Biochemical Function Tests

A Guide to Specialized Investigations in Chemical Pathology

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BIOCHEMICAL FUNCTION TESTS

Foreword

In recent years, due to advances in instrumentation it has become possible to obtain results on many of the analyses most commonly wanted in clinical chemistry from machines simple enough to be operated at the bedside. In parallel with this tendency towards decentralization there has been a tendency towards centralization of some other more specialized techniques which are needed less frequently or which require special expertise. There is now a bewildering array of such specialized assays available at some District, University and Regional Centres and from the Supraregional Assay Service.

The advantages of such centralization of the less common techniques are considerable and include economies of scale, the greater reliability of techniques in continuous use and the accumulation of a body of data for comparison. Among the disadvantages of centralization are the possible lack of awareness as to what is actually available, how best these other tests can be applied to particular clinical problems and integrated with investigations available on site. This is precisely the information provided in this handbook which, in addition gives details for the preparation of patients for the various tests and for the collection, storage and transport of samples.

The information is well organized and clearly presented. It should be of immense value to physician and biochemist alike.

Professor R.V. Brooks
DSc FRCPath

Preface

This handbook has been produced as a practical guide for performing dynamic function tests and other specialized investigations that are currently available in clinical biochemistry. It has been designed to enhance coordination between medical, laboratory, pharmacy and nursing staff to ensure the tests are correctly executed in a standardized manner to allow interpretation of the results thereby obtained. Information on some factors interfering with the tests and any special requirements for preparation of patients is provided. Important notes, such as the possible harmful side effects of pharmacological agents used in the dynamic tests and their management and also clinical conditions where such tests may be contraindicated are included. It should be noted that prior notice may be required by the pharmacy for some pharmaceutical preparations. Such occasions where this may arise are outlined in the text. The procedure for administration of pharmacological agents with their appropriate dosage is suggested and details of sample collections, including correct volume and type of specimen, the necessity for specimen preservatives and storage of specimens before dispatch are outlined. Suggested formats of biochemical investigations for suspected pathological conditions are included and should be used in association with other investigations that are available. In many instances it will not be necessary to perform all of the tests to establish a diagnosis.

We would strongly recommend the clinician to contact the local laboratory before starting the test to alert the laboratory that a specialized investigation is taking place and to ensure that an alternative protocol is not preferred. Investigations include a spectrum of methodologies; hence reference ranges may be

marginally different from those given in the text and should be checked with the local laboratory. The handbook has adopted the recommendations of the Regional (South East Thames and West Midland, UK) and Supraregional Assay Services (SAS) for Hospital Laboratories (UK) for the more specialized tests. Interpretation of results has been included generally as a consensus of opinion from such specialized hospital centres. *However, there are a number of methodologies, mostly involving hormone analyses, where reference ranges and response to dynamic stress tests may differ considerably between centres and the data for interpretation are only given as guidelines.*

Assays performed at Regional or Supraregional Centres are generally technically more demanding, requiring greater expertise and more expensive equipment which limits the workload capabilities of such centres. The handbook outlines all the necessary clinical, biochemical and other information regarding the patient which should accompany the assay request and is generally required by the specialized centres. Follow up tests after the initial investigation are considered and alternative tests which are available in certain clinical circumstances are suggested.

Finally we would welcome comments and criticisms regarding the information presented in this handbook.

Acknowledgments

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Any errors or omissions are entirely our own and we would be pleased to have these brought to our attention.

M.S. Billingham
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R.A. Hall

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1 Suggested scheme for biochemical investigation of suspected pathological conditions

1.1 Adrenocortical hyperfunction

Prolonged and inappropriately elevated circulating cortisol concentrations result in the symptoms and signs of Cushing's syndrome. However, the typical features of Cushing's syndrome may not be apparent if the hypercortisolaemia is of recent and rapid onset, as may occur in ectopic ACTH secretion.

Diagnosis of adrenocortical hyperfunction

A normal serum cortisol circadian rhythm excludes Cushing's syndrome, but lack of cortisol suppression at midnight or raised random serum cortisol concentrations may also occur in patients with acute stress, endogenous depression, gross obesity, alcoholism and pregnancy. Urine free cortisol and dexamethasone suppression test (overnight) will be helpful in differentiating patients with adrenocortical hyperfunction from the majority of patients presenting with obesity. The overnight dexamethasone test is a simple and reliable test, with all healthy individuals adequately suppressing cortisol concentrations whereas less than 2% of Cushing's patients suppress. About 13% of obese controls will also fail to suppress on 1 mg dexamethasone but their urine free cortisol will remain within the reference interval.

Non-suppression may occur with non-compliance (check dexamethasone on post-dexamethasone cortisol sample if suspected), drugs inducing hepatic metabolism (phenytoin, rifampicin, alcohol), high oestrogen states (raised cortisol binding protein), acute stress (hospitalized chronically ill) and psychiatric disease. Unfortunately urinary free cortisol may also be elevated in patients with acute stress or psychiatric disease. Endogenous depression is the commonest cause of non-suppression and may be distinguished from Cushing's syndrome patients by a normal cortisol response to insulin induced hypoglycaemia. Cushing's

syndrome patients show a lack of response and also a suppressed growth hormone response which may be useful in confirming a diagnosis. The overall incidence of false response is less for the low dose dexamethasone test (0.5 mg/6 h for 2 days) which may be used in combination with the high dose dexamethasone test (2 mg/6 h for 2 days) in the differential diagnosis of adrenocortical hyperfunction.

Differential diagnosis of adrenocortical hyperfunction

Cushing's syndrome is most often caused by excessive administration of glucocorticoids. The approximate distribution of non-iatrogenic pathological conditions of endogenous cortisol hypersecretion are listed:

1 Cushing's disease caused by excessive pituitary ACTH secretion from microadenoma. It accounts for 70% of cases with endogenous cortisol hypersecretion and occurs predominantly in women of child-bearing age.

2 Ectopic ACTH secretion accounts for 15% of cases with endogenous hypercortisolism.

3 Adrenal tumours occur predominantly in females, with a mean age of 35 years for adenomas and 50 years for carcinomas.

The dexamethasone suppression test (combined low and high dose), ACTH and DHAS will give an indication of the site of the lesion and additional tests may then be used to confirm the diagnosis.

Distinguishing adrenal tumour from ACTH dependent disease

Patients with adrenal tumour will have low or undetectable ACTH concentrations and do not suppress cortisol concentrations in response to high dose dexamethasone. DHAS concentrations are frequently below the reference range in adrenal adenoma and usually above the reference range with adrenal