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Prototype Misidentification Makes Conclusions about Pathotype Growth Characteristics Uncertain

To the Editor—Miyairi et al. [1] suggest that their careful measurements of growth rates and developmental cycles of several Chlamydia trachomatis isolates may reflect genomic differences that define chlamydial pathotypes. For their purposes, isolates were divided into ocular strains (endemic trachoma) versus genital strains (a lymphogranuloma venereum strain and trachoma biovar isolates from the genital tract). The validity of such differentiation depends on the accurate identification of prototype strains. Unfortunately, in this case, one of the ocular prototypes is misidentified. The E/Bour isolate is described as coming from “a patient with endemic trachoma” (p. 351). In fact, the patient had lived in the San Francisco Bay area for many years [2]. Although endemic trachoma was still prevalent among southwestern American Indians at that time and had been endemic in the United States into the 1930s, the San Francisco Bay area was not an area where trachoma was endemic in the 1950s.

It had long been known that chlamydial infection of the genital tract could spread to the eye, causing inclusion conjunctivitis in adults or newborns exposed to the organism during delivery [3]. Indeed, with the advent of egg isolation for C. trachomatis, studies in the early 1960s of “inclusion conjunctivitis” in San Francisco and in London began to reveal the widespread genital-tract reservoir of C. trachomatis [4, 5].

In the late 1950s, the clinical diagnosis of trachoma was thought to be clearer and easily differentiated from the oculargonal cases. In the article reporting the isolation of E/Bour, the patient’s eye disease was described as “early trachoma.” This diagnosis was based on the degree of corneal inflammation and minimal corneal vascularization in this patient, who had follicular conjunctivitis of acute onset involving the upper lid. Similar sporadic cases in adults had previously been called “acute trachoma” by the same clinician [6]. With subsequent experience gained from experimental human inoculations and cases of genital-tract origin, it became obvious that the inflammatory stages of trachoma and acute inclusion conjunctivitis in adults were very similar. Indeed, Barrie Jones, who pioneered these studies in London, resurrected the older term “paratrachoma” to describe cases of genital-tract origin that fit the diagnostic criteria for trachoma [7].

There are other reasons to consider that E/Bour is not a typical trachoma strain. When inoculated into the conjunctiva of subhuman primates, it causes a relatively severe conjunctivitis similar to the disease seen with other ocugonital strains, rather than the milder disease typically seen with trachoma strains [8].

When serotyping procedures were developed and the Micro-IF test became the method of choice, Bour was identified as an E serovar [9]. This is characteristic of genital-tract strains (typically D-K serovars) rather than trachoma strains (typically A-C serovars).

More critical, the identification of E/Bour as a trachoma strain breaks the recently established trachophan synthase paradigm of ocugonital versus trachoma strains. This paradigm was established through the evaluation of hundreds of C. trachomatis isolates for the gene sequences for the enzymes involved in trachophan synthesis. In addition to the prototype strains, there were 94 ocular isolates and 214 from the genital tract. It was found that all of the endemic trachoma strains lacked an active trachophan synthase, whereas those of genital-tract origin encoded a functional trachophan synthase. E/Bour was included in this functional genetnic evaluation and fell into the genital-tract group of isolates [10].

Thus, the preponderance of evidence suggests that E/Bour is not representative of endemic trachoma strains. The only reason to consider it as a trachoma strain is a questionable clinical diagnosis. The general hypothesis presented by Miyairi et al. is consistent with our observations (made over the course of 45 years of attempting to isolate C. trachomatis from ocular and genital sources): lymphogranuloma venereum strains tend to be more productive (they produce a higher titer after passage in cell culture) and grow faster than genital-tract strains, which, in turn tend to grow faster than endemic trachoma isolates. However, we have also found a fair amount of variation from this theme. For example, we see “good” growing strains from any infected site, as well as “poor” growers, even to the stage of obtaining isolates that simply cannot be maintained, because they die out after several passages. We do not know the genetic basis or the potential pathological implications for these different behaviors in cell culture, nor do we know what selective pressures exist for successful adaptation to cell-culture systems. However, we suggest that the variations in growth that Miyairi et al. observed with their 2 serovar E isolates reflect...
that variation in strain behavior in vitro and are not supportive of an ocular-versus-genital pathotype differentiation.

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References

Reply to Schachter and Dawson
To the Editor—Schachter and Dawson have clarified the origin of the Chlamydia trachomatis serovar E/Bour strain as a clinical isolate from a patient with inclusion conjunctivitis rather than endemic trachoma [1]. It is worth noting that we were not the ones who misrepresented the origin of E/Bour. The strain was, in fact, originally identified as a clinical trachoma strain in a report that appeared in Science in 1959, and Dr. Dawson was a coauthor on that study [2]. Schachter and Dawson suggest that because E/Bour is not a true “trachoma” strain, growth differences observed among the E serovars tested are more likely a matter of in vitro variation than a property allied directly to pathobiotype. This is an appropriate concern, and it highlights limitations inherent in using reference strains with uncertain identities that have been passed extensively in numerous laboratories. Indeed, as we have indicated, a definitive generalization regarding growth rate with pathotype distinction needs to be validated with extensive investigation using clinical strains as demonstrated by tryptophan synthase polymorphism [3]. However, it seems to us to be premature to state that there is no correlation between growth rate and pathotype distinctions, as suggested by Schachter and Dawson. Growth differences among strains are affected by multiple genetic factors, some of which most likely contribute to differences in pathogenesis such as pathotype, tissue tropism, and invasiveness. We appreciate the extensive experience Schachter and Dawson have in isolating ocular and genital strains for >45 years and the knowledge they convey regarding slow-growing ocular strains and fast-growing lymphogranuloma venereum (LGV) strains. If the general observation is that C. trachomatis can be grouped into LGV, genital-tract, or endemic trachoma isolates according to growth rates, then the evaluation of strains with clear genetic differences could help explain deviations in chlamydial growth.

Investigation of growth variants has already yielded interesting phenotypes such as IncA mutants [4] and genital serovar B strains with intact partial tryptophan synthase operons [3]. Our initial observations were intended to set the stage for developing a more codified means of sorting out pathotypes based on the investigation of tractable biological parameters.

There is no doubt that E/Bour was isolated from the conjunctiva of a patient with chronic chlamydial ocular disease, despite its designation as a genital-tract serovar. If most genital-tract strains do grow relatively quickly, why does this particular strain grow more slowly? The current assumption is that isolates capable of infecting the eye and the genital tract are identical, but this has not been systematically investigated. In fact, there is no indication that the individual infected with E/Bour had a concomitant genital-tract infection. As we proposed in our article [5], a comparison of growth rates in paired mother-infant or genital tract–conjunctival isolates would be informative in this context. For example E/Bour has a 5′ tarp deletion that distinct from all other sequenced strains [6]. The relevance of this finding is unknown, but it could reflect growth rate distinctions.

Research in the area is presently in the initial stages of uncovering genetic explanations for pathotype distinctions for these closely related pathogens [3, 4, 6]. In the absence of a gene-transfer system for Chlamydia, the key to discovery is to work through biological differences among pathotypes as a basis for understanding mechanisms that contribute to differing disease for ocular and genital strains. Our study focused on demonstrating consistent growth rate differences based on pathobiotype (A-C vs. D-F and LGV) or disease manifestations (E/Bour vs. E/UW5/Cx). Future work needs to expand the repertoire of clinical isolates representing a much greater pool of strains with diverse genetic and pathogenic potential. Although growth rates are tractable measures, the integration of other biologic dis-