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Is procalcitonin increased in cases of invasive amoebiasis? A retrospective, observational study

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ABSTRACT

Procalcitonin (PCT) levels are commonly used for diagnostic guidance in routine bacterial infections. By contrast, little data are currently available regarding PCT in parasitic diseases, and its role in cases of invasive amoebiasis has not yet been described. For this purpose, 35 adult patients with a proven diagnosis of invasive or digestive amoebiasis were included in a 4-year study period. Serum PCT was retrospectively assessed. Results were analysed with regard to the usual inflammatory biomarkers, like C-reactive protein (CRP). PCT was significantly higher in patients with proven invasive amoebiasis than in digestive amoebiasis (mean value: 4.03 μg/L versus 0.07 μg/L, respectively; $P < 0.001$), but the SD was greater than with CRP, and the effect was less than that demonstrated in bacterial infections. By contrast, PCT was not shown to be elevated during digestive amoebiasis.

1. Introduction

Procalcitonin (PCT) is the precursor peptide of calcitonin, a hormone involved in calcium homeostasis. Several cell types can produce PCT in response to proinflammatory stimuli. A high PCT level is usually compatible with serious bacterial infections and sepsis (Van den Bruel et al., 2011; de Azevedo et al., 2012; Domínguez-Comesaña and Ballinas-Miranda, 2014) and plays a prognostic role in evaluating their clinical outcome (Van den Bruel et al., 2011; de Azevedo et al., 2012; Ugajin et al., 2014; de Azevedo et al., 2015). Thus, PCT measurement has been implemented into routine clinical practice for diagnostic guidance in bacterial infections (Long et al., 2011; Prkno et al., 2013; Wacker et al., 2013). In addition, substantial elevations in PCT levels have been reported as being correlated with high levels of parasitaemia during malaria attacks (Chiwakata et al., 2001; Diez-Padrisa et al., 2011). The role of PCT has also been widely discussed in invasive fungal infections (Dou et al., 2013; Marková et al., 2013; Cortegiani et al., 2014). Overall, it is considered that low levels (<0.50 μg/L) (Al-Dorzi et al., 2014) usually rule out all of the above-mentioned infections and point towards virus (Piacentini et al., 2011) or nonspecific inflammatory diseases (Tsalik et al., 2012; Anand et al., 2015).

Amoebiasis is a parasitic infection caused by the digestive protozoan *Entamoeba histolytica*, which has recently been differentiated from its morphologically similar species *Entamoeba dispar* (Stanley, 2003). The intestinal clinical forms range from asymptomatic colonisation to amoebic dysentery. *E. histolytica* can, however, disseminate from gut mucosae to other organs such as the liver. Here it generates abscesses (Stanley, 2003; Oku et al., 2012; Petri and Haque, 2013), which define invasive amoebiasis. This condition is a medical emergency and may lead to death (up to 70,000 deaths per year worldwide (Stanley, 2003)), in the absence of a rapid and reliable diagnosis. Nowadays, amoebic serology represents the gold standard for this purpose, but this requires time and a seasoned laboratory. Very few alternative biomarkers are currently available for predicting the invasiveness of amoebiasis, and those that are in use are not specific. For instance, hyperneutrophilia is inconsistent; there is no hypereosinophilia in invasive amoebiasis (Stanley, 2003; Wuerz et al., 2012); and liver enzymes show variable blood levels, with no major increase (Wuerz et al., 2012). These limitations may delay the initiation of effective treatment; hence, additional biomarkers that indicate invasive amoebiasis are needed.

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Since no study concerning the association of PCT with *E. histolytica* infection has been reported thus far, the main purpose of this retrospective, observational study was to investigate whether there is an increase in PCT in cases of invasive amoebiasis.

2. Materials and methods

2.1. Inclusion criteria

The study was carried out retrospectively using automated, computerised extraction of clinical data from our laboratory software. The search engine was programmed to find all the recorded cases of invasive amoebiasis (January 2010–September 2014), which had been confirmed by at least 1 positive specific anti–*E. histolytica* serological test, either indirect immunofluorescence assay (IFA by Amoeba Spot-IF®; BioMérieux, Marcy-L'Etoile, France) or indirect haemagglutination (IHA by Amibiase HAI FUMOUZE®; Fumouze Diagnostics, Levallois-Perret, France) in 1 of the 3 teaching hospitals involved in the study (Tours, Nantes, and Angers, France). Titres above 1:100 for IFA and/or above 1:160 for IHA were defined as positive (Hartmann et al., 1980).

A second automated search was carried out to extract all the patients who had been detected with *Entamoeba* spp. in stool samples. Detection methods followed standard practice in the microbiological labs: direct examination of freshly emitted faeces, followed by Bailenger's technique of concentration and merthiolate–iodine–formaldehyde concentration (Lawson et al., 2004). Microscopic identification of *E. histolytica* was achieved by skilled microbiologist and/or by specific amplification of the 16S-like SSU rDNA by PCR. Briefly, the DNA was extracted using QIAmp DNA mini kit® spin columns (Qiagen SA, Courtaboeuf, France). The amplification reactions were performed using 5 μL of a DNA sample in a volume of 20 μL of a mixture that contained a TaqMan Fast Universal PCR Master Mix 2x® (Applied Biosystems™, Saint Aubin, France), internal positive control (Applied Biosystems™), and the oligonucleotide primers for *E. histolytica*: Eh-196F (5′-AAA TGG CCA ATT CAT TCA ATG A-3′) and Eh-294R (5′-CAT TGG TTA CTT GTT AAA CAC TGT GTG-3′) and the probe Eh-245 (6FAM)-AGG ATG CCA CGA CAA-(NFQ). The thermal cycling conditions consisted of 20 seconds at 95 °C, followed by 50 cycles of 3 seconds at 95 °C, and 30 seconds at 60 °C, using a TaqMan 7500® Fast Real-Time PCR System (Applied Biosystems™). The detection and the data analysis were performed with TaqMan Fast 7500® software version 1.4.0 (Applied Biosystems™) (Ben Ayed et al., 2008). If not done previously, an anti–*E. histolytica* serological test was performed retrospectively on these patients, according to the above-mentioned references (IFA and IHA tests), in order to rule out any subclinical invasive infection.

For both of these automated searches, the noninclusion criteria were age <18 years old, to avoid the expected physiological variations in biomarker levels during childhood, and lack of biological specimens in the serum collection (frozen at −80 °C). For each selected patient, demographic, biological, clinical, and radiological data were collected on the basis of a standardised survey. Evidence of one or more liver abscess(es), detected by abdominal ultrasound and/or computed tomodensitometry scan, was recorded. Potential undercurrent bacterial infections, malaria, and chronic or acute viral/nonviral hepatic diseases were also noted.

2.2. Biological assay

Serum PCT was measured by immunoassay using the B·R·A·H·M·S Kryptor compact® (Thermo Fisher Scientific, Waltham, MA, USA), according to the manufacturer's instructions. The assay was retrospective and monocentric and was performed once. A normal PCT value was expected to be below 0.06 μg/L (Syvanen et al., 2014), whilst the cutoff for sepsis was established at 0.50 μg/mL (Al-Dorzi et al., 2014), according to the manufacturer's recommendations (http://www.procalcitonin.com/).

C-reactive protein (CRP) was measured using rabbit anti-CRP antibodies coated on latex particles (CRP Latex reagent® on the AU2700®; Beckman Coulter, Pasadena, CA, USA). Normal CRP values were taken to be those under 6 mg/L. Aspartate aminotransferase (AST), alanine transaminase (ALT), γ-glutamyltransferase (GGT), and alkaline phosphatase (ALP) were assessed using the AU2700® (Beckman Coulter), according to the methodology recommended by the International Federation of Clinical Chemistry and Laboratory Medicine (Schumann et al., 2002). Normal values of AST, ALT, and ALP were considered to be 0–40 U/L, 0–30 U/L, and 50–160 U/L, respectively (Siest et al., 2013). Normal values for GGT ranged from 8 to 61 U/L for males and from 5 to 36 U/L for females. α-2-macroglobulin was measured by immunonephelemetric methods using a BN ProSpec Analyser® (Siemens Diagnostics, Saint-Denis, France). Normal α-2-macroglobulin values were taken to be 1.50–3.50 g/L for males and 1.75–4.20 g/L for females (Siest et al., 2013).

2.3. Statistical analysis

Statistical analysis was performed using "The R Project for Statistical Computing version 3.1.2." software (http://www.r-project.org/). The Fisher test was used for the comparison of qualitative variables; and the Mann–Whitney test, for quantitative variables. The Student *t* test was used for comparison with theoretical values. The Spearman's rank correlation coefficient was used to assess the correlation of biomarkers. The alpha-risk was adjusted to 0.05.

2.4. Ethics

All personal data were anonymous. Approval was given by the ethics committee at our teaching hospital (Espace de Réflexion Ethique, Région Centre, France). The study registration number 2015_003 was issued by the Technology and Freedom Committee (Commission de l'Informatique et des Libertés) on January 10, 2015.

3. Results

3.1. Inclusion

Overall, 18 patients were identified as invasive amoebiasis cases. Two individuals had previously been excluded, the first because he was under 18 years old at the time of diagnosis and a second individual due to an unclear diagnosis. The latter patient had neither a history of foreign travel nor typical symptoms and showed discordant serology (IFA = 1:400; IHA = 0).

By means of the second automated extraction, 17 patients were included in the digestive amoebiasis group on the basis of at least 1 positive stool examination. Seven patients had previously been excluded because their respective ages were below 18 years old. None of the selected individuals had a positive anti–*E. histolytica* serological test, which ruled out any possibility of invasive amoebiasis (Fig. 1).

3.2. Demographics of the 2 populations

Mean age was 47.00 for the patients included in the invasive amoebiasis group and 48.29 for those in the digestive amoebiasis group ($P = 0.88$) (Table 1). The sex ratio displayed a majority of male subjects, 72.23% for the invasive amoebiasis group and 70.59% for the digestive amoebiasis group; however, there was no significant difference between these 2 groups ($P = 0.93$) (Table 1). In the former group, abscesses were mostly located in the liver (94.44%). African ethnics were significantly more prevalent in the digestive amoebiasis group than in the invasive group (41.18% versus 11.12%; $P = 0.03$). By contrast, Caucasian patients were more highly represented in the latter group (52.94% versus 88.88%; $P = 0.03$) (Table 1).

None of the included patients were reported to have acute malaria, and no individual experienced invasive bacterial infection at the time of the study. One patient in the invasive amoebiasis group had an uncomplicated lower urinary tract infection due to *Escherichia coli*,

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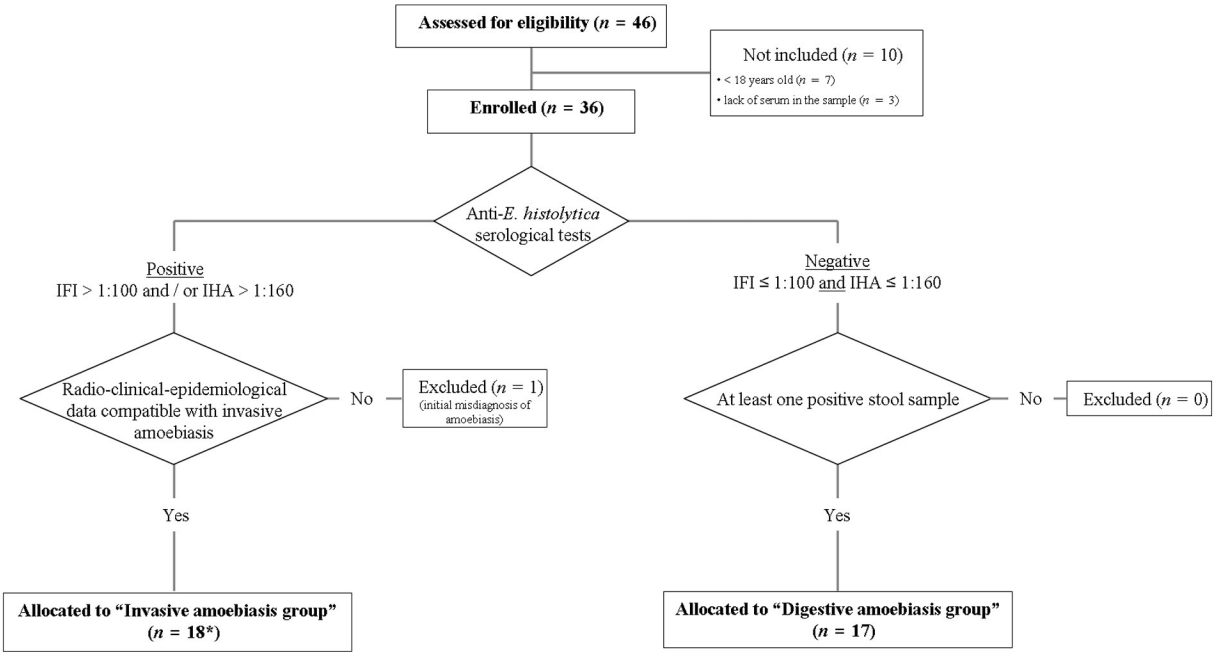

Fig. 1. Study flowchart. Abbreviations: IFI = indirect immunofluorescence; IHA = indirect haemagglutination; * including 17 with liver abscess(es) and 1 with severe colitis.

whereas another individual in the digestive amoebiasis group had an ear infection caused by *Serratia marcescens*. Liver diseases, including viral hepatitis, were insignificantly more frequent in the digestive amoebiasis group (29.41% versus 5.55%, respectively; $P = 0.09$) (Table 1).

3.3. Assay results

PCT values ranged from 0.02 μg/L to 45.66 μg/L in the sera of patients with proven invasive amoebiasis (Fig. 2A). PCT mean levels were significantly higher in this group than in the group with digestive amoebiasis: 4.03 μg/L versus 0.07 μg/L, respectively; $P = 3.32 \times 10^{-5}$ (Fig. 2B). In the latter group, the PCT mean value did not differ from the theoretical physiological value ($t = 0.27$). CRP was significantly higher in the invasive amoebiasis group (209.79 mg/L versus 9.56 mg/L; $P = 8.14 \times 10^{-6}$). The coefficient of variation for CRP (SD = 97.92 mg/L) was much lower than for PCT (SD = 10.60 μg/L): 46.68% versus 263.28%, respectively. In invasive amoebiasis, PCT and CRP values did not appear to be correlated, according to Spearman's rank correlation coefficient (0.44; $P = 0.08$). Noteworthy in 1 patient, PCT levels have been sequentially assessed over a 6-month period: they showed a rapid decrease right from the initiation of the antiamoebic therapy (Table 2).

There was no significant difference in mean AST and ALT levels between the 2 groups (25.06 UI/L versus 19.71 UI/L, $P = 0.20$, and 21.88 UI/L versus 14.24 UI/L; $P = 0.14$). By contrast, GGT and ALP appeared significantly

Table 1
Epidemiological characteristics and biological results of the enrolled patients.

Variable (units)	Invasive amoebiasis group[a] (n = 18) (quantitative values: mean (SD); qualitative value: %)	Digestive amoebiasis group[b] (n = 17) (quantitative values: mean (SD); qualitative value: %)	*P* (significant when <0.05)
Age (y)	47.00 (7.35)	48.29 (7.92)	0.88[c]
Female/male (%)	27.77/72.23	29.41/70.59	0.93[d]
Ethnic group: African/Caucasian/Asian (%)	11.12/88.88/0	41.18/52.94/5.88	0.03[d]
Amoebic liver abscess (%)	94.44	0	NC
Amoebic severe colitis (%)	5.56	0	NC
Acute malaria (%)	0	0	NC
Bacterial infection (%)	5.55[e]	5.88[e]	0.94[d]
All liver diseases[f] (%)	5.55	29.41	0.09[d]
Including viral hepatitis (%)	0	17.64	0.10[d]
Foreign travel to: Europe/Africa/Asia/America (%)	0/72.22/44.44/27.78	5.88/41.18/5.88/0	0.10[d]
PCT (μg/L)	4.03 (10.6)	0.07 (0.15)	3.32×10^{-5}[c]
CRP (mg/L)	209.79 (97.9)	9.56 (13.9)	8.14×10^{-6}[c]
AST (UI/L)	25.06 (12.9)	19.71 (11.5)	0.20[c]
ALT (UI/L)	21.88 (18.6)	14.24 (10.3)	0.14[c]
GGT (UI/L)	146.47 (84.0)	47.24 (55.1)	1.41×10^{-4}[c]
ALP (UI/L)	139.35 (58.0)	71.94 (31.6)	5.36×10^{-4}[c]
α-2-macroglobulin (g/L)	1.78 (0.49)	2.48 (1.04)	0.03[c]

Abbreviations: ALP = alkaline phosphatase; AST = aspartate aminotransferase; ALT = alanine transaminase; CRP = C-reactive protein; GGT = γ-glutamyl transferase; NC = not calculable; PCT = procalcitonin.

[a] Proven by anti–*E. histolytica* serological tests.
[b] Proven by at least 1 positive stool examination.
[c] Mann–Whitney test.
[d] Fisher exact test.
[e] Only superficial infections (e.g., low urinary tract infection or ear infection).
[f] For example, viral hepatitis, autoimmune hepatitis, alcoholic hepatitis, cirrhosis, hepatitis due to therapeutic side effects.

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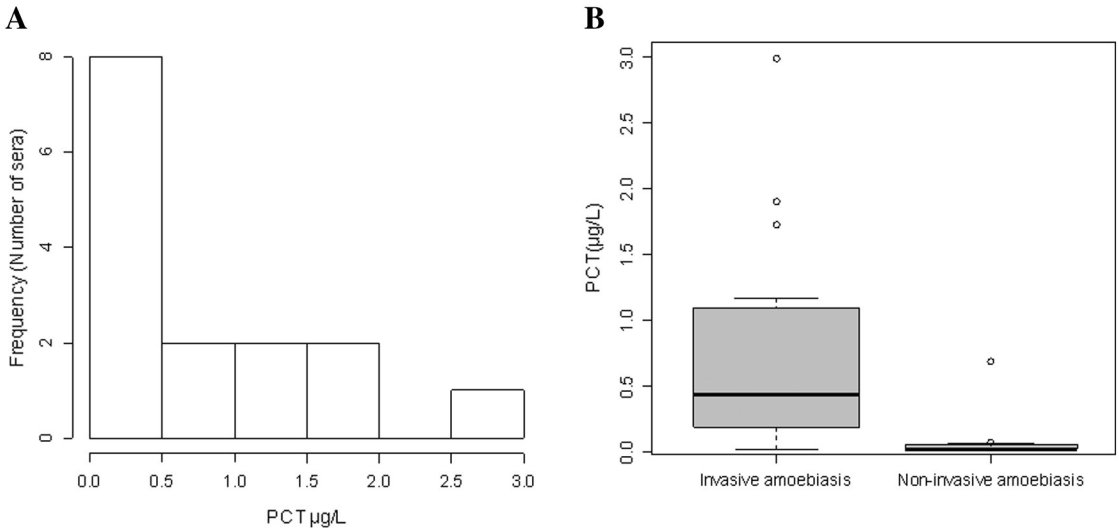

Fig. 2. Results of PCT measurements. A. Histogram showing the distribution of the serum PCT values in patients with proven invasive amoebiasis (for improved readability, the 2 highest values, 45.6 µg/L and 14.65 µg/L, were excluded from the histogram). B. Boxplot of PCT values in the invasive amoebiasis group and the digestive amoebiasis group (the 2 highest values of PCT in the invasive amoebiasis group were outside the upper limit of the graphic: 45.6 µg/L and 14.65 µg/L). Abbreviations: PCT = procalcitonin.

higher during invasive amoebiasis (146.47 UI/L versus 47.24 UI/L, $P = 1.41 \times 10^{-4}$, and 139.35 UI/L versus 71.94 UI/L, $P = 5.36 \times 10^{-4}$). The α-2-macroglobulin blood concentration was lower in cases of invasive amoebic infection (1.78 g/L versus 2.48 g/L; $P = 0.03$).

4. Discussion

Invasive amoebiasis is a parasitic disease of low incidence in Western countries but with potentially severe consequences. Significant immigration flows and frequent foreign travel mean that the biological diagnosis of this condition has become an important concern in healthcare centres. Biochemical and cytological biomarkers have been uninformative thus far (Stanley, 2003; Wuerz et al., 2012), and serological tests are not compatible with an emergency context. Practitioners need tests that are quick and easy to perform, in order to guide the aetiological diagnosis in cases of strong presumption. PCT may be theoretically helpful in such a context. In this study, we attempted to establish its role during amoebiasis, by recruiting patients with a well-documented diagnosis. The number of proven cases was limited because of its low incidence, but their demographics were comparable with the epidemiological data previously reported (Acuna-Soto et al., 2000; Cordel et al., 2013). For example, invasive amoebiasis is known to be observed most commonly in men over 50 years (Acuna-Soto et al., 2000), which was consistent with our population. Additionally, our control group of patients with digestive amoebiasis was shown to be very relevant, since the overall demographic characteristics were very similar to those of the invasive amoebiasis group.

Overall, PCT was significantly higher in patients with proven invasive amoebiasis. To our knowledge, our study is the first to display this finding in such a context. Only 1 case of PCT elevation has previously been reported, in a Japanese patient (Oku et al., 2012). However, it was not easy to distinguish the role of this patient's amoebic liver abscess from his underlying disease. As it has been reported in cases of bacterial sepsis (de Azevedo et al., 2012; Prkno et al., 2013; Wacker et al., 2013), the mean PCT level in our study (4.03 µg/L) was well above the threshold of 0.50 µg/L that is sometimes used in practice (Al-Dorzi HM et al., 2014; Syvanen J et al., 2014) for distinguishing between bacterial infection and viral disease (Piacentini et al., 2011) or other causes of unspecific inflammation (Anand et al., 2015; Tsalik et al., 2012). However, it is worth noting that individual values appeared heterogeneous and were globally lower than the rates observed during bacterial sepsis (de Azevedo et al., 2012; Prkno et al., 2013; Wacker et al., 2013). This finding is not likely to be related to degradation during frozen storage previous the assay, since PCT is known to be a stable protein (almost 100% conservation when kept below −20 °C). Degradation has previously been reported to reach only 2% after 3 cycles of cooling-heating (Meisner et al., 1997); therefore, it should be noted that we only took the serum samples out of storage on a single occasion. To investigate further the large distribution of PCT values, we looked at the potential prognostic value of PCT in relation to the clinical presentation. Analysis of the personal data of a patient with a particularly high PCT level (45.66 µg/L) showed that he had a very rare and severe radiological presentation, with 19 large liver abscesses (Desoubeaux et al., 2014). Noteworthy, PCT level rapidly decreased for him after initiation of antiamoebic therapy. Likewise, another patient with a low initial PCT level (0.02 µg/mL) was actually already under therapy at the time of dosage. These findings lead us to speculate that the PCT level could also be related to parasite burden.

The liver is the most commonly involved organ in invasive amoebiasis. It was therefore surprising to note that liver enzyme assays did not show any major variation in the study group and were globally in accordance with a cholestasis syndrome. These markers have scarcely been reported in previous amoebic disease studies (Wuerz et al., 2012). The results concerning α-2-macroglobulin were more questionable, since this biomarker is usually implicated in the regulation of liver fibrosis mechanisms. The study control group, consisting of digestive amoebiasis cases, was shown to include more patients with chronic liver disease and viral hepatitis. According to our results, PCT testing appeared to be less accurate than CRP measurement in determining cases of invasive amoebiasis. In addition to greater latitude in the results, this analysis is also more expensive than CRP measurement. The mean cost of the 2 tests is estimated at 29.70€ versus 6.75€, respectively, in our laboratory.

Table 2
Example of evolution of PCT levels in 1 patient under antiamoebic therapy.

Date[a]	PCT (µg/L)
d0	45.66
d + 4	4.85
d + 20	0.15
d + 67	0.07
d + 168	0.04

[a] d0 being the date of diagnosis and the initiation date of the antiamoebic therapy for a 2 weeks duration.

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5. Conclusions

PCT measurement seemed less efficient than CRP for predicting the invasiveness of amoebiasis. Besides, it was not elevated in cases of digestive forms. Nonetheless, PCT may be a useful aid for distinguishing between invasive amoebiasis and bacterial infections, since the observed values were globally much lower in the former. These preliminary results need to be confirmed by further studies.

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