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## INVESTIGATION OF THE PATIENT WITH 'CRYPTIC ANEMIA'

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**T**HE term 'cryptic anemia' may not have originated with the late Dr. Russell L. Haden, but he popularized it, particularly among his students, for many years. The adjective *cryptogenic* seems to have no real advantage over the similar *cryptic*—defined as pertaining to that which is hidden, occult, secret, or mysterious. This is basically the meaning of the term cryptic anemia as applied to a pale patient whose complete and detailed history and physical examination fail to reveal specific and convincing evidence of the type or the cause of the anemia. The clinical investigation of such a patient is a challenge to the physician, first, because he already has prima facie evidence that the patient has a significant organic disease, and secondly in that it behooves him to establish as accurately as possible a specific diagnosis before consideration of therapy.

The physician, then, assumes the role of a detective who must utilize all of his resources, including diagnostic acumen, selected laboratory studies, and roentgenographic examinations. However, the physician is in charge of this investigation and it is a responsibility that cannot be transferred to the laboratory specialist or to others. An important facet of the investigation involves arriving at the diagnosis in the shortest possible time, with a minimum number of laboratory studies, and with the least cost to the patient. Therefore, the physician also must emulate the expert chess player and must try to establish a checkmate promptly.

### History-Taking

Certain features of history-taking from the pale patient are particularly important, with regard to cryptic anemia, in excluding known causes for the hemoglobin deficiency. In this respect the physician often must play the role of a sympathetic trial lawyer and the patient the role of witness. It is essential that the symptoms that result from the anemia *per se*, for example dyspnea on exertion, be differentiated from those that may be due to the primary disease causing the anemia. It is most important to make every effort to establish the time of onset of the symptoms. The anemias of short duration are usually considerably different in type from the chronic anemias of long duration. It is also important to determine accurately whether or not the presence of anemia has been definitely documented in the past, and at times to review this information from previous records. The physician must try to determine whether or not the prior anemia responded or failed to respond to a specific type of treatment. It is vitally important to obtain specific details regarding the patient's nutrition, menstrual periods in the female patient, and symptoms referable to the urinary tract and the gastrointestinal system.

### Physical Examination

By the strict rules of the investigation the anemia cannot be termed cryptic, before the completion of a comprehensive physical examination. Most physicians have learned the hard way that it is a great help to have adequate light, preferably daylight, even to differentiate the various forms of pallor, such as waxy pallor, sallowness, and lemon-yellow pallor. The faint yellow of mild jaundice may be masked in artificial light. It is particularly difficult at times to detect pallor beneath a rather deep suntan, heavy cosmetics, or blushing which may be present. In the darkly pigmented races the skin color is rarely helpful in this regard, and the appearance of the mucous membranes must be utilized. Most physicians will agree that as a general rule it is more difficult to determine pallor of the mucous membranes than of the skin.

The skin should be carefully inspected for petechiae, nevi, and purpuric lesions. Spooning of the fingernails is characteristic of iron-deficiency anemia unless one can prove it to be a hereditary defect. The examination of the tongue may give helpful information if only in supplying negative evidence. Sturgis<sup>1</sup> has emphasized that he never saw a patient with pernicious anemia, in relapse, with an unmistakably coated tongue. Careful palpation of superficial lymph nodes can hardly be over-emphasized, because this may lead to suspicion of malignant lymphoma, or to an unsuspected metastatic disease. Upon abdominal examination, a large, soft spleen may escape detection because the palpation is begun at the level of the umbilicus and the splenic border may descend into the pelvis. At times a spleen is more readily palpable with the patient lying in the right lateral position with his knees flexed. It is important for the physician to utilize his olfactory sense and to note the

patient's breath for the ammoniacal odor that will prove the presence of azotemia and, in turn, renal insufficiency, which may be the cause of the anemia. It should be emphasized that the edentulous patient with significant azotemia will not have an ammoniacal odor on his breath because of the lack of urease enzyme that is normally present around the gingival pockets of the natural teeth.

### Laboratory Investigation

Upon completing the history and physical examination, the physician may have accumulated an abundance of negative data and the one positive conspicuous finding of pallor. All of this is promptly fed into the physician's computer which is located in his frontal lobes and the answer comes out *cryptic anemia*. At this point, many diagnosticians are not only frustrated, but find it difficult to decide on the next logical steps to pursue.

Urinalysis is usually completed at this point. The next step is a complete hematology study, which should include a red blood cell count, in duplicate, a white blood cell count, a differential count, a hematocrit determination, and an estimation of the number of platelets on the stained films. As a screening procedure the icterus index can be obtained from the hematocrit tube. To save repeated venepunctures, such additional studies as blood glucose content, blood urea or creatinine determination, or other studies may be performed at the same time. A careful study of the stained blood films will disclose any significant deviations in the size, shape, and color of the red cells. In addition, certain abnormalities, if present, such as rouleaux formation, the presence of target cells, spherocytic red cells, or elliptocytes give excellent clues. A reticulocyte count is always performed when anemia is present. When the pallor is obviously severe and the clinical findings indicate the need for urgent treatment, then blood grouping and crossmatching are requested on the first venepuncture and the patient is promptly hospitalized. However, when the patient is comfortable and free of dyspnea at bed rest, transfusion therapy is deferred until the investigation is complete or nearly complete.

### The Investigation Continues

Upon completion of the study of the peripheral blood, a specific diagnosis may be established and few additional studies may be needed. At this point the anemia often remains cryptic and the blood study has served to classify the type of anemia into several broad groups; namely, (1) normocytic normochromic anemia, (2) microcytic hypochromic anemia, or (3) macrocytic anemia. All of the anemias can be so classified for practical purposes, but the obvious hemolytic anemias can often be separated at this point into various categories. Whereas the red cell indices such as the MCH, MCV, and the MCHC are helpful, they are no more accurate than the determination of the red blood cell count, the blood hemoglobin value, and the

**Table 1.**—*Analysis of data of 100 patients with cryptic anemia*

| Type of anemia and associated disease                                                              | Number of patients |
|----------------------------------------------------------------------------------------------------|--------------------|
| <b>NORMOCYTIC NORMOCHROMIC</b>                                                                     | <b>55</b>          |
| Renal insufficiency (chronic nephritis; pyelonephritis; prostatic hypertrophy; hypervitaminosis D) | 16                 |
| Primary refractory anemia (hypoplastic and hyperplastic marrow)                                    | 10                 |
| Leukemia (usually chronic), leukopenic                                                             | 10                 |
| Plasma cell myeloma                                                                                | 8                  |
| Metastatic tumor cells in bone marrow                                                              | 3                  |
| Hemolytic anemia                                                                                   | 3                  |
| Cryptic                                                                                            | 2                  |
| Carcinoma of rectum (during iron therapy)                                                          | 2                  |
| Recent acute blood loss (peptic ulcer)                                                             | 1                  |
| <b>MICROCYTIC HYPOCHROMIC</b>                                                                      | <b>27</b>          |
| Esophageal hiatus hernia                                                                           | 5                  |
| Gastric carcinoma                                                                                  | 3                  |
| Small-bowel neoplasms                                                                              | 3                  |
| Carcinoma of right side of colon                                                                   | 3                  |
| Polyyps of colon                                                                                   | 2                  |
| Bleeding hemorrhoids                                                                               | 2                  |
| Thalassemia minor (Mediterranean anemia)                                                           | 2                  |
| Renal insufficiency                                                                                | 2                  |
| Cryptic                                                                                            | 2                  |
| Gastric ulcer                                                                                      | 1                  |
| Amebiasis of cecum                                                                                 | 1                  |
| Subacute bacterial endocarditis                                                                    | 1                  |
| <b>MACROCYTIC</b>                                                                                  | <b>18</b>          |
| Pernicious anemia                                                                                  | 7                  |
| Primary refractory anemia                                                                          | 3                  |
| Leukemia, leukopenic                                                                               | 2                  |
| Cirrhosis of liver                                                                                 | 1                  |
| Nutritional                                                                                        | 1                  |
| Nontropical sprue                                                                                  | 1                  |
| Myxedema                                                                                           | 1                  |
| Acquired hemolytic anemia                                                                          | 1                  |
| Reticulocytosis (severe hemorrhage)                                                                | 1                  |
| <b>Total</b>                                                                                       | <b>100</b>         |

hematocrit value. It is most important to check the accuracy of these indices by careful inspection of the stained blood film, and if there is any question about the accuracy, the red blood cell count, the blood hemoglobin and hematocrit determinations should be repeated. If the physician is not experienced in studying blood films, he should at least know the extent of the hematology technician's capability and experience. Physicians have been responsible for errors in diagnosis because they were dependent upon hematology technicians who were not competent to recognize subtle morphologic changes in the blood films.

Frequently the next logical procedure is to perform a marrow aspiration, and a definite diagnosis will often be established, particularly in cases of leukemia, plasma-cell myeloma, or megaloblastic anemia.

It is beyond the scope of this report to outline the various diagnostic procedures in each type of anemia, but it is obvious that the investigation will often proceed along different lines in the various groups. For example, the normocytic anemias are frequently associated with failure in marrow function, either primary or secondary. The microcytic hypochromic anemias usually indicate chronic blood loss, with the notable exceptions of thalassemia of the minor types and the rare pyridoxine-responsive anemia. The macrocytic anemias strongly suggest a megaloblastic anemia and, in turn, a deficiency of vitamin B<sub>12</sub> or folic acid unless proved otherwise.

### Results

The records of 100 consecutive patients who had cryptic anemia were analyzed. Of this group, 55 had normocytic normochromic anemia, 27 had microcytic hypochromic anemia, and 18 had macrocytic anemia. Specific diagnoses are listed in *Table 1*. The analysis of 100 consecutive patients is of little statistical importance, and is probably not applicable in the year of 1964, because of the fewer number of patients now observed who have occult renal insufficiency causing the anemia.

Fortunately, the number of patients remaining in the cryptic anemia group after exhaustive investigation, has decreased, but there remains a small number who seem to defy a complete solution to their problems, even with the inclusion of all of the present-day refined technics of red cell enzyme analysis and isotopic studies such as those using iron<sup>59</sup> and chromium<sup>51</sup>. Many of the diagnoses in these cases will be clarified by prolonged observation.

### Summary

The investigation of a patient who has cryptic anemia can be both a rewarding and a frustrating experience. The suggestions outlined here proved helpful to us in attempting to establish a correct diagnosis in the shortest possible time and with the least cost to the patient.

Reference

1. Sturgis, C. C.: Hematology. Springfield, Illinois: Charles C Thomas, 1948, 915 p.; p. 204.