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## INTRODUCTION

Micro miniaturization of analytical procedures will have a significant impact on all aspects of diagnostic testing as we move into the 21st century. It will enable highly complex clinical testing to be miniaturized, and hence permit testing to move from the central laboratory into non-laboratory settings. These new personal laboratories will enable relatively unskilled operators to perform highly complex clinical tests, once only available from large specialized central laboratories. Many factors will determine the extent of the implementation of this type of testing, including prevailing regulations that govern laboratory testing, cost-benefit considerations, and the interest by members of the general public in performing self-testing. This article briefly reviews the current state of the micro technology that would underlie the development of personal laboratories

## MICROANALYTICAL DEVICES

There is already a diverse range of micro analytical devices - e.g., microchips, gene chips, bioelectronic chips (Cheng and Kricka, 2000; Kricka, 1998; Service, 1998). These silicon, glass, silicon-glass, quartz, or plastic devices contain um-sized components and sub-uL volumes, and are fabricated using techniques borrowed mainly from the microelectronics industry (Fig 1 and 2). They have been applied to a series of clinically important assay techniques and assays (e.g., PCR, immunoassay, capillary electrophoresis). The main advantages of the new devices are integration of multiple steps in complex analytical procedures (particularly sample preparation), diversity of application, sub-uL consumption of reagents and sample, and, because of their small size and light weight - portability. The latter feature makes possible devices that would serve as personal laboratories. Based on the current state of the art, the user would still have to collect a sample (e.g., blood, urine, saliva), but once introduced into the personal laboratory, all subsequent analytical steps would be performed automatically and a result displayed and stored in memory. A two-way wireless communication feature would allow the results to be communicated to a physician for comment or interpretation, or for downloading of interpretive information from the internet. The following sections describe some of the core components of a future personal laboratory. A further degree of simplification can be envisaged with the development and miniaturization of non-invasive testing, but this type of technology is still at the very early development stage.

Microchips This type of chip contains a range of microfluidic elements (microchannels, microchambers) designed for specific analytical tasks. These include chambers for performing PCR or immunoassay reactions, microchannels for intra-chip transfer of fluid or for electrophoretic separations, and posts and dams for cell separation and isolation. Sample loading and dispensing can be conveniently controlled using external electrodes to generate electrical fields in a microchannel (Alarie et al., 2000; Hadd et al., 1997). Various detection methods are used for on-chip detection, principally fluorescence (Colyer et al., 1997a,b; Hadd et al., 1997), but other techniques such as chemiluminescence (Mangru and Harrison, 1998) and electrochemical detection (Wooley et al., 1998) are also effective. A range of analytical techniques have been adapted to a microformat including gas chromatography (Bruns, 1994), micellar electrokinetic chromatography (Rodriguez et al., 1999) isoelectric focussing (Wen et al., 2000), and isotachophoresis (Walker et al., 1998). Miniaturization of capillary electrophoresis is currently one of


Figure 1 Plastic microchip for in vitro fertilization fabricated by Jenoptik (Jenna, Germany) (mikrotechnik@jenoptik.com) (channel at the left contains eggs and is connected via 100 um wide sperm selection microchannel to the semen chamber.

the most successful microchip applications (Colyer et al., 1997a,b; Dolnik et al., 2000; Hashimoto et al., 2000; Hofgartner et al., 1999; Huang et al., 1999; Liu et al., 1999; Munro et al., 1999; Rodriguez et al., 1997a,b; Rossier et al., 1999; Schultz-Lockyear et al., 1999; Ueda et al., 2000) and an analyzer is now available commercially (www.agilent.com). Considerable effort has also been expended in developing PCR chips (Belgrader et al., 1998; Ibrahim et al., 1998; Kopp et al., 1998; Ross et al., 1998; Shoffner et al., 1996), and in the simplification of PCR by integrating other analytical steps onto the same microchip device - e.g., sample preparation, detection of PCR products (Cheng et al., 1998a,b; Waters et al., 1998a,b, 1999; Wilding et al. 1998). Other microchips have been con-

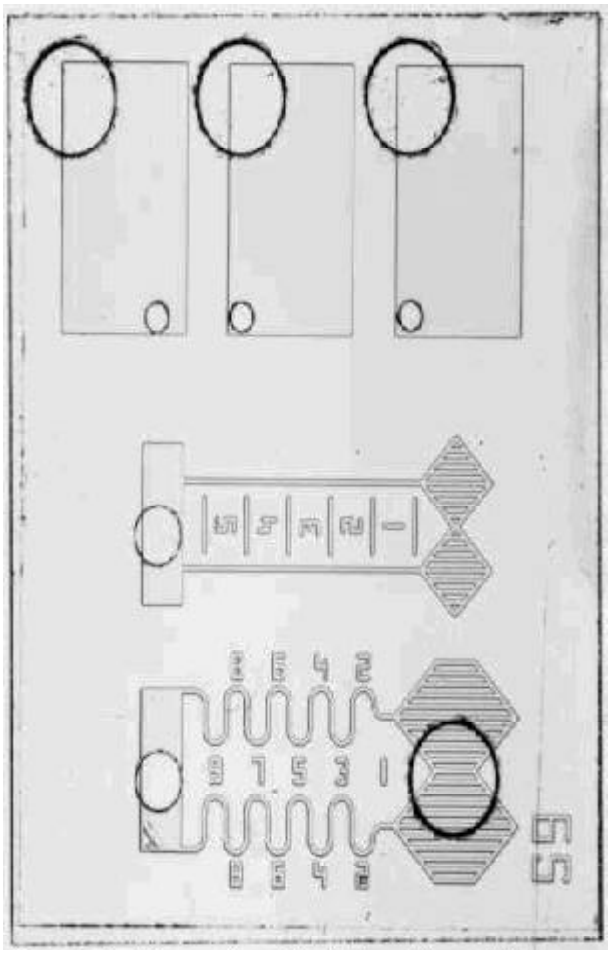

Figure 2
Glass microchip (15 x 17 mm) for semen testing (from left to right: sperm motility tester, penetration tester (microchannels filled with hylauronic acid), three tests chambers for other semen tests, e.g., sperm count, vitality test, sperm antibody test).

structed for performing enzyme assays (e.g., protein kinase A, beta-galactosidase)(Cohen et al., 1999; Hadd et al., 1997), immunoassays (e.g., thyroxine, cortisol)( Chiem and Harrison, 1998a,b; Koutny et al., 1996; Schmalzing et al., 1997; Song et al., 1994), mass-spectrometric assays (Xue et al., 1997), semen testing (Kricka et al., 1997)(Fig 2), and microdigestion of proteins coupled to MALDI-TOF mass spectrometry (Ekstrom et al., 2000). Silicon or glass has been the most popular material for fabricating microchips but increasingly, plastics (e.g, poly(methylmethacrylate) are being for microchip fabrication (Chen and Chen, 2000; Chen et al., 1999; Rossier et al., 1999; Soper et al., 1999; Yu et al., 2000) because of the availability of flexible, low-cost high-throughput manufacturing methods for this type of construction material (Fig 1).

### Bioelectronic chips

The presence of electrical components differentiates this type of chip from the simple microfluidic chip. Electrodes can be incorporated within the microfluidic compartments of a chip and used for a variety of analytical functions, including DNA hybridization, cell separation, cell lysis, and reagent positioning (Gilles et al., 1999; Livache et al., 1998; Vo-Dinh et al., 1999; Westin et al., 2000). Highly complex integrated bioelectronic chips can be fabricated that incorporate electronic components. For example, the Pharmaseq chip (www.pharmaseq.com) is a 500 um x 500 um x 500 um cube of silicon containing a light-powered microtransponder with an outside surface coated with a molecular recognition reagent. The chip can be programmed with a unique identifier, thus combining analytical reagents and an identification system on a single microchip. Bioelectronic chips from Nanogen (www.nanogen.com) incorporate arrays of platinum electrodes (80 um diameter) coated with streptavidin. Manipulation of the electrode (positive, negative, neutral charge) permits manipulation of molecules to and from each electrode. This type of device has been used for single nucleotide polymorphism (SNP) assays using fluorescently labelled reporter probes and biotinylated amplified patient DNA samples (Gilles et al., 1999). Similar bioelectronic chips have been adapted for multiplex strand displacement (SDA) amplification for factor V DNA using probes immobilized onto the surface of the electrodes within the microchip (Westin et al., 2000).

### Microarrays

Arrays of proteins (antigens, antibodies, enzymes) (Arenkov et al., 2000; Ekins and Chu, 1991), oligodeoxynucleotides (Drobyshev et al., 1999; Dubiley et al., 1999; Sachadyn and Kur, 1999), DNA (Proudnikov et al., 1998), and cDNAs (Pollack et al., 1999), have proved valuable analytical tools in the biological and clinical sciences. The range of techniques adapted to a microarray format includes simultaneous multianalyte immunoassays (Ekins and Chu, 1991), mutation analysis (Gerry et al., 1999; Hacia et al., 1996), expression assays (Lockhart et al., 1996; Schena et al., 1996), tumor cell analysis (Pappalardo et al., 1998), and sequencing (Dubiley et al., 1999; Liu et al., 1999; Sachardyn and Kur 1999).

Nanochips Beyond the um-dimensioned microchips lie the nanochips (Drexler, 1991). These are analytical devices constructed from individual atoms and molecules to form functional analytical devices that have um-sized dimensions. They will mimic the biomolecular machinery of biological cells, but as yet there are no examples of working nanochips. Some basis for optimism is to be found in the work on self-assembling molecular structures (e.g. nanotubes and other molecular systems)(Ghadiri et al., 1993; Stevens and Richards, 1997), however, at this stage they are still a distant prospect.

## CONCLUSIONS

The new microchip devices form the basis of new and smaller analyzers (e.g., capillary electrophoresis instruments) and may ultimately be used in even smaller devices useful in decentralized testing, e.g., hand-held monitors (lab-on-a-chip, personal laboratories). In contrast to previous analytical technologies, microchips offer an enlarged and unified menu of tests, and this will modify thinking on deployment of such devices and may have far reaching effects on the future of central laboratories. The impact of microchips on healthcare costs could be significant via timely intervention and monitoring, combined with improved treatments (e.g., microchip-based pharmacogenomic tests)(Housman and Ledley, 1998). Empowerment of health consumers to perform self-testing is limited, but microchips could accelerate this

process and so produce a level of self-awareness of biochemical and genetic information hitherto unimaginable. The next level of miniaturization is the nanochip (nm-sized features) and the technological foundation for these futuristic devices can be discerned in nanotubes and self-assembling molecular structures

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