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# From the Archives, in Recognition of the 75th Anniversary of AALAS: The Development of Practical and Effective Filtered Cage Caps to Exclude Viral Diseases from Mouse Breeding Colonies (1964–1967)

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## Commentary

Previous articles republished as part of the *From the Archives* series documented historical considerations of laboratory rodent housing options such as proper diet and bedding as well as practical cage construction. Plastic shoebox-style cages in various sizes were being used in the 1950s, but these were provided in an open-top configuration. The specific-pathogen-free rat colony described in the last installment was managed using exclusion methods focused on maintaining a barrier at the room level. However, it was soon recognized that, in both academic and commercial colonies, there were situations that would benefit greatly from a system that significantly reduced or eliminated cage-to-cage transmission within a single room. This would increase the efficiency of both space utilization and labor and also allow scientists to conduct more robust infectious disease experiments without inadvertent cross-contamination between groups.

Dr. Lisbeth Kraft, DVM (1920 to 2002) was an AALAS Griffin Award winner (1972) and has been acknowledged as the inventor of the barrier at the cage level.[1] Dr. Kraft used her first filter cages as part of research studies investigating the diarrheal diseases of infant mice. Much of her work involved study of a disease referred to as the "epizootic diarrhea of infant mice" (or EDIM), which she characterized for many years, eventually identifying a virus as the etiological agent in an article published in the journal *Science*.[2] Electron microscopy of the causative virus revealed a reovirus-like particle that was later classified as mouse rotavirus. While she was studying EDIM, another viral diarrheal disease of neonatal mice became recognized, but this syndrome was associated with much more mortality so it was referred to as the "lethal intestinal virus of infant mice" (or LIVIM), which she described in a paper also published in *Science*.[3]

For her own viral research projects, the filtered cages used were cylinders that had been custom-made from galvanized wire mesh with the curved sides fully covered with thick layers of fiberglass. These cages were only opened within a transfer hood consisting of a filtered glove box maintained under negative pressure.[4] But to adapt the principles of filtered caging more broadly in commercial or academic colonies, it was recognized that what would be more useful would be a filtered cap that could be placed on top of existing shoebox caging.

The first of the following papers describes such a system designed by Dr. Kraft and her collaborators that used standard caging with a fiberglass-covered wire mesh cap added.[5] In order to allow clear visualization of the food and water above the cage top, these filter caps were designed with one clear side toward the front that was created using a transparent polyester film approximately 0.2 mm thick. The transfer hood

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remained an important part of cage-level exclusion practices, but rather than the complicated glove box she originally described, the system depicted here used a filtered positive-pressure hood with a basic design that is quite familiar to us 60 years later.

The second paper reproduced in this issue was published in *Laboratory Animal Care* a few years later, and it describes a number of additional approaches that had been taken to develop effective filter tops that were as durable and economical as possible.[6] The author is Mr. Samuel Poiley, a 1965 AALAS Collins Award winner who was head of the Mammalian Genetics and Animal Production Section for one of the NIH institutes at the time. He had worked his way up to that position after 30+ years working in animal care management positions at the NIH, so he was able to provide detailed background information on EDIM in mouse colonies and to describe various prevention and remediation strategies that had been attempted. One of the important developments in cage-level exclusion he described was the use of thin and pliable nonwoven synthetic fabric filter materials as a substitute for the more bulky and friable fiberglass pads used previously in filter tops. This sheet-like material could be cut and sewn into a rectangular shape that used a minimal wire frame for internal support, rather than the full wire mesh supports previously used. Looking at the figures from the Poiley paper, it is not difficult to envision the final change from a wire frame to a polymeric support shell, which led to the modern plastic microisolation-style cage design.

The final reprinted article brings the story of LIVIM to a conclusion. Although the full scientific report on the etiological agent would eventually be published in *Infection and Immunity* in 1979,[7] the authors from the Centers for Disease Control knew that this was an important finding to those in the laboratory animal and comparative medicine field, so they quickly provided a preview to the readership of *Laboratory Animal Science* by publishing a Brief Report that identified a strain of mouse hepatitis virus (MHV) as the causative agent of the transmissible and lethal enteritis.[8] This was the beginning of our understanding of the pathobiology of enterotropic strains of MHV, which would go on to cause significant issues for research mouse colonies in years to come. As time went on and the use of filter tops began to be more common, the enterotropic strains of MHV proved more difficult to exclude than the more classically studied polytropic (also known as respiratory-tropic) strains.[9]

In the 'Letters' section of that same issue of *Laboratory Animal Science*, Dr. Kraft commented on this news regarding MHV as the etiological agent, and she graciously concurred that the designation 'LIVIM' should be retired. Her note is appended below.

**[From "Letters" in the December 1976 issue of *Laboratory Animal Science*]**

Dear Sir:

A recent Brief Report in this journal (Broderson JR, Murphy FA, Hierholzer JC; Lethal enteritis in infant mice caused by mouse hepatitis virus. *Lab Anim Sci* 26:824, 1976) discusses a lethal enteritis of infant mice caused by murine hepatitis virus. From morphologic as well as serologic evidence, the authors indicate that lethal intestinal virus of infant mice (LIVIM) is none other than a variant of murine hepatitis virus and they suggest that the designation "LIVIM" be dropped.

Having described the clinical entity (which has become known as LIVIM) in 1962, but not having been able to characterize the agent further at that time (for a variety of nonscientific reasons), I am now delighted that at last its etiologic agent seems to have been identified. I should therefore like to concur with Broderson and his colleagues that, based on their data, the "LIVIM" designation be dismissed and that we speak instead only of lethal intestinal disease of infant mice caused by murine hepatitis virus.

What a joy to be able to shorten the list of murine viruses rather than to add to it!

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## Conflict of Interest

The author has no conflict of interest to declare.

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# PRACTICAL CONTROL OF DIARRHEAL DISEASE IN A COMMERCIAL MOUSE COLONY[1]

LISBETH M. KRAFT,[2] ROYAL F. PARDY,[3] DAVID A. PARDY,[3] AND HERBERT ZWICKEL[2]

ABSTRACT. Adaptation of research type filter cages for the practical control of airborne diarrheal disease in a commercial colony of mice is described.

Filter cages have been used to control airborne infection in the study of epizootic diarrhea of infant mice (EDIM) and lethal intestinal virus infection of infant mice (LIVIM) (Kraft, 1958; Kraft, 1962). It seems feasible, therefore, to attempt to apply the same principle of the filter cage in the practical control of diarrheal disease in a naturally infected commercial colony of mice. In the present instance the mice are ICR-derived; monogamous mating and random breeding are practiced.

In the cages described previously (Kraft, 1958) it was found necessary for the comfort of the animals to place the filter material on the vertical screened sides of the cages so that gaseous exchange would occur horizontally through the filter. Ordinary pan, shoebox, or glass jar cages could not be used when the filter material was placed directly upon the cover, for, when the number of animals in the cage was at the same maximum as in an open cage, the mice perspired and became frantic, stopped nursing if they had a litter, and occasionally became cannibalistic.

It is unrealistic for a commercial breeder of mice to discard all regular breeding cages (usually of the shoebox or pan variety) and reinvest in relatively expensive filter cages of the research type. Therefore, some other arrangement had to be devised. Thus, it was found possible to utilize existing cages, cage covers, feeders, and water bottles and, furthermore, to do this with little additional expense by the addition of a filter cap (Fig. 1) and a transfer hood (Fig. 2).

The regular cages used in the present study (Figures 2 and 3) measure approximately 8 x 12 x 5 inches. The filter cap (Figure 1), which covers the entire cage top, is about 4 inches high, and is made of wire mesh lined with PF 105 Fiberglas (Corning) ½ inches thick. Either absorbent or non-absorbent cotton can be used instead of the latter, but both of these materials are more difficult to handle during construction and less durable than Fiberglas. Clips keep the cap square on the cage cover. The end facing the aisle (see Fig. 3) is made of 750 gauge Mylar Type D (DuPont) for visibility in observing feed and water supply without having to remove the cap. The entire cap may be autoclaved.

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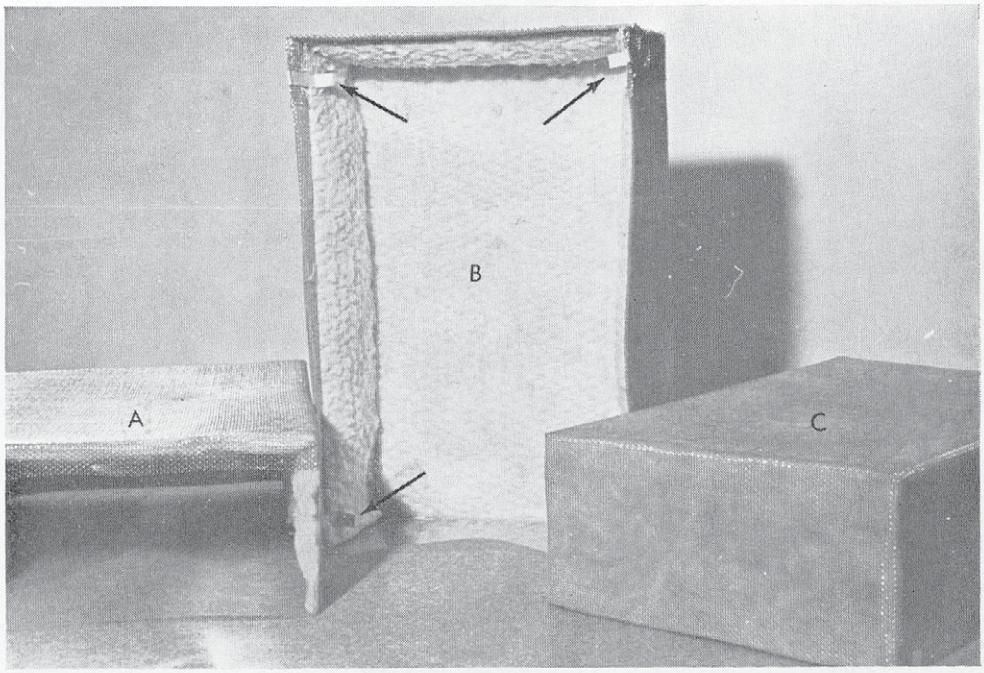


FIG. 1. The filter cap viewed from the front (A), the under side (B), and the rear (C). Arrows point to support clips.

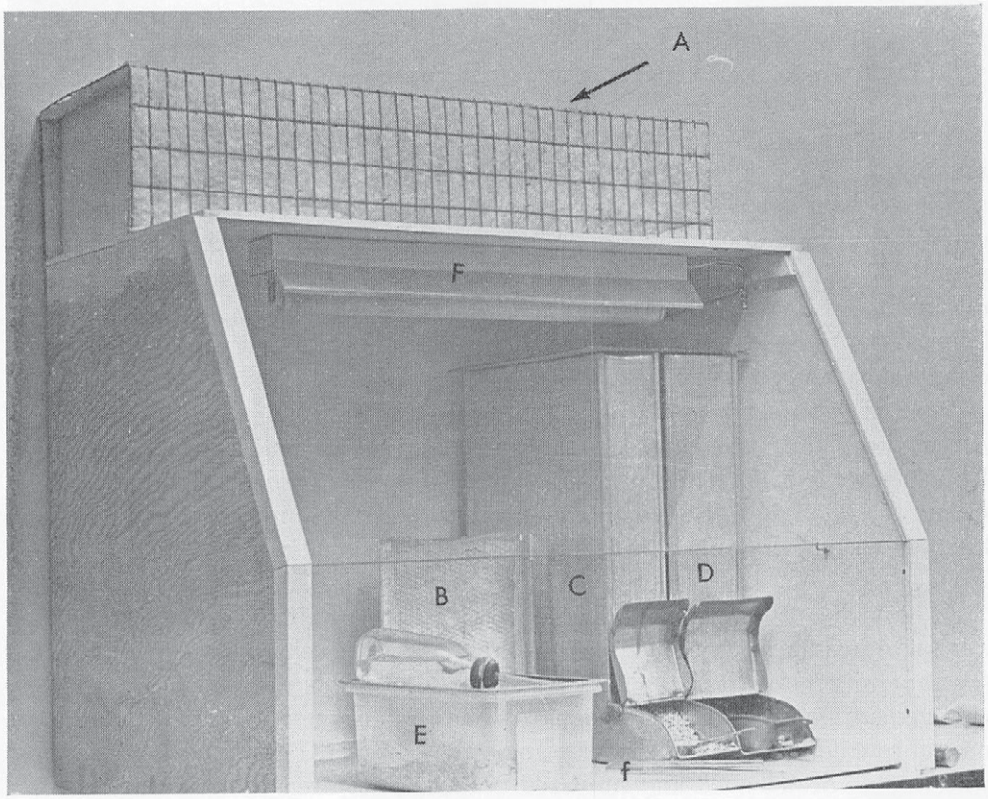


FIG. 2. Plywood transfer hood. The intake filter housing (A) encloses a fan. The sloping portion of the hood front is made of plate glass beneath which the hood is open. B, filter cap; C, D, feed hoppers; E, regular mouse cage; F, fluorescent lamp. Forceps (f) rest in a protective tube.

FIG. 3. Cages with filter caps in use. Note viewing ease as indicated at arrows

The success of the cap in maintaining the animals' comfort lies in the following facts: if filter material were placed directly upon the cover of the cages, the available filter surface would be about 96 square inches. In the case of a filter cap 3 inches high above the clips, the available filter surface increases twice to about 192 square inches (taking into consideration the viewing window). The minimum available filter area which will allow the animals' comfort is not known; the present dimensions were determined fortuitously and arbitrarily in order to accommodate the water bottle employed.

A portable transfer hood (Fig. 2) is used in conjunction with the filter caps. Air movement is provided by a fan and pressure is positive within the hood. Entering air is filtered through Fiberglas. Cages are opened and serviced only within the hood. Feed is provided in hoppers (Fig. 2, C and D). All animals are handled with 10-inch forceps that are changed frequently and disinfected (Fig. 2, f).

At servicing time sufficient feed and water are given to last one week, and adequate bedding is provided so that animals are apparently comfortable for the same period of time. The entire box bottom and water bottle are both exchanged each week for freshly prepared ones. The same cover and filter cap are used throughout the life of the breeding cage, however. Dirty cages, bottles, and water tubes are cleaned and sanitized in a separate area before being returned to use.

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The time necessary for caring for mice by the method described and by usual means in open cages of the same design is approximately equal. This communication has been submitted with the hope that the information will be of benefit to others experiencing diarrheal disease in mouse colonies.

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# THE DEVELOPMENT OF AN EFFECTIVE METHOD FOR CONTROL OF EPIZOOTIC DIARRHEA IN INFANT MICE

SAMUEL M. POILEY[1]

ABSTRACT. Recurring outbreaks of Epizootic Diarrhea of Infant Mice (EDIM) continue to be a matter of concern in many mouse colonies. Although a medication such as tetracycline hydrochloride has beneficial effect, treated animals are not acceptable for many bio-medical studies. The most advanced mouse producers, however, have managed to avoid the use of antibiotics or other therapeutic compounds by resorting to the use of the hysterotomy-isolator techniques for the development of clean colonies. Many organizations in this industry, however, are unable to afford the investment that is required to support this system.

The encouraging results obtained through the use of the Kraft filter cap stimulated interest in the development of similar devices. An evaluation of materials available resulted in the development of an inexpensive and reusable device. It consists of a bonnet fabricated of a non-woven material of synthetic fibers supported by a light weight welded wire frame. A modified form of the frame consists of two wire shapes which can be stored in minimal space. Mouse colonies protected with this filter cap have been free of EDIM for a period of one year.

Epizootic diarrhea of infant mice (EDIM) has been a scourge in mouse populations for many years. Early attempts to correct the condition were based upon the assumptions that it was related to inadequate diets, or the inability of mice to properly digest and assimilate dietary ingredients. Efforts to offset these presumed effects resulted in the concoction of "kitchen" formulated diets and the haphazard selection of dietary supplements to the basic pelleted rations. The supplements consisted of diverse substances such as wheat, oats, and "Grandmother's" cure-alls. The latter included blackberry jam, bacon fat, Coca Cola syrup, and boiled rice, individually or in various combinations. In final desperation, attempts were made to alleviate the condition by means of Kaopectate (The Upjohn Co., Kalamazoo, Michigan). Apparent improvement was of short duration and coincidental because all of these efforts in the final analysis were unsuccessful. In addition, infected litters and their parents were killed, and caging equipment was sanitized and sterilized prior to reuse.

Syverton and Olitzky (1934) described a similar condition which they concluded was caused "by a bacterium of salmonella type". Cheever and Mueller (1947) speculated that the disease might be caused by a virus.

With the accumulation of evidence that this disease might be agent-inspired, investigations were undertaken to identify the causal organism. In the interim, medications found to be promising for other enteric conditions were offered for

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this disease in hopes that, by chance, a solution for this troublesome problem would be forthcoming. Although the agent was subsequently identified as a virus (Kraft, 1958, 1966), suitable therapeutic compounds, until recent times, were unavailable.

## Therapeutic Trials Using Antibiotics

With the advent of a variety of antibiotics, it was felt that the chance application of one of these might demonstrate promising results. It was speculated that effects upon secondary organisms might be beneficial. Our objective was directed towards the development of a suitable prophylactic technique rather than the cure of a disease. Preliminary efforts were based upon the use of penicillin, chloramphenicol, and aureomycin for corrective purposes. These efforts were unproductive.

Consideration was then given to the selection of a broad spectrum antibiotic, particularly one that had been shown to be effective for certain enteric organisms. Tetracycline was chosen since it appeared to comply with these criteria. Since our approach, as previously noted, was chancy, it was felt that a sulfa derivative should also be evaluated for contrast. Sulfamerazine was selected based upon effectual usage for the alleviation of chronic respiratory disease in rats (Hambermann, et al., 1963).

The occurrence of an epizootic of EDIM in our colonies afforded an appropriate opportunity for us to undertake several pilot studies (Poiley and McEleney, 1957). Strain $C_3H/HeN$ inbred mice were selected for these investigations because they were known to be extremely susceptible to EDIM.

Since the purpose of these studies was to determine the efficacy of these compounds for control purposes, it was felt that it would be most desirable for the regimen to cover the period from late pregnancy through the weaning of the subsequent offspring.

Pregnants were selected during the third trimester of gestation or, more specifically, at five days before term. On day 1, or the starting day of this study, 88 pregnant mice were available for division into three groups. Rather than waste the 88th mouse, it was assigned to sulfamerazine in Trial №1 as the outcome of coin tosses.

Each pregnant mouse, and its subsequent litter, was maintained in a one gallon capacity glass provision jar enclosed with a perforated stainless steel cover. Coarse white pine sawdust was used for bedding, and the animals were transferred to sanitized equipment twice weekly. Food consisted of laboratory mouse blocks provided in a stainless steel receptacle suspended from the edge of the jar. Dietary supplements were not used.

The medications were supplied in the drinking water, ad libitum, at dose levels of 5 mg/20 cc for sodium sulfamerazine and 200 mg/gallon for tetracycline hydrochloride.

The pregnants were selected from a production colony which, under normal

circumstances, produced 500 to 700 weanlings per week. However, at the time of this study, while undergoing the massive epizootic of EDIM, survivors were being weaned at the rate of 150 to 200 per week. Treated mice and untreated controls were maintained in these environs in a room measuring 30′ x 30′ x 10′ high. The air handling system provided 100% fresh air in six changes per hour at a temperature range of 72–76° F. The system was not capable of humidity control and the range fluctuated from 40–75%, dependent on a combination of outside climatic conditions and moisture in the ambient atmosphere. Husbandry practices were optimal, with the exception that equipment, food, and bedding were not sterilized, and personnel locks were not available.

Because of the known tendency for mouse mothers to cannibalize or lose interest in their mouselings, equipment was not changed until the sucklings were 8–10 days old. Counts of young at birth were not made for these reasons. Trial No. 2 was undertaken in order to confirm or refute the first study as a chance occurrence. The results are shown in Table 1.

The results obtained through the use of tetracycline hydrochloride indicate that this material is quite effective in controlling EDIM. The litter survival rate, weaned litter averages, and litters with diarrhea are normal levels for this strain of mouse. Diarrhea was identified grossly based upon color and appearance of the fecal material. Litters with diarrhea survived the nursing period of four (4) weeks, but were discarded due to poor quality.

Sodium sulfamerazine apparently exerted limited effect, but the surviving mouselings from litters with diarrhea were of poor quality. They presented an emaciated appearance, weighed between 7 to 9 grams at weaning, and failed to gain weight during the following four weeks. The results reported for un-

TABLE 1

*Comparison of the effects of tetracycline hydrochloride and sodium sulfamerazine in controlling EDIM in a $C_3H/HeN$ inbred mouse population*

| | Tetracycline hydrochloride* | | Sodium sulfamerazine | | Untreated controls | |
|---|---|---|---|---|---|---|
| | Trial #1 | Trial #2 | Trial #1 | Trial #2 | Trial #1 | Trial #2 |
| No. of pregnants | 29 | 29 | 30 | 29 | 29 | 29 |
| Pregnants died | 1 | — | — | — | 3 | — |
| Litters born | 28 | 29 | 30 | 29 | 26 | 29 |
| Litters died | — | 1 | 10 | 8 | 13 | 11 |
| Litters weaned | 28 | 28 | 20 | 21 | 13 | 18 |
| Total young weaned | 171 | 192 | 94 | 116 | 45 | 65 |
| Weaned litter average | 6.11 | 6.85 | 4.70 | 5.52 | 3.46 | 3.61 |
| Males weaned | 87 | 99 | 32 | 49 | 21 | 28 |
| Females weaned | 84 | 93 | 62 | 67 | 24 | 37 |
| Weaned litters with diarrhea | 3 | 4 | 21 | 13 | 6 | 9 |

* Veterinary—25 gm. per pound.

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treated controls are characteristic of those noted for the production colony during epizootics.

These studies were discontinued for several reasons. In the first place, even though the effects of tetracycline hydrochloride seemed to be promising, the end results indicated that it was merely palliative. This is evidenced by the fact that litters with diarrhea were observed. Secondly, mice receiving continuous medication are not acceptable for many types of research. Finally, organisms that are not affected by this antibiotic can create additional undesirable problems. Nevertheless, some colony managers continue to offer medications to mouse populations. However, they do provide a suitable withdrawal period prior to shipment of animals to laboratories.

### Prophylactic Trials Using Protective Devices

During the recent past, several methods have served to provide a means for the control of this disease. Reference is made to the hysterotomy-isolator technique for the development of clean laboratory animals, and the filter cap developed by Kraft, et al. (1964), and the similar device by Schneider and Collins (1966). The methods employed for the former are amply described in published literature and consequently will not be discussed in this report. Its principal and probably sole disadvantage for many commercial and institutional colonies stems from the cost of equipment and maintenance.

The several types of filter caps have been demonstrated to be extremely effective for the control of EDIM. Jennings and Rumpf (1965) reported satisfactory results based upon the use of the Kraft filter cap. In our experience, identical and similar devices have served to mitigate an epizootic in a commercial colony, and to prevent similar occurrences in our colonies. Although these devices are beneficial, they are rather costly and possess several disadvantages. The outside dimensions exceed those of the cage and, as a result, the number of cages which can be housed on a rack is reduced. Fiber glass is autoclavable but not washable, and in the course of time its porosity diminishes. The replacement of fiber glass is a troublesome chore and the material, due to its bulk, requires a disproportionate amount of storage space.

In order to reduce labor and material cost, some individuals replace unserviced filter caps upon freshly sanitized animal care equipment. The filter caps are not discarded or sanitized until the completion of a lactational period or breeding cycle. Proponents for this system contend that the animals are stabilized with respect to their environment, negating requirements for clean caps. Be this as it may, this author has witnessed rapid increases in ectoparasite populations due to this concept.

The filter cap design selected for this first study was similar to the Kraft cap, with the exception that a sheet metal angle frame located at the bottom of the wire box served to position the device upon the cage cover. The plastic window was found to be unnecessary for our purposes and was eliminated

in the interest of economy. A further reduction in cost was accomplished by using FM 018 fiber glass (Owens-Corning) ¼″ thick. This thinner material is equally as effective in the control of EDIM as is the FG 50 suggested by Kraft. The caps were sanitized weekly by means of a peracetic acid spray, which also removed loose dust particles. Although the cost was significantly reduced, the disadvantages of space requirement and the need for precautionary measures associated with the use of peracetic acid imposed limitations for the application of this design in large scale production colonies.

An ingenious approach to a simple and inexpensive method was developed by Oleson (1965). He found that pieces of filter paper placed upon the covers of glass jars used for mouse production were quite effective. In principle, this material served as a barrier between particle fallout and the mice. We subsequently used paper towels, paper napkins, and wrapping paper for plastic cages. It was found necessary to interpose a piece of screen wire between the cage cover and the paper in order to prevent the mice from gnawing the paper and/or displacing it from the cage cover. This method was abandoned for the reasons noted above and the lack of adequate ventilation.

Since the results of the evaluations of the various protective devices at this point had not been wholly satisfactory, it was felt that consideration should be given to a commercially available filter cap at this writing. Observations conducted in a commercial animal colony indicated that it was effective in controlling EDIM when applied during the course of an epizootic. However, it was incapable of withstanding the stress of machine washing, and its outside dimensions exceeded the dimensions of the cage lid. The additional space required would result in a reduction of the number of cages per shelf. Although this material was autoclavable, many of our colonies are not equipped with suitable autoclaves. The cost per unit was such as to prohibit its use as a disposable item.

Efforts to develop a suitable and inexpensive disposable filter cap suggested that we explore the application of cardboard for this purpose. After a period of trial and error, a satisfactory boxlike shape was eventually developed. Ventilation openings were protected with the FM 018 fiber glass, with an assembled cost of 10–15 cents.

The design provided a friction fit with the cage cover, solving space requirements. Washing being obviously impossible, autoclaving was attempted. The attrition rate per exposure cycle was 25%, and surviving items were generally distorted. The cost per unit did not justify disposal on a semi-weekly or even on a weekly basis. Reuse could be prolonged if serviced with peracetic acid but, as noted above, the use of this compound created additional problems.

A search for suitable filtering material was crowned with success when this problem was discussed with a member of the garment industry. He described non-woven fabrics of synthetic fibers that are used to stiffen portions of men's and ladies' clothing. These materials are produced as noted above for a variety

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of applications with a wide range in thickness. These fabrics are available in bolts 42″ wide by 300 or 500 yard lengths.

We initially selected six types for evaluation, with the final choice confined to two types, the first of 50% rayon and 50% nylon and the other of 100% rayon. The former is more dense than the latter and, of course, more expensive. The first type is recommended for SPF colonies and as filter covers for shipping boxes during cold weather. The second type is satisfactory for conventional colonies and as filter covers for shipping boxes during warm weather.

The fabric is cut to size and sewn in the form of an open bottom box (Fig. 1). The absence of a window is of no special concern because very little effort is required to raise the bonnet in order to observe animals, food, and water. This material is autoclavable, and exposure for one hour at 250 degrees Fahrenheit has not resulted in detectable deterioration. The bonnets are readily washed in cage washing machines and automatic clothes washers. Although they air dry in a few minutes, it is more expeditious to use a clothes dryer. A combination washer-dryer would be a valuable adjunct to a program based upon the use of this filter cap.

The supporting frame (Fig. 2) is fabricated of 12 gauge bright basic wire or 12 gauge stainless steel wire, formed and spot welded as shown. The sides, back, and front are tapered in order to conserve storage and shipping space. The configuration and position of the legs supply an element of versatility with respect to the use of this frame on a variety of cage covers. It is being used for perforated covers (Fig. 3) as well as those fabricated of woven wire or welded rods. When the legs are twisted into positions parallel to the bottom wires of the frame, bulk can be further reduced for shipping purposes. These frames are easily washed or autoclaved. The height of these frames is governed by the height of the water bottle above the upper surface of the cage cover. When

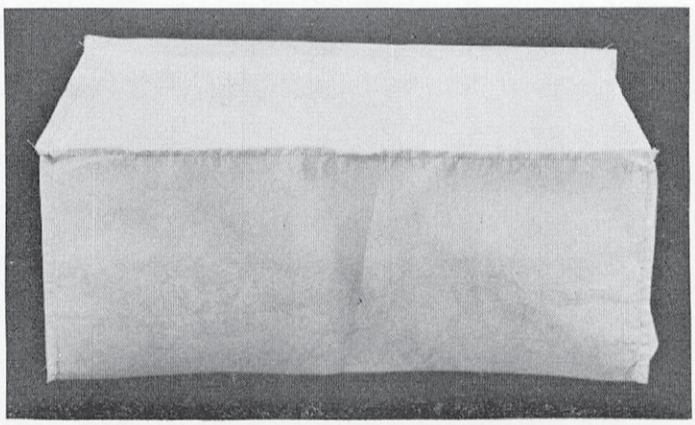

FIG. 1

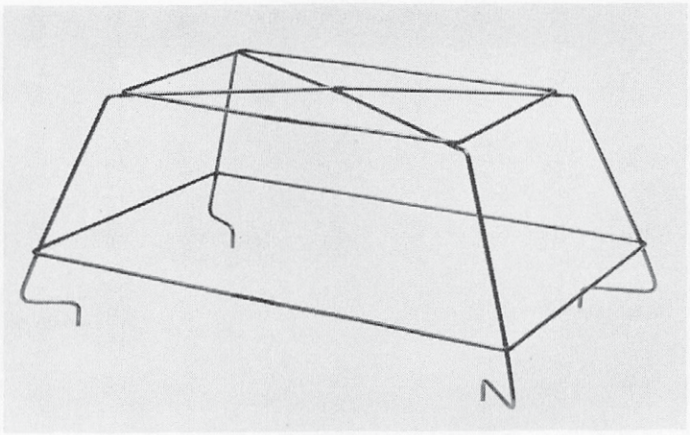

FIG. 2

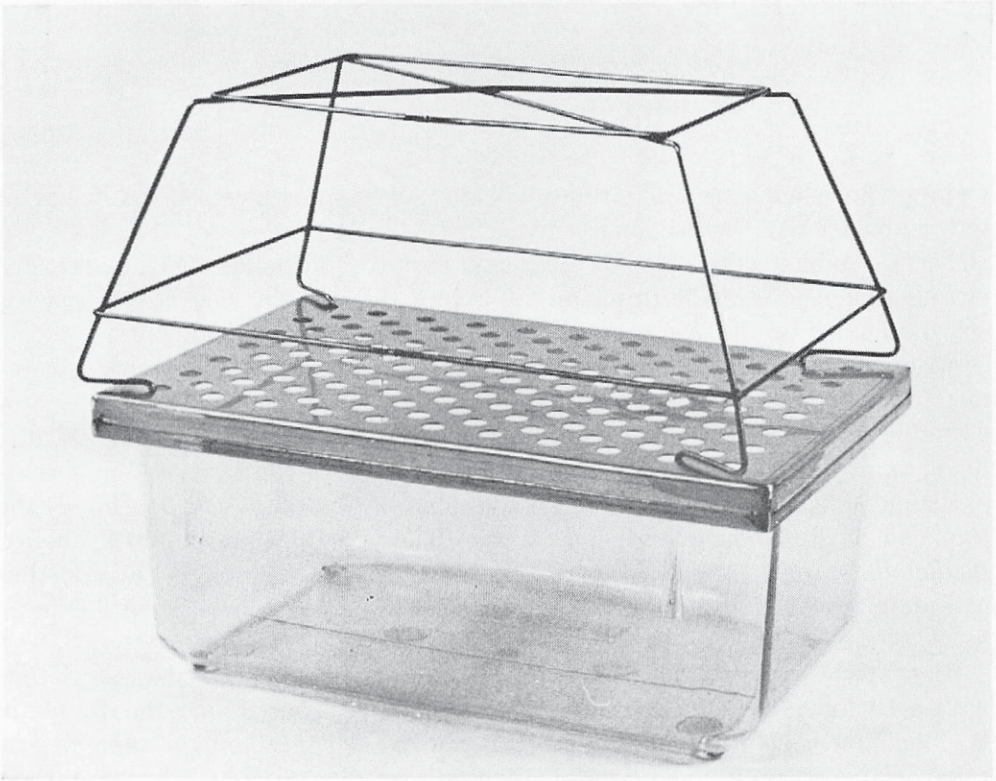

FIG. 3

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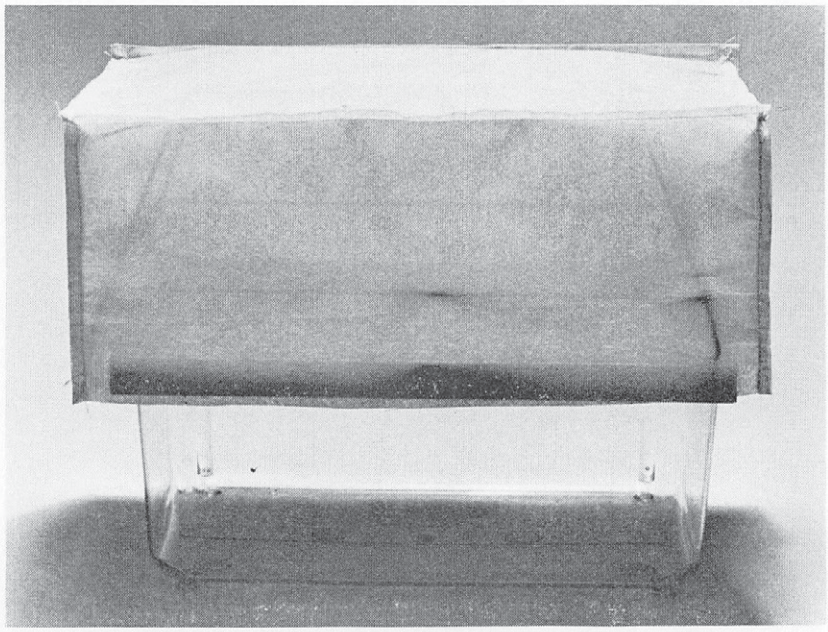

FIG. 4

frames whose height is 4½″ are nested, they overlap or increase the height of the combination of the two devices by ½″.

The assembled unit (Fig. 4) does not require additional shelf space. The outside dimensions of the frame do not exceed those of the cage cover, and the space occupied by the overlapping edges of the bonnet is insignificant.

Space is a valuable asset whether it be in governmental, academic or commercial institutions. Consequently, storage space for equipment, no matter how valuable, even though it be on a temporary or in-out basis, is frequently difficult to acquire. Although the frames described above can be stored in a compact manner (10 frames measuring 10½″ long, 7½″ wide, 5½″ high minus the legs, can be stored in a space measuring 10½″ long, 7½″ wide, 10½″ high), storage for stand-by units pose space problems. For this reason, we suggest that consideration be given to the take-apart filter bonnet support shown in Figure 5.

Elements A and B (Fig. 5) are formed of ⅛″ diameter stainless steel rods with a 4B finish. When assembled, the dimple in A is fitted over the dimple in B. This joint is held in place with either masking tape, cellophane tape, plastic tape, or any other similar material. We find that two turns of ½″ wide tape is sufficient. The assembly is shown in position in Figure 6. The final arrangement, including the bonnet, will be equivalent to that shown in Figure 4. We have found that it is not necessary to remove the tape for storage. The frame assembly is withdrawn from the cage cover, collapsed, sanitized, sterilized and

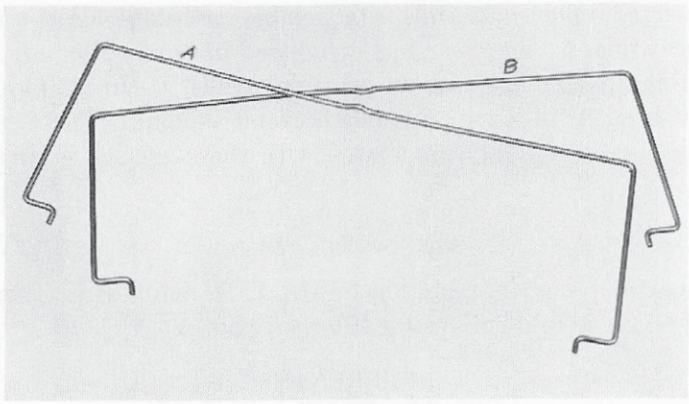


FIG. 5

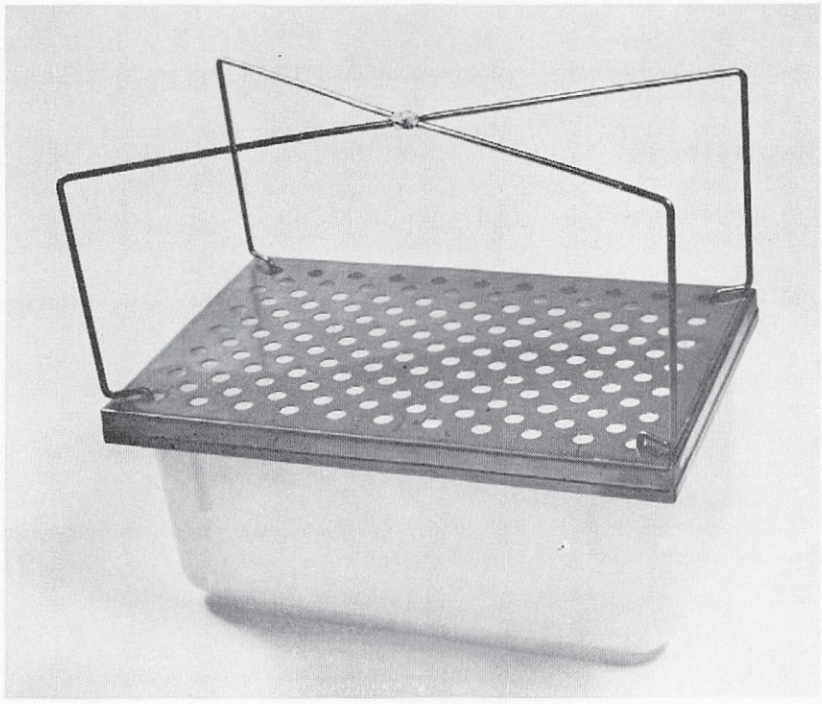

FIG. 6

stored in a container. If the frame is to be sanitized and immediately reused, we prefer to remove the tape and use a fresh piece for assembly.

Cages are changed without the use of a transfer hood, for exposure during this maneuver is generally less than two minutes.

The filter cap assemblies described above have solved the problems posed by other devices evaluated in the past. The combined cost of each unit is significantly less than $1.00 and, as a reusable item, the initial financial outlay is

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quickly amortized. The materials are readily available. Experience for a period of approximately one year has convinced us that either of these assemblies can eliminate EDIM from susceptible mouse colonies. Similar devices have recently been installed in rat and hamster colonies. Their usefulness in controlling diseases commonly associated with these species is currently being evaluated.

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We wish to express our appreciation to Mr. A. R. Schmidt for suggesting that consideration be given to a collapsible filter support.

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# BRIEF REPORTS

## LETHAL ENTERITIS IN INFANT MICE CAUSED BY MOUSE HEPATITIS VIRUS[1,2]

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Recently a devastating epizootic of diarrheal disease was experienced in mice [Cdc: (ICR) ] from the pathogen-free colony at this institution. The disease occurred when purchased mice (many strains, from several suppliers) came in contact with a "nursery" used to produce suckling mouse litters. The epizootic was characterized by high mortality during the first 7–10 days of life; mothers were not clinically affected. Most litters were cannibalized within a few hours of death. Macroscopically, continuously flaccid distention of the small intestine and colon was noted, and intestinal contents were yellowish and watery. Histologic changes in tissues of moribund mice were identical to those described by Kraft and others in mice infected with "lethal intestinal virus of infant mice" (LIVIM) (1, 2, 3). The intestinal lesions included blunting of villi with syncytium formation, cytonecrosis and desquamation of epithelium. No lesions were found in any other organ.

In an attempt to find the etiology of this infection, we expressed the intestinal contents from moribund mice and examined them by negative contrast electron microscopy. Large numbers of coronavirus particles were present. The particles were about 100-130 nm in diameter and had the large petal shaped surface projections which are characteristic of coronaviruses. No evidence of EDIM virus or any other virus was found despite extensive searching.

By thin-section electron microscopy, large numbers of the same virus particles were found in intestinal epithelium and in macrophages in the lamina propria of the jejunum and ileum.

Mice which had cannibilized their litters were held for 3 weeks, and their sera were then tested for antibodies to mouse hepatitis virus (MHV) and other murine pathogens. Tests were also made for adenovirus, lymphocytic choriomeningitis virus, ectromelia, psittacosis, Sendai virus, reovirus 3, pneumonia virus of mice, Kilham rat virus, Theiler's GDVII virus, polyoma, K virus, minute virus of mice and Toolan H-1 virus. Titers as high as 256 were obtained against polyvalent MHV antigen[3] using the complement fixation test, but there was no evidence of antibody to other murine viruses. In reciprocal tests, antigens prepared from gut suspensions of moribund suckling mice gave the same titers with MHV polyvalent antiserum as did control MHV antigens. Gut suspensions from control mice did not react with MHV antiserum.

MHV has been described as a common cause of enteric infection in baby mice (4, 5). It is highly contagious and highly lethal when initially introduced into a colony. In epizootics such as the one described here, there is no maternal antibody protection of the new-born mouse. Diagnosis and understanding of this disease have been obscured by two continuing difficulties. First, the description of LIVIM as a distinct syndrome has led, erroneously, to the assumption that a distinct but unknown etiologic agent must be responsible, although at one time, LIVIM infection was also thought to be the product of two interacting viruses (EDIM and MHV) (Parker J C, Microbiological Associates, personal communication). Second, there has been too little appreciation of varying organ tropisms of MHV.

In infection of adult mice, a necrotizing hepatitis may predominate, but in suckling mice, death may result from encephalitis or enteritis (5). It is not clear whether the serologically distinct strains of MHV have differing tropisms and disease patterns. A detailed study of the pathogenesis of this disease and complete serologic and virologic characterization of the MHV isolate is in progress.

In view of this direct etiologic association of MHV with lethal enteritis of newborn mice (in the absence of other detectable viral agents), it now seems that the term LIVIM should be discarded. Moreover, if the extraordinary contagiousness of MHV is appreciated when this kind of enteritis is seen, eradication procedures may be adjusted accordingly.

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[2] Accepted for publication 15 September 1976.
[3] Microbiological Associates, Bethesda, MD.