Contemporary Themes

Biochemical Screening Programme in General Practice: A Clinical Follow-up

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Summary

Follow-up studies of findings obtained during a short programme of biochemical screening conducted on 1,041 patients attending their general practitioners in January 1967 showed that this yielded 64 results that led to a change in diagnosis or method of treatment. These results were obtained in 57 patients (5·5% of patients screened), whereas only 15 abnormal results would have been revealed on 14 of the 1,041 patients if the tests performed had been restricted to those requested on the basis of clinical features. Hence a screening programme can make an important contribution to the recognition of otherwise unsuspected disease.

Introduction

A limited programme of biochemical screening in general practice was conducted in 1967 as part of an intensive trial of the SMA 12/30 (Technicon Instruments, Ardsley, New York) sequential multiple analyzer. The results of the chemical evaluation of this equipment have been published[1] and a preliminary account has been given of the abnormalities shown in the patients who underwent biochemical screening.[2] These early reports, and decisions taken by the general practitioners at the time of the screening survey, were based on values read direct off the chart records generated by the SMA 12/30 but with use of the "normal ranges" quoted by this laboratory. Clearly sequential multiple analysers are subject to drift,[3] and the raw analytical data derived from the initial survey in 1967 have since all been corrected for any drift which had been observed. The corrected data have been examined and used to establish the appropriate normal ranges for different groups of patients, and a review of the subsequent medical histories of the patients has been conducted. These further findings are presented and their relevance in helping to define the potential role of biochemical screening in general practice is discussed.

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Preliminary Study

PATIENTS

During a two-week period in January 1967 all patients over 21 years of age attending the surgeries of two group general practices in Edinburgh were invited to participate in the screening programme. The patients presented themselves at the surgeries in the normal way; there was no attempt at selection, nor were any patients especially invited to attend. About 95% of them agreed to provide a blood sample. Specimens were collected in the non-fasting state with a minimum of haemostasis; patients were seated at the time. After the blood sample had been taken serum was separated within two hours and determinations were carried out on the same day or the sera were stored at −20°C until analysed; a sample of blood was also obtained from most patients for haemoglobin estimation.

BLOOD ANALYSIS

Analyses were performed on an SMA 12/30 analyzer on loan from Technicon Instruments; these determinations consisted of serum sodium, potassium, chloride, bicarbonate, total protein, albumin, calcium, alkaline phosphatase, bilirubin, urea (as urea nitrogen), sugar, and aspartate aminotransferase measurements. Details of the standardization and operation of the equipment have been published.[1] During each run a drift-correcting standard was analysed in every tenth sampling position and the controls of the recorder were adjusted as necessary by hand. Apart from this regular resetting of the instrument the SMA 12/30 results were read off the charts and reported without adjustment or correction, except that blood urea nitrogen readings were converted into blood urea concentrations. In addition to the analyses performed on the SMA 12/30, serum protein-bound iodine and uric acid and the haemoglobin content of whole blood were determined whenever enough blood had been collected from the patients. The measurements of protein-bound iodine and uric acid were carried out on single-channel AutoAnalyzers and were corrected for any instrumental drift before being reported. The haemoglobin determinations were carried out in the department of haematology with the use of a manual cyanmethaemoglobin method by kind permission of Dr. S. H. Davies.

Specimens were collected from 1,089 individuals, and complete sets of data for the SMA 12/30 analyses were obtained on 1,072 samples; the reasons for 17 sets of data being incomplete have been explained elsewhere,[2] and these patients have been excluded from the follow-up. Another 31 individuals have also been excluded from follow-up because they were not in fact patients but various categories of inter-

ested volunteers—for example, drug firm representatives and the general practitioners themselves.

CALCULATION OF NORMAL RANGES

Since the completion of the preliminary reports of this study all the results for the patients' samples, as read direct off the SMA 12/30 chart records, and the readings shown on the charts for the drift-correction standards before the adjustment of the recorder have been entered on to Hollerith cards. A programme was written for correction of the results as read direct off the charts for any drift that had occurred on the basis of linear interpolation between adjacent pairs of drift-correction standards.

Age and Sex Groupings.—The corrected data for the patients were divided into three age groups (21-40, 41-60, and over 60 years) and subdivided by sex; the 21-40 group of women was further subdivided so as to separate out those women known to be pregnant at the time of the survey. These groupings were selected in order that each (apart from the group of 62 pregnant women) should have a minimum of 100 patients, thus permitting satisfactory statistical analysis. Each of the seven groups of results for the 15 sets of measurements included in the screening programme was next broken down into suitable class intervals and their distribution studied by means of contrasting cumulative probability charts.[4] Both the original data and the log-transformed data were plotted and the graphs used to decide whether normal ranges could be calculated from the data without transformation; it was found necessary to apply logarithmic transformations to the results for potassium, alkaline phosphatase, bilirubin, and urea determinations in both men and women in all of the age groupings.

Mean and Standard Deviations.—The mean and standard deviation for each determination, subdivided into the seven groups detailed above, were determined by using a standard statistical package (M.V.C. Survey Program used at the Atlas Computer, Chilton, Berkshire, U.K.); with potassium, alkaline phosphatase, bilirubin, and urea the calculations were performed on the logarithms of the observed results. The normal ranges (mean values ± 2 S.D.) on which the further assessments of the data from the screening programme have been based, together with the number of patients included in each calculation, are contained in tables, copies of which are available on request from the librarian of the Royal Society of Medicine, London. Before the data for the protein-bound iodine results were examined by the computer programme truncation was applied to exclude results in excess of 10 μg/100 ml, except for the results from the group of pregnant women, on the grounds that many of these higher values reflected either overt disease or artificial elevation due to drugs; altogether 24 results (range 10·2-24·7 μg/100 ml) were excluded. Truncation was also applied to the bilirubin results for values in excess of 1·6 mg/100 ml, a total of 10 results (range 1·7-2·5 mg/100 ml) being thereby excluded.

Results of Screening Programme

The normal ranges obtained from the screening programme were used to review the corrected values for the findings obtained in 1967 on individual patients. The total number of investigations performed in respect of each analysis and the number of abnormally high and abnormally low results observed that were considered by the practitioners to be sufficiently abnormal as to need further special consideration of a patient's medical record are shown in the Table; as would be expected many abnormal results were only marginally abnormal, and the Table shows the distribution of the 333 findings that were given special consideration. Altogether 15,110 analyses were performed, and the 333 markedly abnormal results were observed on 258 different patients (24·8% of all the patients studied). Of these 333 results, 64 findings in 57 patients (5·5% of the patients studied) led to a change in the diagnosis or in the method of treatment, leaving a total of 259 unexplained results observed in 201 patients (19·3% of those studied).

At the time of the initial screening survey the general practitioners were asked to record those laboratory investigations that they would have requested regardless of the fact that a laboratory screening programme was being conducted. The number of times each of the tests would have been asked for on the basis of clinical assessment ("discretionary tests," as defined by Whitehead[5]) and the total number of abnormal findings (high and low findings not differentiated) that the screening programme revealed in respect of these discretionary requesting procedures are also given in the Table. Altogether 390 investigations would have been requested on a discretionary basis, and the results for these tests included 15 definitely abnormal values observed in 14 patients (1·4% of the patients seen).

FOLLOW-UP

About two years after the original screening survey the general practitioners were asked to review their records for all the 1,041 patients investigated in 1967 and on whom complete sets of results had been obtained with the SMA 12/30 analyzer. They were given lists of these patients along with the diagnosis made in January 1967 and a further list for those patients in whom the survey had revealed abnormal

Results of Biochemical Studies in 1,041 *Patients Attending their General Practitioners*

	Total No. of Analyses performed in the Screening Programme	Abnormally High Results		Abnormally Low Results		Total No. of Abnormal Results revealed by Screening	No. of Analyses that would have been Requested on a Discretionary Basis	No. of Abnormal Results for Discretionary Tests
		Total	Needing Special Consideration	Total	Needing Special Consideration			
Sodium	1,041	6	0	5	2	11	29	1
Potassium	1,041	3	0	9	2	12	30	3
Chloride	1.041	5	0	5	1	10	28	0
Bicarbonate	1,041	11	0	7	0	18	43	0
Total protein	1,041	15	3	11	2	26	0	0
Albumin	1,041	10	1	16	3	26	0	0
Calcium	1,041	13	2	11	0	24	12	0
Alkaline phosphatase	1,041	19	10	0	0	19	27	0
Bilirubin	1,041	38	6	0	0	38	22	0
Sugar	1,041	19	5	3	1	22	21	4
Aspartate aminotransferase	1,041	6	2	0	0	6	5	0
Urea	1,041	15	3	0	0	15	79	3
Uric acid	640	29	5	6	0	35	1	0
Protein-bound iodine	937	30	11	11	4	41	33	2
Haemoglobin	1,041	6	1	24	0	30	60	2
Total	15,110	225	49	108	15	333	390	15

results that appeared particularly to require consideration, together with a note of these findings. The opportunity was taken with this second list to eliminate from special consideration a number of slightly raised serum bilirubin values which had been observed in 1967 but which had been discounted at that time because of the lack of other abnormal data, either clinical or laboratory; the rationale for discounting these isolated observations from further consideration in 1967 had been the fact that the SMA 12/30 analyzer does not make a correction for blank values on the bilirubin channel. Out of the 1,041 patients requiring follow-up assessment 14 had died before the follow-up and another 46 could not be traced, the majority of these latter patients having left the area.

The general practitioners were asked a series of questions designed to assess the medical value of the screening programme and to decide the extent to which the investigations had served as pointers to the subsequent course of each patient's clinical history. They were asked to state whether a new diagnosis had been made or a change in the patient's treatment had been required on the basis of the biochemical results; they were also asked to record any new illnesses that had occurred during the two-year period following the initial survey.

The 1967 survey had unmasked several important facts about the patients. Nevertheless, it could be misleading to select from the follow-up a few "typical" case histories as evidence of the value of biochemical screening, and the present account instead considers some general points that derived from these reviews.

Urea, Sodium, Potassium, Chloride, and Bicarbonate.—The preliminary account of the survey[2] reported much larger numbers of abnormal findings than are shown in the Table. This applies especially to the chloride and bicarbonate analyses. Instrumental factors were responsible for these differences; most of the results that appeared abnormal in 1967 when read direct off the charts became normal when correction for drift was applied. Five of the 11 patients with genuinely raised blood urea values who were followed up had already been under treatment at the time of the survey; another patient with an abnormal result was a diabetic, newly diagnosed as a result of the survey. As a whole, this group of investigations yielded little useful information, apart from confirming the value of estimating serum potassium concentrations periodically on patients receiving hypotensive drug treatment.

Bilirubin.—Immediately after the 1967 survey 11 patients having raised serum bilirubin concentrations (as read direct off the SMA 12/30 chart records) were found to have other abnormalities suggesting mild hepatic disorder—for example, raised serum alkaline phosphatase—and three developed acute infectious hepatitis shortly afterwards. At follow-up two years later 13 of the 38 patients in whom raised serum bilirubin concentrations were observed (see Table), but who had had no other clinical or laboratory evidence suggesting liver disease, had at no time developed symptoms or signs suggesting liver disease; none of these patients was recalled especially for reassessment. Since 1967 one of the remaining patients found then to have a raised bilirubin had developed congestive cardiac failure secondary to rheumatic heart disease, another had developed chronic myeloid leukaemia, a third had developed carcinoma of the lung, and a fourth was already known to be suffering from systemic lupus erythematosus.

Alkaline Phosphatase.—Many of the abnormal alkaline phosphatase results found in 1967 were observed in patients with other features of mild liver disease, but moderate rises were found in eight patients for whom no explanation was forthcoming at that time. One of these patients has since died of carcinoma of the breast with skeletal metastases, another has since been shown to have a mild form of cholangitis, and a third has been diagnosed as having osteomalacia.

Total Protein and Albumin.—The main interest in these observations derived from the patients found to have hypoalbuminaemia. Two cases of intestinal malabsorption, one associated with total villous atrophy, have since been identified, and another patient (a known chronic bronchitic) has since developed anaemia and been shown to have multiple opacities on *x*-ray examination of the chest; a fourth patient has since been shown to have osteoporosis. No patient with dysproteinaemia was revealed by the survey.

Aspartate Aminotransferase.—One patient with raised aspartate aminotransferase activity has since been diagnosed as having alcoholic cirrhosis, while a second patient developed carcinoma of the body of the uterus 16 months after the survey; this latter patient had been taking meprobamate regularly, and this could have accounted for the high level of aspartate aminotransferase.

Calcium.—A few patients were found to have hypercalcaemia in 1967 but no explanation has been found as yet for this among the patients since followed up; no patient had a serum calcium exceeding 11·5 mg/100ml. The observation of hypocalcaemia led towards the diagnosis of malabsorption syndrome (total villous atrophy) in one patient and to the recognition of postgastrectomy malabsorption in two other patients.

Glucose.—A diagnosis of diabetes mellitus was made in three patients as a result of the screening programme, and a further six known diabetic patients were shown to have their disease inadequately controlled.

Uric Acid.—The main value of this investigation proved to be in respect of patients receiving a number of different drugs. Five hypertensive patients being treated with methyldopa and a diuretic, and two patients receiving isoniazid for tuberculosis, had their treatment reviewed and modified following the detection of hyperuricaemia.

Protein-bound Iodine.—One case of hyperthyroidism, one of Hashimoto's disease, and three of idiopathic hypothyroidism were recognized as a result of the survey. In addition two patients with raised levels of protein-bound iodine and who were receiving replacement thyroxine have since had the dosage adjusted.

Haemoglobin.—One patient with a raised haemoglobin concentration has since been shown probably to have polycythaemia vera and the others remain asymptomatic. Reduced haemoglobin values responded to treatment with oral iron in five patients, and in another three patients provided part of the evidence for the diagnosis of intestinal malabsorption. In addition two pregnant women were found to have reduced haemoglobin concentrations; one of these required iron therapy and the second required iron accompanied by folic acid for correction of the anaemia.

Discussion

Whitehead and his colleagues[5-8] have pioneered the approach to biochemical profile techniques in Britain. As a result of profile examinations carried out, at first on hospital patients and later on patients attending their general practitioners, information of diagnostic value affecting many of these patients and a better understanding of what is "normal" have derived from the Birmingham studies.

The present findings confirm and extend the observations reported by Whitehead and his colleagues—automatic analysis, particularly when planned to embrace a range of chemical investigations, provides much useful information which can contribute to the better understanding of patients' illnesses. The data reported here show that abnormalities demanding reconsideration of the patient's condition were found in 5·5% of the patients screened. The yield of abnormal results was

unevenly distributed among the 15 determinations performed, and the data given in the Table indicate that haemoglobin, protein-bound iodine, alkaline phosphatase, bilirubin, and sugar estimations were the five analyses that provided the largest number of medically interesting findings. This pattern of yield might well be different in another general practice or in hospital work and cannot be used to do more than indicate some of the more appropriate screening tests for use in general practice.

The present findings again show how small a percentage of profile results might be described as clinically significant in terms of their immediate relevance to initiating a change of diagnosis or method of treatment—64 out of the 15,110 tests performed. This small percentage (0·4%) does not detract from the potential value of chemical screening, but it highlights the danger that important observations may be overlooked in a welter of data.[9] Research is needed to define the best way of presenting the results of multiple laboratory tests so as to assist in decision-making. These clinically siginificant results, leading to a new diagnosis, an alteration in diagnosis, or a change in the method of treatment, were observed in 57 (5·5%) of the patients and can be considered to be of "diagnostic" significance. In another screening programme involving patients in general practice, Carmalt *et al.*[8] found that unrequested biochemical tests led to a new diagnosis in 50 (16·9%) out of a group of 296 patients. The difference between these figures for the frequency with which a screening programme may reveal results of diagnostic value in general practice may be partly due to the use of different definitions for the word "diagnostic," and partly to slight differences in the range of investigations performed.

Abnormal results which initially were unexplained were found in 201 (19·3%) of the patients examined in the present survey. This figure is similar to the findings of Carmalt *et al.*,[8] who reported unexplained abnormal results in 64 (21·6%) of their 296 patients. An important fraction (about 15%) of the 259 abnormal findings initially unexplained in the present programme of screening could be explained at follow-up two years after the original survey, emphasizing the importance of clinical follow-up in such groups of patients.

A valuable outcome of large-scale laboratory testing has been the securing of information about normal ranges relevant to different sectors of the population. Laboratories carry out large numbers of tests routinely on patients' specimens, and normal ranges can be extracted from these data.[10-14] The findings from the present investigation contained several examples where different normal ranges were applicable to different groups in a population of ambulant patients. Several of these variations in normal values have been reported before, but the importance of the present findings is to draw attention to the fact that there may be local variations in the patterns of normality; these need to be defined and taken into account if the maximum information is to be derived from profile or screening data obtained on individual patients. It can often be difficult to interpret abnormal results shown by screening programmes of chemical investigations carried out on the healthy population (well-population screening). This fact, and the potential psychological trauma of unexplained abnormal findings, has been discussed by Illingworth.[15] It is important, however, not to overemphasize these difficulties. Moreover, probably, carefully planned screening examinations will permit better definition of normal ranges, and clinical follow-up at regular intervals should allow assessment of the significance to be attached to abnormal results found by screening the apparently healthy population.

This paper indicates some of the benefits of screening by means of chemical investigations in general practice. We would, however, agree with Irwin and Neill[16] that the millennium has not yet arrived, since several problems remain to be solved before any laboratory-based screening programme of chemical tests conducted on patients attending general practice can be contemplated except on a research basis. These problems include the selection of the most appropriate tests, the organization of the collection of specimens, transport of specimens to the laboratory, the performance of the analytical work itself, and the associated operations of data processing. The fact that instrument manufacturers have shown great ingenuity in developing equipment, such as the SMA 12/30 analyzer and other automatic analytical instruments with higher rates of throughput, does not provide the complete answer to these problems. Such instruments may ease the physical burden of performing the analytical work and the attendant data processing operations, but the very ease with which they undertake these tasks distracts attention from fundamental questions such as whether they are performing the most appropriate range of investigations and are performing these reliably.

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