

# RECKLINGHAUSEN'S DISEASE: ITS RELATION TO THE ENDOCRINE SYSTEM

REPORT OF AN ILLUSTRATIVE CASE \*

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Throughout this article the term "Recklinghausen's disease" is used for all cases presenting the varying syndrome usually indicated by the name "generalized neurofibromatosis." Von Recklinghausen<sup>1</sup> and Adrian<sup>2</sup> have both long since objected to the latter term as giving an incorrect impression of the nature of the growths characteristic of the disease. Many French physicians have also made the equally valid objection that the name "generalized neurofibroma" has thrown undue emphasis on only one aspect of the syndrome and has thus limited the disease, in the minds of many, to its most common forms, to the exclusion of the unusual and incomplete forms, "formes frustes," which are not so unusual as one is led to believe. The latter, of which the author's case is an example, almost invariably shows pigmentation, and the accompanying psychic, nervous, and trophic disorders frequently play a more important part in the life of the patient than do the cutaneous disorders themselves.

The form of Recklinghausen's disease most frequently seen is that with multiple molluscosus fibromas and neuromas, with or without pigmentation, and no obvious nervous or trophic troubles. Parkes Weber,<sup>3</sup> in 1909 (page 52), makes this classification: (1) plexiform neuroma unaccompanied by multiple molluscosus tumors of the skin, with or without cutaneous pigmentation, (2) multiple molluscosus tumors of the skin without obvious neurofibromatosis of the nerve trunks, with or without cutaneous pigmentation, (3) pigmentation of the skin not (at least as yet) accompanied by obvious neurofibromatosis of the nerve trunks or molluscosus tumors (cutaneous neurofibroma), and (4) anomalous cases of neurofibromatosis complicated by the coexistence of bony or epidermic (papillomatous) changes. Weber and

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1. Von Recklinghausen, F.: Ueber die multiplen Fibroma der Haut und ihre Beziehung zu den multiplen Neuomen, Berlin, Hirschwald, 1882.

2. Adrian, C.: Ueber Neurofibromatose und ihre Komplikationen, Bruns Beitr. klin. Chir. **31**:1-98, 1901. Multiple Neurofibromatose, Centralbl. Grenzgeb. d. Med. u. Chir. **6**:81, 1903.

3. Weber, F. P.: Cutaneous Pigmentation as an Incomplete Form of Recklinghausen's Disease, Brit. J. Dermat. **21**:49-53, 1909.

Little<sup>4</sup> state that an early incomplete form of the disease is seen in cutaneous pigmentation (diffuse brownish café-au-lait patches or sheets of pigmentation, discrete spots and patches, lentigo, and pigmented nevi) which may be present a long time, usually in young people, frequently from birth, before any molluscos skin tumors appear. There are many cases in the literature in which melanoderma is the only cutaneous symptom of Recklinghausen's disease.

#### THE ADDISONIAN SYNDROME

Besides the cutaneous conditions of Recklinghausen's disease, and, significantly, particularly in those cases characterized by marked pigmentation, there is quite frequently seen a more or less complete syndrome indicative of dysfunction of the glands of internal secretion, and recalling the picture of insufficiency of the suprarenal glands in Addison's disease. This condition may include any or all of the following:

1. Sensory Disorders: Arthralgic or rheumatoid pains, general or localized particularly to the lombo-abdominal region and the calves of the legs; formications; vague esthesias; hyperesthesias.

2. Motor Disorders: Vertigoes; motor incoordinations; trepidations; augmentations of reflexes; diminution of muscular force; asthenia, sometimes progressive to death. Landowski<sup>5</sup> (Thèse, Paris, 1894) states that "what dominates with these patients is a state of general depression or torpor similar to that of Addison's disease. They can hardly move themselves—walking is painful—the slightest movement is a labor. All intellectual effort is fatiguing. The face is dull and stupid, the body more or less bent, thin, and meager."

3. Psychic Symptoms: Difficulty in learning at school is most commonly mentioned; apathy, indifference; hesitations of speech, stammering; loss of memory; melancholia; fatalism; sometimes imbecility and idiocy of the cretinoid type. The adenoid facies is noted. Charpentier,<sup>6</sup> 1910, states that 63 per cent. of the cases of Recklinghausen's disease are accompanied by psychic defects symptomatic of mental degeneracy. The disease is rare in veritable aliens. As is obvious, these conditions are quite different from those present in the same disease when the neurofibromatosis has invaded the cerebrospinal nerves or even the central nervous system itself; in this case, there are symptoms common to any condition of cerebrospinal pressure.

4. Little, G.: Meeting Roy. Soc. Med., Dermat. Sec., June 17, 1909, Brit. J. Dermat. **21**:253, 1909.

5. Landowski, L.: La neuro-fibromatose généralisée. Gaz. hôp., Paris **69**: 946, 1896.

6. Charpentier, J.: Maladie de Recklinghausen et psychose périodique, L'Encephale **5**:460-465, 1910.

4. Defects of Development and Faulty Nutrition: Stigmas of degeneracy usually congenital, such as nevi, arched palate, facial asymmetry, prognathism, malformation of ears, syndactylism, badly spaced teeth, troubles with the nails. The adult, usually of small stature, shows lack of complete development, infantilism, faults of the hairy system, dwarfism and sexual underdevelopment with frigidity. There is frequently scoliosis, kyphosis, osteomalacia and friability of the bones.

5. Digestive Complaints: Anorexia, nausea, cramps, vomiting.

6. Examination of the urine may reveal glycosuria and albuminuria, and the blood may show a certain degree of eosinophilia.

Few patients have all of the symptoms mentioned in the foregoing, but many possess a sufficient number of them to present an unmistakable syndrome which various French writers, notably Charpentier, call the classic picture of Recklinghausen's disease, regarding the psychic symptoms as practically habitual.

#### REVIEW OF THE LITERATURE <sup>7</sup>

A somewhat detailed account of characteristic cases is here presented, since, except in the article of Elliott and Beifeld<sup>8</sup> (1914), which attempts to connect Recklinghausen's disease with the condition status thymolymphaticus, there has been no review in English of the work of many foreign writers, notably of the French and Italian, who have endeavored to establish a connection between Recklinghausen's disease and glandular dysfunction. Although many cases are reported in which the writer's interest was so entirely dermatologic as to exclude any other information, and although there are others in which the authors state that no nervous or functional symptoms were present, there is also considerable literature on cases in which involvement of the endocrines, sex glands, pituitary and thyroid glands, and suprarenals is unmistakable. The picture is one of general glandular dystrophy with varying emphasis on different glands in different cases.

*Sex Glands.*—It is significant that many cases, some with no particular Addisonian complex, are influenced by the onset of menstruation, by pregnancy and by the menopause. Pigmentation and tumors usually first appear or rapidly increase between the twelfth and the eighteenth years; it is quite a common statement in the histories of both male and female cases that the disease developed at the onset of puberty.

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7. An excellent review of the literature up to the year 1903 may be found in Adrian's article of that year.

8. Elliot, C. A., and Beifeld, A. F.: Generalized Neuromatosis. Report of a Case Showing a Superficial Resemblance to Hodgkin's Disease. J. A. M. A. **63**:1358-1362, 1914.

Menstrual anomalies figure in certain cases, as in Meige and Feindel's <sup>9</sup> (1903) myxedematous case of infantilism, in which menstruation was barely established, and in a similar case of Orzechowski's <sup>10</sup> (1912) of a girl of 18 in whom it had never been established.

Bourcy and Laignel-Lavastine <sup>11</sup> (1900) reported a case in which tumors first developed at the age of 15; more appeared after marriage; and immediately after the menopause a molluscum pendulum appeared. Hirst <sup>12</sup> (1911) and Sutton <sup>13</sup> (1914) had cases in which tumors appeared during pregnancies, but not between pregnancies. In Sutton's case, the tumors shriveled up after the first delivery, but some of those of the second pregnancy persisted.

Bérard <sup>14</sup> (1902) reported a case without an Addisonian picture, in which an enormous cyst of the ovaries was associated with multiple cutaneous and subcutaneous tumors. After ovariectomy, the tumors progressively disappeared until at the end of three years only the smallest remained. Pascalis <sup>15</sup> (1911) and Oddo <sup>16</sup> (1905) report similar cases.

Many of the male cases also develop or become active at puberty, and an incomplete or delayed sexual development, cryptorchidism and lack of pubic hair and other characteristics are mentioned in cases without any other obvious signs of glandular involvement. Harbitz <sup>17</sup> (1909) reports the case of a man of 28, who showed pigmentation at birth and developed generalized cutaneous fibromas at the age of 15. There was cryptorchidism. Bénaky <sup>18</sup> (1904) had a patient, a man of 40, with congenital pigmentation, generalized neurofibromatosis and

9. Meige, H., and Feindel, E.: *Infantilisme myxoedémateux et maladie de Recklinghausen*, *Rev. neurol.* **11**:857, 1903.

10. Orzechowski, K., and Nowicki, W.: *Zur Pathogenese und pathologischen Anatomie der multiplen Neurofibromatose und der Sclerosis tuberosa*, *Ztschr. Neurol. u. Psychiat.* **11**:237-307, 1912.

11. Bourcy, P., and Laignel-Lavastine: *Un cas de maladie de Recklinghausen*, *Soc. méd. hôp.* **22**:21-26, 1905.

12. Hirst, B. C.: *Etiological Influence of Pregnancy on Molluscum*, *Am. J. Med. Sc.* **147**:419, 1914.

13. Sutton, R. L.: *A Clinical Note on Fibroma Molluscum Gravidarum, Fibrosum*, *Am. J. Obst.* **63**:256, 1911.

14. Bérard, L.: *Ancien kyste de l'ovaire et tumeurs cutanées multiple*, *Bull. Soc. Chir. Lyon.* **5**:15 (Nov. 13) 1902.

15. Pascalis, G.: *Molluscum pendulum volumineux de la cuisse au cours d'une maladie de Recklinghausen*, *Bull. Soc. anat. de Par.* **13**:102, 1911.

16. Oddo, C.: *Maladie de Recklinghausen avec pigmentation des muqueuses*, *Rev. neurol.* **13**:412-415, 1905.

17. Harbitz, F.: *Multiple Neurofibromatosis*, *Arch. Int. Med.* **3**:32 (Feb.) 1909.

18. Bénaky: *Neuro-fibromatose généralisée avec molluscum pendulum de la moitié droite de la face*, *Ann. de dermat. et syph.* **5**:977-982, 1904.

molluscum pendulum, with skeletal deformities, diminution of sensibility, cramps and fatigue, accompanied by sexual underdevelopment. Guinon and Reubsæt<sup>19</sup> (1907) describe the case of a boy of 12 with pigmentation from birth, progressively growing tumors, stupidity, adenoid facies and lack of testicular development. Preiser and Davenport,<sup>20</sup> Elliott and Beifeld, Poisson and Lebat,<sup>21</sup> and Graham Little report similar conditions in young boys.

*Pituitary Gland.*—It is to be expected that cases of Recklinghausen's disease should be associated with hypophysis dysfunction, as there seems to be some connection between hypopituitarism and certain tumor formations, apparent in conditions like multiple lipomatosis, etc.

Evidences of pituitary dysfunction in Recklinghausen's disease are found in many cases showing a partial acromegalic tendency, such as prognathism, cheironmegaly, and in the confluent elephantiasic form of the disease, as well as in the few cases in which generalized fibromas appear with outspoken acromegaly. The latter, six in number, are the cases of Feindel and Froussard<sup>22</sup> (1899), Piollet<sup>23</sup> (1902), Cushing<sup>24</sup> (1912), Nicolas and Favre<sup>25</sup> (1910), de Castro<sup>26</sup> (1912), and Wolfsohn and Marcuse<sup>27</sup> (1912). The cases of the two latter (de Castro, and Wolfsohn and Marcuse) both showed typical pigmentation and generalized tumors, together with typical acromegaly. Both were characterized by nervous phenomena; headache, pains in the limbs, psychic depression, sexual frigidity and general asthenia. Wolfsohn and Marcuse found that roentgenoscopy of the sella turcica showed an increase of measurements from normal to abnormal within three

19. Guinon, L., and Reubsæt: Un cas de maladie de Recklinghausen fruste, Soc. pédiat. **9**:263-267 (June 16) 1907.

20. Preiser, S. A., and Davenport, C. B.: Multiple Neurofibromatosis (von Recklinghausen's Disease) and Its Inheritance, Cold Spring Harbor, 1918.

21. Poisson and Lebat: Maladie de Recklinghausen, Gaz. méd.-chir, Nantes, May 3, 1913, p. 357.

22. Feindel, E., and Froussard, P.: Dégénérescence et stigmates mentaux, malformation de l'ectoderme, myoclonie épisodique, acromégalie possible, Rev. neurol. **7**:46-54, 1899.

23. Piollet, P.: Neuro-fibromatose généralisée, Gaz. d. hôp. **75**:1345-1350, 1902.

24. Cushing, H.: The Pituitary Body and Its Disorders, Philadelphia and London, 1912, p. 148.

25. Nicolas, J., and Favre, M.: Acromégalie et maladie de Recklinghausen, Lyon méd. **114**:786, 1910.

26. De Castro, A.: Sur la coexistence de la maladie de Recklinghausen avec l'acromégalie, Nouv. iconog. de la Salpêtrière **25**:41-44, 1912.

27. Wolfsohn, G., and Marcuse, E.: Neurofibromatosis und Akromegalie, Berl. klin. Wchnschr. **49**:1088, 1912.

months' time. Jeanselme<sup>28</sup> in an article descriptively entitled "Anomalies of the Sight, the Intelligence, and the Skeleton Associated with Generalized Neurofibromatosis," recorded an accompanying narrowness of the sella turcica. Breton<sup>29</sup> (1903), in a case of Addison's syndrome, found at necropsy an enlarged pituitary gland and a sella filled with lymphoid tissue. Spillman<sup>30</sup> found a tumor of the sella, and Mossé and Cavalie,<sup>31</sup> an enlarged and hard hypophysis.

Harbitz (1909) has a valuable article on the allied condition of elephantiasis in connection with generalized neurofibromatosis. He reports a case of a woman, a mongolian imbecile, with an elephantiasis-like growth of the whole thigh and generalized cutaneous tumors. The characteristic mongolian appearance had developed at puberty. Perthes<sup>32</sup> (1902) reports a similar case (which Wolfsohn and Marcuse included in the acromegalic cases) and gives the literature of similar conditions. Alexis Thomson's<sup>33</sup> monograph (1900) has a particularly fine illustration of the condition.

Weber (1909) mentions patients with cases accompanied by bony overgrowth of whom the "elephant man" described by Sir Frederick Treves<sup>34</sup> is the most extreme example.

A single case of generalized neurofibromas associated with Fröhlich's syndrome, dystrophia adiposogenitalis, is reported by Lier<sup>35</sup> (1914) in a boy of 9. Roentgenoscopy showed evidence of a tumor close to the hypophysis.

*Thyroid.*—Instances of cretinism in patients with Recklinghausen's disease are recorded by Adrian (1903), Strohmeyer,<sup>36</sup> 1844, and Schuh,<sup>37</sup> 1851, 1854 (Adrian, page 461). Schiffner observed true

28. Jeanselme, E.: Anomalies de l'appareil visuel, de l'intelligence et du squelette associées à la neurofibromatose généralisée, *Bull. et mém. Soc. méd. d. hôp. de Paris* **31**:1136-1139, 1915.

29. Breton, A.: La neuro-fibromatose généralisée, *Rev. gen. chir. et thérap.* **17**:17-20, 1903.

30. Spillman: Neurofibromatose et tumeurs cérébrale, *Gaz. hebd. de méd.* **5**:320, 1900.

31. Mossé, A., and Cavalie: Tumeurs multiples de l'encéphale et de la moelle allongée. Neurofibromatose central, *Gaz. hebd. de méd.* **2**:789, 1897.

32. Perthes, G.: Ein Fall von Fibroma molluscum, vorwiegend der linken Hand mit Steigerung der Knochenwachstums, *Deutsch. Ztschr. f. Chir.* **63**: 103-110, 1902.

33. Thomson, A.: *Neuroma and Neurofibromatosis*, Edinburgh, 1900.

34. Treves, Sir Frederick: *Trans. Path. Soc. London* **36**:494, 1885.

35. Lier, W.: Ueber Neurofibromatose, *Ztschr. f. klin. Med.* **80**:261, 1914.

36. Strohmeyer, quoted by Adrian: *Centralbl. Grenzgeb. Med. u. Chir.* **6**: 461, 1903.

37. Schuh, F.: Ueber die Erkenntnis der Pseudoplasmen, 1851. *Pathologie und Therapie der Pseudoplasmen*, 1854. Quoted by Adrian, 1903, p. 461.

cretinism in two brothers with the disease (Jullien). Ottolia<sup>38</sup> (1908) regarded his case as cretinoid. Debove<sup>39</sup> (1905) gives the case history of a man with multiple cutaneous tumors, tumors along the course of the nerves, generalized pigmentation, in connection with thyroid infantilism.

Myxedematous persons are found in the cases of Meige and Feindel, and of Pic and Rebattu.<sup>40</sup> At necropsy, Bourcy and Laignel-Lavastine found among other glandular lesions, a typical fibrous goiter, with bloody infiltration and diminution of colloid. Muto<sup>41</sup> also found thyroid changes at necropsy. Ehrmann<sup>42</sup> observed a small thyroid in one case, and the absence of the gland in another. Hallopeau and Ribot<sup>43</sup> report typical pigmentation and tumors in a woman in whom exophthalmic goiter was making its appearance. Schlesinger<sup>44</sup> (1911) saw a case with an associated tetany, the only recorded instance of parathyroid involvement with Recklinghausen's disease.

*Suprarenals.*—A far from complete review of the literature has disclosed about fifty cases in which a so-called Addisonian syndrome, entirely or partially developed, indicated clinically a suprarenal involvement. Many other cases characterized by these symptoms would doubtless have been found if the reporter's interest had not been entirely taken up by cutaneous and nerve tumors. The author believes that in a great majority of cases of Recklinghausen's disease there will be found certain indications of glandular insufficiencies. A few typical cases showing the clinical picture of Addison's syndrome are detailed:

1. Pic and Rebattu (1907): A man, aged 47; complaint: progressive asthenia; multiple cutaneous molluscous tumors, neurofibromas along the course of the spinal nerves, and widely scattered café-au-lait patches present from birth, together with deep brown punctiform pigmentation of the lower legs; extreme kyphoscoliosis; a myxedematous appearance, caused by infiltra-

38. Ottolia, D.: Considerazioni sopra un caso di morbo di Recklinghausen, *Riforma méd.* **24**:1243-1247, 1908.

39. Debove: Sur un cas de neuro-fibromatose de Recklinghausen, *J. de méd. et de chir. prat.* **76**:566-568, 1905.

40. Pic and Rebattu: Un cas de maladie de Recklinghausen, *Lyon méd.* **108**:636-643, 1907.

41. Muto, A.: Contributo allo studio del morbo di Recklinghausen, *Riv. di patol. nerv.* **15**:656-670, 1910.

42. Ehrmann: Zwei Fälle von Neurofibromatose, *Wien. klin. Wchnschr.* **16**: 139-140.

43. Hallopeau and Ribot, A.: Un cas de maladie de Recklinghausen avec prédominance des troubles pigmentaires et volumineuse tumeur profonde, *Ann. de dermat. et syph.* **3**:613-615, 1902.

44. Schlesinger, H.: Multiple Neurofibroma der peripheren Nerven und der Nervenwurzeln, mit Beinphänomen, *Mitt. d. Gesellsch. f. inn. Med. u. Kinderh.* **10**:124-125, 1911.

tion of the integument down to the shoulders; intellectual faculties formerly intact, weakened. The extreme asthenia was accompanied by hypotension and vasomotor troubles evidenced by Sergeant's white adrenal line.

2. Ottolia (1908): A small underdeveloped man, cretinoid; scoliosis and deformation of bones of head; generalized tumors; pigmentation all over the body including the buccal mucous membranes; intellectual inferiority; slowness of movements; obtused and diminished sensibilities.

3. Thiebierge<sup>45</sup> (1898): A woman, aged 56; pigmented patches small and large, identical with those of neurofibromatosis, over trunk since birth; no tumors, extreme asthenia and gastric troubles for two years; with onset of this condition there occurred generalized discoloration of the skin of the face and body; alteration of character, melancholia, loss of memory.

4. Thiebierge: A man, aged 50; typical tumors and deep brown pigmentation; gastric trouble progressive to death.

5. Jullien<sup>46</sup> (1910): A woman, aged 43; tumors at 2½ years of age; pigmentation and bronzing of the face at 7; irregular menstruation; at puberty, headaches, gastric distress and vomiting. At present, pigmentation of neck and hands, Addisonian mask, large pigmented patch on mucous membrane on inside of cheek; gastric disorders; lumbo-abdominal pains; quickly fatigued. There was a recurrence in situ of a plexiform neuroma removed from the hypogastrium.

6. Kahn<sup>47</sup> (1910): A man, aged 42; at the age of 33 pigmentation and multiple tumors occurred; since that time there have been anorexia, vomiting, lumbar pains, exophthalmos, asthenia and pulmonary tuberculosis. Kahn reports this case as one of Addison's disease, but the tumors, the absence of pigmentation on the mucous membranes and the lack of necropsy findings fail to support this diagnosis.

Such is the picture—one of degeneracy and lack of resistance. The exciting causes which bring into activity the underlying tendencies (congenital, hereditary, or familial<sup>48</sup>) in these persons, may be any one of many varying stimuli, such as puberty, pregnancy, the menopause, trauma and infections—such as typhoid fever or tuberculosis—but I believe that the stimulus, whatever it may be, is purely accidental, and that only the inherent tendency is constant.

#### NECROPSIES IN WHICH THE GLANDS OF INTERNAL SECRETION HAVE BEEN EXAMINED

So far as the writer knows, there have been fourteen necropsies with examination of the ductless glands. Twelve of these were cases

45. Thiebierge, G.: Un cas de maladie de Recklinghausen sans fibromes cutanées ni fibromes nerveux, Soc. méd. hôp. de Paris 15:143-149, 1898.

46. Jullien, A.: Neurofibromatose généralisée, Thèse, Paris, 1910.

47. Kahn, I. N.: Report of a Case of Molluscum Fibrosum, Addison's Disease and Pulmonary Tuberculosis, New York M. J. 2:114, 1910.

48. As regards the familial character of Recklinghausen's disease, Preiser and Davenport found that out of 115 children of parents affected with neurofibroma, fifty (43.5 per cent.) were affected with the disease.



in which a more or less complete Addisonian syndrome had been found; two cases lacked such phenomena. In twelve of the cases, or 85 per cent., including the two without Addison's syndrome, involvement of the suprarenals and other glands was found. In two cases, both of which clinically indicated suprarenal involvement, there were only minor histologic changes in the suprarenals.

The proof of glandular dystrophies offered by changes in the glands found at necropsy, even though so large a proportion of the few cases examined were positive, is, nevertheless, interesting rather than convincing; even in undoubted Addison's disease, the suprarenals are occasionally intact at necropsy. Furthermore, as is well known, a general dysfunction of the glandular system may be clinically manifest for a considerable time before any great changes appear in the structure of the glands. No stronger proof of glandular involvement is needed than the clinical conditions shown. However, as the necropsy examinations in question have not formerly been assembled, they are here detailed, together with a case in which a tumor of the suprarenals was found in a living subject afflicted with neurofibromatosis.

*Necropsy Examinations.*—1. Chauffard<sup>49</sup> (1896): A man, aged 37; pigmentation, neurofibromatosis; increasing digestive disturbances; death, cachetic marasmus. Necropsy: voluminous adenomatous tumor of cortical origin, involving pancreas, suprarenals and lymphatic ganglions; capsular degeneration. Absence of tuberculous transformation of suprarenals characteristic of Addison's disease.

2. Branca<sup>50</sup> (1897): A case of Marie's disease; a man, aged 43, alcoholic, had multiple pigmented nevi; molluscous tumors; cachetic; tuberculous; intelligence and memory diminished; speech embarrassed. Necropsy: Kidneys red, hard, small; cysts and adhesive capsule; suprarenal capsule congested; no sympathetic nerve involvement.

3. Marie and Couvelaire<sup>51</sup> (1900): Adult male; disease developed late after freezing hands and feet; progressive asthenia; neurofibrosis, becoming generalized with pigmentation; alterations of sensibility; nervous troubles—apathy, anorexia, etc. Extreme skeletal changes; photographs show appalling progressive kyphosis. Death, extreme asthenia. Necropsy: Osteomalacia; intestinal fibromatosis; pancreas sclerotic; splenic artery extremely sclerosed; spleen hard; suprarenal cortex intact.

4. Bréton (1903): A man, aged 48; complaint, extreme asthenia; five years previously, attack of pain in hands and feet; when pain receded, generalized subcutaneous tumors appeared with pigmentation and nevi; no tumors along nerve trunks; had always been sexually frigid; death, profound marasmus.

49. Chauffard, A.: Dermo-fibromatose pigmentaire (ou neuro-fibromatose généralisée). Mort par adénome des capsules surrénales et du pancréas, Soc. méd. et chir. prat. **76**:566-568, 1905.

50. Branca, A.: Neuro-fibromatose intestinale, Soc. Anat. Par. **72**:166-173, 1897.

51. Marie, P., and Couvelaire, A.: Neuro-fibromatose généralisée, Autopsie. Nouv. iconog. de la Salpêtrière **13**:26-40, 1900.

Necropsy: Suprarenal capsules replaced by two masses of sarcomatous tissue; spleen, kidneys and lymphatic ganglions involved; no tuberculosis. Sella turcica occupied by voluminous lymphoid tissue; pituitary gland size of large bean.

5. Bourcy and Laignel-Lavastine (1905): A woman, aged 58; tumors at 15, increased after marriage; generalized lentigo; molluscum pendulum after menopause; many infections; pains, cramps, formication, changes in sensibility; asthenia. Death, after five years. Necropsy: Fibrous goiter; changes in suprarenals, spleen and kidneys.

6. Merk<sup>52</sup> (1905): A man, aged 34 (?); neurofibromatosis and pigmentation; intellect diminished; asthenia. Necropsy: Changes in left suprarenal.

7. Raymond and Alquier<sup>63</sup> (1908): A woman, aged 74; cutaneous fibroma; pigmentation; no neuromas; headaches; vertigo; profound asthenia. Necropsy: Suprarenals occupied by generalized sclerosis; at one point that had escaped sclerosis, there was a hyperplastic nodule of spongiocytes; kidneys sclerotic. Hypophysis showed alternating layers of sclerosis and hyperfunctionating tissue.

8. Jullien (1910): A man, aged 70; pigmentations and molluscos tumors since birth; augmentation at puberty; extreme asthenia; apoplectic death. Necropsy: Suprarenal capsules voluminous with brown points of epithelial hyperplasia; spleen, voluminous, sclerotic.

9. Muto (1910): A woman, aged 53; gross tumor from infancy; in mature life, generalized eruption of small papules, 3,000 at death. No nervous symptoms. Death, general marasmus. Necropsy: Intense pigmentary infiltration of all the cortical zone of the suprarenals; modification of cervical sympathetic. Histologic changes of pituitary and thyroid.

10. Vignolo-Lutati<sup>64</sup> (1911): A man, aged 25; pigmentation at birth; skin tumors at puberty. Three years before death, loss of strength, cramps, nausea, vomiting, bronzing of face. Death, cachexia. Necropsy: Sclerosis of the suprarenals.

11. Orzechowski and Nowicki (1912): A girl, aged 18; multiple neurofibromatosis; menstruation never established; intelligence low; troubles of eye and ear. Necropsy: Chromaffin system hyperplastic; pituitary gland only slight abnormalities.

12. Saalman<sup>65</sup> (1913): A woman, aged 35; typical Recklinghausen's disease. Death from pulmonary embolism after operative removal of elephantiasic tumor from the arm. Necropsy: Hypernephroma, originating in a suprarenal rest, found in liver. Suprarenals normal.

13. Bosquet<sup>66</sup> (1913): A man, aged 46; cutaneous and nerve tumors; skin a uniform dirty yellow as in Addison's disease; inferior psyche; sexual

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52. Merk, L.: Ueber die multiple Neurofibromatose, Arch. Derm. u. Syph. **73**:139-145, 1905.

53. Raymond, F., and Alquier, L.: La maladie de Recklinghausen. Ses variétés nosologiques, L'Encephale **3**:6-35, 1908.

54. Vignolo-Lutati, C.: Recklinghausenschen Krankheit, Monatschr. f. prakt. Dermat. **52**:51-70, 1911.

55. Saalman: Ueber einem Fall von Morbus Recklinghausen, mit Hypernephrome, Virchows Arch. f. path. Anat. **211**:424, 1913.

56. Bosquet, T.: Maladie de Recklinghausen et capsules surrénales, Echo méd. du Nord **17**:329-332, 1913.

frigidity; anorexia; pains in extremities; profound asthenia. Necropsy: Right suprarenal almost entirely transformed into an epithelial tumor; polymorphic cells; cystic and hemorrhagic formations.

14. Preiser and Davenport (1918): A man, aged 45; after lead poisoning, twelve years previously, generalized tumors and pigmentation; headache; dizziness, palpitations, vomiting, generalized pains. Death, general asthenia. Necropsy: Pigmentation of liver and spleen; slight histologic changes in suprarenal, pituitary and thyroid glands.

15. Kawashima<sup>57</sup> (1911): Woman in puerperium; multiple cutaneous and nerve tumors; marked kyphoscoliosis. Tumor of suprarenal medulla consisting of atypical hyperplasia of giant multinuclear cells.

#### TREATMENT BY OPOTHERAPY

This should apparently be a suggestive subject, but the literature contains next to nothing on it. Revilliod,<sup>58</sup> 1900, in a typical case of Recklinghausen's disease with Addisonian syndrome, controlled the symptoms by use of suprarenal extract. When the extract was discontinued, the asthenia reappeared, and disappeared again when suprarenal extract was again used. Gabriel,<sup>59</sup> 1911, reported good results in two patients also with the use of suprarenal extract. Preiser and Davenport obtained no results with either thyroid or suprarenal extract in their case in which death occurred from progressive asthenia. One case is reported (Schoonheid<sup>60</sup>) in which ovarian extract was tried without effect.

In diseases of somewhat similar type, adiposis and lipomatosis, Lyon<sup>61</sup> states that thyroid preparations have given better results than any other medication, and that other forms of glandular therapy should also be tried. As is obvious, the glandular field of therapy is practically untouched in Recklinghausen's disease, and should be given a thorough trial, especially as epinephrin, thyroid and pituitary extract have all given good results in the condition of osteomalacia, which so frequently attends the disease.

#### REPORT OF A CASE

##### *Recklinghausen's Disease with Evidences of Endocrinic Dysfunction*

*History.*—A white unmarried girl, aged 20, born in the United States, and having no regular occupation, was admitted, March 8, 1919, to the Skin Clinic of the Beth Israel Hospital, complaining of progressive cutaneous troubles.

57. Kawashima, K.: Ueber einem Fall von multiplen Haut fibromen mit Nebennierengeschwulst. Ein Beitrag zur Kenntnis des sogenannten Morbus Recklinghausen, Virchows Arch. f. path. Anat. **203**:66-74, 1911.

58. Revilliod, H.: De la neurofibromatose généralisée et de ses rapports avec l'insuffisance des capsules surrénales, Thèse, Genève, 1900.

59. Gabriel: Fall von Recklinghausen'scher Krankheit mit Osteomalacie, Berl. klin. Wchnschr. **48**:133-134, 1911.

60. Schoonheid: A Case of Multiple Neurofibromatosis of the Skin, Nederlandsch Tijdschr. v. Geneesk. **2**:1639, 1913.

61. Lyon, I. P.: Adiposis and Lipomatosis, Arch. Int. Med. **6**:28-120, 1910.

Her father and mother were alive and well; her maternal grandparents died of old age; her paternal grandfather, 76 years of age, was well; her paternal grandmother died of a disease the nature of which was unknown; one brother and three sisters were alive and well; another brother was suffering from a nervous breakdown due to recent business troubles. There was no history of miscarriage or of dead brothers or sisters. Syphilis, tuberculosis and cancer were denied.

The patient had had measles in early childhood; she had had no other infectious diseases, but gave a history of constant complaints and suffering from minor ailments. For several years there had been severe drawing frontal headaches; these appeared weekly, lasting for three days, and were worse on rising. During damp and changing weather, there were indefinite pains in the extremities. For the past eight years the vision of the left eye had been gradually decreasing. For three years she had suffered once a fortnight, from attacks of weakness, faintness and precordial pressure of one day's duration. Appetite and digestion were poor; there was no increased frequency of urination, excepting occasionally at night. During the past year, nocturnal restlessness and insomnia had been present. The patient had always had difficulty in learning; she did not progress with her classmates, and was finally compelled to leave school while still in a low grammar grade. She had always had attacks of depression and melancholia.

Menstruation, which began at the age of 14, was regular every four weeks, lasting three days and accompanied by severe bearing down abdominal pains during the first two days; the flow on the first day was profuse, but was scant for the remaining period.

*Cutaneous Conditions.*—The mother stated that while the patient was but a few months old it was noticed that the right side of her face seemed to grow more rapidly than the left, and that it was of a darker color. This nevoid growth increased in height and extent; it finally spread down the neck to the collar bone. At the age of 4, freckles appeared on the skin of the trunk; these increased rapidly in number and distribution so that the face, neck, trunk and extremities became covered with numerous yellow and brown spots. Round, painful tumors later appeared on the scalp and the lower vertebral region and were excised when the patient was about 8. In 1915, when she was about 16, she was in Mount Sinai Hospital, from March 1 to 15, for the removal of painful tumors of the dorsal and sacral regions. The pathology of these growths was that of neurofibroma. At this period, 1915, the pigmented nevus on the face and neck had become darker in color and was covered with small warty growths and painful soft tumors resembling those of the back and scalp; the latter were also removed. In 1919, two months prior to her admission to the clinic, the painful tumors on the face and neck began to recur.

*General Examination.*—The patient was short and obese, with mental and physical underactivity. Her movements were slow and clumsy; she answered questions with difficulty; the facial expression was stupid and she never smiled. The head was large; the face, flat and asymmetrical and drawn to one side in talking. The nose was broad; the lips, thick; the right half of the tongue, hypertrophied. The ears were large, and the right auricle was involved by the nevoid lesion of the face and neck. The upper and lower jaws were enlarged; there was a wide space between the two upper central incisors and a small space on each side between the middle and lateral incisors; the canine teeth were small, pyramidal and pointed. The fingers were short and thick and show hyperextensibility.

Examination of the nose, eyes, ears and throat revealed nothing abnormal. The neck was short and fat, and the thyroid gland was of moderate size and soft. The lungs, heart, spleen and liver were apparently normal. The breasts were large and pendulous. The temperature was normal; repeated pulse rate determinations varied between 72 and 80 a minute; the respiratory movements were normal. The blood pressure varied from 106 to 122, systolic, and 60 to 66, diastolic; it was not taken during any of the attacks of faintness, and possibly at these periods it might have been much lower. Stroking the skin produced a mild erythema which disappeared rapidly.

Repeated urinary examinations disclosed nothing abnormal. Chemical examinations of the blood gave these results: blood sugar, 0.07 per cent.; carbon dioxid, 60 per cent.; urea nitrogen, 8 per cent.; nonprotein nitrogen, 30 per cent.; creatinin, 1.2 per cent. The low level of the normal blood sugar finding and the low urea nitrogen content indicate a tendency to a diminished metabolism. The Wassermann reaction, the tuberculosis and the gonorrhea complement-fixation tests of the blood were negative, as was also the radiograph of the skull.

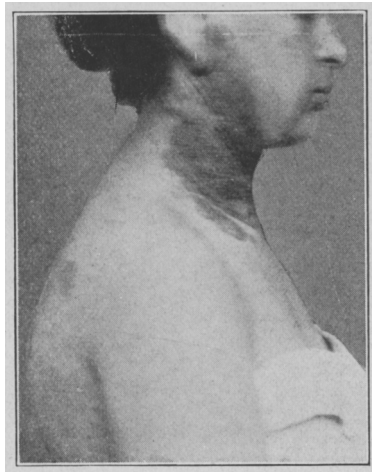


Fig. 1.—Pigmented nevus on face and neck of author's patient.

*Dermatologic Examination.*—The general cutaneous surface showed the presence of uncountable yellow, café-au-lait and dark brown macules, round, oval and irregular in shape, and varying in size from that of a pin-point to that of a quarter dollar. These were most numerous on the trunk and less in number on the face, neck and extremities. There was no pigmentation of the buccal mucous membranes. There was increased pigmentation, especially at the nipples, the anterior axillary folds and points of pressure. Covering the right half of the neck from the midline in front to the anterior border of the trapezius, there was a dark brown, elevated soft growth, with a surface of pedunculated and nonpedunculated soft, warty papules, ranging from the size of a pinhead to that of a large pea, some of which were tender on pressure. This nevoid growth extended up the cheek over the lower maxillary region and down to the clavicle. An egg-sized pendulous mass, tender to pressure, was situated on the upper posterior portion. From the upper anterior portion depended a large orange-sized, pigmented, soft, tender mass which gave a

larger and lower aspect to the right side of the face than the left. The auricle of the right ear was also disproportionately large, as its lower one-third was hypertrophied, pigmented, thickened and extended into the nevus growth. A 3 inch linear scar ran parallel to and over the lower maxillary bone.

Situated about the middle of the sternum there was large pea-sized, globular, doughy painless tumor which could be compressed, and imparted to the finger a sensation as if it were growing through a hernial ring in the skin. Nowhere else on the skin was another fibroma of this nature found.

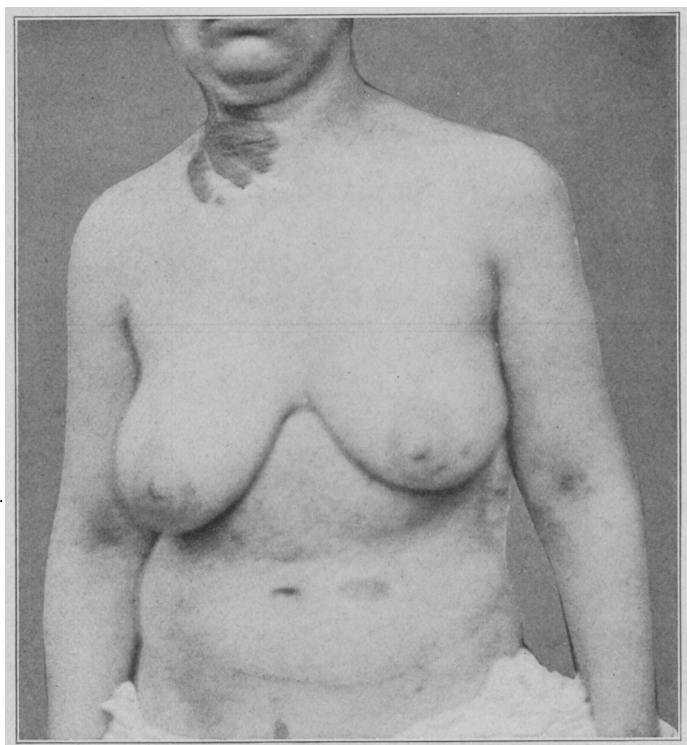


Fig. 2.—Dark brown macules on body and arms of patient.

The hair of the scalp was brownish-black, dry, curly and thick, and extended down the temples almost to the eyebrows. The scalp itself was the site of a seborrheic eczema. In the right parietal region there was a 3-inch round, flat smooth scar devoid of hair, the result of an operation for the removal of a painful growth. The eyebrows were heavy, shaggy and wide, but thinned in the outer one-third. The space between the eyebrows was wide and partially covered with hair. There was a moderate hypertrichosis with the presence of hair on the chin, abdomen and back, while the axillary hairs formed a dense bushy growth. Several linear scars were present in the mid-dorsal and sacral regions where painful tumors had been removed.

*Course and Treatment.*—This case was presented at the meeting of the Manhattan Dermatological Society, March 11, 1919, with the diagnosis of Recklinghausen's disease. There were some doubts expressed as to the correctness

of the diagnosis, because of the absence of neuromas and fibromas. Dr. Wise, however, agreed with the author that the pigmentation, the nevus and the one fibroma of the chest fully justified the diagnosis. As a matter of fact, in spite of the lack of tumors, this was an outspoken case of Recklinghausen's syndrome, one of the well-known *formes frustes*, but destined, as so many of them are, to develop a fuller cutaneous picture.

The patient was irregular in attendance at the clinic, and indifferent to treatment except to that which would give relief from pain. Organotherapy was attempted but it was impossible to test its value in so unreliable a patient. In April, 1920, she appeared complaining of severe pain in the pendulous masses of the face; this was relieved by large doses of coal-tar analgesics. At this time, there were found about two dozen pedunculated, soft, pigmented fibromas, from pinhead to lentil-size, on the right side of the abdomen. In December, 1920, she returned with a request for the removal of the disfiguring masses of the face. Examination of the skin revealed several new large pea-sized fibromas of the right forearm; the small fibromas of the abdominal skin had disappeared, but several, flat, hardly elevated, soft, purplish, hernial growths were found instead. A plastic operation is to be performed on the face and radium is being applied to the nevoid growth. It is hoped that she may agree to try organotherapy.

*Summary.*—A report has been made of a case of Recklinghausen's disease showing evidences of pluriglandular dyscrasia, with stigmas of suprarenal and pituitary dysfunction predominating. Beginning early in life, there were indications of suprarenal disorder in the form of cutaneous pigmentations, painful new growths, and physical and mental weakness; the history and the physical findings suggest Addison's disease. The abnormal anatomic markings point to faulty pituitary activity. The thyroid gland and the gonads appear to have played only minor rôles in the production of the picture.

The cutaneous symptom, pigmentation, is generally accepted as depending on a disturbance of the chromaffin system, of which the suprarenals are an important constituent. According to Lyon (page 107), pigmentation has long been considered as symptomatic of insufficiency of the suprarenal (nervous) cortex. It is present in many other conditions besides Recklinghausen's disease, "having known or supposed relations with certain glands of internal secretion, e. g., acromegaly, exophthalmic goiter, myxedema, Dercum's syndrome, adiposity and lipomatosis, . . . arthritis deformans, bronzed diabetes, uterine and ovarian affections, etc." It "suggests a possible relation to the suprarenal glands or to the chromaffin system in general." The fibromas, neurofibromas, plexiform neuromas, and nevi depend for their presence on a congenital or local predisposition and a faulty endocrine-sympathetic system.

It has been shown that the cortex in man constitutes about 90 per cent. of the suprarenal gland, and that in lower animals it is much smaller. The more developed intellectually is the person the more developed is the brain, and the larger is the cortex of the suprarenal glands. It is therefore possible that the mental symptoms in Recklinghausen's disease have some relation to some trouble in the suprarenal cortex.

The following tabulation gives a tentative suggestion of the relationship between the various symptoms of the case to the various endocrines.

**Suprarenals:** Attacks of weakness, faintness and precordial pressure; hyperesthesia; muscular pains; poor vasomotor tone—diminished skin stroking reaction, low blood pressure; diminished metabolism—low blood sugar and urea nitrogen; anorexia; nocturnal frequency of urination; insomnia; mental

symptoms; abnormal hair growth—hypertrichosis of face, back, axillae, abdomen and between the eyebrows; obesity; dermatologic condition—pigmentation, fibromas, neurofibromas, nevus.

**Pituitary:** Periodic, frontal headaches; poor vasomotor tone; low blood sugar; nocturnal frequency of urination; insomnia; mental symptoms; low downgrowth of hair of scalp; structural defects—short and obese, shape, size and asymmetry of face and head, prognathism, enlarged right ear, spacing and character of teeth, hyperextensibility of fingers.

**Thyroid:** Hyperesthesia; poor vasomotor tone; low urea nitrogen; thinned outer one third of eyebrows; obesity.

**Gonads:** Menstrual symptoms; abnormal hair growth; obesity; dull lethargic mentality.

#### COMMENT

Ewing,<sup>62</sup> writing on the origin of fibromas, states that the exact point of origin is still undetermined. That many of them arise from misplaced islands of tissue according to Connheim's theory, is very probable. Other fibromas may depend on local irritation and disturbance of nutrition. In a third group, the clinical features point to a congenital or local predisposition, of which multiple neurofibroma is the best example. It is especially in the second and third etiologic classes that one encounters the less definite tumorlike processes which it is sometimes difficult to classify, and in which one must recognize the cumulative influence of inflammations and chronic disturbance of nutrition and the passage of inflammatory into self-perpetuating neoplastic processes. Recklinghausen showed that the fibroma molluscum arises from the cutaneous nerve filaments. In 1882, he traced degenerating nerve fibers in several characteristic cases and stated that all these tumors arise from nerve trunks or filaments.

"Many authors trace a connection between neurofibroma and many angiofibromas and naevi. They are sometimes associated with xanthoma (Delore, Poncet), and rarely with multiple lipoma (Vallas, Mouchet). Some early lesions suggest an origin from the connective tissue about the sweat-glands, but even here the process has been traced from nerve fibers belonging probably to the sympathetic system." Ewing also asserts that "it is probable that the great majority of actively growing fibromas and fibrosarcomas of the limbs are of neural origin."

"It is generally assumed that the victims of fibromatosis are the subjects of congenital malformation of the ectoderm which under a great variety of exciting causes may slowly or rapidly develop one or more of the manifestations of the disease."

62. Ewing, J.: *Neoplastic Diseases*. New York, 1919, p. 151.



The Italian endocrinologist, Pende,<sup>63</sup> has presented a most suggestive theory as to the causation of Recklinghausen's disease—a theory which is particularly interesting in view of the facts set forth in the present article. Pende<sup>64</sup> (1909) expressed his opinion (with, to quote Muto, "many learned arguments") that the sympathetic nervous system and the glands of internal secretion constitute two physiologically and pathologically synergic systems, so that a morbid process localized in one system makes its effects felt in the other; he maintains that a whole series of affections which have been included either under diseases of the nervous system or in the group of disorders of the glands of internal secretion should be combined into one family group of endocrine-sympathetic dystrophies. The common symptomatic picture would consist essentially of a more or less complex dystrophy (disturbances of metabolism and anomalies in tissue development), accompanied by symptoms due to disturbances in the functioning of one of the endocrinic glands. Among such dystrophies, he places scleroderma, chronic dystrophic rheumatism, painful lipomatosis and neurofibromatosis. For the production of these conditions, two factors are required: (1) a constitutional factor represented by an abnormality of the endocrine-sympathetic system, which may be hereditary, intra-uterine, or extra-uterine during the period of growth; and (2) an accidental factor, such as shock, trauma, toxic poison, infection, etc., which through its effects on the endocrine-sympathetic system acts as a stimulus to embryonal elements of the sympathetic system and the skin.

Much the same idea is expressed by Lyon,<sup>65</sup> who concludes that the various clinical groups of fatty deposit, Dercum's syndrome, the lipomatoses, "adipositas cerebialis," etc., are essentially identical, being only variations of a common morbid process. "They all show a tendency to be characterized by constitutional symptoms of wide variety including especially psychic, sensory, motor, vasomotor, secretory, and trophic manifestations." Special attention is called to various arthralgic and arthritic and neuralgic and neuritic manifestations as belonging to the constitutional symptomatology of the morbid process.

The etiology of the process, thus broadly considered is unknown. Only two views, connecting the process with disturbances of the nervous system or of

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63. Pende, N.: Sistema nervoso simpatico e glandole a secrezione interna. *Il Tommasi* **31**: 1909. *Pathologia dell apparecchio surrenale e degli organi parasimpatica*, Soc. Editrice Libreria, 1909. *I nuovi orizzonti della fisiopatologia delle secrezioni interne*, *Med. ital.* **6**:129-132, 153-157, 1910.

64. The translations from Pende are from exact quotations found in Muto's article, *Riv. di patol. nerv.* **15**:656-670, 1910. The original sources were not available.

65. Lyon: *Adiposis and Lipomatosis*. 1910. In this work Lyon makes no specific mention of Recklinghausen's disease, but what he says is equally applicable to this condition, and is quoted here for this reason.

the glands of internal secretion, seem broad enough to harmonize with all the facts. These two views are not necessarily opposed, but can be resolved into one, by assuming that the nervous system is secondarily disturbed by a primary disturbance in the glands of internal secretion, or vice versa. The pathological findings and the general evidence suggest the view that the process is related to alterations in the glands of internal secretion, many writers laying special stress on implication of the pituitary gland in the pathogenesis.

However, the complex mutual relationships between all the glands suggests that one or more or all of them may be concerned in the pathogenesis, and that the variation in symptomatology of the different groups and cases may depend on the varying degrees of involvement of these several glands and the nervous system.

As experimental work tending to show the relationship between the internal secretions and the production of tumors, pigmentation, etc., in conditions such as Recklinghausen's disease is almost prohibitive, it is interesting to note, even though the bearing be remote, the conclusions of Loeb<sup>66</sup> on the internal secretions as a factor in the origin of tumors in mice. He found that for the development of cancer three factors were necessary: (1) the hereditary, (2) the physical stimulation, irritation, and (3) the chemical stimulation, the internal secretions. The internal secretion seems to cause cancer only in cooperation with hereditary factors. On the other hand, hereditary factors need, at least in some cases, the cooperation of hormones in a definite quantity, if cancer is to develop.

#### CONCLUSIONS

In view of the previously reported cases, and my observations in other cases as well as in the one here reported, I believe: (1) that Recklinghausen's disease is a complex of cutaneous and general symptoms depending essentially for its etiology on endocrine dysfunction.

(2) That the great majority of cases would show definite signs of endocrine-vegetative disorders, if they were carefully examined for these findings.

(3) That all cases of Recklinghausen's disease tend finally to develop such symptoms, unless there is some compensatory halting of the glandular dystrophy, and that eventually death, unless from inter-current diseases, will in all probably result from progressive asthenia.

(4) That the term neurofibromatosis should not be used synonymously with Recklinghausen's disease, as neurofibroma or fibroma constitutes only one type of the cutaneous lesions.

(5) Pigmentation is a frequent skin lesion and may be present without any signs of fibromatosis.

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66. Loeb, L.: Internal Secretions as a Factor in the Origin of Tumors, *J. M. Res.* **40**:477, 1919.

(6) A syndrome covering a multiplicity of symptoms must be designated by a term broad enough to include them all. At the present time we have no better name than Recklinghausen's disease.<sup>67</sup>

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67. In addition to the references already given, the following cases in which endocrine dysfunction is apparent, may be of interest:

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