and where the central edentulous fragment has become depressed below the level of the two adjoining fragments. There is no doubt that for immediate fixation in the majority of cases intermaxillary or interdental wiring is the method of choice. It is quick, easily applied at short notice, and requires no elaborate dental fitting or apparatus. Metal cap splints, when properly applied, undoubtedly give the most accurate fixation, and should be used where intermaxillary wiring has failed, where delayed union makes the most perfect fixation necessary, or preparatory to bone grafting. They are particularly indicated where, with standing teeth in both fragments, rigid fixation may be obtained without immobilizing the temporo-mandibular joint.

COMPLICATIONS INVOLVING THE SOFT PARTS

Obliteration of the Buccal Sulcus

In nearly all cases which have been bone-grafted loss of the alveolar ridge obliterates the inferior buccal sulcus. In a few severe fractures of the lower jaw also the injury is so extensive that the sulcus is partly or completely destroyed. In riding, flying, or motoring accidents, or in those resulting from explosions, the lower lip or cheek may be so severely lacerated that the same effect is produced. Other causes are extensive destruction of the alveolar ridge and continued sepsis at the site of fracture. When the fracture heals and the sepsis clears up it is found that the buccal sulcus is so shallow as to make the fitting of a stable denture impossible. The treatment of this complication is exceedingly satisfactory. By the Sidcup modification of the method of Esser, called the "buccal inlay," the adhesions between the mandible and the lower lip or cheek are separated, and the resulting raw area grafted with a Thiersch graft cut from a hairless portion of the body, preferably the inner side of the upper arm. Pressure is maintained on the graft by means of a Stent mould of the defect held by a dental appliance previously fitted to the lower teeth. After ten days, when epithelialization is complete, the mould is removed and is replaced by a gutta-percha or vulcanite mould of similar shape. This is maintained *in situ* until all tendency for the cavity to contract has ceased. When this period is over the denture can be fitted.

Facial Deformities Resulting from Fracture of the Mandible

In dealing with mal-union mention was made of the treatment of irregularities of contour of the jaw, such as the "flat" or too prominent angle. Any such unevenness may be simply dealt with, on the one hand, by means of fat grafts introduced at appropriate sites, and on the other by the removal of excess bone, so that the jaw line is smoothed out and normal symmetry regained. In addition to concealing the defects of bony contour, it is frequently necessary to excise and resuture depressed scars of the chin or cheek caused by the original injury. These are frequently associated with the deep depressions adherent to the bone, which indicate the former presence of sinuses. Careful excision of all scar tissue and freeing of the skin from deep structures, together with local rearrangement of fat flaps or the introduction of fat from elsewhere, followed by resuture, will do much to obliterate all trace of what would otherwise remain as an unsightly disfigurement.

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THE CRONIN LOWE SERUM REACTION FOR MALIGNANCY

BY

JOCELYN PATTERSON, M.Sc., Ph.D.

BIOCHEMIST TO CHARING CROSS HOSPITAL

AND

JOSEPH ADLER

(From the Biochemical Department, Charing Cross Hospital, Institute of Pathology)

Widespread interest has been aroused by the recent publication by Cronin Lowe¹ of a reaction claimed to be diagnostic of malignancy. This new test is a development of the vanadic acid flocculation reaction devised by Bendien² which, when coupled with a means of subjecting the precipitated protein to a spectrophotographic examination, was said to lead to results of diagnostic value. It has now been generally accepted, following upon the serious criticisms levelled against the value of the spectrophotographic examination by Smith, Holiday, and Marrack,³ that the serum reactions as described by Bendien do not provide any basis for arriving at a diagnosis of malignancy; hence the need of replacing them by others likely to prove more successful.

The test devised by Cronin Lowe is of a triple nature, the vanadic acid preparation of Bendien being performed on (1) untreated serum, (2) heat-inactivated serum, and (3) ether-extracted serum. In general, with a given vanadic acid mixture in the region of "first precipitation," if A, B, and C are used to denote the yields of protein deposit resulting respectively from each phase, then A is greater than B and less than C. If from these values a ratio be computed in the form of $\frac{C-A}{A-B}$, then a ratio greater than unity is observed for malignant cases, while other serums show a ratio less than unity. It is claimed that on this basis an accurate diagnosis as to the presence or absence of malignancy can be made in at least 95 per cent. of cases, and if certain grossly septic cases held to be responsible for introducing a complication into the reaction be left out of account the figure is raised to 98 per cent. These results are so striking that if the necessary confirmation be forthcoming the Cronin Lowe reaction would represent practically the most valuable diagnostic test known to clinical medicine. The present investigation was undertaken with a view to formulating an opinion with regard to the value of the test.

Our initial results fell lamentably short of the success which had been reported, and, after full investigation, and seeing no hope of reconciling our findings with his, one of us communicated with Dr. Cronin Lowe, who thereupon kindly provided us with very full technical details upon all the points of procedure which were regarded as being likely to cause discrepancies in results. Further work performed with the aid of this extra information still left us far short of achieving a diagnostic reaction, and we are thus obliged to conclude our investigation by presenting results which provide no confirmation of the usefulness of the triple reaction as a test for malignancy. It should be made clear that the present paper deals solely with results obtained subsequent to receiving the private communication from the original author.

TECHNIQUE ADOPTED

Every precaution was taken to reproduce exactly the conditions laid down by Cronin Lowe. Unfortunately, however, the interferometric apparatus employed by him in the estimation of the protein deposits was not part of the equipment of this laboratory, and is too expensive an instrument to acquire solely for the purpose of this investigation. It was thus necessary to substitute an alternative method of protein estimation. This may account for some of the difference in the accuracy of our diagnostic results as compared with the original, but it could only affect those near to unity ratio and could make no serious alteration in the general trend of the findings. Moreover, the original author has himself expressed the opinion that the interferometer is by no means to be regarded as indispensable to the success of the test. After testing the application of several different methods of protein estimation we adopted the Wu colorimetric method¹ as being the most suitable for the purpose as well as accurate and convenient.

The procedure adopted is exactly that described in the original paper up to the point of estimating the protein deposits. These are dissolved in 2 c.cm. of N/70 NaOH, allowed to stand until practically colourless, then transferred to a 10 c.cm. graduated tube, 5 to 6 c.cm. of distilled water being used for the purpose. After the addition of 1 c.cm. of 20 per cent. sodium carbonate and 0.1 c.cm. of the special Wu "phenol reagent," the volume is made up to the 10 c.cm. mark with the distilled water. Following thorough mixing, the colour is allowed to develop for twenty minutes and then compared in the colorimeter with a standard similarly prepared from 0.5 c.cm. tyrosine standard solution (containing 0.02 per cent. of the amino-acid), 2.5 c.cm. of the sodium carbonate, and 0.25 c.cm. of the phenol reagent in a total volume of 25 c.cm. This standard provides a colour intensity in close approximation to that from 1 mg. of protein deposit, corresponding to 40 units, which is the index of "first precipitation" accepted by Cronin Lowe. (Actually, if the whole of the protein deposit consisted of serum globulin the figure would be 1.04 mg.; if albumin, 1.10 mg.)

TABLE I.—Malignant Cases

Case No.	Reactions		Clinical Conditions	Evidence of Disease H. = Histological O. = Operative C. = Clinical
	Malignant	Non-malignant		
3	—	5. 0.9/26.2	Epithelioma of cheek	H.
6	1. 21.9/0.5	—	Carcinoma of oesophagus	C.
8	—	7. 4.2/28.6	Carcinoma of breast	H.
9	—	4. 8.8/11.4	" " "	C.
10	5. 18.4/8.8	—	" " "	H.
12	—	6. 4.6/11.0	Rodent ulcer	C.
15	—	B.* 21.6/23.6	Carcinoma of breast; died	C.
18	A.* 12.5/9.9	—	Carcinoma of rectum	H.
23	4. 9.9/8.4	—	Carcinoma of transverse colon	O.
27	5. 12.6/3.1	—	Malignant papilloma of bladder	H.
30	—	5. 2.6/19.8	Malignant thyroid; glands in neck	H.
37	—	B.* 5.3/19.2	Carcinoma of right alveolar margin	C.
38	—	2. 0.8/3.8	Epithelioma of palate; glands in neck	C.
43	2. 1.2/-1.6	—	Carcinoma of stomach; died	P.M.
45	O.* 12.2/7.8	—	Carcinoma of colon, ulcerating through skin	C.
50	—	3. 5.4/15.4	Carcinoma of bladder; died	O.
52	—	3. 3.6/21.1	Carcinoma of lung; died	P.M.
54	3. 9.2/0.9	—	Carcinoma of breast	C.
55	3. 24.8/5.8	—	Carcinoma of sigmoid	O.
57	4. 0.0/-1.1	—	Carcinoma of caecum	O.

* The usual Bendien scale has been extended below 1 in successive steps in the order: 1, O, A, B.

TABLE II.—Non-malignant Cases

Case No.	Reaction		Clinical Condition	Evidence of Disease H. = Histological O. = Operative C. = Clinical
	Non-malignant	Malignant		
1	4. 7.0/29.4	—	Peptic ulcer	H.
2	5. 8.7/16.5	—	Appendicitis	H.
4	—	5. 17.8/12.0	Peptic ulcer	H.
5	—	5. 20.8/12.5	" "	H.
7	5. 10.0/14.1	—	Alveolar abscess	O.
11	1. 0.0/15.9	—	Chronic nephritis	O.
13	O. 4.2/23.8	—	Tabes	C.
14	O* Ether throw markedly negative	—	Chronic nephritis	C.
16	—	O. 12.4/3.7	Intestinal obstruction; died	P.M.
17	—	5. 34.6/11.4	Chronic mastitis	H.
19	—	5. 8.2/3.5	Hyperpiesis and arthritis	C.
20	—	6. 27.4/19.4	Hyperpiesis	C.
21	—	6. 27.0/6.8	"	C.
22	6. 12.0/31.0	—	"	C.
24	5. 3.6/13.6	—	Disseminated sclerosis	C.
25	—	5. 19.0/8.0	Hyperpiesis	C.
26	6. 1.6/21.6	—	Fatty hernia	O.
28	5. 1.7/15.1	—	Pulmonary tuberculosis	C.
29	6. 6.3/15.0	—	Cholelithiasis	O.
31	3. 15.0/20.4	—	Transverse myelitis	C.
32	—	5. 15.8/3.2	Nephritis	C.
33	—	4. 21.6/10.0	Pulmonary tuberculosis	C.
34	6. 11.8/22.7	—	Simple enlargement of prostate	H.
35	6. 9.1/10.7	—	Suspected lactating carcinoma of breast, shown to be non-malignant on section	H.
36	—	5. 18.5/17.9	Simple chronic lobular mastitis	H.
39	—	4. 19.8/10.9	Chronic nephritis	C.
40	3. -3.8/6.0	—	Pulmonary tuberculosis	C.
41	6. 5.6/24.8	—	Lipoma of breast	H.
42	6. 2.9/9.6	—	Tuberculous hip	C.
44	5. 6.9/15.7	—	Virilism	O.
48	—	5. 11.7/7.5	Duodenal ulcer	O.
49	3. 0.0/19.4	—	Food poisoning (mental case)	C.
53	4. 8.6/18.7	—	Rectal obstruction; no abnormality following barium enema	C.
56	—	6. 16.1/9.7	Benign tumour of breast	H.
58	5. 0.0/23.4	—	Haematuria proved to be non-malignant	C.

* A markedly lipaemic serum in which it was very obvious on inspection that C was much less than A, and A only slightly greater than B. The enumerator was therefore clearly less than the denominator; hence, according to rule, the reaction must be styled non-malignant.

INTERPRETATION OF FINDINGS

The present investigation has dealt with a series of fifty-nine cases, of which twenty were definitely malignant and thirty-five were non-malignant but pathological, while four cases remain unclassified because the presence or absence of malignancy could not be decided upon with certainty. No normal healthy cases were included. The essential data furnished by the investigation has been assembled in Tables I and II, wherein the reaction ratios are shown for each case, immediately preceded by the Bendien number denoting the first precipitation tube. With the diagnosis is given the nature of the evidence upon which it is based. For convenience in the tabulating of results reactions have been recorded as malignant or non-malignant according as to whether the calculated ratio falls

greater or less than unity, without reservation in the first instance in regard to those which are likely to be affected by the experimental error of the method. In the final review of the results of this type it is essential that such inherent errors be brought into account. The notable absence of any such qualification about Cronin Lowe's results constitutes a serious criticism of his findings, a point which will be raised again at a later stage.

In determining the extent to which results are strictly reproducible we have found that, in general, duplicate results lie within 5 per cent. of the mean, and that it is impossible to ensure consistently any better agreement than is represented by this margin; in other words, an individual reading cannot be guaranteed as being within a narrower range than two units—that is, 5 per cent. of forty—of the correct figure. Allowance must therefore be made for a possible maximum error of four units on both numerator and denominator. Thus only those cases in which the difference between numerator and denominator is greater than eight units may be regarded as lying clearly outside possible error, and these are described as "frankly" malignant or non-malignant in reaction according as to whether the ratio exceeds unity or not. Those in which the difference is between four and eight units can only be regarded as "presumably" malignant or non-malignant. The remaining results cannot be classified by the reaction formula. On this basis the results recorded in the tables may be summarized thus:

A. Malignant cases.

(1) Number giving frankly malignant reactions ...	5
(2) Number giving presumably malignant reactions...	1
(3) Number giving frankly non-malignant reactions...	6
(4) Number giving presumably non-malignant reactions ...	1
(5) Number impossible to classify ...	7

B. Non-malignant cases.

(1) Number giving frankly non-malignant reactions ...	17
(2) Number giving presumably non-malignant reactions ...	3
(3) Number giving frankly malignant reactions ...	9
(4) Number giving presumably malignant reactions...	4
(5) Number impossible to classify ...	2

In practice, using the reaction for diagnostic purposes, one would probably be obliged to reserve judgement on those which did not fall into Groups A1 and B1, A3 and B3. In such circumstances, so far as our present series is concerned, a verdict could be given on thirty-seven out of fifty-five cases submitted for investigation (67 per cent.). Of these the reaction, according to our findings, is only capable of providing the correct result in twenty-two cases, or 60 per cent. By carrying out duplicate or triplicate tests, the majority of the cases falling into Groups A2 and B2, A4 and B4 would find satisfactory confirmation on the malignant or non-malignant side as they now stand. If, therefore, we include these cases for the purposes of calculating the correctness of results, we have a verdict given on forty-six cases out of fifty-five—that is, 84 per cent.—which is right in twenty-six instances—amounting, that is, to 57 per cent. correct.

In view of the large percentage error on the series taken as a whole, little is to be gained by an analysis of the malignant cases into groups according to the site of the tumour, or of the non-malignant cases into the types of disease which comprise them. Among the malignant diseases the most satisfactory group is that associated with the gastro-intestinal tract. The results in all six cases examined fall on the right side, but of these only one gives what is described as a frankly malignant

reaction. A less satisfactory conception of the possible value of the test in relation to the diagnosis of malignancy in the gastro-intestinal tract is obtained when we turn to the corresponding group on the non-malignant series, for they likewise have, if anything, a tendency to a ratio exceeding unity, four out of seven cases responding in this manner, and thus represent a large error. The only other prominent feature is to be discovered in the group of cases of well-marked hyperpiesis, of which four out of five give a frankly malignant reaction. Finally, attention might also be directed to Cases 3, 7, and 12, which represent superficial and highly localized growths, and which give reactions of the non-malignant type.

DISCUSSION

It is at once obvious that, from whatever angle one looks at these results, they conflict sharply with those of Cronin Lowe. His diagnostic test has clearly been of no diagnostic value in our hands. The total discrepancy is so wide that there appears to us at present no means of fully accounting for what are really diametrically opposed findings. A different choice in the method of protein estimation could scarcely have made any appreciable difference to the most important groups of our series, as has already been explained. Indeed, many of the major errors which have been encountered could quite well be noted on naked-eye inspection of the three deposits before engaging on the estimation stage. The technique involved in the preliminary treatment of the serum and its fractional precipitation might be held responsible as leaving sufficient latitude for notable discrepancy. It should be emphasized, however, that before commencing upon the series we were at pains to ensure that quite independent interpretation of the technique described in full detail by the original author in the personal communication already mentioned gave reasonably close agreement in the final formula (within the range of ± 2 units of the mean as noted in an earlier section). We hope, therefore, to make it plain that we have adopted throughout every practicable measure to ensure the avoidance of discrepancies arising out of possible differences in technique.

Coming now to the examination of the results published in Cronin Lowe's original paper, it is possible to direct serious criticism against some of the important aspects of the reaction as a diagnostic test. Neither from the text nor from the tables does it appear as if there were any borderline cases. Every ratio, no matter how near to unity, is given significance according as it falls on one side or other. Thus, to take examples, from Table II there is a 15/17 ratio recorded as a non-malignant, and a 38/40 ratio as a malignant, result. Accepting for the moment that this last ratio has somehow crept into its wrong place, and laying stress only upon the practical equality of numerator and denominator, it seems to us wholly unjustifiable to rely upon these and similar figures for diagnostic purposes, since, even supposing the protein estimation is itself capable of the highest degree of accuracy, the preliminary procedure does not lend itself to mathematically precise results. It involves a somewhat crude and inefficient form of lipid extraction, followed by a flocculation reaction of a type which can sustain no claim to being capable of providing knife-edge partition of protein. One is therefore justified in assuming a critical attitude towards figures which depend for their significance upon minute differences in protein deposits. In the cases cited they amount to 0.05 mg. of protein.

Moreover, this ratio upon which the diagnosis rests cannot be held to be an expression of any special property (or simple interplay of properties) belonging to the particular blood serum against which it is recorded. There are

no general terms by which it is possible to relate the inactivated "throw" with the ether "throw." Quite an arbitrary standard is chosen upon which to fix the reagent to be applied. Move one to the right or left on the Bendien scale and the ratio becomes numerically quite different, and may even be reversed in regard to the sign of the numerator-denominator difference. In other words, a serum showing a non-malignant reaction when associated with one Bendien number may show a malignant reaction with the next. If the ratio were an expression of some property of the serum then there ought to be at least some semblance of order to be made of the changing results as conditioned by slight systematic alterations such as that mentioned. In practice we find these changes as recorded by the ratio to be chaotic, and this fact alone raises doubts as to whether diagnosis based upon this highly unstable factor could be made dependable to the extent of 98 per cent.

One final point confirms our scepticism. We have found no evidence that the ratio has any relation whatever either to the general condition of the patient or to the degree of malignancy. In the large number of cases dealt with in the original paper no connexion was traced either. Such correspondence as existed between clinical malignancy and the reaction was arrived at on the basis of the primary Bendien reaction, not of the ratio. It would be extremely unlikely that any factor capable of picking out so exactly one type of disease from all other

pathological cases, and especially one that was capable of being recorded in arithmetical form, would not reveal in the course of extensive examination some directional evidence of the course or severity of the disease which it diagnoses.

SUMMARY

The application of the Cronin Lowe reaction as a diagnostic test for malignancy has been studied in the course of an examination of a series of fifty-nine pathological cases. In our hands the reaction gives a correct result in only 60 per cent. of cases. Attention is drawn to certain inherent defects in the method as a means of diagnosis. Our conclusion is therefore that the method has no diagnostic value.

We have to express our warmest thanks to the physicians and surgeons of Charing Cross Hospital, and to Dr. Avery of the London Jewish Hospital, for permitting access to their patients and lending their helpful assistance in points of diagnosis; to Dr. H. W. C. Vines for placing at our disposal his histological and post-mortem findings; to Mr. L. D. Scott of the biochemical department for his co-operation and technical assistance; and also to the ward sisters for their kind help.

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SIMPLE ACHLORHYDRIC ANAEMIA IN ADULT MALES

BY

F. PARKES WEBER, M.D., F.R.C.P.

SENIOR PHYSICIAN TO THE GERMAN HOSPITAL, LONDON

AND

W. WEISSWANGE, M.D.

HOUSE-PHYSICIAN TO THE HOSPITAL

Cases of ear diseases were formerly somewhat wittily divided into those which benefited by syringing and those in which syringing did no good. Similarly, cases of anaemia could be divided into (1) those which benefited by iron, and (2) those in which iron did no good. Cases of anaemia of the first group might well have been supposed to be due to a deficiency in the amount of iron ingested or to a defect in its assimilation, but if we were to carry our analogy further we should come to divide ear diseases into (1) "syringing-deficiency" cases, and (2) all the other cases. With regard to cases of auricular fibrillation in which digitalis is a necessary "food," one may truly speak of "digitalis-deficiency symptoms" arising on the omission of digitalis. In regard to anaemia, some cases are now acknowledged to be really due to iron deficiency in some way or other, notably a large proportion of the cases in which anaemia is associated with gastric achlorhydria or extreme hypochlorhydria, and which have been grouped together by Wits under the heading "simple achlorhydric anaemia."

We cannot here enter into the history of the clinical separation of this group of cases from those of pernicious anaemia (Addison's anaemia, Biermer's anaemia), in nearly all of which there is gastric achlorhydria or achylia, but which are not markedly benefited by the administration of iron. It will be sufficient for us to point out that L. J. Wits¹ found that of cases of chronic microcytic (hypochromic) anaemia 86 per cent. occurred in women, and that the women affected were mostly in

the reproductive period of life and of the so-called "asthenic constitution"; gastric achlorhydria was present in 80 per cent. of the women, constituting cases of "simple achlorhydric anaemia" (Wits and others). In regard to the occurrence of "simple achlorhydric anaemia" in children, we would refer especially to papers of F. M. B. Allen and G. P. McCullagh²—three of whose cases were in one family—and of L. G. Parsons,³ who thinks that simple achlorhydric anaemia of adults is very similar to, if not identical with, "nutritional anaemia of infancy."

During recent years we have seen four cases which we class as simple achlorhydric anaemia in adult males. During the same period under observation at the hospital there have been at least forty typical cases of simple achlorhydric anaemia in women. Thirty of these were summarized by Dr. O. B. Bode and Dr. W. Weisswange,⁴ and Dr. O. B. Bode and Dr. G. Krumm⁵; these patients were mainly between 40 and 50 years of age, and an "asthenic constitution" was not specially noted in them. Following are résumés of the four cases in adult males.

CASE REPORTS

1. A dock labourer, aged 56, came under observation in September, 1930. He was a fairly well built man, but pale, and had for several months been troubled with breathlessness on exertion. Blood count: haemoglobin, 40 per cent.; erythrocytes, 3,700,000; colour index, 0.54; leucocytes, 4,650 per c.mm. (basophils 1 per cent., eosinophils, 6 per cent., polymorphonuclears 73 per cent., lymphocytes 27 per cent., monocytes 3 per cent.). Fractional examination of the gastric contents showed complete achlorhydria, even after subcutaneous injection of histamine. Negative Wassermann reaction. Brachial blood pressure: 130/80 mm. Hg. Nothing special was noted by ordinary examination of the thorax, abdomen, urine, etc.

The patient was treated with ferrum reductum and with hydrochloric acid and pepsin with meals. In January, 1933 (about two and a quarter years later), the blood count gave: haemoglobin, 95 per cent.; erythrocytes, 4,800,000. He still had complete achlorhydria, even after subcutaneous injection of histamine; the gastric contents contained a little