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Animal Models of Inflammatory Bowel Disease—An Overview

WARREN STROBER, MD

Many diseases, including those characterized by inflammation of the gastrointestinal tract, are due to an array of factors which act independently or in concert to produce pathologic change. This has led investigators to center their efforts on studies of isolated tissues and cells wherein the various causative elements can be independently controlled. A complementary approach involves the establishment of animal models of disease. The latter allow studies of intact organisms under conditions in which environmental and/or genetic factors are more or less completely defined; in addition, they provide a source of tissue at disease stages and from anatomic sites that are not obtainable from humans with disease.

In this conference we will consider what is known about a promising animal model of inflammatory bowel disease (as well as intestinal carcinoma), the ulcerative colitis-like illness occurring spontaneously in the cotton-top tamarin. Before we do this, however, it is well to review some of the characteristics of animal models of inflammatory bowel disease developed previously, to discover what we have learned about IBD from such models and where research into the disease in tamarins should tend.

IDEAL ANIMAL MODEL OF INFLAMMATORY BOWEL DISEASE

At the outset of our discussion it is well to confront the question of what constitutes an ideal animal model of inflammatory bowel disease (IBD). The answer that presents itself most immediately and that seems incontrovertible is that the ideal model consists of a disease in an animal that is identical in every respect to human IBD. By identical we mean that the animal disease is induced by the same primary factors (has the same cause) and is maintained by the same secondary factors (has the same pathophysiology) as human IBD. With this sort of identity one could be sure that the animal disease has an equivalent spectrum of clinical and pathological manifestations and a similar response to possible therapeutic agents. Table 1 contains a list of characteristics associated with an ideal animal model of IBD. In addition to the point already made about the necessity for identity, the table indicates that the ideal model must also be a practical tool of study in that the animals involved must be accessible, must lend themselves to experimental manipulation, must be hardy enough to allow easy maintenance and rapid expansion and, finally, must be treatable with therapeutic agents which can ultimately be tested in humans.

The rather uncompromising definition of an ideal animal model of IBD outlined above exposes an important theoretical problem with the models so far devised or even those proposed for future study. The fact is that there are huge gaps in our knowledge of IBD, both from the point of view of the exogenous and endogenous etiologic factors involved and of the nature of the disease mechanisms present. In addition, IBD has not yet been associated with a finding that can be considered a sure marker of the disease such as the presence of a characteristic autoantibody or an elevated level of an unique isoenzyme. The problem is, therefore, that one cannot define a model of an entity that is itself poorly defined. In all, these considerations lead one to the view that the animal disease states so far observed are most properly called models of gastrointestinal inflammation generally, rather than

Address for correspondence and reprint requests: Dr. Warren Strober, Mucosal Immunity Section, Laboratory of Clinical Investigation, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland 20205.

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TABLE 1. IDEAL ANIMAL MODEL OF IBD

A. A disease in an animal identical to human IBD having the:
   1. Same causal factors
   2. Same pathology and pathophysiology
   3. Same clinical spectrum
B. A disease occurring in an animal that:
   1. Is accessible and reasonable inexpensive
   2. Has a defined genetic background
   3. Has a similar immune system to that in humans
   4. Can be manipulated as to its:
      a) Dietary intake
      b) Immunologic status
      c) Exposure to infectious agents
C. A disease occurring in an animal that is susceptible to various forms of treatment

models of IBD specifically. This does not mean that the study of such animal disease states should be abandoned; on the contrary, knowledge of gastrointestinal inflammations occurring in animals under various conditions can help resolve many questions about the human disease (see Table 2) and, as we shall see, can even lead to hypotheses concerning IBD pathogenesis.

CATEGORIES OF ANIMAL MODELS OF GASTROINTESTINAL INFLAMMATION

There are two broad categories of animal models of gastrointestinal inflammation, one in which the disease arises naturally, ie, without the introduction of exogenous factors, and one in which the disease is induced experimentally, either by exposure to a disease-producing agent or by manipulation of otherwise normal physiologic processes (Table 3). In the former category are diseases in which the animal is naturally exposed to an organism which causes the disease or diseases in which the animal is genetically programed to manifest disease, possibly in response to materials (causative agents) that are commonly found in the normal environment. In the latter category are diseases due to exposure to nonliving materials such as dietary substances or pharmacologic agents or to exposure to living materials such as organisms derived from human tissues or to newly discovered organisms isolated from extraneous sources. Finally, this category includes diseases induced by manipulation of the animal's immune system, either by immunization with living or dead antigenic materials or by deliberate exposure of the animal to living agents that affect immune function.

TABLE 2. POTENTIAL QUESTIONS ANSWERABLE BY STUDY OF ANIMAL MODELS OF GASTROINTESTINAL INFLAMMATION

A. Is a given factor capable of causing an IBD-like gastrointestinal inflammation?
B. What genetic factors are necessary for disease expression?
C. How do various factors interact to cause disease?
D. Is a given disease characteristic a primary or secondary phenomenon?
E. Does a given therapeutic agent have value in treating an IBD-like illness?

TABLE 3. CATEGORIES OF ANIMAL MODELS

A. Naturally occurring gastrointestinal inflammation
   1. Due to an exposure to infectious agent
   2. Due to a genetic defect
B. Experimentally-induced gastrointestinal inflammation
   1. Due to exposure to toxic dietary substances, pharmacologic agents, or other environmental materials
   2. Due to exposure to materials derived from patients
   3. Due to manipulation of the animal's immune system

NATURALLY OCCURRING ANIMAL MODELS OF GASTROINTESTINAL INFLAMMATION

Turning first to naturally occurring models of gastrointestinal inflammation, there is given in Table 4 a list of gastrointestinal infections that have been observed in animals and that are in some fashion suggestive of human IBD. [This table is abstracted from a more complete listing appearing in a review by Mayberry et al (1)]. The kind of pathology noted in these naturally occurring gastrointestinal inflammations was similar to that seen in ulcerative colitis or to that occurring in Crohn's disease; in some cases, however, epithelial hyperplasia was also observed. These diseases cannot be called animal models of IBD because in most (if not all) cases, an organism (usually an intracellular

TABLE 4. NATURALLY OCCURRING GASTROINTESTINAL INFLAMMATIONS IN ANIMALS

Animal	*Agent*	*Feature(s)*
Hamster	"Rod-shaped bacteria"	Hyperplasia, microabscesses, necrosis
Mouse	*Bacillus pyliformis*	Hyperplasia, ulceration, crypt abscesses
Rat	Unknown	Ulcerative cecitis
Dog	?*Chlamydia*-type organism *Trichuris*	Colitis, enteritis
Horse	Unknown	Granulomatous enterocolitis
Cattle	*Chlamydia* Cw 613	Terminal ileal disease
Pig	*Camplyobactor sputorum*	Adenomatous proliferation, ulceration
Sheep	Unknown	Mucosal hypertrophy, ulceration

organism) was found, whereas in IBD a causative organism has not been identified. They nevertheless add to our knowledge of IBD because they establish that identifiable infectious agents, especially when they cause chronic inflammation, can give rise to a pathologic picture that is similar to that seen in either ulcerative colitis or Crohn's disease. Stated differently, the pathologic picture in IBD so far described does not seem to be a unique aspect of the disease, but rather an inflammatory response of the intestine that can also be induced by a variety of infectious agents. One further point concerns the fact that the existence of a variety of IBD-like gastrointestinal inflammations in animals, each caused by an identifiable organism, gives rise to the expectation that if IBD were caused by an infectious agent, that agent would be more or less apparent using current technology. The fact that this is not so suggests that either IBD is caused by an unusual organism or is not caused by an organism at all.

Among the best known naturally occurring models of gastrointestinal inflammation is one occurring in dogs. In one variant of such canine gastrointestinal inflammation, that observed in boxer dogs, a granulomatous colitis is observed which appears to be caused by an intracellular organism that may be related to the *Chlamydia* organism (2). The pathologic picture in this case is dominated by macrophage infiltration so that the disease seems to be more akin to Whipple's disease than to IBD. In other variants of canine gastrointestinal inflammation, in this case noted in a wide variety of dog breeds, an ileitis or colitis that was pathologically and clinically similar to human IBD has been noted (3). This form of canine inflammatory disease of the bowel appears to be unassociated with an identifiable organism, although this has hardly been given careful study. There is no evidence that any particular form of canine IBD is characteristic of a particular breed, but this interesting possibility merits further study.

IBD-like illness in subhuman primates has been reported in a few gibbons, orangutans, and other primates prior to the report of IBD in the cotton-top tamarin (4–6). In the best-studied instances, a pathologic picture identical to that seen in ulcerative colitis was observed, except that the illness was very severe and led to death within days. The disease observed in primates was not likely to be due to a bacterial organism since stool cultures were pathogen-negative in some of the cases, and there was no evidence that the animal disease was part of an epidemic of gastrointestinal illness in any of the cases. Interestingly, in some instances, gastrointestinal inflammation in primates had its onset during periods of psychological stress, suggesting that neuroendocrine factors are involved in the gastrointestinal inflammation of subhuman primates as it appears to be in that of humans. Because of their close relationship to humans, subhuman primates are inherently more suitable than other animals as a host species for models of gastrointestinal inflammation. This advantage, however, is mitigated by the fact that subhuman primates are expensive, difficult to obtain and maintain, and in some cases, are among the endangered species.

EXPERIMENTALLY INDUCED GASTROINTESTINAL INFLAMMATION

Gastrointestinal Inflammation Produced by Immune System Manipulation

Turning now to experimentally induced colitis in animals, we come upon a number of situations in which gastrointestinal inflammation was induced as a result of immunologic manipulation. These models include, first of all, "B-cell models" in which antibodies were the main disease-producing factors. The major studies relevant here were those conducted by Kirsner and his colleagues in the 50s and 60s (7). In their initial work, these investigators induced intestinal inflammation by the local induction of the Arthus reaction and Schwartzman reactions (7). In the former instance, animals were first sensitized to an antigen by systemic antigen administration; later, an intestinal inflammation was invoked by direct injection of the antigen into intestinal tissue. In the latter case, the animals were administered bacterial lysates, again in a sequential systemic and local fashion. In general, these procedures led to hemorrhagic lesions originating in perivascular areas which later progressed to ulcerations. Lesions caused in this way resolved quickly but did leave a residue of granulomata and areas of atrophy/fibrosis.

A more interesting kind of B-cell model devised by Kirsner and his associates involved the production of colonic inflammation via the "Auer procedure" (8). In this case, animals (rabbits) were initially immunized with an antigen (such as egg albumin), then subjected to colonic irritation with formalin, and then finally given systemic or local injection of the original antigen. The underlying

strategy here was to create a site of altered vascular permeability in the intestine which then becomes subject to increased entry of circulating antibody that can react with locally applied antigen to form intraintestinal immune complexes. It was found that this procedure causes a colonic inflammation not unlike that seen in ulcerative colitis. In particular, the lesion produced was marked by a cellular infiltration with granulocytes and lymphocytes (especially plasma cells) which was associated with a disappearance of intestinal glandular cells and, ultimately, the occurrence of intestinal ulceration. Repeated induction of the Auer lesion in the same animal led to more profound inflammation characterized by hemorrhage, cystic dilatation of the crypts, and ulceration. In all, this model of gastrointestinal inflammation indicates that immune complex deposition in the bowel wall initiates an inflammatory cascade that ultimately produces an ulcerative colitis-like lesion; on this basis, one of the possible mechanisms contributing to the production of IBD (at least in its early stages) is local immune complex deposition.

A key difference between the gastrointestinal inflammation induced by the Auer procedure and the inflammation characterizing IBD is that the former is not self-sustaining and tends to resolve fairly rapidly if local irritant and antigen are not constantly reapplied. This difference was apparently erased by Mee and his coworkers, who once again induced colitis by a modification of the Auer procedure, except that they first immunized the animals with an *E. coli* antigen (9). In this case, an ongoing colitis, not dependent on reexposure to formalin and antigen, was obtained. These interesting results require confirmation; if true, they indicate that a gastrointestinal inflammation can move to chronicity if the animal has a predetermined capacity to react to one or more normal constituents of the gastrointestinal flora.

This last point finds resonance in earlier work (now more or less forgotten) by Halpern and his coworkers, who induced chronic ulcerative colitis-like lesions in rats by injection of the latter with live or dead *E. coli* incorporated into Freund's adjuvant (10). In these studies, the capacity to induce gastrointestinal inflammation was not seen with all *E. coli* strains, implying that specific antigens present only in certain *E. coli* strains were necessary for disease production. Furthermore, induction of gastrointestinal inflammation could be prevented by feeding animals the *E. coli* used in the immunization schedule, suggesting that the colitis-producing effect was due to elimination of certain *E. coli* from the normal flora. These findings, as in the case of the results obtained by Mee and coworkers mentioned above, seem to indicate that experimental production of colitis (at least those forms of colitis that are chronic) is more related to the response of the mucosal immune system to bacterial elements present in the gastrointestinal environment than to a primary reaction against the animal's own cells.

A second approach to the production of experimental gastrointestinal inflammation by manipulation of the immune system involves stimulation of T cells. This has been accomplished by the administration of the contactant, dinitrochlorobenzene (DNCB), a substance that has long been known to stimulate T-cell-mediated reactions (11, 12). In the relevant studies, animals are first sensitized with DNCB at a cutaneous site and then reexposed to DNCB at an intestinal site (11). It is observed that an ulcerative colitis-like gastrointestinal inflammation develops at the intestinal site, but as in the case of the Auer procedure, the inflammation is not sustained. This model of gastrointestinal inflammation indicates that T-cell-mediated immunologic events, no less than B-cell-mediated events, can lead to an ulcerative colitis-like inflammation. The fact that the inflammation obtained in both instances is similar suggests that the inflammatory response in the gastrointestinal tract (as detected by conventional morphologic study) is a rather stereotyped process that does not reveal much about initiating immunologic events. Alternatively, one must consider the possibility that the original immunologic manipulation does not determine the nature of the lesion ultimately produced, but instead, serves as an initiator of a final common immunopathologic pathway.

Experimental Gastrointestinal Inflammation Due to Infection of Animals with Materials Derived from Patients

A totally different approach to the creation of an animal model of gastrointestinal inflammation resembling IBD is embodied in the many attempts to inject various species of animals with materials obtained from IBD in an attempt to: (1) utilize animals as culture tubes in which causative organisms can be expanded and identified; or (2) actually establish an IBD-like disease in the animals so injected. This approach was pursued by Mitchell and Rees, who injected homogenized, filtered

Crohn's disease tissue into the footpads of mice and obtained granulomas at the site of injection or, in several instances, in the ileum as well (13). On the basis of these observations, these investigators drew the conclusion that a transmissable agent, probably a virus, was responsible for IBD. The matter was not settled so easily, however, because subsequent attempts to establish lesions in animals by injection of patient material yielded highly equivocal results: in some instances, evidence of man to animal transmission of disease was found and in some instances it was not (14, 15). In the most recent study bearing on this issue, Cohen and his colleagues showed that filtered Crohn's disease tissue homogenates injected into the footpads of mice do indeed result in granulomatous lesions, particularly when the C57BL/10 or BALB/c strains of mice are used as recipients, whereas control tissue homogenates are much less likely to do so (16). In these studies, however, gastrointestinal lesions were not produced and, perhaps more importantly, histologic examination of the granulomas produced frequently disclosed the presence of foreign bodies, suggesting that the granulomas were nonspecific lesions that are not caused by living agents.

In the light of these and other data, most students of IBD now assume that IBD lesions probably cannot be passed into animals by injections of homogenized, filtered materials acquired from patients. This conclusion is in general agreement with the negative results obtained in the extensive studies centered on the attempt to grow viruses from lesion materials *in vitro* (17). In spite of these negative studies, one is not entitled to draw the conclusion that a transmissable agent is not the cause of IBD. In this regard, one must be constantly aware of the fact that genetic factors in the recipient animal may be important in whether or not an agent present in the lesion material will be capable of causing disease in the recipient. Such genetic factors could operate through the immune system by affecting the kind of immune response elicited by infection with a given organism.

Recently, two additional sets of studies in which animals have been used as a way of identifying potential infectious causes of IBD have come to the fore. In the first, those conducted by Das and his colleagues, nude (athymic mice) were injected with homogenates of Crohn's disease tissue and subsequently found to develop either lymphoid hyperplasia or frank lymphoid neoplasms (18). Key facts concerning these results are: (1) the hyperplasia/neoplasm formation did not follow injection of nude mice with control tissue; (2) C-type RNA viruses (most probably of murine origin) were found in the neoplasms; and (3) the hyperplasia and neoplasms involved cells of B-cell origin. Finally, Das and his associates found antibodies in Crohn's disease patients (but not in ulcerative colitis patients) that reacted with the hyperplastic and neoplastic tissue.

The original explanation of these findings was that an IBD-associated virus was being transferred to the nude mice and eliciting lymphoid cell hyperplasia or neoplastic transformation of lymphoid cells in the latter. In keeping with this view, the occurrence of patient antibodies which react with the mouse hyperplastic/neoplastic tissue was thought to be due to the patient's immune response to viral protein present in lesion tissue which was also expressed in or on the hyperplastic/neoplastic cells induced in the mice. While this argument cannot be ruled out, other interpretations of the same data which do not involve the possibility that a virus is being transmitted from man to mouse should also be considered. For example, it is possible that IBD is characterized by a particular disease-associated nonviral antigen which can evoke a hyperplastic B-cell response in nude animals which is ultimately transformed into a neoplastic proliferation by murine viruses. In this construction, the antibody found in patients which reacts with the hyperplastic neoplastic cells is an antiidiotypic antibody which reacts with antigen receptors on patient lymphoid cells and cross-reacts with antigen receptors on mouse lymphoid cells. On the basis of this possibility (and others not mentioned), one must be cautious in assuming that the nude mouse data developed by Das and his colleagues constitutes unequivocal evidence that viruses cause IBD.

In another set of studies involving transfer of patient-derived materials to animals, Chiodini et al isolated an as yet unclassified mycobacterium from resected Crohn's disease tissue by *in vitro* culture techniques and subsequently fed this organism to goats and produced granulomatous lesions of the ileum and proximal colon of the recipient animals (19). The most straightforward explanation of these findings is that a mycobacterium is the cause of the IBD illness in both the individual from whom it was isolated and in the experimental animal to whom it was transferred. Before it can be accepted, how ever, one must be able to show that the agent

causing disease in the secondary host (in this case, the goat) is not, in reality, a secondary invader of the IBD lesion which becomes manifest only because of a preexisting inflammation. This caveat is, of course, applicable to the interpretation of all studies in which animals are used as recipients of patient materials.

Gastrointestinal Inflammatory Disease Produced by Physical or Pharmacologic Agents

Yet another class of animal models of gastrointestinal inflammation are those caused by physical or pharmacologic agents. These models open the door to the possibility that materials in the environment can contribute to the initiation and maintenance of the inflammation found in IBD. One must hasten to add, however, that no environmental exposure or dietary component has been convincingly demonstrated as an etiologic factor in IBD, despite considerable effort to demonstrate such factors.

Among the physical and pharmacologic agents that have been found to cause gastrointestinal inflammation are materials as diverse as acetic acid and parasympathomimetic agents (20, 21). Acetic acid instillation causes an inflammation similar to that found in ulcerative colitis which is not simply due to the physical effects of acid *per se,* since instillation of dilute HCl having the same pH as the acetic acid does not have the same effect (20). Administration of parasympathomimetics causes vascular congestion of the gastrointestinal tract culminating in local bleeding; in this case, inflammation is minimal initially but if drug administration is continued, ulceration can develop (21).

The best-studied example of a physical agent causing gastrointestinal inflammation is carrageenin-induced enteritis (Table 5). The salient fact concerning this model of gastrointestinal inflammation is that oral administration of acid-hydrolyzed iota carrageenin (a sulfated polysaccharide derived from the red seaweed, *E. spinosum*) induces a cecal colitis in virtually every animal to which the material is fed (including mice, guinea pigs, and primates) (22). It is felt that the mechanism of the inflammation involves uptake of the carrageenin by intestinal macrophages followed by release of lysosomal enzymes into the mucosal tissue and consequent tissue destruction and inflammation (23). Recently, several investigators have tried to modify carrageenin-induced inflammation with antibiotics (24). It was found that metronidazole (an antibiotic capable of killing anaerobic organisms), but not gentamycin (an antibiotic capable of killing gram-negative aerobic organisms), could prevent carrageenin-induced colitis if given early in the course of carrageenin administration. This indicates once again that gastrointestinal inflammation frequently involves both specific inflammatory factors and host responses to normal gut constituents.

TABLE 5. CARRAGEENIN-INDUCED COLITIS

A.	Oral administration of degraded carrageenin
B.	Production of cecal inflammatory lesions in a wide variety of species
C.	Pathogenesis: macrophage uptake of carrageenin followed by leakage of lysosomal materials into the microenvironment
D.	Contributory factors: gut flora; inflammation can be modified/prevented with metronidazole
E.	Chronic carrageenin administration: colorectal cancer

ANIMAL MODELS OF GASTROINTESTINAL CARCINOMA

A well-known observation in human colitis is that long-standing disease, particularly of the large bowel, can result in colonic carcinoma. Some insight into why this is so is afforded by studies with a known intestinal carcinogen, dimethyl hydrazine (DMH), wherein it was shown that sensitivity and resistance to the carcinogenic effect of DMH in different species correlates with the rate of epithelial cell proliferation and the fraction of epithelial cells proliferating at any given time (25). In addition, it was found that these epithelial cell characteristics are in turn determined by genetic and environmental factors including the presence or absence of infectious agents, colonic injury, and exposure to toxic physical agents, such as carrageenin. On the basis of these observations, it may be presumed that chronic inflammation of the gastrointestinal tract from any cause, including that due to a disease entity such as IBD, also results in an increased incidence of carcinoma because of primary changes in epithelial cell proliferation rates. It need only be added that since animal models of IBD result in chronic inflammation, such models are also models of gastrointestinal carcinoma.

SUMMARY

It is obvious from the above discussion that, whereas no really clear-cut animal model of IBD has been established, a number of specific insights

into the nature of the human illness can be derived from the study of naturally occurring and induced gastrointestinal inflammations occurring in animals. One of the most important emerges from the finding that both immune complex deposition in the gastrointestinal tract as well as stimulation of the mucosal T-cell system results in an ulcerative colitis-like gastrointestinal inflammation. The simplest explanation of the fact that vastly different methods of inducing immune-mediated injury in the gastrointestinal tract can lead to a similar kind of gastrointestinal inflammation is that the inflammatory response in the gastrointestinal tract is rather restricted in its overall pathologic appearance and that the histologic lesions characteristic of ulcerative colitis and Crohn's disease can arise from primary disturbance of the B-cell system, the T-cell system, or both. Another explanation of this fact, however, is that no matter what the initial immunological disorder may be, the mechanism underlying the gastrointestinal inflammation ultimately comes to involve a response to materials in the mucosal environment so that pathologic events are inevitably channeled into an inflammatory pathway that is either ulcerative colitis-like or Crohn's disease-like in its final configuration.

This second explanation is buttressed by other findings derived from the study of animal models which, in general, suggest that no matter what the initial result, an immunologic interaction against a constituent of the bowel flora determines the ultimate course of the gastrointestinal inflammation. This is seen in the studies of Mee and his colleagues, wherein preimmunization with *E. coli* led to chronicity of the Auer reaction, as well as in the study of the colitis associated with *E. coli* immunization, wherein feeding of *E. coli* seemed to prevent colitis, presumably by correcting a microbial imbalance which might otherwise stimulate an abnormal mucosal immune response against bacterial antigens. Finally, it is seen in the study of carrageenin-induced colitis, wherein antibiotic therapy which eliminates anerobic organisms seemed to prevent colitis. In all, these findings suggest that IBD in humans results from an initial inflammation which serves as a stimulus for a more chronic and irreversible reaction against normal gastrointestinal constituents.

The relevance of these considerations to studies of the cotton-top tamarin are fairly straightforward. First, investigation of the ulcerative colitis-like condition found in this primate should include the search for immunologic factors that predispose the animal to a mucosal immune response to materials which are not ordinarily immunogenic; this could set up an initiating inflammation equivalent to the induction procedures used to produce the various animal models of gastrointestinal inflammation. Second, investigation of the tamarin should involve the search for evidence that such initial gastrointestinal inflammation, perhaps for reasons peculiar to the tamarin, becomes prolonged and chronic as a result of an abnormal regulation of the mucosal immune response to normally occurring materials in the mucosal environment. Such studies would be parallel to those currently being conducted in humans, wherein mucosal system immunoregulatory defects are being intensely sought.

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