dose was enough to demonstrate adequate immune efficacy. The epidermal delivery route did not produce an immune response against the rabies vaccine [140].

The use of "poke and patch" techniques (Figure 39.2A) has mostly been replaced by more sophisticated MN devices. For example, it was demonstrated that antigen-coated, pH-sensitive MNs were superior to a poke and patch approach in terms of antigen-specific $CD4^+$ and $CD8^+$ T-cell responses [141]. Nonetheless, many studies using this technique have focused on delivery of diphtheria vaccine. In diphtheria toxoid intradermal immunization, MN array pretreatment of the skin was essential to achieve substantial IgG and toxin-neutralizing antibody titres [142]. Studies have also focused on adjuvants administered alongside the diphtheria toxoid vaccine and concluded that the potency and quality of the immune response can be modulated by the presence of adjuvants [143, 144].

MN-based systems, specifically dissolving MNs, appear to have huge potential for vaccine delivery. Many studies demonstrate dose-sparing effects compared to traditional vaccine administration routes, and the ability to formulate vaccines in the dry state could save huge amounts of money, as well as benefitting developing countries. Studies have demonstrated that studies are moving past "proof of concept" stages and into clinical trials [109, 145, 146]. If the maintenance of vaccine component stability can be assured, it is likely that a MN-based vaccine device will soon be available to use clinically as an alternative to traditional vaccine delivery methods.

39.5 MNs FOR COSMETIC APPLICATIONS

Skin health is affected by many factors such as lifestyle, genetics, hormones, nutrition, and aging [147]. Skin blemishes, be they wrinkling, stretching, or scarring, regardless of their causation, often resulting in reduced self-confidence. Considering the importance of the latter, it is unsurprising that, fueled by the rise of social media, the global cosmetic skincare market was valued at $135 billion USD in 2018 [148]. Successful use of cosmetic MN devices to rejuvenate and treat the skin was reported in 1995, and since then, growth has been exponential [149].

The earliest record of an MN-type therapy used solely for the treatment of skin blemishes was reported by Orentreich and Orentreich in 1995 [149]. Termed "SC incisionless surgery" or "subcision," this work described the successful treatment of acne scars through the promotion of substratum collagen production by needle application as deep as the dermis layer [149]. Based on the principle of subcision and in conjunction with subsequent advancements in the field of cosmetic MN therapy, Fernandes developed the first handheld device for cosmetic microneedling in 2002 [150]. This device comprised a handle with a rotating drum-shaped head that bore outwardly protruding fine needles and was designed to be rolled over skin blemishes such as scars or wrinkles to induce the aptly named process of percutaneous collagen induction (PCI) [150]. MN-mediated PCI (Figure 39.5) occurs in two distinct steps. The first step involves the disruption of preexisting collagen fibers that tether a scar or wrinkle to the underlying dermis by controlled incisions upon needle application [150, 151]. The second step aims to heal these microscopic wounds through angiogenesis and collagenesis as part of the skin's natural posttraumatic inflammatory cascade [150, 151]. The inflammatory cascade in this case is composed of three sequential phases: (1) initiation/inflammation, (2) proliferation, and (3) remodeling. Phase 1, i.e., after MN penetration, is characterized by the recruitment of platelets, neutrophils, and macrophages that stimulate the release of growth factors, including epidermal growth factor (EGF), transforming growth factor- alpha (TGF- α), TGF- beta (- β) and platelet-derived growth factor (PDGF) [152]. Growth factor release induces fibroblast proliferation and signals the commencement of phase 2 [151, 152]. In combination with keratinocytes and monocytes, which now increasingly replace neutrophils, these fibroblasts continue to produce growth factors [151, 152]. This sustained growth factor release results in angiogenesis leading to fibronectin matrix formation. Simultaneously, collagen III and other intercellular matrix proteins, including elastin, proteoglycans, and glycosaminoglycans (GAGs), are deposited at the wound site [152]. The final phase, remodeling, is the slowest phase and in some cases can take several months to complete [152]. This phase is characterized by the conversion of collagen III to collagen I through