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Does the capsule component of the Cryptococcus neoformans glucuronoxylomannan impair transendothelial migration of leukocytes in patients with Cryptococcal meningitis? (letter)

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Reply

To the Editor—We apprecia e he commen s of Thompson [1], who kindly provided some da a supplemen ary o our findings [2]. As originally s a ed, we failed o find an associa ion of serum reac ivi y wi h clinical profiles, including pa ien age or sex or dura ion, si e, or number of molluscum lesions. Al hough Thompson did no repor a correla ion be ween he rela ive an ibody i er in heir ELISA sys em and clinical symp oms [3], we hink i should be no ed ha 1 of he weakly posi ive sera lacked reac ivi y wi h 33/35-kDa polypep ides [1]. These resul s sugges ha he ypes of an ibody may differ according o heir reac ivi y measured by ELISA. Fur her longi udinal s udies wi h a large popula ion is necessary o clarify he clinical significance of he wo ypes of an ibody.

Unfor una ely, we did no purify molluscum con agiosum virus (MCV) virions separa ely, since i was our purpose o ob ain a sufficien amoun of viral DNA o es ablish a library. The ac ual propor ions of MCV sub ypes 1, 1v, and 2 in our pooled samples remains unknown. However, we hough ha mos of our samples consis ed of MCV 1v because a previous large epidemiologic s udy revealed ha sub ype 1v accoun ed for 96% of he s rains isola ed in he Tokyo area [4], and we previously es ablished a genomic library of MCV 1v [2]. I appears o be possible o discrimina e minor differences in molecular masses when various isola es are compared on he same polyacrylamide gel. In addi ion, we do no hink i is appropria e o es ima e he molecular masses of pro eins wi h ~70 and ~34 kDa on he same polyacrylamide gel. Thompson [1] poin ed ou ha he size of larger an igenic polypep ides may have been underes ima ed (figures 1, 2, and 6 in [2]), which could be due o he use of higher percen age acrylamide. We repea edly performed elec rophoresis using gels a differen concen ra ions and finally de ermined he molecular masses of he wo major an igenic polypep ides.

Oda e al. [5] analyzed he s ruc ural polypep ides of MCV by SDS-PAGE. They found ha only wo polypep ides, designa ed A and D, which were coinciden ally demons ra ed o be wo major an igenic pro eins [2], among seven major polypep ides differed in heir mobili y on acrylamide gel according o he isola es. Assuming ha , as Thompson repor ed [1], he variabili y of hese wo an igens depends on he ypes of MCV DNA, i migh be immunologically impor an because MCV may have undergone changes in i s surface pro eins during he evolu ionary process in response o he hos . However, i remains o be clarified why each of he polypep ides A and D is recognized as a wide, blurred band, ra her han wo discre e bands, when pooled un yped MCV are analyzed on SDS-polyacrylamide gel [5]. We believe ha some unknown fac ors o her han sub ypes of MCV DNA par icipa e in he divergence of he wo an igenic polypep ides.

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Does the Capsule Component of the *Crypt c ccus ne f rmans* Glucuronoxylomannan Impair Transendothelial igration of Leukocytes in Patients with Cryptococcal eningitis?

To the Editor—The encapsula ed yeas -like fungus *Cryptococcus neoformans* is he leading cause of mycological infec ion of he cen ral nervous sys em in pa ien s wi h compromised cell-media ed immuni y [1]. Recen ly, we demons ra ed ha he cerebrospinal fluid (CSF) of pa ien s wi h cryp ococcal meningi is con ains high levels of he neu rophil chemoa rac an in erleukin (IL)-8, despi e he fac ha he CSF con ains few neu rophils [2].

The cryp ococcal capsular polysaccharide glucuronoxylomannan (GXM) is presen in serum and CSF of pa ien s wi h cryp ococcal meningi is, and GXM is known o in erfere wi h neu rophil migra ion [3]. We demons ra ed in vi ro ha GXM is capable of inducing he produc ion of IL-8 by brain cells, and i also preven s neu rophils from migra ing oward IL-8 [4]. Consequen ly, a high ra io of GXM in serum and CSF should correla e wi h a low CSF leukocy e cell coun in pa ien s wi h cryp ococcal meningi is. Therefore, we compared re rospec ively he GXM i ers in serum and CSF wi h he CSF leukocy e cell coun s of 35 Du ch human immunodeficiency virus–infec ed pa ien s wi h a cul ure-proven diagnosis of cryp ococcal meningi is be ween 1986 and 1996.

An igen i ers for he pa ien s were measured wi h commercial ki s rou inely used for diagnos ic de ec ion of cryp ococcal an igen

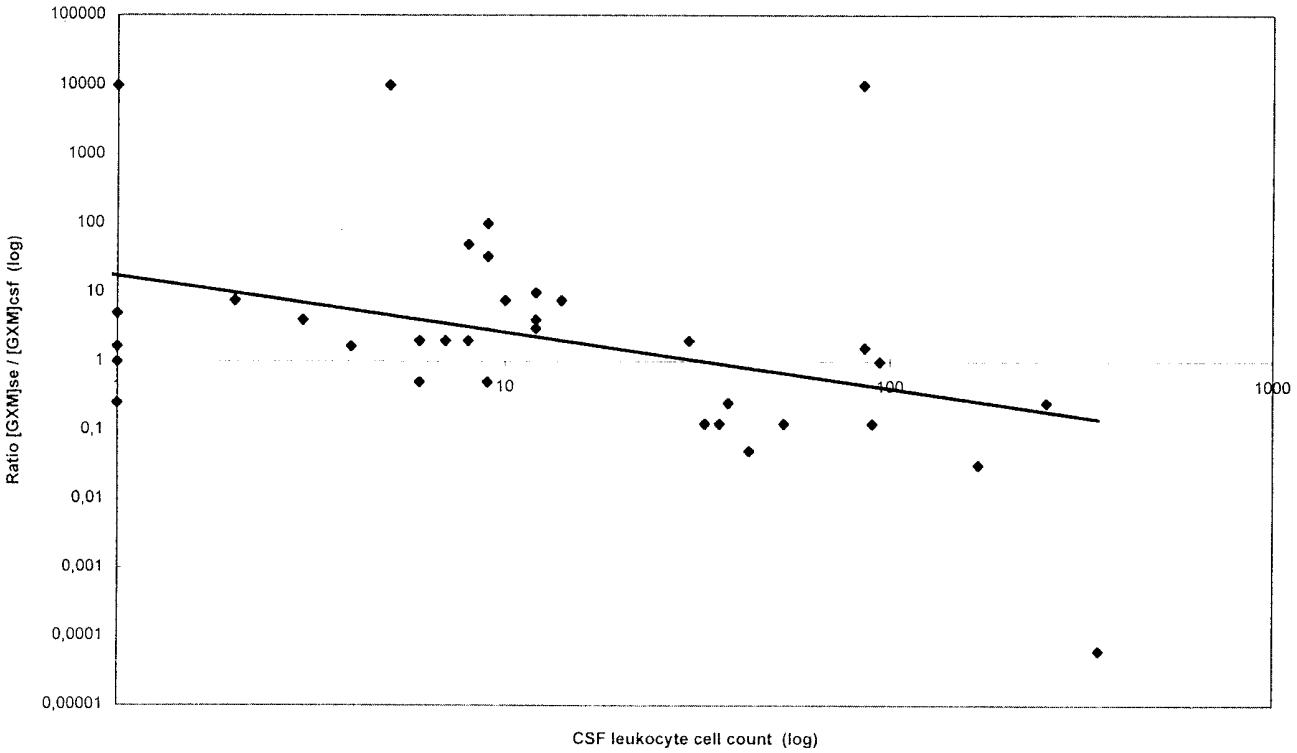

Figure 1. Inverse correla ion be ween ra io of leukocy e coun in cerebrospinal fluid (CSF) and cryp ococcal glucuronoxylomannan i ers in serum ([GXM]se) over hose in CSF ([GXM]csf) in 35 pa ien s wi h cryp ococcal meningi is.

(mainly Murex Cryp ococcus Tes ; Murex, Ken , UK) and were ob ained wi hin 5 days of he CSF leukocy e cell coun s. Since GXM can a rac neu rophils [4], he GXM concen ra ion gradien over he blood brain barrier (expressed as he ra io of i ers in serum vs. CSF) is expec ed o be more cri ical o he CSF leukocy e cell coun han are absolu e GXM concen ra ions. Figure 1 demons ra es a significan inverse correla ion be ween he (log) GXM ra io and he (log) CSF leukocy e cell coun in pa ien s wi h cryp ococcosis. (Correla ion coefficien of log values: -0.54, $n = 35$; wo-sided $P < .001$). These da a sugges ha he in vi ro finding of in erference of GXM wi h neu rophil migra ion may indeed represen a pa hogene ic mechanism in cryp ococcal meningi is.

yriam . Lipovsky, Leontine J. R. van Elden, Annemiek . E. Walenkamp, Jacob Dankert, and Andy I. . Hoepelman

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