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NUTRITIONAL AND ENVIRONMENTAL MEDICINE
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'Looking at Health from the Molecular to the Global for 25 years'

- Trace and Toxic Elements
- Water Soluble Vitamins
- Fat Soluble Vitamins
- Essential Fatty Acids
- Amino Acids
- Peptides
- Antioxidant Profile
- Nutritional Status
- Osteoporosis Profile
- Gut Fermentation
- Gut Permeability
- Allergy Tests
- Health Risk Profile
- Iodine *and many more...*

NEWSLETTER - SUMMER 2010

Introduction

With an ever increasing interest in the role of micronutrients in health and disease, and fascinating scrutiny by researchers around the globe, Biolab strives to always provide you with the very best measurements of micronutrient status. This newsletter covers the latest developments at Biolab, bringing news of new & updated tests, and provides further opportunities for you to learn about the application of nutritional biochemistry.

If you would like to discuss any items covered in this newsletter, or any other aspects of our work, please don't hesitate to contact us directly.

Biolab Workshop for Clinicians - September 2010, London (BANT CPD applied for)

Following on from our *Introduction to Biolab Tests* workshop in March 2010 (audio and video recordings available on request), our next workshop will include a series of case presentations by doctors and nutritional therapists demonstrating the responsible use of Biolab tests in treating patients.

This workshop, to be held in London on Saturday 11th September 2010, will cover a variety of topics including effective allergy testing, nutrition & cancer, and the importance of making a comprehensive nutritional assessment, plus an update on recent developments at Biolab. The workshop registration fee may be offset against future test referrals.

Contents

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Reference Intervals for Plasma Minerals by ICP-MS

Biolab is now processing most samples submitted for plasma element analysis by inductively coupled plasma-mass spectrometry (ICP-MS), using only blood collected into a trace element-free potassium EDTA tube. These elements include calcium, chromium, copper, magnesium, manganese, selenium, sodium and zinc.

Atomic absorption spectrometry (AAS) was the mainstay of elemental analysis for some 30 years, but is now being replaced in all sectors by ICP-MS, which is much more sensitive and specific. This is because ICP-MS measures the actual mass of the atoms, rather than an effect of the atoms on light rays, which is a comparatively indirect approach. Most hospital laboratories use even less specific and sensitive methods than AAS for measuring plasma elements because such techniques fit in with the requirements of their large analysers.

The Biolab reference intervals for plasma elements have been updated with the current improvement in technique (see table 1).

Hair Analysis for Minerals and Toxic Metals

Hair analysis at Biolab has recently been re-standardised and, with the introduction of the state-of-the-art trace element analysis, ICP-MS technology, we now report hair mineral analysis results with an adjusted reference range relevant to this technology.

Hair mineral analysis remains an important tool in the nutritional and environmental assessment of patients. In spite of various objections in the literature that the analyses may be poorly controlled, that different laboratories produce may different results from the same sample and also that the clinical interpretation of the results may be obscure [1], a measurement of the elemental concentration in recently-grown hair provides an integrated view of the element status in the follicular cells and their blood supply, unaffected by short term fluctuations in the nutrient intake of the subject.

Hair growth

The structural proteins of hair are formed as a filament arising from the matrix of follicular cells in the epidermal epithelium. Human hair is approximately 80% protein

Table 1. PLASMA ELEMENTS REFERENCE INTERVALS (ICP-MS derived)

(based on plasma prepared from whole blood collected into a trace element-free potassium EDTA tube)

Element	Reference Intervals	Comments
Calcium (Ca)	2.10 – 2.60 mmol/L	Unchanged
Chromium (Cr)	6.2 – 33.4 nmol/L	Higher limit increased in value
Copper (Cu)	12.5 – 25.0 µmol/L	Unchanged
Iron (Fe) (male)	14.3 – 35.8 µmol/L	Higher limit increased in value
Iron (Fe) (female)	10.7 – 32.1 µmol/L	Unchanged
Magnesium (Mg)	0.70 – 1.20 mmol/L	Unchanged
Manganese (Mn)	9.0 – 40.0 nmol/L	Higher limit increased in value
Selenium (Se)	1.00 – 1.90 µmol/L	Se levels in the population appear to be on the increase
Zinc (Zn)	11.5 – 20.0 µmol/L	Unchanged

and 15% water, with smaller amounts of lipid and inorganic substances [2]. Hair growing from the human scalp normally follows a definite growth cycle: anagen (the growth phase), catagen (a period of controlled regression of the hair follicle, when the cells become inactive and the hair fibre stops growing) and telogen (when the follicle is in a resting state and the hair may fall out) [3]. Normally more than 90% of human head hair is in the growth phase and it is at this stage that elements from the follicular cells and their blood supply are incorporated into the structure of hair.

These may be nutrient elements, such as zinc and magnesium, present in the follicular cells as enzyme co-factors, or toxic elements, poorly handled by renal excretion, which are dumped into the hair as part of a detoxification mechanism. Hence mercury, lead and arsenic show considerable enrichment in hair as compared to blood levels. Other elements, such as zinc and magnesium, show some enrichment over blood levels (reflecting their high intracellular concentrations), while others, such as iron, show no enrichment over blood levels (which for iron are, of course, much higher than serum levels).

So elements are normally incorporated into the filamentous structure of hair for plausible, predictable biological reasons. As the hair follicle emerges through the skin surface, the process of keratinisation (incorportation of cysteine residues) seals the formed elements within the protein structure, making the hair a resilient and long-lasting tissue [4] that can be used for a variety of analyses. The presence of sulphydryl groups from cysteine means that hair will selectively chelate and indefinitely retain heavy metals.

Limitations to the use of hair analysis for assessment of minerals status

While the cycle of hair production normally continues for the whole lifespan, other factors, such as adverse reactions to drugs and tumors, radiation damage and other toxic reactions, may lead to the physical destruction of the hair follicle. This will affect the overall rate of hair growth and the incorporation of elements into the hair shaft. Human hair normally grows at about 1.0 cm per month, but, for example, prolonged zinc deficiency, or protein-energy malnutrition [5], slows down hair growth and may thus elevate the concentration of heavy metals in the hair (since the same mass of mercury, lead and cadmium is being incorporated into a smaller volume of hair tissue).

Many cosmetic treatments and colourants contain metals, especially magnesium and copper. If hair that has had such treatments in incorporated into the analytical sample, very high values will be recorded for these elements, which may mask deficiencies. Shampoos may contain sodium, potassium, zinc and selenium in substantial amounts and it is not always possible to wash these elements from the hair, either with normal rinsing in the bathroom or *ex-vivo* in the laboratory [6].

Interpretation of results: are hair element concentrations of clinical significance?

A variety of scholarly and US government-funded studies have concluded that hair element analysis is a valid means to screen for mineral deficiencies and for toxic element exposure [2, 9, 10, 11]. A comprehensive review conducted by the U.S. Environmental Protection Agency (1979), which examined over 400 studies, concluded that …"if hair samples are properly collected and cleaned, and analyzed by the best analytic methods, using standards and blanks as required, in a clean and reliable laboratory by experienced personnel, the data are reliable" [9].

Systemic deficiencies of magnesium, zinc, selenium, chromium, manganese or copper will be reflected in low hair concentrations of these elements. Toxic levels of nutritionally important minerals will also be reflected in their hair concentration [6].

Enhanced exposure to, or ingestion of, aluminium, arsenic, cadmium, lead, mercury and nickel will result in higher than normal levels of these elements in hair tissue. This may not correlate directly with blood levels or with clinical symptoms, since it is part of a detoxification mechanism, in which toxic metals are sequestered into hair to prevent the expression of their adverse biological effect. Hair toxic metal concentrations are, however, a sensitive measure of exposure to these elements [9, 10].

Much work, too extensive to detail here, has also been published by outstanding researchers on the relationship between measured hair elements and various clinical conditions, for example cardiovascular disease and myocardial infarction. A Finnish-Austrian study [12] reported in 2001 that men with the highest hair mercury content had double the risk of suffering a myocardial infarction and three times the risk of dying of cardiovascular disease, as compared to men with the lowest hair mercury content (this is a reflection of the transition metal activity of mercury and its ability to catalyse the oxidation of low-density lipoprotein). Another study [13] reported on low hair magnesium levels (along with other elements) which were recorded in subjects who had already suffered a myocardial infarction.

Our conclusion is that hair element concentrations, based on appropriate samples and analysed using the best methods, can provide important and valid information over a wide variety of clinical conditions.

The test fee for the Biolab hair element analysis is £40.

Details of our hair element reference intervals and comments on the interpretation of each element are included in the original document from which this article has been extracted, which can be downloaded from www.biolab.co.uk/docs.hair.pdf (or search our web site for "hair datasheet").

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The Physiological Role of Coenzyme Q

Coenzyme Q_{10} is a "semi-vitamin": a nutrient which can be synthesised in the body - but in amounts that are insufficient for metabolic needs - and which is also present in food. First isolated in 1957 [1], it acts as a cofactor in the electron transport system, carrying electrons from Complex I and Complex II to Complex III; CoQ_{10} also an important antioxidant component of the membranes and tissues within which it is located [2]. Research into this compound's role in electron transport was the subject for the Nobel Prize in Chemistry in 1978.

The dietary requirement for CoQ_{10} is not known and is presumed to be variable, depending on the condition of the individual. Inhibition of HMG CoA reductase by statin drugs to reduce serum cholesterol has the effect of reducing endogenous coenzyme Q_{10} synthesis, thus increasing the dietary requirement. Various medical conditions, including renal and ischaemic heart disease, cardiac failure, neurological disease (such as Parkinson's) and muscular degenerative disorders (such as mitochondrial myopathies) have been reported as lowering CoQ_{10} levels. As such, knowledge of CoQ_{10} physiology is progressing into the description of the long latency effects of CoQ_{10} deficiency, in which energy production requirements may be satisfied, but nevertheless there are deficiency effects that may be observed around the body.

The short term effect of a marked deficiency of CoQ_{10} is thus malfunctioning of mitochondrial energy production. There has been interest in a therapeutic role for CoQ_{10} in a variety of medical conditions. In 1961 it was first examined as an agent for the treatment of cancer [3], when low levels were noted in the blood of breast cancer patients. Coenzyme Q_{10} has been shown, in animal models, to stimulate the immune system, enhancing antibody production as well as the activities of macrophages and T cell lymphocytes [4,5]. Coenzyme Q_{10} has also been reported to increase IgG antibody levels and to increase the CD4 to CD8 T-cell ratio in humans [6,7,8].

A number of clinical trials have been done testing the effects of CoQ_{10} in hypertension, which has been the

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subject of a recent meta-analysis [9]. This suggests that CoQ_{10} supplementation has the potential to lower systolic blood pressure by up to 17 mm of Hg and diastolic blood pressure by up to 10 mm of Hg, without significant side effects. This finding, as well as providing an interesting insight into the effect of a shortage of Q_{10}, underlines the dictum that nutrients are required by all tissues and organ systems, and that nutritional treatments have a role to play in a wide variety of human diseases and disorders beyond the condition that was originally associated with the deficiency of a particular nutrient.

Serum CoQ_{10} levels can be measured at Biolab for £29 (test kit available on request)

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Post arthroplasty blood toxic metal profile - blood levels of cobalt, chromium, manganese and molybdenum after hip replacement.

With the introduction of new materials for surgical prostheses, joint replacement has become the operation of choice for the treatment of chronic hip problems. Other joints, such as the knee, can also be treated in this fashion. However the potential for long term complications from metal toxicity, metal hypersensitivity, and metal carcinogenicity after these operations are causes for concern, since they usually involve the implantation of a prosthesis made from a metal alloy into the tissue of the subject. Since the metallic surface is subject to wear and degradation (and needs replacing or re-surfacing after a period of years) there is metal leakage into the tissues. The particular nature of the prosthesis used, as well as other factors, can affect the rate of leakage. Also it is now suggested that more than 50% of all joint arthroplasties will, by the year 2011, be performed on patients of less than sixty-five years of age. This projection has a number of implications for joint arthroplasty procedures and their follow up.

Little is known about the long-term systemic effects of enhanced levels of these metal components in the extracellular fluid. At the present time there is no defined and confirmed risk involved, but as patients live longer carrying metal prostheses, the risk potential becomes more apparent.

A prudent approach is to monitor the blood levels of the component metals, probably annually. Biolab is offering a blood profile involving measurement of chromium, cobalt, manganese and molybdenum – whole blood being the specimen of choice in this situation. This will help in the risk assessment to such patients, who may subsequently require metal resurfacing operations or further implants.

The fee for this profile is £45 (test kits available on request).

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Extended Health Risk Profile

The Biolab Health Risk Profile includes a wide range of minerals, vitamins, antioxidants and other biochemical markers of health & disease. We now also offer an extended profile which includes a number of important additional tests (see table 2 overleaf). Any of these tests can of course also be requested individually.

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Table 2. Extended Health Risk Profile

	Health Risk Profile	Extended Health Risk Profile (additional tests & samples)
Minerals	Plasma zinc, copper, chromium, selenium & red blood cell magnesium	
Vitamins	A,C,E, carotene, lycopene & lutein	B_1, B_2, B_3, B_6, biotin, vitamin D
Essential fatty acids (red cells)	Omega 6 series: Gamma-linolenic acid, Di homo gamma-linolenic acid, arachidonic acid. Omega 3 series: Eicosapentaenoic acid, docohexaenoic acid	
Enzymes	Glutathione peroxidase 1 & 3, superoxide dismutase, paraoxonase, alkaline phosphatase, acid phosphatases, LDH, GGT & GST	
Others	Total bile acids, albumin, globulin, CRP & HbA1c	Homocysteine
Additional lipids profile	Plus £29.70	
Sample requirements (blood collection tubes) – kits available on request	1 x navy blue (trace element free EDTA), 1 x gold (SST), 1 x green (heparin), 1 x lavender (EDTA) tubes	1 x green (heparin), 1 x gold (SST) & 1 x lavender (EDTA – with prior addition of inhibitor by Biolab)
Total cost	£200	£330

Urine iodine:creatinine ratio

Urine iodine can be co-analysed with creatinine to check the completeness of a 24 hour urine collection, or to correct for urine dilution in a shorter collection (6 hours, early morning urine or random urine collection). Corrected for creatinine, the reference interval for urine iodine is 18 – 47 micrograms per gram of creatinine (equivalent to 0.018 – 0.47 mg/24 hours) (142 – 370 nmol/ gm creatinine or 1.26 – 3.27 mmol/mmol creatinine). According to a recent paper "Urine Iodine Measurements, Creatinine Adjustment, and Thyroid Deficiency in an Adult United States Population" by James E. Haddow, Monica R. McClain, Glenn E. Palomaki, and Joseph G. Hollowell, Journal of Clinical Endocrinology & Metabolism 2007;92:1019–1022, whose purpose was to determine whether low urine iodine is associated with hypothyroidism, neither TSH nor total T4 values are associated with urine iodine. However, if the urine iodine to creatinine ratio is calculated, there is an apparent positive relationship between this ratio and TSH measurements. This suggests that the urine iodine/creatinine ratio can be used as an adjunct test in the diagnosis of hypothyroidism.

Ethanol Consumption and Metabolism

The principal pathway for ethanol degradation pathway in the liver begins with conversion of ethanol to acetaldehyde by the enzyme alcohol dehydrogenase, which is lo-

cated in the cytosol of the hepatocyte. This is a "phase 1" detoxification reaction, or, more appropriately, "retoxification" reaction, since acetaldehyde is more toxic than the ethanol from which it is derived. It is believed that acetaldehyde is associated with much of the liver damage that may follow ethanol ingestion. The resulting acetaldehyde passes into the mitochondrial compartment of the hepatocyte, where it is converted to acetate by the action of mitochondrial aldehyde dehydrogenase. The acetate so produced then leaves the hepatocyte and is metabolised by extra-hepatic tissues [1]. The prevailing high ratio of NADH + H / NAD+ within the liver mitochondrial matrix precludes the oxidation of acetate via the Krebs cycle in situ, so it is left to extra hepatic tissues to metabolise the acetate so formed in the liver [2].

Oxidative and non-oxidative pathways of ethanol metabolism

Four distinct pathways for ethanol degradation have been described in the human - three oxidative pathways and one non-oxidative pathway. Each of the oxidative pathways starts with the oxidation of ethanol to acetaldehyde, which is then oxidized to acetate for subsequent extra-hepatic activation to acetyl-CoA [2]. The three oxidative pathways can be differentiated on the basis of the enzyme and the mechanism by which ethanol is oxidized to acetaldehyde. The first pathway utilizes cytoplasmic alcohol dehydrogenase, as described above, the second oxidative pathway uses the endoplasmic reticulum Microsomal Ethanol Oxidizing System (MEOS) and the third pathway uses peroxisomal catalase. MEOS is better known as Cytochrome P450 2E1. The nonoxidative pathway for ethanol metabolism is less well characterized but produces fatty acid ethyl esters (FAEEs) as primary end products [3].

Alcoholic liver damage appears to take place primarily as a result of the saturation of the alcohol dehydrogenase pathway and the induction of the other pathways for ethanol metabolism, particularly the Microsomal Ethanol Oxidizing System (MEOS) pathway.

Oxidative and nonoxidative pathways for ethanol metabolism have also been demonstrated in a range of tissues outside the liver, including the stomach, the pancreas and the lung. Inhibition of oxidative ethanol degradation pathways raises both hepatic and pancreatic FAEE levels, demonstrating that oxidative and non-oxidative pathways are alternative pathways which are metabolically linked. Pancreatic ethanol metabolism occurs predominantly by the nonoxidative pathway but the oxidative routes to acetaldehyde have also been demonstrated in the pancreas [4].

Ethanol metabolism occurs predominantly in the liver and the resulting oxidative metabolite acetaldehyde is thought to play the key role in alcohol-induced liver injury. Additionally, there is now solid evidence that FAEEs also play a role in alcoholic pancreatitis [5]. Blood and organ levels of FAEEs are raised by ethanol consumption with the highest concentration observed in the pancreas. FAEE generation from ethanol is greater in the pancreas than in any other organ suggesting that the pancreatic pathway contributes to raised blood and organ FAEE levels [5].

Under conditions of acute consumption, the majority of ethanol consumed is degraded by the hepatic oxidative pathways, predominantly the alcohol dehydrogenase-mediated pathway. However, under conditions of chronic ethanol consumption, both hepatic MEOS activity and the non-oxidative pathway are induced and quantitatively make a greater contribution to ethanol catabolism. The induction by ethanol of Cytochrome P450 2E1 levels has a profound effect on the development of alcoholic liver disease, resulting in increased oxygen consumption, production of excess free radicals and increased metabolic wasting of vitamins and hormones. The chronic effects of increased free radical production contribute to depletion of the antioxidant activity of the cells involved. Antioxidant deficiency (glutathione, vitamin E) and excess free radicals are believed to subsequently contribute to the progression of liver damage [6].

How much alcohol and can it be good for you?

Polymorphic loci for genes encoding the enzymes of ethanol degradation pathways have been identified. The resulting variant isoenzymes have been characterized and found to exhibit distinct kinetic properties. Genetically determined differences in ethanol metabolism may, in part, account for the variability of individual susceptibility to the physical complications of alcohol abuse

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[7]. Few subjects who exceed the recommended levels of alcohol intake actually develop bridging fibrosis and irreversible liver damage, but some individuals (who are presumably genetically susceptible) can develop serious hepatic problems with quite modest levels of alcohol intake.

According to the proposition put forward by Renaud and de Lorgeril [8] alcohol, particularly in the form of red wine, can have a cardioprotective effect when taken at the levels regularly consumed in France (20 – 30 gm per day, or 160 – 240 mL of 12.5% wine). Other data have suggested that the protective effect of alcohol, or of red wine, is exerted at much lower levels of regular consumption. While specialists in the U.K. are generally less enthusiastic about this approach than their counterparts in France and Italy, it is agreed that any health beneficial effects are derived from a modest daily intake – it is not advisable to save up the weeks' units of alcohol for consumption on a Friday night; this will result in adverse health effects on the liver.

The effects on laboratory test results

A high proportion of the samples received by Biolab for health screening are from subjects who are experiencing the effects of chronic over-consumption of ethanol. Typically, serum gamma-glutamyl transferase activity is elevated after moderate to prolonged ethanol consumption. This does not actually indicate liver damage, but is due to hepatic enzyme induction and an increase in the permeability of the hepatocyte membrane, which allows the gamma-glutamyl transferase enzyme to leak from the hepatocyte into the extra-cellular fluid at a greater-than-normal rate. There is no observable effect on glutathione -S-transferase activity, since glutathione conjugation is not directly involved in ethanol metabolism. Serum bile acids may be elevated if there is a developing cholestatic component to the liver dysfunction. Alkaline phosphatase, which is a biliary tract enzyme, is usually found to have elevated serum activity somewhat after the elevation in serum bile acids and this suggests more severe cholestatic disease. With established chronic liver disease comes an elevation in serum bilirubin (suggesting the presence of obstructive cellular damage), but this is a late effect of alcoholic liver damage. Serum lactate dehydrogenase activity, while not specific for the liver, also rises with on-going hepatocellular damage. The pattern of results can be less than simplistic, depending on the exact state of liver dysfunction or recovery at the time the sample is taken.

An elevation in red cell superoxide dismutase (as a response to the development of oxidative stress) and depletion of intracellular glutathione can also be seen early on in the development of alcoholic liver damage. Vitamin levels, especially vitamin B1 and vitamin B6, are seen to fall. Paradoxically, we often observe a rise in serum vitamin A levels, which can be explained as the displacement of retinol from hepatic binding sites by ethanol and which can further contribute to on-going liver damage. Magnesium and zinc also tend to be lost from the body via the urine.

Chronic alcoholics have low serum total and nutritional antioxidant activity (TAA) [9], but subjects in the earlier stages of alcoholic liver damage will still have values for these parameters that are within the reference interval. TAA can still be a useful test if applied sequentially over a period of months, looking for a modest improvement in antioxidant activity with treatment. In the same way, nutritional recovery from the effects of alcohol excess should be associated with an improvement in antioxidant enzyme status.

Conclusions

Nutritional biochemical monitoring of the damaging effects of excess alcohol consumption can help both the patient and the physician to appreciate the pathological process that is taking place and to take remedial action to avoid the establishment of alcoholic liver disease.

Biolab tests to consider

Health Risk Profile, red cell magnesium, plasma zinc, functional B vitamin profile, blood glutathione, serum total antioxidant activity and nutritional antioxidant activity, antioxidant enzymes (red cell superoxide dismutase activity, red cell glutathione peroxidase activity, plasma glutathione peroxidase activity, red cell glutathione reductase activity, serum paraoxonase activity).

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Breath Hydrogen and Methane tests (home sampling kits)

Biolab offers a comprehensive breath hydrogen and methane testing service for the diagnosis of intestinal bacterial dysbiosis, and lactose and fructose malabsorption. These tests are performed over a 3 - 4 hour period collecting breath samples at regular intervals. We now offer kits for these tests so that patients can collect breath samples in their own home and return the samples by post for analysis.

Breath hydrogen and methane test prices:

For small intestine bacterial overgrowth	£95.00
For lactose malabsorption	£55.00
For fructose malabsorption	£55.00

A deposit of £35 is required for each postal test kit supplied.

Other laboratory investigations available at Biolab

In addition to Biolab's own specialist investigations we also offer all routine pathology tests (referred to The Department of Pathology at The London Clinic) and we can now provide access to a number of other tests via referral arrangements with laboratories in Europe and the USA. Tests include MELISA toxic metal sensitivities, pantothenic acid (B5), vitamin K, urine porphyrin screens, D-glucaric acid, urine methylmalonic acid, urinary 8-hydroxy-2'-deoxyguanosine (8-OHdG) and platelet neurotransmitters.

All tests referred from Biolab to other laboratories are charged at cost price, with a small sample handling fee (plus international courier fees if necessary), ensuring that patients receive all tests at the lowest possible price.

For further details of any of any of these tests, or any other investigations you would find helpful if available at Biolab please contact us.

Consulting room availability

We currently have consulting rooms available on a number of days each month. Rooms are available for half or full-day bookings, and our nurses are available for phlebotomy if required. If you are working in the field of nutritional medicine and would be interested in seeing your patients at Biolab, please contact Helen Hayes for details (e-mail: helen@biolab.co.uk).

Biolab Exhibitions

Biolab will be exhibiting at a number of scientific and academic meetings over the coming months, so please make yourself known to us if you are attending any of these events. If you work with a group that might be interested in a contribution from Biolab at conferences, meetings or in newsletters please contact Mark Howard at Biolab (e-mail: mark@biolab.co.uk, or telephone 020 7636-5959).

www.biolab.co.uk

New web site launch scheduled for July 2010