In the present series skin rashes have occurred in six patients: in four the drug was given again without causing reappearance of the rash, and in two the rash reappeared and the thiocyanate had to be stopped. Koffler and Freireich (1944) have reported femoral thrombophlebitis in four of a series of 40 cases treated, and observed that the lesion tended to recur if the drug was repeated. In the present series this complication has occurred twice. In a larger series of other cases under the observation of one of us it has not occurred at all. Goitre is reported to have followed the long-continued administration of potassium thiocyanate. Wald *et al.* (1939) report 11 cases in 246 patients treated. We have not seen this complication. Our opinion is that, apart from skin rashes which may occur at low serum thiocyanate concentrations, toxic effects are uncommon provided that the dosage of the drug is properly controlled. The necessity for close control, especially in the early stages of thiocyanate therapy during which the adequate maintenance dose is being ascertained, cannot be over-emphasized.

It is said that thiocyanate therapy may be responsible for retinal, cerebral, and coronary thrombosis, but this opinion takes no account of the fact that a proportion of patients with persistent hypertension are suffering from active arteriosclerotic disease and that this disease is the cause, or may be the cause, of thrombotic phenomena occurring during the administration of thiocyanate.

Summary

An attempt has been made to assess the value of thiocyanate therapy in hypertension. A scheme of dosage has been given together with indications for treatment. Patients with hypertension have been classified according to phases and types of hypertensive disease. Taking the cases as a whole, symptomatic relief and a significant fall in blood pressure were observed in roughly 60% of the cases. The further observation of 42 patients shows that the effect of thiocyanate therapy can be correlated with the phases of the arteriosclerotic process, and that whereas symptomatic relief is given and blood-pressure reduction is maintained in approximately 40% of the cases, the continued administration of potassium thiocyanate does not prevent, in individual cases at least, the continued progress of arteriosclerotic disease.

REFERENCES

- Allen, E. V. (1942). *Proc. Mayo Clin.*, **17**, 519.
 Barker, M. H. (1936). *J. Amer. med. Ass.*, **106**, 762.
 D'Silva, J. L., and Evans, G. (1944). *Brit. J. Urol.*, **16**, 1.
 Evans, G. (1943). *Lumleian Lectures, R.C.P.*
 Fishberg, A. M. (1944). *Hypertension and Nephritis*, Lea and Febiger, Philadelphia.
 Koffler, A., and Freireich, A. W. (1944). *Amer. J. med. Sci.*, **207**, 374.
 Kurtz, C. M., Shapiro, H. H., and Mills, C. S. (1941). *Ibid.*, **202**, 378.
 Massie, E. (1941). *Int. Clin.*, **3**, 198.
 Moschowitz, E. (1945). *Vascular Sclerosis*, Oxford Medical Publications.
 Page, I. H., and Corcoran, A. C. (1945). *Arterial Hypertension*, The Year Book Inc., Chicago.
 Pauli, W. (1903). *Munch. med. Wschr.*, **50**, 153.
 Ravin, A. (1940). *J. Lab. clin. Med.*, **25**, 1204.
 Treupel, G., and Edinger, A. (1900). *Munch. med. Wschr.*, **47**, 717, 767.
 Wald, M. H., Lindberg, H. A., and Barker, M. H. (1939). *J. Amer. med. Ass.*, **112**, 1120.

The Minister of Food has issued a General Licence (S. R. & O., 1947, No. 595) under the Food Rationing (General Provisions) Order, 1946, which regularizes the arrangements for the supply of glucose barley sugar, free of personal points rationing, to persons for whom it is prescribed by registered medical practitioners. It prescribes the maximum quantity which can be supplied and provides for prescriptions covering a certain number of repeat purchases. Ration-free sales to the public can be made only by registered pharmacists and the responsibility for checking the prescriptions is placed upon them and manufacturers. The licence indicates how registered pharmacists may obtain glucose barley sugar from manufacturers to fulfil prescriptions or to replace stocks sold ration free. The Order came into operation on April 6.

AUTOHAEMAGGLUTINATION AND RAYNAUD'S PHENOMENON

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Autohaemagglutination has been defined by Boxwell and Bigger (1931) as "a clumping of the erythrocytes into irregular masses, visible to the naked eye, occurring in the presence of the individual's own serum, without bacterial action, at air temperature and reversible at body temperature." The phenomenon has been fully studied by these authors and by Landsteiner (1903), Clough and Richter (1918), Yorke (1911), and others both in animals and in human subjects. As a result of their investigations a number of criteria have been established; these may be briefly summarized: (1) Autohaemagglutinins in the serum of an "auto-agglutinator" will produce agglutination of his own corpuscles at temperatures below that of the body. They are most active at 0° C., less active at room temperature, and inert at blood heat. (2) Autohaemagglutinins are capable of agglutinating, at low temperatures, not only autologous corpuscles but also those of other individuals irrespective of their blood group, and in some cases the corpuscles of various animals as well. (3) The reaction is reversible. Corpuscles which have been agglutinated at low temperatures will disperse on heating to body temperature and reagglutinate on cooling.

Because of their activity at low temperatures auto-agglutinins are often referred to as "cold" agglutinins. The terms are not strictly synonymous. Broadly speaking, however, an auto-agglutinin may be regarded as non-specific "cold" agglutinin of such potency that it is active at room temperature. The difference then is largely one of "titre" and thermal range. The phenomenon is quite distinct from pseudo-agglutination which is due to excessive rouleaux formation, bacteriogenic haemagglutination which may occur when sera or cell suspensions are contaminated with certain organisms of the diphtheroid group (Thomson phenomenon), and from polyagglutinability, in which phenomenon the individual's corpuscles are agglutinated at low temperatures by most normal sera irrespective of their group agglutinins, but not by autologous serum (Gaffney and Sachs, 1943).

The sera of normal healthy individuals frequently contain small amounts of cold agglutinins which will produce weak macroscopic agglutination when the serum is mixed with corpuscles of the same group (or group O) at refrigerator temperature (0–7° C.). The reaction is seldom demonstrable on dilution of the serum beyond 1:16 (Turner and Jackson, 1943). Rarely a serum will stand considerable dilution (1:32; 1:64), and in very exceptional cases the agglutinin will be present in such strength as to produce obvious naked-eye agglutination at room temperature—that is, auto-agglutination.

Of 10,000 sera from presumably healthy individuals 0.29% were found by Shooter (1943) to contain cold agglutinins active at room temperature. Errors in blood-group determination are occasionally caused by the presence in an individual's serum or plasma of such an agglutinin. The small amount of plasma that is present in a citrate or saline suspension of the individual's corpuscles may be sufficient, even on further dilution with test grouping sera, to cause marked clumping of his own corpuscles, and a false diagnosis of group AB may be made. This source of error can be eliminated by carrying out the grouping test at 37° C., at which temperature

auto-agglutinins, but not the ordinary iso-agglutinins, anti-A and anti-B, are inactive.

Autohaemagglutination occurs rarely and inconstantly in a variety of pathological conditions which have little or no nosological affinity. Boxwell and Bigger could find in the literature only 22 cases which they considered to be undoubted examples of the phenomenon. Of these, five were normal subjects and the remainder suffered from such diseases as severe anaemia, cirrhosis of the liver, syphilis, and leukaemia. Cold and auto-agglutinins, however, are found with some degree of regularity in the sera of patients with primary atypical pneumonia (Peterson *et al.*, 1943; Turner *et al.*, 1943), tropical eosinophilia (Viswanathan and Natarajan, 1945), and trypanosomiasis (Yorke, 1911), and their demonstration has been used as a laboratory aid to the diagnosis of these conditions.

Table Showing Cases of Autohaemagglutination with Peripheral Vascular Manifestations

No.	Author	Case Notes
1	Iwai and Mei-Sai (1925) ..	Male, 36; Raynaud's phenomenon (R.P.)
2	Alexander and Thompson (1925)	Male, 48; R.P., atypical leukaemia, haemoglobinuria, W.R. negative
3	Iwai and Mei-Sai (1926) ..	Female, 78; R.P.
4	Stieffel (1928)	Male, 60; R.P., haemoglobinuria, hepatomegaly
5	Davidson (1932)	Male, 60; macrocytic anaemia, "suffered from cold hands"
6	LeGoff (1933)	Male, 67; R.P., chilblains
7	Roth (1935)	Male, 59; R.P., haemoglobinuria
8	Salén (1935)	Male, 50; acrocyanosis, haemoglobinuria
9	Ernstene and Gardner (1935) ..	Male, 38; R.P., haemoglobinuria
10	Sézary, Kipfer, and Gharib (1938)	Male, 60; R.P., haemolytic anaemia, arteriosclerosis, splenomegaly, and hepatomegaly
11	Hanns and Sommer (1938) ..	Male, 32; R.P., anaemia, splenomegaly
12	Gautier, Heimann, and Laudat (1939)	Female, 52; R.P., anaemia
13	Benians and Feasby (1941) ..	Female, 65; R.P., anaemia
14	Davidsohn (1942)	Female, R.P.
15	Stats and Bullowa (1943) ..	Male, 64; R.P., dry gangrene of digits
16	Helwig and Freis (1943) ..	Male, 38; acrocyanosis, primary atypical pneumonia
17	McCombs and McElroy (1937)	Male, 57; R.P., haemoglobinuria, arteriosclerosis

The association of autohaemagglutination with symptoms of a peripheral vascular nature has been observed on several occasions. Iwai and Mei-Sai (1925, 1926) reported two cases of Raynaud's phenomenon with associated high-titre auto-agglutinins, and were of the opinion that the peripheral vascular manifestations in their cases resulted from intravascular haemagglutination when the extremities were subjected to low environmental temperatures.

In 1937 McCombs and McElroy reviewed the literature on autohaemagglutination with special reference to its association with Raynaud's phenomenon. They were able to collect five case reports of this association, and they themselves added one more to the list. According to Stats and Bullowa (1943), 14 accounts of this combination of phenomena had appeared in the literature by 1943. To these I would add four other case reports. They are by LeGoff (1933), Ernstene and Gardner (1935), Davidsohn (1942), and Helwig and Freis (1943).

Laboratory findings are given pride of place in most of the accounts in the literature and full clinical details are not always available. Intermittent pallor or cyanosis of the extremities, precipitated by exposure to cold, is the predominant clinical feature, and the demonstration of high-titre cold or auto-agglutinins in the blood is a constant laboratory finding. Attendant clinical features such as anaemia, haemoglobinuria, hepatic dysfunction, and organic occlusive disease of the peripheral vessels are found in the case reports. Males are affected more often than females and there is wide variation in age incidence. Few, if any, of the patients appear to have been suffering

from the true clinical entity called Raynaud's disease (see Table). The following account of a case which I investigated recently is submitted as an illustrative example of the association of autohaemagglutination and Raynaud's phenomenon.

Case Report

A 24-year-old American sergeant was admitted to hospital with the complaint that his fingers became blue and numb on exposure to cold environmental conditions. He had had several attacks in the course of a few days before admission, during which time the weather was moderately cold. An attack would develop if his hands were uncovered while out of doors or in bed at night. Each attack would last for 10 to 20 minutes and would be rapidly relieved by warmth. He stated that changes first appeared at the tips of his fingers. As a rule the tip of one finger of either hand would first become involved and the change would gradually extend to all the fingers of one or both hands. The palms and the dorsa of the hands were affected to a less degree than the fingers; the wrists and forearms were unaffected. Colour changes during an attack were rather variable and depended to a certain extent on whether he was in the upright or the recumbent position, and whether or not he took immediate steps to alleviate the condition. From his description it seems that the fingers assumed a mottled dusky tint with white and purple patches and areas of normal colouring. In one attack the white patches would predominate, in another the purple. During the recovery phase the fingers would become first pale orange in colour, gradually intensifying to red and then fading to the normal skin colouring. He stated that his fingers felt numb during an attack and that they "throbbed" for a short time afterwards. Occasionally the tip of his nose and the lobes of his ears would become blue. His toes and feet were not affected at any time.

His past history was essentially negative. Despite the fact that he had lived for many years in a very cold part of the United States he had not previously suffered from this complaint. He acted as a volunteer blood donor a few months before admission and at that time no abnormality was found on blood examination. There was nothing in the past history to suggest that he had suffered from trypanosomiasis. Mastoidectomy had been performed at the age of 6 years. Eight months before admission a small tumour situated at the right angle of the jaw had been removed. The patient (a highly intelligent man) stated that microscopical examination of the tumour revealed "inflammatory change only."

A few slightly enlarged lymph nodes in both axillae and in the left supraclavicular fossa were the only abnormal findings on physical examination. There was no wasting of the small muscles of the hands or clubbing of the fingers. Normal pulsation was felt in the main limb vessels. The skin over the extremities (when examined between attacks) appeared perfectly healthy and his hands felt quite warm. The spleen was not enlarged. Radiological examination of the chest revealed no abnormality.

During the patient's short stay in hospital the weather became much warmer and attacks did not develop spontaneously. However, by immersing his hands in cold water it was possible to induce an attack. The colour changes already described were reproduced after a 15-minute immersion, with a rapid return to normal on placing his hands in warm water.

Laboratory Findings

That the patient was an "auto-agglutinator" was first suspected when an attempt was made to do a blood count. Capillary blood issuing from a small puncture wound in the lobe of the ear was seen to agglutinate spontaneously and large clumps of corpuscles were present in the diluting pipette. Under these circumstances it was impossible to carry out an accurate blood count, but by warming the patient's ear with a hot-water bottle and using pipettes and diluting fluids which had been warmed to 37°C. before use agglutination was temporarily prevented and a reasonably accurate blood count obtained. This count showed: haemoglobin, 98% (Haldane); red cells, 4,900,000 per c.mm.; white cells, 6,000 per c.mm. (neutrophil polymorphs, 3,180; lymphocytes, 2,520; monocytes, 300); platelets, 370,000 per c.mm. A film revealed nothing

abnormal. The patient's blood group was determined by carrying out the test at 37° C. He was found to belong to group B. The bleeding time and clotting time were normal. The erythrocyte sedimentation rate (Wintrobe) at 37° C. was 1 mm. in 1 hour (the true reading); at 22° C., 47 mm. in 1 hour—a false result owing to the rapid sedimentation of cell clumps; at 4° C. large cell masses prevented sedimentation. The Kahn and Donath-Landsteiner reactions were negative, as was the Paul-Bunnell reaction when carried out at 37° C. The urine revealed nothing abnormal.

Venepuncture was next performed and the blood sample placed in both oxalate and plain containers. These were immediately transferred to the incubator, clot retraction was allowed to take place at 37° C., and the following experiments were carried out, using the serum thus obtained.

1. One drop of the patient's serum was added to one drop of a 5% saline suspension of his own corpuscles on a porcelain tile at room temperature. Complete agglutination of the corpuscles occurred almost immediately. The porcelain tile with the serum-corpuscle mixture, still showing marked agglutination, was then transferred to the incubator at 37° C. The tile was re-examined after 10 minutes at 37° C. Dispersion of the corpuscles had occurred so that a homogeneous suspension of corpuscles in serum resulted, and there was no trace of agglutination. Reagglutination of the corpuscles took place when the tile was left at bench temperature (22° C.) for several minutes. Agglutination or de-agglutination could be produced indefinitely by alternate cooling and warming of the serum-corpuscle mixture.

2. The above experiment was repeated, using several suspensions of group AB, A, B, and O corpuscles instead of autologous corpuscles. The same result was obtained with B and O suspensions. With AB and A suspensions agglutination persisted at 37° C. because of the anti-A iso-agglutinin in the patient's serum.

3. A 1% saline suspension of washed autologous corpuscles was added to a series of dilution tubes containing progressive geometric dilutions of the patient's serum, so that the final dilutions of serum were 1:4 to 1:4096. The tubes were placed in the refrigerator at 4° C. overnight. The following morning the corpuscles were resuspended in the supernatant fluid by rapidly inverting each tube three times, and the highest dilution which showed naked-eye agglutination was taken as the end-point. A titre of 1,024 was thus obtained. The same titre was reached when the patient's serum was titrated against suspensions of O and B corpuscles. This titre remained constant throughout the patient's stay in hospital.

Comment

It has been shown experimentally that the abnormal agglutinin in this patient's serum was a true autohaemagglutinin. The disease or factor responsible for its presence was not, however, determined. The fact that no abnormality was detected on physical and radiological examinations of the chest does not altogether exclude the possibility that he had suffered recently from a subclinical attack of primary atypical pneumonia, a disease which was encountered not infrequently among Service personnel in North-West Europe at the time of his admission. It is known that primary atypical pneumonia may assume a very mild subclinical form, and Turner *et al.* (1943) record a case of the disease in an ambulant female patient, radiologically negative, whose serum contained cold agglutinins to a titre of 1,000, and whose only complaint was of a bad cough.

There can be little doubt that the peripheral vascular manifestations in the case presented were due to mechanical blockage of the small peripheral vessels by aggregations of corpuscles within their lumina, the activating factor being exposure to cold. Cold exerted its influence in a twofold manner: (a) by lowering the temperature of the exposed extremities to the critical level for auto-agglutination to occur, and (b) by producing simultaneously a constriction of these vessels—the normal response of peripheral vessels

to cold stimuli (Lewis, 1936). The lumina of the vessels were thus almost completely occluded and the clinical features of Raynaud's phenomenon produced. In true Raynaud's disease obliteration of the vessel lumen is brought about by intense spasm of the vessel. Although the mechanism of production of vascular obliteration is different in the two conditions the end-result is essentially the same (see diagram). The peripheral vascular manifesta-

Diagram showing the effect of exposure to cold on the lumen diameter of small arteries: A, in normal subjects; B, in true Raynaud's disease; C, in Raynaud's phenomenon due to auto-agglutination.

tions readily disappeared when heat was applied to the affected extremities, owing presumably to dilatation of the peripheral vessels and dissolution of the corpuscle aggregations. A free flow of blood to the parts was thus re-established.

The patient informed me by letter three months after his discharge from hospital that he was then symptom-free and that a blood examination for cold and auto-agglutinins was negative.

Summary

The literature on autohaemagglutination, with particular reference to its association with symptoms of a peripheral vascular nature, has been reviewed. Some 18 cases of this combination of phenomena are on record.

A case of autohaemagglutination with peripheral vascular crises has been described. It is suggested that the Raynaud-like attacks which followed exposure of the patient's extremities to low temperatures resulted from blockage of the small peripheral vessels with corpuscular aggregations. The results of *in vitro* experiments on the blood lend support to this contention and are probably a true reflection of the changes which occurred *in vivo*.

The aetiological factor responsible for the presence of the abnormal agglutinin was not determined.

REFERENCES

- Alexander, H. L., and Thompson, L. D. (1925). *J. Amer. med. Ass.*, **85**, 1707.
 Benians, T. H. C., and Feasby, W. R. (1941). *Lancet*, **2**, 479.
 Boxwell, W., and Bigger, J. W. (1931). *J. Path. Bact.*, **34**, 407.
 Clough, M. C., and Richter, I. M. (1918). *Johns Hopk. Hosp. Bull.*, **29**, 86.
 Davidsohn, I. (1942). *J. Amer. med. Ass.*, **120**, 1288.
 Davidson, L. S. P. (1932). *Quart. J. Med.*, n.s., **1**, 543.
 Ernest, A. C., and Gardner, W. J. (1935). *J. clin. Invest.*, **14**, 799.
 Gaffney, J. C., and Sachs, H. (1943). *J. Path. Bact.*, **55**, 489.
 Gautier, C., Heimann, V., and Laudat, M. (1939). *Bull. mém. Soc. méd. Hôp. Paris*, **55**, 59.
 Hanns, A., and Sommer, A. (1938). *Strasbourg-méd.*, **98**, 172.
 Helwig, F. C., and Freis, E. D. (1943). *J. Amer. med. Ass.*, **123**, 626.
 Iwai, S., and Mei-Sai, N. (1925). *Japan med. World*, **5**, 119.
 — (1926). *Ibid.*, **6**, 345.
 Landsteiner, K. (1903). *Münch. med. Wschr.*, **50**, 1812.
 LeGoff, J. M. (1933). *Presse méd.*, **41**, 628.
 Lewis, T. (1936). *Vascular Disorders of the Limbs*, London.
 McCombs, R. P., and McElroy, J. S. (1937). *Arch. intern. Med.*, **59**, 107.
 Peterson, O. L., Ham, T. H., and Finland, M. (1943). *Science*, **97**, 167.
 Roth, G. (1935). *Proc. Mayo Clin.*, **10**, 609.
 Salén, E. B. (1935). *Acta med. scand.*, **86**, 570.
 Sézary, A., Kipfer, H., and Gharib, M. (1938). *Bull. mém. Soc. méd. Hôp. Paris*, **54**, 1710.
 Shooter, R. A. (1943). *Lancet*, **1**, 202.
 Stats, D., and Bullowa, J. G. M. (1943). *Arch. intern. Med.*, **72**, 506.
 Stieffel, R. (1928). *Contribution à l'Etude des Hémoglobinuries*, Louis Arnette, Paris.
 Turner, J. C., and Jackson, E. B. (1943). *Brit. J. exp. Path.*, **24**, 121.
 — Nisnewitz, C., Jackson, E. B., and Berney, R. (1943). *Lancet*, **1**, 765.
 Viswanathan, R., and Natarajan, B. (1945). *Ibid.*, **1**, 148.
 Yorke, W. (1911). *Ann. trop. Med. Parasit.*, **4**, 529.