Wearable electrochemical sensors
for monitoring performance athletes.

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ABSTRACT

Nowadays, wearable sensors such as heart rate monitors and pedometers are in common use. The use of wearable systems such as these for personalized exercise regimes for health and rehabilitation is particularly interesting. In particular, the true potential of wearable chemical sensors, which for the real-time ambulatory monitoring of bodily fluids such as tears, sweat, urine and blood has not been realized. Here we present a brief introduction into the fields of ionogels and organic electrochemical transistors, and in particular, the concept of an OECT transistor incorporated into a sticking-plaster, along with a printable "ionogel" to provide a wearable biosensor platform.

Keywords: Wearable Systems, Fluid Handling, Smart Textiles, Ionic Liquids, Microfluidics, Enzyme Biosensors, Ionogels.

1. INTRODUCTION

1.1 The Need For Wearable Sensors

Wearable sensors allow the continuous monitoring of a person's physiology in a natural setting. At present, health-monitoring systems using electronic textiles are mainly targeting applications based upon physiological parameter measurements, such as body movements or electrocardiography (ECG). However, due to their relative complexity, there is very little activity in the development of real-time wearable chemo/bio sensing for sports applications.

Micro-Total-Analysis-Systems and Lab-on-a-Chip technology are widely used in analytical chemistry and biotechnology[1] but they are still rarely used in other areas like sports science. In this field, wearable sensors are becoming increasingly employed, through the use of embedded transducers or smart fabrics for monitoring parameters like breathing rate, heart rate and footfall[2]. These sensors require that the desired sample of analysis, usually a body fluid such as sweat is delivered to the sensor's active surface, whereupon a reaction happens and a signal is generated. Moreover the system must be low cost, while still being robust, miniature, flexible, washable, reusable or disposable[3]. All these requirements point to micro-fluidic devices as the key tools for improving wearable chemo-/bio-sensing[4].

To open a dramatically wider field of applications, chemical measurements on body fluids (blood, sweat, and urine) are needed. This area of research is unfortunately still poorly developed due to the difficulty in sampling such fluids. The BIOTEX project tackled some of these problems by developing a textile-based system to collect and analyze sweat by using a textile-based sensor capable of performing chemical measurements[3]. The great advantage of analyzing sweat for health monitoring is that it is noninvasive, reasonably accessible, with the potential to provide valuable

physiological information[5, 6]. levels. However, advances in this direction have been limited due to the difficulty in obtaining uncontaminated samples.

Nowadays, wearable sensors such as heart rate monitors and pedometers are in common use. Several products are already on the market, such as the Lifeshirt®, developed by Vivometrics®, the body monitoring system developed by BodyMedia® and the Nike-Apple iPod Sports kit which facilitates individualized feedback control of performance during exercise periods. The use of wearable systems such as these for personalized exercise regimes for health and rehabilitation is particularly interesting.

This area is growing exponentially, as the economics of healthcare increasingly point to the need to provide remote monitoring of patient progress, rather than the current hospital-focused model. In particular, the true potential of wearable chemical sensors for the real-time ambulatory monitoring of bodily fluids such as tears, sweat, urine and blood has not been realized. This is due to the difficulties associated with sample generation, collection and delivery, sensor calibration, wearability and safety issues[3].

1.2 Wearable electrochemical sensors.

Wearable sensors ideally should have the ability to monitor the physiology of the wearer and the surrounding environment. A wearable sensor may respond to physical changes, such as body temperature or movements of the joints. A chemical sensor (chemosensor) detects and measures a particular chemical in its environment. Biosensors are closely related to chemical sensors, distinguished by the molecular recognition element which is biological in nature (*e.g.* enzyme, receptor, DNA, antibody, or microorganism)[7]. The integration of chemical sensors into a textile substrate is a challenging task as chemical sensors typically involve a molecular interaction or reaction in order to generate a signal. This involves delivery of a sample to an active sensor surface where the signal generation process happens. Often, the sample is mixed with a reactive reagent, and mixing of samples and reagents results in waste products.

It is estimated that 70% of all illnesses are preventable, and if suitable screening measurements were introduced, this could produce dramatic reductions in costs for treatments and medication[8]. For example, by adopting suitable exercise and diets, many lifestyle-related illnesses can be prevented. Exercise generates sweat naturally, and sweat contains very rich information about the physiological condition of the subject as it contains a matrix of essential ions and molecules[9]. Real-time sweat analysis during exercise can give valuable information on dehydration and changes in the amount of important biomolecules and ions[9]. This information has been shown to be very important for monitoring the subject's physiological conditions during training/exercise and can be used to determine optimised approaches to rehydration. In the case of elite athletes and people who enjoy endurance sports, it is well-known that sweat composition changes during exercise as a result of dehydration[9], and therefore a wearable non-invasive sensor that can provide information on optimum personal re-hydration regimes could offer significant benefits.

To monitor sodium concentrations of sweat in real time, Schazmann *et. al*[10] developed, in our laboratories, the sodium sensor belt (SSB). The SSB consisted of an Ion Selective Electrode (ISE) selective to sodium, integrated into a platform that was interfaced with the human body during exercise Fig 1. No skin cleaning regime or sweat storage technology is required as the sweat is continually wicked from the skin to a sensing surface and from there to a storage area via a fabric pump

Figure 1: the SSB sensor assembly showing signal display and the SSB mounted onto the lower back of a high performance sports athlete[10].

Using the SSB, Schazmann *et. al*[10] demonstrated real-time analysis of sweat electrolytes via in-situ measurements using an on-body sampling and sensing platform. Exercise trials using the platform generated values of sodium concentrations in sweat that were broadlyin agreement with literature ranges and verified using an AAS reference method. Future work for on-body sensing systems would be to monitor the onset of dehydration, (resulting in extended trial exercise periods). In theory a large number of cations and anions can be selectively analysed according to the many ionophores available for use in ISEs. The authors state that they simply replace the current sodium selective ionophore or be used as part of a sensor array. Location of these sensors closer to the sweat sampling inlet, coupled with system miniaturisation could reduce the delay time between sweat emission and its subsequent analysis[10]. In parallel, the integration of wireless communications is relatively straightforward and could result in truly individualised applications such as those found on smart phones / devices[10].

1.3 Ionogels: A diverse material for sensing platforms.

Ionic liquids (ILs) are molten salts that exist at low temperatures, i.e., liquids that are comprised entirely of cations and anions. According to the current convention, a salt melting below the normal boiling point of water is known as an "ionic liquid" or by one of many synonyms including low / ambient / room temperature molten salt, ionic fluid, liquid organic salt, fused salt, and neoteric solvent[11]. Recently the most commonly employed IL anions are polyatomic inorganic species. Most common among these is $[PF_6]^-$, a "workhorse" anion that Wilkes and Zaworotko[12] paired with imidazolium cations in preparing early water stable hydrophobic ILs. It, and the related $[BF_4]^-$ ion, are probably the most popular anions used in IL research and the variation in properties between salts (with a common cation) of these species is dramatic. For example, butylmethylimidazolium hexafluorophosphate $[C_4mim][PF_6]$ is immiscible with water, whereas butylmethylimadazolium tetrafluoroborate $[C_4mim][BF_4]$ is water soluble[13]. This sort of variation in physical properties arising from different anion choice gave rise to Seddon's description of ILs as "designer solvents"[14]. The number of potential anion-cation combinations available reputedly equate to one trillion (10^{12}) different ILs[11]. Ionic liquids have received much attention of late because of their potential application in green chemistry and as a range of novel electrochemical materials. They have indeed become "designer solvents" with many ILs now being designed for a specific application, for example as potential electrolytes for various electrochemical devices[15-27], including rechargeable lithium cells,[28, 29] solar cells,[30-32] actuators[33-35] and double layer capacitors (DLCs).[36-38]

Along with electrochemical applications, ILs have gained momentum in bio applications. Recent work in the area include ILs as biocatalytic reactions[27, 39], biosensors[40], protein stabilization[41] and biopreservation[42]. They have been proposed as unique solvents for biomolecules such as proteins / enzymes because of their unusual solvation characteristics. Work by Fujita *et al*.[40, 43] and others[41, 44] have shown that some proteins are, in fact, soluble, stable and remain active in some ILs. As a case study Cytochrome c (cyt. c) was found to have enhanced solubility and stability in a biocompatible IL solution based on the dihydrogen phosphate anion[43]. This is an important observation since proteins are sometimes unstable when handled in vitro, and stabilizing agents are a necessary component to ensure their long-term stability. This is especially true of proteins that have pharmaceutical potential since lack of stability is a limitation to widespread use of some protein therapeutics. It has been well documented that enzyme performance in an IL is affected by several parameters including water activity, pH and impurities[45]. Other important factors that play a role in enzyme stability / activity include IL polarity, hydrogen bond basicity and nucleophillicity of anions, ion kosmotropocity and viscosity. Although outside the scope of this discussion, these areas have been discussed in an excellent review on the topic by Zhao[46]. Abe *et. al*[47] recently synthesized a number of phosphonium salts that have an alkyl ether group present. The phosphonium salts moiety is commonly found in living creatures, and it was hypothesized that this family of ILs have good affinity with enzyme proteins and may provide a good environment for enzymes.

Currently for applications in materials science, there is a growing interest in 'ionogels', i.e. polymers with ionic liquids integrated such that they retain their specific properties within the polymer/gel environment. An excellent review by Bideau *et. al*.[48] discusses ionogels as a new class of hybrid materials, in which the properties of the IL are hybridized with those of various components, which may be organic (low molecular weight gelator, (bio)polymer), inorganic (e.g. carbon nanotubes, silica etc.) or hybrid organic–inorganic (e.g. polymer and inorganic fillers) as shown in Fig 2.
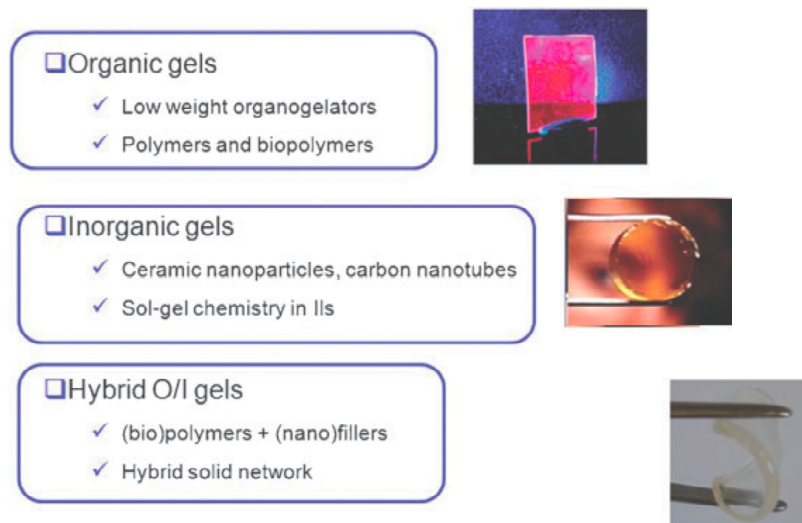
Figure 2: Types of Ionogels synthesised as outlined by Bideau *et. al*[48].

The use of ionogels in electrochemical and biosensors has been well documented and is an ever growing field. Examples include onogels that manifest a highly selective response to the hydrophilic sulfate anion. Coll *et. al*[48]. described for the first time the preparation of PVC membranes containing 1-butyl-3-menthyl-imidazolium hexafluorophosphate [C$_4$MIm][PF$_6$] IL and polyazacycloalkane as an ionophore. Pletnev *et. al.*[49], using the same concept, described the use of PMMA and PVC membranes containing bis(trifluoromethanesulfonimidate) salts of 1-butyl-2,3-dimethylimidazolium and dodecylethyl- diphenylphosphonium, [BDMIm][NTf$_2$] and [DEDPP][NTf$_2$], respectively. These ion-selective membranes demonstrated good and extremely stable responses to both cations and anions (including surfactants)[49]. The use of an ionogel as a biosensor has been shown by Sun *et. al.*[50]. ILs are known for their good biocompatibility with biomolecules and enzymes and they improve their reusability and stability. Some examples are based on the immobilization of enzyme-IL systems in chitosan[51] or Nafions[52]. Thus, catalytically active proteins and enzymes may also be confined for biosensors applications in order to achieve direct electron transfer within ionogels. It is therefore proposed that having "Ionogels" is a particularly attractive strategy in the field of biosensing. These materials, in theory, will inherit all of the favourable IL properties whilst being in a solid, semi-solid gel like structure[53].

1.4 Applications of Ionogels: Sweat on a chip

Within our group, the development of optical pH sensors using ionogels has been reported[3, 7, 54]. There are several factors that correlate sweat pH and health. Changes in the pH of the skin are reported to play a role in the pathogenesis of skin diseases like irritant contact dermatitis and acne, among others.[55] Patterson *et al*[56]. showed that inducing metabolic alkalosis through the ingestion of sodium bicarbonate led to increased blood and sweat pH. Furthermore, it has been reported that sweat pH will rise in response to an increased sweat rate.[57] A relationship was also observed between pH and sodium (Na^+) levels in isolated sweat glands in that the greater the concentration of Na^+, the higher the sweat pH will be[58]. As exercising in a dehydrated condition has been shown to lead to increased levels of Na^+, it can be seen that such changes can be measured directly (e.g. using a Na^+ selective sensor) or indirectly by monitoring sweat pH.[59] In order to provide sensors with good sensitivity, selectivity and stability, various support materials, methods and reagents for immobilization of pH indicators were employed by our group[60, 61]. In particular, ionic liquids (ILs) are rarely used in optical sensors in spite of their excellent chemical and thermal stabilities, low vapour pressure, high ionic conductivity and tuneable hydrophobic and hydrophilic nature[62]. A barcode system shown in Fig. 3 was developed as an initial sweat sensor with an ionogel being an important component in the fabrication of the sensing platform[54]

Figure 3: Barcode system with the four pH indicator dyes and their pH activation range incorporated into phosphonium based ionogels[54].

The ionogel consisted of two monomeric units; poly(N- isopropylacrylamide) (NIPAAm) and *N,N*-methylene- bis(acrylamide) (MBAAm) in the ratio 100:5, respectively. The reaction mixture was prepared by dissolving the NIPAAm monomer, the MBAAm and the photo-initiator dimethoxy-phenylacetophenone (DMPA) into trihexyl(tetradecyl)phosphonium dicyanamide [$P_{6,6,6,14}$][dca] ionic liquid. The barcode (18 x 10 mm), consisted of four independent reservoirs, and was easily fabricated in poly(methyl methacrylate) and pressure-sensitive adhesive in five layers using CO2 ablation laser[54]. The stability of the barcode was studied by immersing the barcode in de-ionised water, and then varying the pH from 0 to 14 in intervals of one pH unit. The pH was monitored using a benchtop pH meter and it was repeated at least four times without observing any damage to the barcode and/or ionogel. Benito-Lopez *et. al.*[54] showed that the fabrication, characterization and performance of a wearable, robust, flexible and disposable

barcode system based on ionogels for monitoring in real time mode the pH of sweat was possible. The ionogel matrix proved to be very robust even at harsh pH conditions (0-14) and it was shown that the pH indicators bromocresol green, bromocresol purple and bromothymol blue retained their pH indicator properties within the ionogel. The ionogel-dye interactions ensure no leaching of the dyes during experiments, providing long durability of the device and accuracy on the pH of sweat measurements over time[7, 54].

1.5 Electrochemical biosensing: Organic electrochemical transistors.

The field of organic electronics in recent years has seen a boom in publications, with organic semiconductors being considered for applications in electronic and optoelectronic devices, including light emitting diodes, photovoltaic cells, and thin- film transistors[63]. Advantages of organic electronics include tunability of their electronic properties via chemical synthesis and compatibility with roll-to-roll fabrication, which can yield ultra-low cost manufacturing. An emerging focus in the field involves the use of organic-based devices as transducers in chemical and biological sensors[64-66]. Early OECT fabrication used varying types of conducting polymers, for example: polyaniline[67, 68], polycarbazole[69], polythiophene, and their derivatives[70, 71]. However limitations were also faced when using these devices as biosensors. For example, polypyrrole when exposed to hydrogen peroxide (H_2O_2) undergoes an irreversible conductivity change limiting its use with many enzymes such as glucose oxidase (GOx) that generate H_2O_2 during interaction with suitable analytes[72]. Polyaniline loses its electrochemical activity at a pH higher than 5, limiting the sensing capability of polyaniline-based OECTs in physiological fluid (pH ~ 7.3)[73]. Although attempts have been made to overcome this limitation by modifying polyaniline with high molecular counter ions such as poly(vinyl sulfonate) or poly (styrene sulfonate)[73, 74], the development of a more durable conducting polymer was required[75].

Recently, Zhu *et. al.*[76] demonstrated that OECTs based on the commercially available conducting polymer, poly(3,4-ethylenedioxythiophene) doped with poly(styrene sulfonic acid) (PEDOT:PSS), is capable of sensing glucose in a neutral pH buffer solution[76]. The OECT setup proposed by Zhu *et. al.*[76] showed that the current through the PEDOT:PSS channel, induced by the application of a gate voltage on a platinum (Pt) wire electrode, was dramatically increased when both glucose and GOx were present in phosphate buffer solution (PBS). These result indicates that PEDOT: PSS has good stability both in neutral pH and in the presence of H_2O_2, and the limitations that result from the use of polypyrrole and polyaniline may have been overcome[75].

An enzymatic sensor based on an organic electrochemical transistor (OECT) that employs a room temperature ionic liquid (RTIL) as an integral part of its structure has been described recently [77]. The authors reported that patterning the RTIL over the active area of the OECT enables the RTIL to act as an electrolyte and a reservoir for the enzyme. When the solution containing the analyte is added to the device, it mixes with the RTIL. The analyte, the enzyme, and the mediator are then allowed to interact and the OECT transduces this interaction. An important requirement for the RTIL is that it wets the PEDOT : PSS film, thus allowing the enzyme and the mediator to be patterned over the active area of the device. Moreover, the RTIL should be miscible with the aqueous solution that carries the analyte (PBS). The RTIL triisobutyl-(methyl)-phosphonium tosylate ([P$_{1,4,4,4}$][Tos], Fig. 4a, supplied by Cytec Industries) satisfies these requirements, as the Tos anion gives it a rather hydrophilic character. Previous studies have also shown [P$_{1,4,4,4}$][Tos] to be a biocompatible medium for glucose consumption by bacteria[78]. The layout of the device is shown in Fig. 4b. Two parallel stripes of PEDOT:PSS, with widths of 100 mm and 1 mm, respectively, were patterned on a glass support using photolithography. Contact pads at the end of the stripes allowed facile electrical connection to the source-measure units. The wide stripe was used as the transistor's channel and the narrow one as the gate electrode, as it has been shown that for enzymatic sensing the area of the channel must be larger than that of the gate electrode[79]. A monolayer of (tridecafluoro-1,1,2,2-tetrahydrooctyl) trichlorosilane (FOTS) was patterned on the surface of the device leaving uncovered only a small area of the channel and of the gate electrode. These areas of PEDOT:PSS which were left uncovered by FOTS served as hydrophilic ''virtual wells''[80] and were shown to be effective in confining the RTIL (and the glucose solution, when it was added) over the centre of the device.

The experiments involved placing a small amount of [P$_{1,4,4,4}$][Tos] that included the enzyme glucose oxidase and the mediator ferrocene [bis(n5-cyclopentandienyl)iron] on the centre of the device and allowing it to be accommodated in the hydrophilic virtual wells. Subsequently, 50 µl of glucose solution in PBS were added to the device and allowed to mix with the RTIL solution, as seen in Fig. 4c.
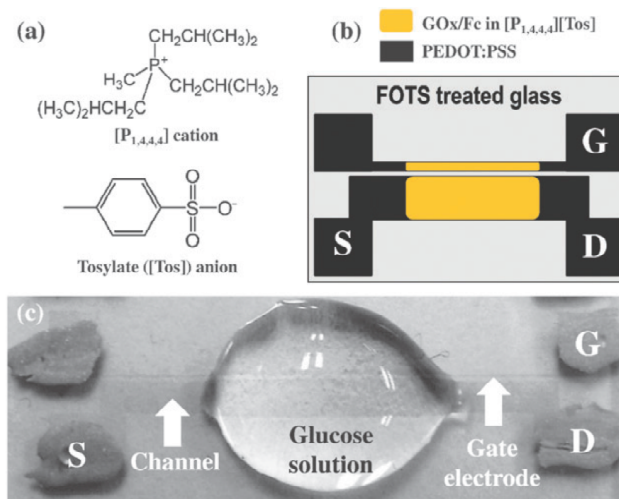

Figure 4: (a) Chemical structure of [P$_{1,4,4,4}$][Tos]. (b) Layout of the OECT, indicating the area where the RTIL was confined. (c) Photo- graph of the OECT with a drop of glucose solution added. The balls at the pads are made of silver paste[77].

1.6 Ionogels & OECTS: The future of biosensing?

Important contributions to current sensor research in the area of lab-on-a-chip micro total analysis systems can be made by integrating OECTs with Ionogels. Many of the applications for OECT / Ionogel sensors will likely involve disposable devices, cheap fabrication and therefore enzyme stability is of the utmost importance. OECT devices are inherently low-power and relatively easy to fabricate. Nilsson *et al*.[81] demonstrated the potential for OECT sensors to be manufactured inexpensively using printing techniques for mechanically flexible single-use tags. They fabricated humidity sensors on thin polyester foils and on paper. A significant challenge exists in how to integrate ILs in these types of solid-state devices, whilst retaining their specific properties. "Ionogels" appear to have the capability to meet this challenge, as the IL remains in an essentially liquid form within the solid/semi-solid gel-like structure[53]. Combining OECT properties with those of ionogels therefore offers significant potential for realizing new generations of solid-state biosensing devices in a variety of form factors, and using ILs to optimise the stability and reactive nature of the host enzyme.
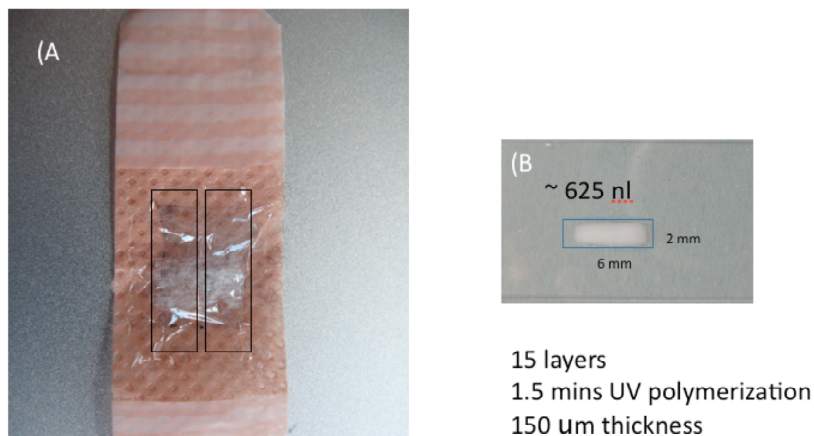
Figure 5: A printable OECT / Ionogel composition incorporated into a widely available fabric (plaster) and the development of printable ionogels. Volumes are in the nano liter range.

The possibility to pattern PEDOT:PSS in a wide variety of substrates such as glass, flexible plastic and textiles, open new routes for the development of wearable biosensors. Such biosensors can therefore be incorporated into fabrics such as t-shirts, sweat bands or shorts allowing for the analysis of real time measurements of the target biomolecules. Fig 5, (left) shows a proof of concept of this type prepared in our laboratories which consists of an OECT transistor incorporated into a plaster, while (right) shows an ionogel formulation printed using an inkjet printer (volume in the nano liter range). However, more studies are needed to understand device degradation mechanisms and improve sensor lifetimes.

1.7 Concluding remarks.

The development of a SSB incorporating ISE's allowed in situ measurements using an on-body sampling and sensing platform for sports athletes. Exercise trials using the platform generated values of sodium concentrations in sweat, in agreement with literature ranges and verified using an AAS reference method. The integration of some commercially available phosphonium based ionic liquids onto electrochemical transistors has been presented. The ionic liquid was confined on the surface of the transistor using a photolithographically patterned hydrophobic monolayer, which defined hydrophilic virtual wells. An enzyme and a mediator were immobilized in the ionic liquid and, when the aqueous solution which carried the analyte was added, they dissolved in it. The enzyme was in a dispersed state in the ionic liquid, which may prove to be a good strategy for improving long-term storage.

It is proposed that having "Ionogels" incorporated with OECTS be an attractive strategy in the field of biosensing. These materials, in theory, will inherit all of the favorable IL / OECT properties whilst being in a solid, semi-solid gel like structure[53]. These properties and flexibility of such materials would render them favorable to be incorporated into fabrics for electrochemical biosensing.

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