There was a correlation between adrenaline excretion and severity of hyperthyroidism, as measured by output of labelled hormone following a tracer dose of ^{131}I .

Possible mechanisms for these changes and relationship to insulin hypoglycaemia are discussed.

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REFERENCES

- Bell, G. H., Davidson, J. N., and Scarborough, H. (1956). *Textbook of Physiology and Biochemistry*, 3rd ed., p. 302. Livingstone, Edinburgh.
- Bischoff, F., and Gray, C. L. (1956). *Fed. Proc.*, **15**, 221.
- Brewster, W. R., Isaacs, J. P., Osgood, P. F., and King, T. L. (1956). *Circulation*, **13**, 1.
- Burn, J. H., Finney, D. J., and Goodwin, L. G. (1950). *Biological Standardization*, 2nd ed. Oxford Univ. Press, London.
- and Marks, H. P. (1925). *J. Physiol. (Lond.)*, **60**, 131.
- Cannon, W. B., McIver, M. A., and Bliss, S. W. (1924). *Amer. J. Physiol.*, **69**, 46.
- Diller, W. F. (1958). *Arch. int. Pharmacodyn.*, **114**, 92.
- Durlach, J., Bouvet, P., and Levillain, R. (1955). *Ann. Endocr. (Paris)*, **16**, 252.
- Fraser, R., and Smith, P. H. (1941). *Quart. J. Med.*, **10**, 297.
- French, E. B., and Kilpatrick, R. (1955). *Clin. Sci.*, **14**, 639.
- Gaddum, J. H., and Lembeck, F. (1949). *Brit. J. Pharmacol.*, **4**, 401.
- Goodall, McC. (1951). *Acta physiol. scand.*, **24**, suppl. 85.
- Goodwin, J. F., Macgregor, A. G., Miller, H., and Wayne, E. J. (1951). *Quart. J. Med.*, **20**, 353.
- Herring, P. T. (1917). *Quart. J. exp. Physiol.*, **11**, 231.
- Hökfelt, B. (1951). *Acta physiol. scand.*, **25**, suppl. 92.
- Kawamoto, K., Yoshida, H., and Sato, H. (1952). *Symposia on Enzyme Chemistry*, **7**, 92.
- Pekkarinen, A., Koivusalo, M., and Pyörälä, K. (1951). *Acta endocr. (Kbh.)*, **6**, 233.
- Peltola, P. (1951). *Acta med. scand.*, Suppl. 262, p. 34.
- Pitkänen, E. (1956). *Acta physiol. scand.*, **38**, suppl. 129.
- Rosenblum, H., Hahn, R. G., and Levine, S. A. (1933). *Arch. intern. Med.*, **51**, 279.
- Schneekloth, R. E., Kurland, G. S., and Freedberg, A. S. (1953). *Metabolism*, **2**, 546.
- Spinks, A., and Burn, J. H. (1952). *Brit. J. Pharmacol.*, **7**, 93.
- Trendelenburg, U. (1953). *Ibid.*, **8**, 454.
- von Euler, U. S., and Floding, I. (1955). *Acta physiol. scand.*, **33**, suppl. 118, p. 57.
- and Hellner, S. (1951). *Ibid.*, **22**, 161.
- (1952). *Ibid.*, **26**, 183.
- and Luft, R. (1952). *Metabolism*, **1**, 528.
- and Orwen, I. (1955). *Acta physiol. scand.*, **33**, suppl. 118, p. 1.
- Wayne, E. J. (1954). *Brit. med. J.*, **1**, 411.

AETIOLOGICAL FACTORS IN PRIMARY RAYNAUD'S DISEASE

BY

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The term "idiopathic," or "primary," Raynaud's disease is currently applied to those patients who present with intermittent attacks of digital pallor or cyanosis in whom careful examination fails to reveal either a local contributory cause or an associated systemic disease in which the digital symptoms might be considered to represent a single feature of a more generalized disease process.

The use of the term primary is in many ways open to individual interpretation by the clinician. This is not only due to the gradually increasing number of diseases with which the digital syndrome is now associated, but is also dependent on the care and accuracy taken to exclude systemic disease and to establish aetiological factors on which such a diagnosis may be accepted or rejected.

Apart from the influence of heredity and the frequent appearance of symptoms during childhood or at puberty (Lewis and Pickering, 1934), little is known about endogenous influences which may affect either the appearance of symptoms or the severity of the disease, and the purpose of this paper is to draw attention to certain features in the histories of a group of patients with this

disease which suggest that they should be regarded as aetiological factors in the evolution of the vascular abnormality of primary Raynaud's disease.

Clinical Material

The 21 cases recorded form part of a group of 42 patients diagnosed as having primary Raynaud's disease. Their symptoms were intermittent attacks of digital pallor or cyanosis of the upper extremities of such severity as to constitute a serious disability in their normal way of life. All were females, aged 23 to 52 years, who had been referred either for upper-limb sympathectomies or because of recurrence of symptoms following previous operations. All fulfilled both the criteria laid down by Allen and Brown (1932a) of a diagnosis of primary Raynaud's disease and those suggested by Hunt (1936) for primary Raynaud's phenomenon. They were otherwise in good general health, and with the exception of one case (No. 10) were non-smokers.

Clinical examination failed to reveal either a local cause for their symptoms or any associated systemic disease. All peripheral pulses were normal and the blood pressure ranged from 110 to 140 mm. Hg systolic and 65 to 80 mm. Hg diastolic. A careful investigation of the E.S.R., serum proteins, and blood excluded the presence of the collagen disease group.

Clinical Histories

Analysis of the clinical histories of the patients obtained by careful questioning of the patients themselves and their close relatives indicated that symptoms either arose for the first time, or pre-existing mild symptoms became greatly exacerbated, following three main events in the patient's life: (1) childbirth; (2) the onset of the menopause; and (3) a period of severe mental stress.

Aetiological Factors in Primary Raynaud's Disease

Case No.	Hereditary History	Age of Onset of Digital Symptoms	Age of Onset of Disability	Aetiological Factor	Progression to Nutritional Lesions
1	+	32	32	Parturition	Yes
2	+	15	29	"	"
3	+	Child	36	"	No
4	+	26	26	"	"
5	+	Child	18	"	"
6	+	35	35	"	"
7	Not known	17	33	"	"
8	+	15	23	"	"
9	+	Child	45	Menopause	"
10	+	"	47	"	"
11	+	Teens	35	Hysterectomy and unilateral oophorectomy	"
12	+	"	34	Hysterectomy	"
13	—	33	33	"	"
14	—	42	42	"	"
15	+	40	40	Mental stress	"
16	+	28	28	"	"
17	+	42	42	"	"
18	—	30	30	"	"
19	+	35	35	"	Yes
20	+	Teens	37	"	No
21	—	25	25	"	"

Childbirth.—In eight patients symptoms severe enough to make them seek medical treatment arose within six months of the birth of a child, the time period between parturition and the onset of symptoms being related to the interval between parturition and the onset of cold weather. In three cases it was following the birth of the first child, in four the second, and in one the third. Two of these cases progressed within a period of five years to nutritional lesions of the digits and sclerodactyly. In three patients the symptoms arose *de novo* and there was no evidence to suggest that previous mild attacks had occurred. In five cases occasional digital pallor had been present for many years, and it was the severity of the attacks that had been modified. These had been converted from occasional and mild to severe and prolonged, with marked pain and disability.

Menopause.—In four of the six patients in this group the digital symptoms followed within a few months of subtotal hysterectomy for fibroids. In only one case (No. 11) was

an associated unilateral oophorectomy performed. In two others the symptoms arose at a time when irregular menstruation was already present which culminated within 18 months in a complete menopause. Although pain and prolonged cyanosis were dominant symptoms in all cases, only one progressed to digital ulceration within the next five years and in only two cases of these did the symptoms arise *de novo*. In four it was established that mild attacks of pallor or cyanosis had been previously present for many years, and the effect of the menopause in these was to exacerbate a pre-existing mild form of the disease rather than to initiate it.

Mental Stress.—In seven cases the digital symptoms followed a period of prolonged and severe mental stress. In four cases symptoms appeared immediately before or after the death of a mother or husband whom the patients had been nursing, whilst in the three remaining cases they arose during a period of unhappy married life leading to separation or divorce from their husbands. In six of these cases the symptoms arose for the first time within a period of one to four months of either the death of the relative or the date of separation, and in only one case (No. 20) was there any evidence that pre-existing mild attacks of pallor or cyanosis had been present, so that the stress was predominantly an initiating rather than an exacerbating factor in this group of patients.

Discussion

The influence of heredity in Raynaud's disease has previously been commented upon, and it could be seen that in 16 of the 20 cases in which a complete family history was available a history of similar attacks was present in one or both of the parents. It would be reasonable to assume, therefore, that there did exist an inherited predisposition to such attacks in the majority of these patients, although the nature of the inherited defect remains unknown. In the first two groups of 14 cases nine had had symptoms before the event which precipitated the disability, but these had been minimal and had given rise to no disability. In only one of the group associated with mental stress were pre-existing symptoms present. In 10 of the 21 cases, therefore, the effect was to exacerbate a pre-existing mild form of the disease, and in all of these cases (with the exception of Case 7, in which the family history was incomplete) a hereditary history of similar attacks was present. In the remaining 11 cases the symptoms were initiated for the first time by the event, and in seven of these a family history of similar attacks was obtained.

Childbirth and mental stress seem to have been largely disregarded as possible aetiological factors in Raynaud's disease, as, apart from the 137 patients recorded by Allen and Brown (1932b), no large series of cases of this disease have been analysed. It is noteworthy, however, that these authors commented that "in a considerable number of cases the disease appears to be initiated by an operation, childbirth, infection, or the death or illness of a loved one, and these factors could doubtless be elicited in a larger percentage of cases if the patients were questioned specifically regarding this."

In this respect Case 5 in Raynaud's (1862) original thesis was a patient in whom symptoms occurred within a month of the death of the mother, and this was recorded by Hunt (1936) as being the only true example of primary Raynaud's disease in Raynaud's series. Hunt's following case (Mrs. H. G.) was also a patient in whom anxiety of the type described above was present, as she was an individual who was separated from her husband.

The menopause has been stated by Jepson (1951) to have occurred often in the condition he described as "the middle-aged female syndrome." I believe, however, that the use of such a term is not entirely satisfactory, as it is non-specific in character and, according to Jepson's description, covers a number of cases in the age group 35–55 years, in which symptoms were initiated in some instances by the menopause and in others by factors which were not discovered. If all cases of primary Raynaud's disease in this

age group are so classified it is quite probable that a number of cases will be included in which other factors in the aetiology would be disregarded. It should be noted also that, although the menopause is often the cause of symptoms severe enough to give rise to a disability and act as an initiating factor, careful questioning may well reveal that mild attacks had in fact occurred before this but were regarded by the patient as being so mild as to be of no importance.

Whether this latter group should be classified as primary Raynaud's disease or included in secondary Raynaud's disease may be regarded as controversial. Such cases do not exhibit any other signs of disease, and clinical examination fails to reveal any evidence of systemic disease—they therefore fulfil the criteria for a diagnosis of primary Raynaud's disease. To regard these cases as secondary in origin owing to their association with the menopause is no more justifiable than to regard the hereditary group, or those which occur at puberty, as falling into this category. It is believed that these cases should therefore still be included in primary Raynaud's disease.

Summary

Twenty-one cases of primary Raynaud's disease are recorded in which the digital symptoms were initiated, or pre-existing mild attacks were converted into a more severe form, at a time so closely related to childbirth, the menopause, or a period of mental stress as to indicate that these three events should be regarded as aetiological factors in primary Raynaud's disease.

These cases represent 50% of a larger series of 42 cases, in the remainder of which no such aetiological factors could be detected.

REFERENCES

- Allen, E. V., and Brown, G. E. (1932a). *Amer. J. med. Sci.*, **183**, 187.
 — (1932b). *J. Amer. med. Ass.*, **99**, 1472.
 Hunt, J. H. (1936). *Quart. J. Med.*, **29**, 399.
 Jepson, R. P. (1951). *Ann. roy. Coll. Surg. Engl.*, **9**, 35.
 Lewis, T., and Pickering, G. W. (1934). *Clin. Sci.*, **1**, 327.
 Raynaud, A. G. M. (1862). "De l'asphyxie locale et de la gangrène symétrique des extrémités." Thèse de Paris.

A CONTRIBUTION TO THE MYCOLOGY OF THE MOUTH

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The published records of fungi obtained from the human mouth demonstrate that fungi of many types can be isolated both from apparently normal mouths and from mouths showing various disorders; in some of these diseases fungi have often been regarded as the causal agents. During recent years particular attention has been paid to mycotic infections of the oral cavity as a complication of antibiotic therapy (Cross, 1949; Tomaszewski, 1951a, 1951b, and numerous others).

The literature on the mycology of the mouth, which is both extensive and confused, will be reviewed elsewhere. Here it is only necessary to note that many of the earlier records are unsatisfactory owing to deficiencies in the clinical and mycological evidence, and that only a few attempts have been made to study the mycology of the mouth in relation to a number of fairly common oral pathological conditions.

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