ELECTROCARDIOGRAPHIC FINDINGS IN ANÆMIA

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It has been known for a long time that anæmia is occasionally associated with cardiovascular disturbances, especially with functional cardiac signs and symptoms and with angina pectoris, but there is still a wide diversity of opinion as to the frequency with which this occurs. Detailed electrocardiographic studies have been made less frequently, and so in the present publication such changes are described in cases of pernicious, acute posthæmorrhagic, and chronic hypochromic anæmias, and the conditions in which they occur are discussed.

Review of Published Cases

Herrick and Nuzum (1918) first pointed out that anæmia may be accompanied by angina pectoris, and reported some cases of pernicious anæmia in which anginal pain occurred after effort. Similar cases have been described later by many authors. Coombs (1926) observed typical attacks of angina pectoris in 8 of 36 cases of pernicious anæmia. Lewis (1934) considered angina pectoris as a frequent complication of anæmia, but Willius and Giffin (1927) found only 43 cases with angina pectoris among 1560 cases of pernicious anæmia. Hochrein (1932) and Scherf (1932) stated that anæmia alone causes neither anginal pain nor myocardial damage, and that the occasional disturbances of the coronary circulation in anæmia are always due to organic disease of the coronary arteries. Jagič and Flaum (1935) supposed that there is always a pre-existent latent myocardial damage which becomes manifest in anæmia.

Electrocardiographic changes in anæmia were mentioned by Ussoff (1911) and later by Coombs (1926). But systematic electrocardiographic studies in anæmia have been made only by later authors. Šerf (1929) found in some cases of pernicious anæmia a flat or isoelectric T wave. Turner (1932) observed low voltage in a great number of cases of pernicious anæmia. Elliot (1934) found in one case of anæmia a slight depression of the S-T segment in leads I and II associated with angina pectoris. He concluded that these findings may be the expression of a functional change resulting from anoxæmia of the myocardium. Bloch (1938) found among 88 cases of anæmia electrocardiographic changes in 47 ; most frequently flattening of the T wave (in

87 per cent. of the positive cases), less frequently depression of the S-T segment and low voltage. De Matteis (1936) studied 32 cases of anæmia ; in 18 of them there were abnormalities, especially changes in the T wave, and it may be of interest that 5 of these 18 were from eighteen to thirty years old, and 10 were younger than fifty years old. Marchal, Soulié, and Roy (1935) reported a case of severe posthæmorrhagic anæmia with low voltage ; immediately after blood transfusion a marked elevation of all waves could be observed. Parade (1933), Bloch (1934), Büchner (1939), Büchner, Weber, and Haager (1935), Aschenbrenner (1934), Herles (1934), Székely (1938), Marchal, Soulié, and Roy (1935), and Dassen and Parodi (1936) have all reported cases in which the electrocardiographic changes disappeared after improvement of the anæmia under treatment.

On the other hand, there are many authors who did not observe any, or only very insignificant, electrocardiographic abnormalities in anæmia, even in those cases in which angina pectoris or intermittent claudication occurred (Reid, 1923 ; Willius and Giffin, 1927 ; Shirley Smith, 1933 ; Pickering and Wayne, 1934 ; Hochrein and Mathes, 1934 ; Misske and Otto, 1937).

Present Observations

Electrocardiographic studies were made in 76 selected cases of anæmia in which clinical examination did not reveal any signs of disturbances of the cardiovascular system, or of any extracardiac affection that may also produce electrocardiographic changes. Cases associated with hyperthyroidism and pulmonary diseases were excluded. The material consisted of 32 cases with pernicious anæmia and 44 with secondary anæmia of the hypochromic type. The erythrocyte count ranged from 850,000 per c.mm. before treatment had begun, to 3,500,000 c.mm., and the value of hæmoglobin from 22 to 75 per cent. We were aware that the majority of the cases of pernicious anæmia were aged patients in whom slight sclerotic involvement of the coronary arteries giving rise to electrocardiographic changes could not be with certainty excluded, in spite of normal clinical findings. But on the other hand, the average age of the patients with electrocardiographic changes was 47·8 years and of those without such changes 44·7 years, which seems to justify the statement that the abnormalities could not be exclusively ascribed to the age and to latent coronary sclerosis. For considering the influence of anæmia on the coronary circulation those cases are of great importance, in which the clinical and electrocardiographic signs suggestive of disturbances of the coronary circulation were only transient and entirely disappeared when the anæmia improved, and those in which the anatomically normal state of the coronary arteries could be verified by post-mortem finding. But owing to the low mortality in anæmia such cases with anatomical verification are very sporadic.

Normal sinus rhythm was present in all cases except in two with auricular and ventricular extrasystoles respectively. The P-R interval was within the usual limits. Lengthening of the intraventricular conduction time was never observed. Left axis deviation was encountered in 10, right axis deviation in

4 cases. In general the following abnormalities were noted : (1) changes of the T wave ; (2) depression of the S-T segment ; and (3) low voltage.

In the series of 32 cases of pernicious anæmia there were electrocardiographic abnormalities in 11 (34 per cent.). The alteration of the T wave was the most frequent abnormality observed. It was seen in 8 cases ; in 2 there was a flat T in leads I and II, in 3 a flat T in leads I, II, and IV, in 2 there was an isoelectric T wave in the three standard leads, and in 1 there was an inverted T in lead I and a flat T in lead II. Depression of the S-T segment was observed in 5 cases and low voltage in 2 cases. Præcordial pain was noted in this group in four cases, but in only one did it have the typical clinical picture, characteristic of angina pectoris. This case had an inverted T wave, especially well marked during the attacks. After improvement of the anæmia, both the anginal pain and the electrocardiographic abnormality entirely disappeared. This case has been followed in our clinic and reported by Prusík and Herles (1934). In the three other cases with præcordial pain the electrocardiogram was normal at rest ; in two of them it was normal even after bodily exercise; in one case there was a slight depression of the S-T segment in leads I and II immediately after exercise.

Among 44 cases of hypochromic anæmia there were electrocardiographic changes in 12 (31 per cent.). In this group also the most frequent abnormality was an alteration of the T wave. It was abnormal in 12 cases ; in 5 it was flat in leads I, II, and III (these changes were associated with low voltage of the initial ventricular complex) ; in 4 it was flat in leads I and II, in 2 in leads I, II, and IV, and in 1 case it was inverted in leads II and III. Depression of the S-T segment in leads I and II was observed in 2, and low voltage in 5 cases. One case with occasional præcordial pain, which had a normal electrocardiogram at rest, but a slight depression of the S-T segment in leads I and II immediately after exercise, is not included. Low voltage was found exclusively in chronic and severe anæmia. From the five with low voltage in this group, two had myelogenous leucæmia which lasted twelve and sixteen months respectively, two had lymphatic leucæmia which lasted eight and ten months respectively. All these four patients were treated by X-rays before our study. The fifth case with low voltage presented clinically an " idiopathic " septicæmia in which the blood culture was repeatedly negative. Anginal pain occurred only in one case in which the electrocardiogram was normal at rest, but slightly pathological after exercise. The other cases of this group were free of anginal pain.

The frequency of the different electrocardiographic changes found in our cases of anæmia is summarized in Table I.

Except in a few cases, repeated electrocardiograms were taken and correlated with the hæmatological condition. No direct relation was found between the degree of anæmia and the electrocardiographic changes. There were cases in our series in which the red blood cell count and also the hæmoglobin were very low (a million or less and 22 per cent. respectively) and yet the electrocardiogram was normal. On the other hand, there were cases of only slight anæmia with marked changes. Neither the red blood cell count nor the hæmoglobin value were found to be in direct relation to the electrocardiographic changes.

TABLE I

CASES OF ANÆMIA WITH ELECTROCARDIOGRAPHIC CHANGES

Number of Cases and Type of Anæmia	Changes of the T Wave			Depression of the S-T Segment	Low Voltage
	Flat	Iso-electric	Nega-tive		
Pernicious Anæmia ; 11 cases ..	5	2	1	5	2
Hypochromic Anæmia ; 12 cases ..	11	0	1	2	5
Total ; 23 cases	16	2	2	7	7
Percentage	87·3			30·4	30·4

However, in some instances the latter entirely disappeared after improvement of the anæmia under specific treatment. In three cases a pathological T wave became normal, and in three a depressed S-T segment became isoelectric.

One case is reported, of interest both from clinical and electrocardiographic point of view, which may help to explain why severe chronic anæmia does not always produce disturbances of the coronary circulation, and on the contrary why anæmia of moderate degree sometimes results in coronary insufficiency. A man, 34 years old, who had never been ill, complained of slight abdominal pain, symptoms having started suddenly three days before with a profuse hæmatemesis. The heart was normal in size, shape, sounds, rhythm, and rate ; and the blood pressure, 140/90 mm. The lungs were normal. There was no rise of temperature and the sedimentation rate of the erythrocytes was 10 mm. in the first hour and 25 mm. in the second hour. The urine contained no albumin and no sugar. The erythrocyte count was 2,910,000 per c.mm., the hæmoglobin 61 per cent. The leucocyte count was 8,800 per c.mm., of which 65 per cent. were mature polymorphonuclear cells, 5 per cent. stab forms, 23 per cent. lymphocytes, and 7 per cent. monocytes. The first electrocardiogram revealed sinus rhythm, a very slight depression of the S-T segment, a flat T_1, and an inverted T_2 and T_3 (Fig. 1A). Next day the inversion of T_2 and T_3 disappeared, only a flat T wave persisting (Fig. 1B). An electrocardiogram five days later was entirely normal (Fig. 1C). The erythrocyte count the same day was 3,080,000 and later 4,100,000 per c.mm. Electrocardiograms were repeatedly taken and all were normal, including one taken after exercise.

DISCUSSION AND COMMENT

Experimental studies in animals have proved that anæmia may produce ischæmic disturbances of the myocardium, even when the coronary arteries are anatomically intact. Büchner (1932 and 1939) found in rabbits, after an acute massive venesection and artificially provoked exercise, marked changes (depression

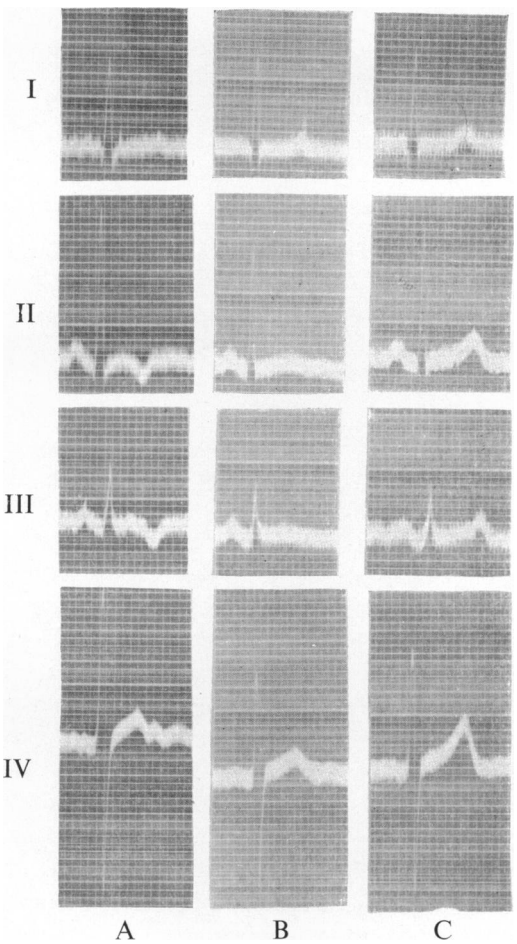

FIG. 1.—(A) Inversion of T_2 and T_3 with hæmoglobin of 60 per cent. (B) T_2 and T_3 flat, one day later, and (C) T_2 and T_3 upright, after six days.

of the S-T segment) which gradually disappeared ; and when these animals were killed after a few days he could demonstrate small areas of recent necrosis in their heart muscle. When they were killed during the first hours after the venesection and exercise, no anatomical changes of the myocardium were found. This author and others (Greene and Gilbert, 1921 ; Rothschild and Kissin, 1932–3 ; and Levy, Barach, and Bruenn, 1938), who experimentally induced anoxæmia and studied the electrocardiogram, found that the specific changes reached their culminating point during the acute oxygen deficiency and disappeared when normal oxygen supply was restored. Ischæmic necrosis of the heart muscle in animals was observed by Büchner only several hours after the condition of supposed acute coronary insufficiency. He concluded that the electrocardiographic changes in these cases are not due to the heart muscle necrosis, but purely to metabolic disturbances of the myocardium resulting from oxygen deficiency, which in anæmia may be caused by diminution of the oxygen-carrying power of the blood.

Laubry and Tzanck (1930) and Marchal *et al.* (1938) pointed out that the pathogenesis of cardiac disturbances seems to be different in acute posthæmorrhagic anæmia and in chronic anæmia. In the first group the anoxæmia of the myocardium is not a decisive factor, but only developes secondarily. The chief and direct cause of the cardiac disturbances may be the insufficiency of the return circulation (insuffisance de la circulation de retour). They could observe that the restoration of the volume of the blood by transfusion or by administration of physiological salt solution was followed by improvement of the clinical signs of cardiac damage and by disappearance of the electrocardiographic abnormalities. On the other hand, in cases of chronic anæmia they attributed a great importance to the anoxæmia of the heart muscle and considered it as the causal factor of cardiac disturbances.

Radnai (1935) made electrocardiographic studies in rabbits after venesection and found approximatively the same progressive changes which were later found by Marchal, Soulié, and Baugé (1938) : accentuation of the T wave, depression of the S-T segment, inversion of the T wave, appearance of a Q wave in lead III, and diminution and enlargement of QRS. Radnai emphasized the identity of these progressive electrocardiographic abnormalities with those found in angina pectoris and considered them anoxæmic in origin.

Experimental findings can only be applied with reserve in the clinical field. Nevertheless there are important clinical facts suggestive of a correlation between anæmia and cardiac disturbances resulting from anoxæmia of the heart muscle ; especially the occasional disappearance of both clinical and electrocardiographic abnormalities after improvement of the anæmia. However, in our cases there was no close parallelism between the degree of anæmia and that of cardiac disturbances. It seems probable that both in acute and chronic anæmia, angina pectoris or electrocardiographic changes are not due merely to the anæmia causing anoxæmia of the heart muscle, but also to another factor. And only the combination of these two factors results in cardiac disturbances. In cases of acute posthæmorrhagic anæmia this additional factor seems to be of reflex vasomotor character. In such instances the coronary volume flow may not be adapted to the acutely altered circulation and acute coronary insufficiency may result with clinical or electrocardiographic manifestations. We believe that our case of acute posthæmorrhagic anæmia, in which the coronary signs in the electrocardiogram entirely disappeared while only a mild improvement of the anæmia was observed, could be explained in this way.

In chronic anæmia the primary myocardial anoxæmia as the direct result of the diminution of the oxygen-carrying power of the blood may play a more decisive role. The experimental results of Marchal *et al* (1938) and of Radnai (1935) may be also in favour of this conception. The small fractional venesections with constant replacement of the volume of the blood by adequate doses of physiological solution may produce, indeed, an important diminution in the hæmoglobin with conservation of the normal blood volume, a condition similar to that in chronic anæmia. And in this experimentally induced anæmia in animals the same electrocardiographic changes were found, especially

flattening of the T wave and depression of the S-T segment, and less frequently low voltage, as in certain cases of chronic anæmia in men. But besides the anoxæmic damage of the heart muscle in chronic anæmia, toxic factors must be also taken into consideration as they may affect the myocardium directly. This might be the fact in our chronic cases with low voltage cases in which the electrocardiographic abnormalities were irreversible in spite of temporary improvement of the anæmia.

SUMMARY

Electrocardiographic studies were made in 76 selected cases of anæmia in which there was no clinical evidence of cardiovascular disease. Electrocardiographic abnormalities were found in 23 cases. Most frequently flattening of the T wave occurred ; less frequently depression of the S-T segment and low voltage.

A case is reported of hypochromic anæmia in which inversion of the T wave in leads II and III occurred after a profuse hæmatemesis. These electrocardiographic changes entirely disappeared at an early stage when only a small improvement of the anæmia had been observed.

The pathogenesis of electrocardiographic changes and of cardiac disturbances in general, in acute posthæmorrhagic and in chronic forms of anæmia, is discussed.

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