

THE CHOICE OF OCCULT BLOOD TESTS IN GENERAL PRACTICE

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IN CHOOSING a suitable test for use in general practice, it is necessary to be guided by the experiences and opinions of others. Dewis (1907) required accuracy, delicacy and simplicity of his occult blood tests. Needham and Simpson (1952) added inoffensiveness to the list of desirable qualities; but it is apparent that there is one further criterion which must obtain in general practice, and that is mobility.

In respect of this matter of essential standards, the words penned by Gregersen (1919) cannot be bettered:

It cannot be expected that the examination of the stools for blood will have the currency which it merits in clinical practice, until a method is devised which is certain, appropriately sensitive, as simple and easy to perform as possible and of which the possible sources of error are known.

A review of the literature was made, each test being studied in turn.

The spectroscopic technique made an immediate appeal on account of its small running costs, but the original paper by Weber (1893) expressed the belief that it was too complex a test for general practice and Schmilinsky (1903) shared the same opinion. Clark (1909) enthused and found he could detect the ingestion of 3.5 ml. of blood. Adler (1921), however, did not share Snapper's elation and he regarded the test as impracticable in the general practice of medicine. Reimann (1923) and Ratnoff (1923) had no strong views on the suitability of this technique, unlike Snapper and Van Greveld (1927), who were gratified with the results of their spectroscopic investigation of gastric cancer. Kiefer (1934) believed that he could detect 3 ml. of ingested blood with the spectroscope, but showed none of the zeal of Mezey (1950), who regarded the technique as

indispensable. More recently, Harrison (1957) was also favourably disposed. In general the attitude towards the method has been that of indifference, while three authors, as recorded above, have found its use in general practice too cumbersome. Because of this, and Reimann's (1923) finding of marked insensitivity, it was felt that the test was undeserving of a general practice assessment. However, a contemporary contributor to the literature of alimentary bleeding places greater reliance on spectroscopic techniques than on any chemical test for blood (Kay, 1962).

The guaiac test. Since 1893, when Weber made a clinical test of the more forensic discoveries of Schonbein (1856), Van Deen (1864) and Day (1867), the guaiac test has coloured the fabric of medicine. Furthermore, a modern textbook (Hepler, 1960) and a recent medical paper (Spiro and Frucht, 1960) acknowledge its usefulness.

Guaiac resin is not a noxious substance and there is no supply difficulty, but Stewart and Dunlop (1958) express doubts about its stability—doubts which are certainly justified in the case of tincture of guaiac (Rossel, 1903). The necessity to use test-tubes makes it rather a slow and inconvenient technique and, as it is also offensive, the tendency in general practice, were there no other procedure, would be to avoid faecal occult blood tests. Additionally, the method has no place in 'bedside medicine' where mobility is essential.

Doubt also exists about its sensitivity. Weber (1893) detected 3 ml. of ingested blood and Boas and Kochmann (1902) found it reliable in cases of gastric cancer. Joachim's (1904) opinions were quite as favourable, indeed there were numerous adherents (Schloss, 1904; Hartmann, 1904; Steele, 1904; Ewald, 1906; Cowie, 1907; Dewis, 1907; Holland, 1907; White, 1907; Clark, 1909).

Joslin (1906), astonishingly enough, found the guaiac test too sensitive, but Leech (1907) found it uncertain and fickle, and Grunwald (1907) regarded it as too insensitive. Boas (1914) was another who found the procedure lacking in delicacy. Gregersen (1916) took the same view and in 12 of 48 cases of gastric cancer the guaiac test was negative (Gregersen, 1919). But he was so impressed by the vital necessity of developing an ideal test for the general practitioner, that he developed his own excellent procedure within a short time (Gregersen, 1919).

Succeeding papers on the guaiac test (Coope, 1920; Koopman 1921; Reimann, 1923; Bell, 1923; Ratnoff, 1923; Aaron, 1924) did little to resolve the controversy until Hurst (1925) claimed that a

negative guaiac test proved the absence of occult blood, and thereby popularized the procedure in English medical schools (Barford, 1928).

Many other original papers and textbooks describe the guaiac test (Rosenthal, 1940; White and Geschickter, 1948; Gradwohl, 1948; Warner, 1950) without having any particular pertinency to general practice. The work of Hoerr, Bliss and Kauffman (1949) is, however, most helpful in the choice of a test for the family doctor, because they applied the guaiac test as a screening procedure; it is of great significance that three of their eight sufferers from gastro-intestinal cancer were passing negative stools. They point out that, in employing a screening test for such cases, it is not the false positive results which are worrisome, but rather the false negatives which may lull the physician into an unjustified feeling of security. Barnett (1952) found that half of his cases of gastro-intestinal cancer never passed positive stools as judged by the guaiac test, while the results of Jemerin and Colp (1952), Mason and Belfus (1952) and Wilcox (1956) were almost as unsatisfactory. Mendeloff (1953) noted that even 50 ml. of blood ingested as a single dose, might fail to produce a positive guaiac test in the faeces.

Therefore, in spite of other more favourable reports (Cancer Detection Conference, 1950; Holt, 1952; Harvey, 1956; Shahon, Horowitz and Kelly, 1956; Morgan and Roantree, 1957), it is apparent that, because of insensitivity, the test is not sufficiently discerning to be used as a screening test in general practice.

The phenolphthalin test. Devised by Kastle and Shedd (1901) as a reagent for oxidizing ferments and utilized by Meyer (1903) as a test for blood, the early authors, among whom was numbered Boas (1911), were favourably impressed with this test (Kastle and Amoss, 1906; Deléarde and Benoit, 1908a, 1908b). The latter authors found it would detect an aqueous dilution of blood of one part in a million. However, Ruttan and Hardisty (1913) condemned the test because of its lack of sensitivity when employed with faecal emulsions. The experience of Grundmann (1916) was precisely the opposite, and he had difficulty in obtaining negative results with normal people; Gregersen (1919) shared this view, and Bell (1923) condemned the test for the same reason and also on the grounds of instability of the reagent, when stored.

Gettler and Kaye (1943) made a searching appraisal of all the popular tests for occult blood and found the phenolphthalin test to

be the most reliable and specific reagent available; their excellent contribution to medical literature was studied, praised and substantiated by Peranio and Bruger (1951). Hughes' (1952) findings were not in accord, however, and Hepler, Wong and Pihl (1953) found that the brown colour of a faecal suspension might mask a positive reaction. Stewart and Dunlop (1958) also believed the reagent to be too non-specific.

The literature concerning the phenolphthalin test is, in its divergence of opinions and contradictory findings, typical of the writings on any, and all, of the tests for occult blood. This confusion of thought has done much to discourage their use. It is unlikely that more will be heard of this technique, and not only because of its safety. The method of preparation of the reagent is, however, complex and because of this and its lack of speed and mobility, the phenolphthalin test is, in its present test-tube guise, unsuitable for general practice.

The aloin test. Schaer (1900), who gave this test its clinical application, recorded that Klunge devised the technique in 1882. The work of Rossel (1903) contains the first description of a technique similar to that of the guaiac test of Weber (1893). Rossel preferred aloin to guaiac because of its availability and constant quality, and Boas (1903a, 1903b) supported this opinion. The clinical usefulness of the test was stressed by succeeding writers (Von Kozicowsky, 1904; Joachim, 1904; Schloss, 1904; Steele, 1904; Petracchi, 1905; Steele and Butt, 1905; Ewald, 1906; White, 1907). Goodman (1907) and Leech (1907) were less pleased with aloin as a reagent; indeed, the latter believed that the red colour of a positive result might be obscured by faecal pigments. Clark (1909) found the procedure very uncertain and later authors (Barker, 1916; Gradwohl, 1948; Forshaw and Mason, 1954) were non-committal. The test has only been described as a test-tube procedure and has never been adequately assessed. It is approximately as sensitive as the guaiac test and therefore must lack delicacy.

The benzidine test and its variations, with a special note on the Gregersen slide test. Since the original paper on the use of this test to detect faecal blood (Adler and Adler, 1904), there have been published many opinions, often conflicting, and many techniques, sometimes unpractical, even mystical. The classical test-tube method of Schlesinger and Holst (1906), although taught to many generations of students, had little use in general practice because it was time-consuming, clumsy, and distasteful to an extent that made it an

undesirable, malodorous procedure in the consulting room. Furthermore, the technique had no mobility whatsoever, requiring, as it did, the use of test-tubes, bottles and a source of heat. The test, therefore, could only be performed with difficulty in patients' homes. In the clinical laboratory, however, the test-tube method has proved an invaluable technique for many years, and the interest which it has excited is widely recorded (Leech, 1907; Goodman, 1907; Dewis, 1907; Stone, 1907; Clark, 1909; White, 1909; White, 1911; Mackay, 1916; Bell, 1923; Abrahams, 1923; Rosenthal, 1940; Hughes, 1952; Hepler, Wong and Pihl, 1953; Hawk, Oser and Summerson, 1954; Thornton and Illingworth, 1955; Levinson and MacFate, 1956).

Groat (1913) increased mobility and simplicity by replacing liquid hydrogen peroxide with barium dioxide, but Wagner (1914) introduced the principle of performing the test on a slide. Further assistance for the general practitioner came from Roberts (1915). With great vision and enterprise, Roberts compounded a five grain tablet of benzidine and sodium perborate. This tablet was placed on the specimen and glacial acetic acid was added. Here indeed was the prototype of the modern tablet and paper-strip tests, which could, as Roberts pointed out, be easily used by a nurse.

Roberts's ideas and conclusions of several decades ago have only recently been accepted; but an even more remarkable example of prescience exists in the literature of occult blood tests, where Barker (1916) pays tribute to the work of Max Einhorn. In this contribution was described a test for occult blood wherein an impregnated paper-strip was dipped in the suspected substance, and if blood were present the strip turned green.

Wagner's (1914) innovation of using the traditional benzidine test ingredients on a glass slide was revived and recommended by Gregersen (1916) and Vaughan (1917), but Gregersen (1919), feeling that this test was too sensitive because of the high concentration of benzidine, described a simple, portable and less delicate test using previously weighed and packeted powders of benzidine and barium peroxide. This method, henceforward designated as the Gregersen slide test, by its very nature made an immediate appeal to general practitioners—indeed it is still in favour.

Another benzidine variant was introduced by Leiboff (1929) with the employment of benzidine dihydrochloride, which was further assessed by Bing and Baker (1931), Gradwohl (1948), Ham (1950), Mendeloff (1953), Hepler, Wong and Pihl (1953), Wilcox (1956), Cook, Free and Free (1956) and Dudley and MacLaren (1957). The

test, as described, is insensitive and has not enough convenience and mobility for general practice purposes. An endeavour to assess the test and improve its delicacy was, however, prevented by the failure of benzidine supplies: in this connection, it is perplexing that four recently published works describe the employment of benzidine in the clinical laboratory (Dawson and Goldie, 1958; Hepler, 1960; Hanks, Cassell, Ray and Chaplin, 1960; Stubbé, Pietersen and Van Heulen, 1962).

The Gregersen slide test (Gregersen, 1919) is now obsolescent but it has had a unique place in clinical laboratory work and in general practice and is still being performed (Stubbé *et al.*, 1962). Early support came from Reimann (1923), Ratnoff (1923) and Aaron (1924); Ogilvie (1927), while admitting the general practice appeal of the test, found it failed to detect the consumption of three ounces of raw meat, and Meulengracht and Jensen (1929) had a significant number of false negative results among their cases of gastro-intestinal cancer.

Much more comforting were the figures of Dahl-Iversen and Nissen (1930) and Samuel Lipetz, an Edinburgh family doctor, has always been a warm supporter of the Gregersen slide test (Lipetz, 1947, 1951, 1952, 1955). Medical textbooks down the years have recommended the procedure (Gradwohl, 1948; White and Geschickter, 1948; Stitt, Clough and Branham, 1948; Kolmer, Spaulding and Robinson, 1952; University of Glasgow Standing Committee on Laboratory Methods, 1952; Todd, Sanford and Wells, 1953; Hunter and Bomford, 1956). But there have been many dissenting voices. Manning (1952) believed that dietary factors could produce false positive reactions and that the test had, therefore, no accuracy as a casual screening test or emergency domiciliary procedure. Hughes (1952), in a fine study of occult blood technique, regarded the Gregersen test as clumsy and unsuited for general practice—a view shared by Hepler *et al.* (1953), but refuted by Ogilvie (1952).

Needham and Simpson (1952) made a meticulous investigation into occult blood tests and praised the Gregersen procedure. It is difficult to reconcile their belief that the ingestion of 3–5 ml. of blood will produce a positive test in a normal person with their finding that five of their 20 cases of gastric carcinoma were passing negative stools, until one recalls the wide variation in the ability of the intestine to destroy blood's reacting power. Confidence in the test was not improved, however, by the fact that Mendeloff's (1953) subjects might ingest 50 ml. of blood and pass stools giving a nega-

tive reaction to a similar test. The findings of Forshaw and Mason (1954) inferred a similar lack of sensitivity. There are other antagonistic opinions (Thornton and Illingworth, 1955; Wilcox, 1956; Dudley and MacLaren, 1957; Harrison, 1957), and, although the test is still in clinical use (Bannerman, 1957; Lange, 1957; Cameron, 1960; Holt, 1960; Winkelman and Summerskill, 1961; Stubbé *et al.*, 1962), the concensus of opinion, from the general practitioner view point, is unfavourable.

Aligned with the modern tablet tests for occult bleeding, the Gregersen slide test is a ponderous, complex technique. Much of its fame has rested on the claim that no dietary restriction is required (Alvarez and Wight, 1929; Kolmer *et al.*, 1952; Todd *et al.*, 1953). However, Gregersen (1919) himself advised a meat-free diet for the subject, and there is a wealth of evidence to support this belief of the originator of the test (Reimann, 1923; Aaron, 1924; Gradwohl, 1948; White and Geschickter, 1948; Stitt *et al.*, 1948; Manning, 1952; Mendeloff, 1953; Lipetz, 1955; Thornton and Illingworth, 1955; Dudley and MacLaren, 1957; Smith, 1958; Alvarez and Summerskill, 1958).

The acknowledged toxicity of benzidine, and the consequent supply failure, signify that there can be no reprieve for Gregersen's brain-child.

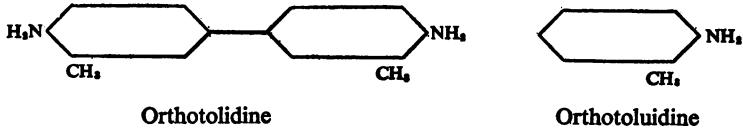
The orthotolidine test. A careful description of orthotolidine's properties and derivation (Ruttan, 1886) long preceded its introduction as a test for occult blood (Ruttan and Hardisty, 1912). In spite of a rapid reprise (Ruttan and Hardisty, 1913), the medical world was unresponsive, until Leiboff (1929) mentioned the method once more. The technique originated, and long persisted, as a test-tube method and made a profound appeal to Kiefer (1934), for whom it was the faecal occult blood test of choice. For the diagnosis of occult haematuria it was also acclaimed by Stone and Burke (1934), Calvin and Carbone (1939), Barach and Pennock (1940) and Caplan and Discombe (1951).

Zwarenstein (1943) simplified the test by using small squares of filter-paper impregnated with orthotolidine solution.

The similarity between the spelling of ORTHOTOLIDINE and ORTHOTOLUIDINE has led to much confusion (Cameron, 1960; Kay, 1962) in spite of Ruttan's (1886) and Zwarenstein's (1943) efforts at clarification.

Differentiation is important, and not least because it is believed, on good authority, that orthotolidine is carcinogenic while orthoto-

luidine is not (Williams, 1961).



Cameron and White (1946), White and Geschickter (1948) and Stitt *et al.*, (1948), in the different textbooks which they published, supported a test-tube technique employing orthotolidine. Paul and Hamilton (1948) and Gradwohl (1948) approved the adoption of the tablet test and the former authors particularly mentioned the stability and portable nature of such tablets; Baron (1951) also appeared to view this occult blood test through the eyes of a family doctor.

Although there is still some support for the test-tube method (Kolmer *et al.*, 1952; Kohn and O'Kelly, 1955; Ogilvie, 1957; Porter, Lewis and Dixon, 1959), the versatile tablet tests now seem to have established themselves.

These tablet tests are manufactured, by the Ames Company Limited, in two strengths—the weaker hematest and the more sensitive occultest. The former is roughly equivalent, in delicacy, to the Gregersen slide test, and the latter to the Schlesinger and Holst (1906) method of performing the benzidine test. Hepler *et al.* (1953) found that hematest tablets gave them false positive results—which were probably of dietary origin, while Morgan and Roantree (1957) and Kay (1962) regarded the hematest tablet as too insensitive. Apart from these dissidents there is general approval of the orthotolidine tablet procedures (Peranio and Bruger, 1951; Levinson and MacFate, 1956; Smith, 1958; Cullis, 1959; Hazell, 1960; Jones and Gummer, 1960; Burnett, 1961), and Stewart and Dunlop (1958) regard them as the method of choice.

The tablets have been successfully used to detect occult uterine bleeding (Stein-Werblowsky, 1954; Bredland, 1958; Hurtig, 1958); their place in detecting occult haematuria is well known (Watson Williams, 1955; Peyman, 1956; Cook, Free and Free, 1956; Free, Free and Giordano, 1956; Rinsler and Gray, 1957; Wells, 1957; Fielding and Langley, 1958; Hoe and Wilkinson, 1958; Peeters and Vuylsteke, 1958; Rees-Evans and Campbell, 1958).

Because there is evidence that orthotolidine is carcinogenic, British production has ceased. However, supplies of the tablets are assured from North America (Vobes, 1961).

There is therefore available a tablet procedure in two degrees of

sensitivity, occultest and hematest (Ames Company Limited), which has a unique suitability in general practice by virtue of speed, simplicity, mobility and lack of offence.

The advent of a standard technique in testing for occult bleeding has rendered obsolete the diverse multitude of previous methods, each with its variations, and all with differing sensitivities.

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SHOWING A TONGUE

... It is often a source of much pleasure to the sick to be allowed to tell in their own way whatever they deem it important for you to know; allow therefore to every such one a courteous hearing, and even though they may be tedious do not abruptly cut them short, but listen with calm, respectful attention. A patient may deem a symptom very important that you know to be otherwise, yet he will not be satisfied with your views unless you show sufficient interest in all the symptoms to, at least, hear them described. When for want of time to listen further, or where the recital become too irrelevant, do not check him by rudely telling him "to stop", but quietly asking him a question, or to show his tongue—which latter will often answer the purpose with garrulous women and others.

The Young Practitioner. JUKES DE STYRAP,
M.K.Q.C.P. (1890). London. H. K. Lewis. p. 30.