient, who also had latent diabetes mell. No evidence of h. in older dau. |
| 5. | Campos (2), 1943 | F., o., h. f., h. | 1 dau. | No evidence of h. in the pat. and her dau. Familial tendency to obesity. |
| 6. | Donini, 1937 | F., o., h. f., m. | 1 dau. | Very similar symptomatology. |
| 7. | Montmollin, 1941 | F., o., h. f., m. | 1 dau. | Moderate o. and many small benign fibromas and papillomas of skin in both pat. and dau. Evidence of goiter only in pat. |



https://doi.org/10.1017/S1120962300027153 Published online by Cambridge University Press

**Continuation table 1**

| | Author | Index Case[1] | Other Affected Members | Clinical Specifications Recorded |
|---|---|---|---|---|
| 8. | Mach and Jeanneret, 1945 | F., o., h. f., h., m. | mother | Hypertension in pat. and her mother, o. in pat. and grandmo., no h. in the mother. |
| 9. | Brunner and Buky, 1947 | F., o., h. f., h., m. | 1 dau. (19 years) | Familial tendency to o. (13 cases). No h. in dau. Amenorrhea in 1 cousin of pat. |
| 10. | Mussio-Fournier, Bazzano and Proto, 1947 | F., o., h. f., h. | 1 sister | Familial tendency to o. Menstrual disorders in pat. and her sister. Diabetes mell. in pat.'s mother |
| 11. | Van Bogaert and Borremans, 1936 | M., o., h. f., m. | 1 brother (under age 20) | Evidence of Lawrence-Moon-Biedl's syndrome in i. c. and brother. Mother said be to mentally disturbed |
| 12. | Bauer, 1945 | F., o., h. f. | 1 sister | Familial tendency to o. and mental disorders. Sister's symptomatology very similar to that of i. c. |
| 13. | Grollman and Rousseau, 1944 | | 1 pat. uncle | |

[1]) o: obesity
h. f.: hyperostosis frontalis interna
h: hirsutism
m: mental disorder

M: male
F: female
i. c.: index case
dau.: daughter



https://doi.org/10.1017/S1120962300027153 Published online by Cambridge University Press

## Summary

Clinical and histopathological data are presented on monozygotic twin sisters concordant as to schizophrenia, Morgagni's syndrome, and adenomatous goiter. The association of the three traits may have been coincidental, but apparently had a common denominator. The genetic theory of Morgagni's syndrome (pointing to autosomal dominance with irregular penetrance and especially low manifestation in the male) is discussed.

## References

APPEL, W.: 1949. *Ueber die klinische Bedeutung des Stewart-Morel-Morgagni'schen Syndroms.* Deut. Arch. klin. Med. 194, 353-366.

BAUER, J.: 1945. *Constitution and Disease.* Ed. 2, New York: Grune & Stratton.

BRUNNER, H. & BUKY, F. R.: 1947. *Hyperostosis frontalis interna.* Eye, Ear, & c. Month. 26, 471-475.

CAMPOS, A. C.: 1943. *El Sindrome de Morgagni.* Buenos Aires: Iglesias & Matera.

DONINI, F.: 1937. Note psichiat., Pesaro. 66, 279-349.

GROLLMAN, A. & ROUSSEAU, J. P.: 1944. *Metabolic craniopathy.* J. Am. M. Ass. 126, 213-217.

HEMPHILL, R. E. & STENGEL, E. 1940. *Morgagni's syndrome.* A clinical and pathological study. J. Ment. Sc., Lond. 86, 341-365.

KALLMANN, F. J.: 1938. *The Genetics of Schizophrenia.* New York: J. J. Augustin.

KALLMANN, F. J.: 1953. *Heredity in Health and Mental Disorder.* New York: W. W. Norton & Co.

KNIES, Ph. T. & LE FEVER, H. E.: 1941. *Metabolic craniopathy: hyperostosis frontalis interna.* Ann. Int. M. 14, 1858-1892.

MACH, R. S. & JEANNERET, H.: 1945. *Hyperostose crânienne diffuse et familiale avec hypertension artérielle et troubles neuro-musculaires.* Schweiz. med. Wschr. 75, 718-721.

MONTMOLLIN, R.: 1941. *Hyperostose frontale interne familiale.* Rev. neur., Par. 73, 15-23.

MOORE, Sh.: 1936. *Calvarial hyperostosis and the accompanying symptom complex.* Arch. Neur. Psychiat. 35, 975-981.

MOREL, F.: 1930. *Hyperostosis Frontalis Interna.* Paris: Gaston & Doin.

MUSSIO-FOURNIER, J. C., BARSANTINI, J. C., & BARBIERI, S.: 1947. *Hyperostose frontale, obésité, narcolepsie, et œdèmes mous des membres inférieures.* Rev. neur., Par. 79, 413-419.

MUSSIO-FOURNIER, J. C., BAZZANO, H. C., & PROTO, A.: 1947. *Syndrome de Morgagni chez deux sœurs.* Bull. soc. méd. hôp. Paris. 63, 561-563.

SAMSON, M., CARON, S., & MARTIN, C. A.: 1942. *Syndrome d'hyperostose frontale interne à caractère familial.* Laval Méd. 7, 140-146.

SCHNEEBERG, N. G., WOOLHANDLER, G., & LEVINE, R.: 1947. *The clinical significance of hyperostosis frontalis interna.* J. Clin. Endocr. 7, 624-635.

SELYE, H.: 1949. *Textbook of Endocrinology.* Ed. 2. Montreal: Acta Endocrinologica.

STEWART, R. M.: 1928. *Localized cranial hyperostosis in the insane.* J. Neur. Psychopath., Lond. 8, 321-331.

VAN BOGAERT, L., & BORREMANS, P.: 1936. *La forme familiale de la rétinite pigmentaire avec cécité et obésité dite cérébrale.* Ann. méd., Par. 39, 54-74.



https://doi.org/10.1017/S1120962300027153 Published online by Cambridge University Press

**SOMMARIO**

Vengono esposti dei dati clinici ed istopatologici riguardanti due sorelle MZ concordanti quanto a schizofrenia, sindrome di Morgagni e gozzo adenomatoso. La concomitanza di queste tre entità morbose poteva essere accidentale, ma è possibile che risultasse da un denominatore comune. Viene discussa la teoria genetica della sindrome di Morgagni (dominanza autosomica con penetranza irregolare e rara manifestazione nel maschio).

**RESUMÉ**

On o presenté des données histopathologiques concernant des sœurs monozygotiques jumelles qui partageaint des traits communs: la schizophrénie, le syndrome de Morgagni, et goître adénomatique. La concurrence de ces trois traits pouvait être accidentelle mais il est possible qu'elle resultait d'un facteur commun. On a discuté aussi la théorie génétique de syndrome de Morgagni. Ce syndrome indique une dominance autosomale avec une pénétration irrégulière et avec une manifestation particulièrement rare chez le mâle.

**ZUSAMMENFASSUNG**

Klinischer und histopathologischer Bericht über eineiige Zwillingsschwestern mit weitgehender Konkordanz für Schizophrenie, Morgagni's Syndrom und Adenom der Schilddrüse. Zufälliges Zusammentreffen der drei Krankheitszustände lässt sich nicht ausschliessen, ist aber nicht wahrscheinlich. Die erblichen Beziehungen des Morgagnischen Syndroms sind noch nicht geklärt.



https://doi.org/10.1017/S1120962300027153 Published online by Cambridge University Press