Progress in the Chick Edema Problem

By Dr. Leo Friedman
Food and Drug Administration

It has been almost four years since I first became aware of the problem that we know today as "chick edema disease." Because of our activity on this problem, my colleagues and I have had the opportunity to become acquainted with many scientific groups and individuals working in the same area with whom we have enjoyed a fruitful cooperation and pleasurable association. We hope that they feel as kindly toward us as we do to them, but sometimes, I know, they wish as we do that they had never heard of chick edema disease.

This problem has been most difficult and progress frustratingly slow. Despite the meager amount of new information that can be added at this time, especially since the most recent advances were reported by Dr. Artman recently, it is nevertheless worthwhile to review the several aspects of this problem and see its present status in full perspective.

As you recall, during 1957 an epidemic disease caused millions of dollars in losses among broiler flocks throughout a large part of the U.S. After elimination in succession of all other possibilities, attention was focused on the fat ingredient of the feed as the etiologic agent. A series of reports in 1958 from several laboratories described the manifestations of the disease and definitely implicated a toxic fat or a toxic substance in fat as the cause. The characteristic symptoms were droopiness, ruffled feathers, labored breathing and high morbidity and mortality. Autopsy findings revealed hydropericardium, abdominal ascites (water belly), subcutaneous edema, swollen liver, swollen and pale kidneys, etc. In laying hens the toxic fat caused a rapid drop in egg production. Pullets receiving toxic fat during the full growing period did not come into production, and mortality was very high. Hydropericardium, the most common lesion found in young birds, was not found in birds of laying age.

Symptoms Different

These differences in susceptibility and symptoms in different age groups of the same species should be noted. The feeding of toxic fat to other species has not produced such striking results as with young chicks, with the exception possibly of monkeys. However, every species that has been tested has shown evidence of deleterious effects. Very little work has been done with rats. Our very limited experience indicates that they are much more resistant than chicks in short-

EDITOR'S NOTE: *This report from the annual meeting of the Animal Nutrition Research Council in Washington is the 10th in a series being published in Feedstuffs. The author, Dr. Leo Friedman, is assistant director of research, division of nutrition, Department of Health, Education and Welfare, Food and Drug Administration, Washington.*

substituted for the usual normal fat, there was poor reproduction and lactation performance. The females on the toxic fat ration whelped pups that were dead or weak, and, furthermore, the mothers seemed to have an insufficient milk supply. When the pups were removed before weaning and fed a normal ration the increase in growth was immediate and dramatic. Also, the females on the toxic fat ration tended to lose hair on their backs and shoulders. With the ration containing toxic fat, post-weaning growth tests (6-18 weeks) with five litters of pups demonstrated inferior growth performance using either weight gain or increases in body length as the criterion.

Work With Other Species

In these experiments with other species, fat that had first been proved to be toxic to chicks had been used. In the case of monkeys, a sample of triolein that had produced irreversible toxic symptoms for no apparent reason later was proved toxic to chicks and was the source from which we isolated a highly purified crystalline "chick edema" factor. At the present time, then, "toxic fat" that produces "chick edema disease" has been demonstrated also to produce deleterious effects in rats, guinea pigs, swine, dogs and monkeys. It should be emphasized that the toxic fat undoubtedly contains many other substances that may have effects in these other species. Definitive information as to the effect of "chick edema factor" (CEF) in other species must await tests with purified CEF. Triolein-fed monkeys probably received the "purest" source of CEF. However, purified CEF should be administered to monkeys to verify the implication that the severe toxic symptoms observed with triolein were due to CEF.

Relatively little has been done to throw light on the mechanism of the toxic effect. Flick and Gallo in our laboratories have reported that in young chicks showing symptoms of reduction in growth without hydr pericardium or ascites."

In chicks, "Microscopic examin tion of the tissues of the test anima revealed lymphocytic foci in the ep cardium and myocardium. Edem tous fluid separated the myocardi fibers. Edema of the lungs was a fr quent observation in the experime tal birds.

". . . Blood pressure indicated t test birds had an elevated avera mean pressure in the right ventri of 6 cm. water and 2 cm. water in t vena cava. Electron micrographs the myocardium revealed shrunk vacuolated mitochondria in the t animals.

"'Toxic fat' produces a reduct in growth rate of experimental a mals. This reduction depends on age of the animal and the level 'toxic fat' added to the diet. Hyd pericardium and ascites are a quent lesion in the animals receiv from 1.0 to 5.0% 'toxic fat.' W this level was reduced to 0.25% the diet, reduced testicular deve ment was a more sensitive crite than hydropericardium, ascites weight gain for evaluating chr toxicity.

"T mechanism by which 't fat' induces hydropericardium ascites appears to be associated degeneration and edema of the r cardial fibers. These data would to eliminate the kidneys, liver endocrines as the primary caus edema. The early development of dropericardium, increased ven pressure, enlarged hearts, mitoc drial changes in the myocardium generalized edema suggest that myocardium may be directly in ed; however, altered capillary pe ability has not been excluded. It lieved that cardiac decompens and increased capillary permeat act together in producing the e sive extravascular fluid collectio the demise of the animal."

The wide range of suscepti within and among species an variety of toxic effects that hav ready been noted would make i year logical that some primary of structure and function such a mitochondrion, may be the tar the toxic factor and that the obs differences may be explained by tors such as absorption, specific ing, transport, detoxication, etc. determine the local concentrati any substance in a specific sit

Another possible mechanism had suggested itself quite ea that the toxic factor interfere the normal regulation of elect

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These differences in susceptibility and symptoms in different age groups of the same species should be noted. The feeding of toxic fat to other species has not produced such striking results as with young chicks, with the exception possibly of monkeys. However, every species that has been tested has shown evidence of deleterious effects. Very little work has been done with rats. Our very limited experience indicates that they are much more resistant than chicks in short-term feedings, but that when fed in sufficient dosage, extracts of the toxic fat produce definite deleterious effects as shown by growth depression, enlarged and fatty livers, and marked involution of the thymus.

I recall few reports of the effects of toxic fat on swine, but again, in our own limited experience we have seen depressed growth . . . and have demonstrated the presence of toxic factor in the meat of hogs that had been fed toxic fat.

I am indebted to Dr. Wilcke of Ralston Purina for reports of studies on guinea pigs and dogs. Guinea pigs fed 2½% toxic fat stopped growing after six weeks, and death losses occurred after eight weeks. At a level of 4½% toxic fat weight losses occurred after three weeks and deaths after four weeks. Control groups receiving non-toxic fats did not show weight loss or deaths. The only observed pathology at the conclusion of the experiment was congestion of the lungs and mottled livers.

In experiments with three different breeds of dogs, using Purina Dog Chow in which 10% of toxic fat was have an insufficient milk supply. When the pups were removed before weaning and fed a normal ration the increase in growth was immediate and dramatic. Also, the females on the toxic fat ration tended to lose hair on their backs and shoulders. With the ration containing toxic fat, post-weaning growth tests (6-18 weeks) with five litters of pups demonstrated inferior growth performance using either weight gain or increases in body length as the criterion.

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Relatively little has been done to throw light on the mechanism of the toxic effect. Flick and Gallo in our laboratories have reported that in young chicks showing symptoms of the disease, the intra-cellular water was not changed. Neither were the total blood and plasma volumes altered so that the observed edema was primarily interstitial. Hemoglobin and hematocrit levels were low and blood glucose levels were decreased in advanced stages of the disease. Plasma sodium, potassium and chloride were not affected. In the liver, neutral fat was decreased and phospholipid increased. Preliminary experiments by Flick give some indication of increased membrane permeability, but these must be repeated under much more rigorous conditions.

Dissertation Abstract

A most interesting study in chicks has been reported by J. R. Allen, Jr. Part of the results were presented at the federation meetings in March, 1961, and the complete study is available as the dissertation of J. R. Allen, Jr., University of Wisconsin, 1961. I will quote portions from the dissertation abstract [Dissertation Abstracts 22, [2], 545 (Aug., 1961)]:

"Experiments conducted to determine the effects of 'toxic fat' on mice, pigeons and turkeys demonstrated a

rate of ex... reduction d... age of the animal and ... 'toxic fat' added to the diet ... pericardium and ascites ... quent lesion in the animals ... from 1.0 to 5.0% 'toxic fat' ... this level was reduced to 0... the diet, reduced testicular ... ment was a more sensitive cri... than hydrope... cardium, ascit... weight gain for evaluating ... toxicity.

"... mechanism by which 't... fat' induces hydropericardium ... ascites appears to be associated ... degeneration and edema of the ... cardial fibers. These data would ... to eliminate the kidneys, liver ... endocrines as the primary caus... edema. The early development of ... dropericardium, increased v e n ... pressure, enlarged hearts, mitoc... drial changes in the myocardium ... generalized edema suggest that ... myocardium may be directly inv... ed; however, altered capillary pe... ability has not been excluded. It i... lieved that cardiac decompens... and increased capillary permeal... act together in producing the e... sive extravascular fluid collection... the demise of the animal."

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Another possible mechanism had suggested itself quite earl... that the toxic factor interferes ... the normal regulation of electr... and water balance. Selye and S... back in 1943, described the pr... tion of edema symptoms in chick... certain steroids and the accentu... of these symptoms by increasin... salt intake of the chicks. Alex... has shown that it is possible to ... duce hydropericardium in chick... increasing the NaCl in the ratio... to prevent its occurrence even ... CEF by eliminating NaCl from ... diet. Work in our own and other ... oratories has illustrated beauti... the interaction of nutritional fa... on the susceptibility of the chic... a toxic agent. For example, the ... ent AOAC bioassay diet for "... edema factor" is probably four ... more sensitive than the assay ... we used originally, although ... have approximately the same ... content.

A point to remember is that h... pericardium as a symptom of to... in chicks is not new. In additi... NaCl and certain steroid horm... chapter 40 in Biester and Selv... on Poisons and Toxins indicates ...

(1) Zinc phosphide, used as ...

(Continued on page 22)

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denticide produces "various degrees of congestion with the accumulation of some serous fluid in the pericardial sac as well as in the abdominal cavity in some cases."

(2) Alpha naphthyl thiourea, the rodenticide ANTU, shows in poisoned chicks evidence of lung edema and excessive quantity of fluid in the pericardial sac.

(3) Sodium monofluoroacetate, compound 1080, another very effective rodenticide, produces in chicks distention of the pericardial sac with clear straw-colored fluid, in addition to other marked pathological changes on the heart and lungs.

(4) Chlordane. "The primary lesions found in all fatal cases were in the heart. Excessive quantities of fluid were found in the pericardial sacs. . . ."

The weed "corn cockle" and several species of Crotalaria produce seeds which are toxic, and in chicks the toxic symptoms include hydropericardium.

However, in each case other characteristic pathology is usually present, and in no case is the purified toxic principle of the same high order of activity as the toxic substances that have been isolated from toxic fats.

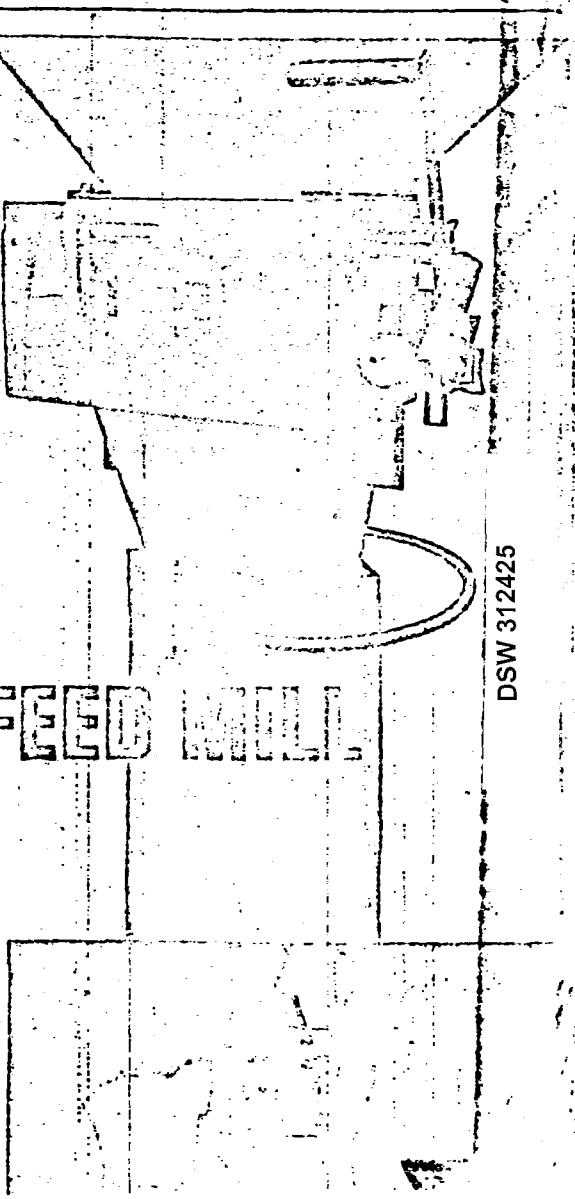
It is well known now that chicks can efficiently utilize large amounts of fat in properly balanced rations. The use of fat as a standard ingredient of poultry feeds grew as the price of fat calories dropped and became competitive with calories derived from corn. The chick edema disease epidemic of 1957 was a totally unexpected consequence of this growing practice. Many of you are familiar with the story of how the toxicity was associated with a fatty by-product of stearic and oleic acid manufacture that had been blended with feed grade fats.

Very large quantities of fatty acids are used industrially in the manufacture of lubricants, rubber, paints, asphalts, roofing, chemicals, and to a much smaller extent in foods. Relatively low grades of fat are split into fatty acids and glycerol at high temperatures and pressures, sometimes with the aid of catalysts. The glycerol is recovered and the fatty acids are distilled under vacuum. The first distillate may be used directly as the highest grade of mixed fatty acids or it may be separated by a new temperature crystallization process into stearic (saturated) and oleic (unsaturated) fractions. The residue from this distillation is resplit and redistilled. The second distillate yields a lower grade of fatty acids. The residue from the second distillation is usually suitable for use on highways or in rubber manufacturing, but occasionally it is again recycled to obtain a third distillate and another residue. It was this third residue that had been blended with feed grade fats for use in feeds.

Every sample of residue of this type from several manufacturers of fatty acids proved to be rich in chick edema toxicity. Our first impression, therefore, was that the toxic factor was produced during the splitting and

7 Ways Richardson G-17 Semi-Automatic Baggers

SAVE MONEY IN ANY FEED MILL



1. FIT ANY SIZE MILL—as the main bagger for the small mill or the small-batch bagger for the larger mill.
2. HANDLE MOST FEEDS—grains, pellets, mashes.
3. HANDLE ALL SIZES AND TYPES OF BAGS—open-mouth textile or multi-wall paper—10 to 140 lb. capacities.
4. LOW COST—little more than an all-manual unit.
5. AUTOMATIC CUT-OFF—no time lost trimming... much faster than all-manual baggers.
6. CONSISTENT ACCURACY—eliminates human error... keeps profits out of the bag and in your pocket.
7. COMPLETE LINE OF ACCESSORIES.

Bagholders—camgrip (shown); also manual and air-operated.
Spouts—quick-change square or oval in a range of sizes.

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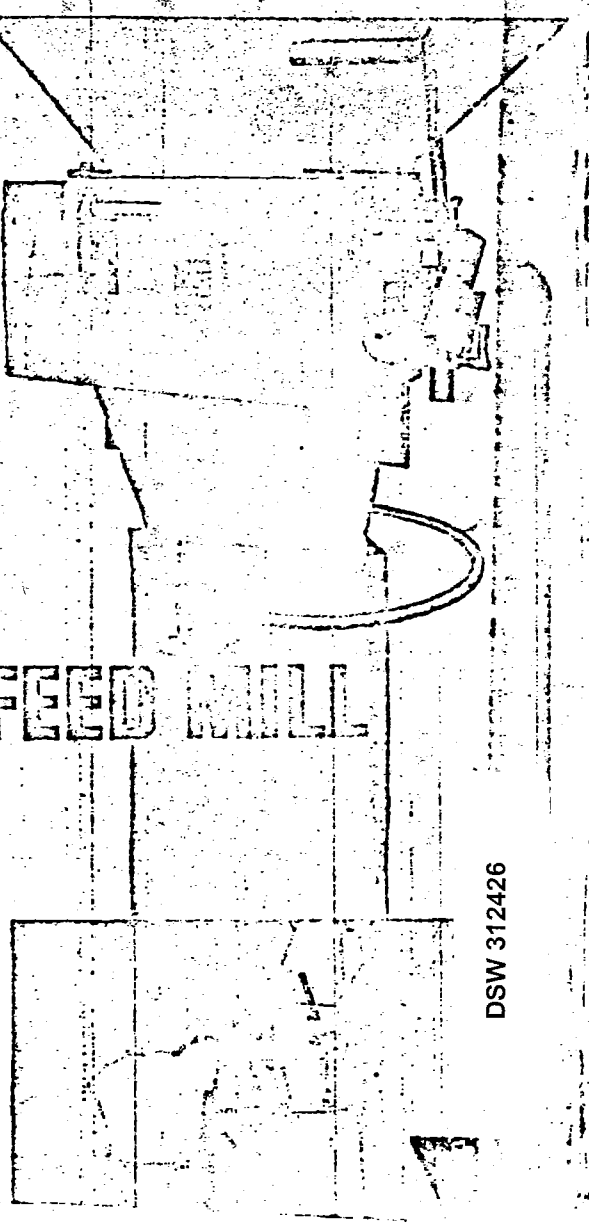

ilation steps and that it was
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vealed that the toxic factor
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vere used for the production of
est grades of fatty acids, and
intended for food purposes. This
overy was made independently
reported by Ames, et al., who
found several samples of oleic
and a monoglyceride made from
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All this happened just after
passage of the Food Addi
Amendment. The fatty acid manu
turing firms were very cooper
in providing us with information
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rial purposes. In our visits and
with their technical people we
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of materials did enter food char
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the technical committee of the
Acid Producers Council became
tively engaged in a study of
problem, and we have enjoyed
whole-hearted cooperation of the
ty acid industry. While they
studies to determine what par
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studies were continuing on the
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of the active substance. Three y
ago at the AOAC meeting a sy
sium on chick edema was hel
which reports from the Purina
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laboratories and the Food and
laboratories described the pro
made up to that time. The
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Every step and experiment h
be followed by the chick bio
However, during the first year a
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about the same rate. First it
demonstrated that the "chick ed
toxicity was entirely in the unsa
fiable portion of the fat. Then, i
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gested the presence of dipalmit
The third fraction consisted of ste
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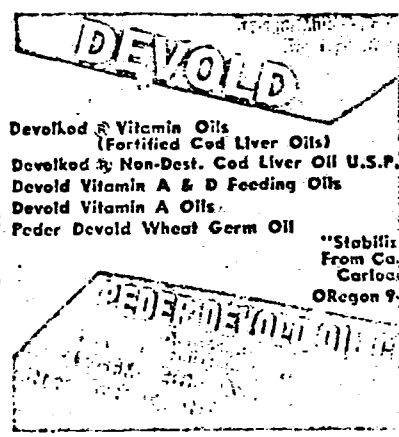
synthetically prepared samples of
lestadiene and dipalmitone sho
that only fraction 2, but not the
palmitone, was toxic.

Several approaches were tried



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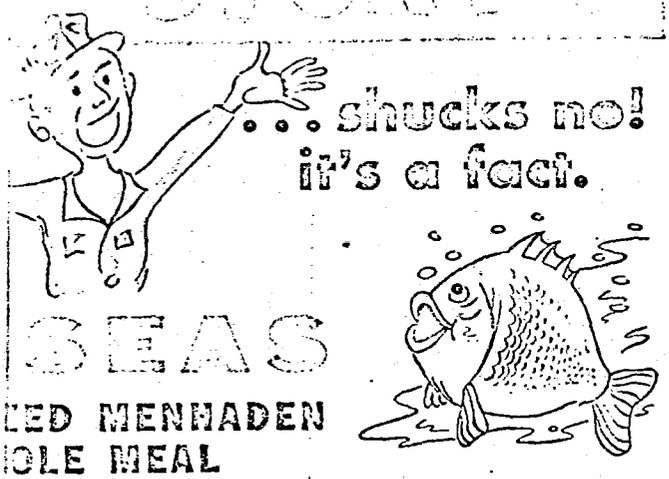
STORY



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multaneously to purify fraction 2. I will not take the time to describe our experiments with a 500 tube counter-current distribution between iso-octane and methanol, or the separation of carbonyls with Girard-T reagent or the consecutive rechromatography on alumina and silane treated Celite. Suffice it to say that as our fractions became more potent we relied more and more on ultra-violet spectrophotometry as an indication of concentration and purity. Two distinct types of fractions were obtained, one with the ultra-violet spectra characteristic of naphthalene compounds and the other of phenanthrene compounds. Both fractions contained the toxic factor. However, the sum of their toxicities was not comparable to that of the starting material in the final purification steps despite the fact that practically all of it was accounted for by weight in the eluates. Since only the fractions that had a significant weight had been tested biologically, the insignificant, hardly visible residue of less than 0.5 mg. in the practically "empty" beaker that represented the cut between the two major fractions was rinsed into a chick diet and to our surprise was very active at approximately 0.1 ppm., representing the most potent material we had obtained. At this stage we had practically exhausted our raw material, and we had to start from the beginning once again.

During the course of these studies we had learned that Drs. Portman and Andrus in the department of nutrition at the Harvard School of Public Health had lost a number of monkeys in a nutritional study. They had used a synthetic triolein as the source of fat and had to abandon the experiment. At a Gordon Research Conference I had the opportunity to discuss this experience with Dr. Portman. Fortunately about 40 lb. of the triolein was still available. It proved to be toxic in the chick edema assay. The triolein was of excellent quality, containing only 0.9% of unsaponifiable material. This unsaponifiable proved to be the richest source of the toxic material we had ever examined.

The toxic fraction was separated from the triglyceride by molecular distillation. The distillate from 17 Kg. of triolein was saponified, and the unsaponifiable was chromatographed on alumina to remove the cholestadiene fraction. The naphthalene and phenanthrene-containing cuts were collected, yielding 670 mg. of material. This fraction was rechromatographed on more retentive alumina with 5% ether in petroleum ether, and 240 mg. of naphthalene-phenanthrene material was separated. This was rechromatographed in the same system and three distinct types of U.V. spectra began to emerge in the fractions: Naphthalene (235 mμ), phenanthrene (260 mμ) and a new peak at 245 mμ. These material were combined and chromatographed on a silane treated Celite-iso-octane column, with 80% alcohol saturated with iso-octane as the mobile phase. The cuts with maximum absorbence at 245 mμ were further purified by two more chromatographic treatments on alumina at a very high sample:adsorbent ratio (1:2,009 and 1:25,000). The final fraction was completely free of absorption peaks near 235 and 260 mμ. This fraction was evaporated to dryness, dissolved in a small volume of boiling iso-octane and stored overnight in the refrigerator. White crystals were out [illegible] weighing 2.6 mg. and represent [illegible] concentration over the original triolein of three million-fold. This material at 1 ppm. in the [illegible] chicks in 12 days and produced typical hydropericardium when fed .05 ppm. in a 21-day test.

During the last stages of this work the Merck group [Harmon, et al. JACS 82, 2078 (1960)], announced the isolation of a crystalline chick edema factor from a toxic fat. On July 1960, the Merck group informed that they had found 47% chlorine in their crystalline material. The presence of chlorine in our material was quickly confirmed by the use of Dohrmann microcoulometric chromatograph.

In this test, a few micrograms sample is injected into a gas chromatograph and the components they emerge are pyrolyzed at 8 under oxidizing conditions. The halogen acid formed from halogenated materials is titrated automatically a microcoulometer.

Of interest also is the isolation a crystalline material that had ultra-violet absorption spectrum identical with that of the toxic mate but shifted 3 mμ so that the m peak was at 248 mμ instead of mμ. It behaved like the toxic substance in the microcoulometric chromatograph, showing a similar tention time and halogen cont However, it was completely inac in the chick edema test when fe 1 ppm. in the diet.

The finding of chlorine in the substance was a major breakthr It was no longer necessary to in terms of a naturally occur [illegible]

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When You SELL
"SNOW FLAKE"

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Haynie. First-in-the-field research has devel-
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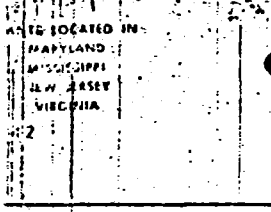

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The toxic fraction was separated

235 and 260 mμ. This fraction evaporated to dryness, dissolved a small volume of boiling iso... and stored overnight in the ref... tor. White crystals were ... weighing 2.6 mg. and repre... concentration over the ori... lein of three million-fold. ... rial at 1 ppm. in the ... chicks in 12 days and produced cal hydropericardium when fe... .05 ppm. in a 21-day test.

During the last stages of this the Merck group [Harmon, e... JACS 82, 2078 (1960)], announce... isolation of a crystalline chick e... factor from a toxic fat. On Jul... 1960, the Merck group inform... that they had found 47% chlori... their crystalline material. The ... ence of chlorine in our material quickly confirmed by the use o... Dohrmann microcoulometric chromatograph.

In this test, a few microgra... sample is injected into a gas ... matograph and the component they emerge are pyrolyzed at under oxidizing conditions. The ... gen acid formed from halogen materials is titrated automatical... a microcoulometer.

Of interest also is the isolati... a crystalline material that ha... ultra-violet absorption spectrum ... tical with that of the toxic mat... but shifted 3 mμ so that the n... peak was at 248 mμ instead of ... mμ. It behaved like the toxic ... stance in the microcoulometric chromatograph, showing a simil... tention time and halogen con... However, it was completely ina... in the chick edema test when fe... 1 ppm. in the diet.

The finding of chlorine in the ... substance was a major breakthr... It was no longer necessary to t... in terms of a naturally occurring ... terial that had changed chemi... under the conditions of indus... fatty acid production. The possi... of contamination with one of ... familiar chlorinated hydrocar... was obvious. Samples of tetrach... naphthalene and hexachloron... thalene, kindly provided by F... and Bell of Virginia Polytechnic ... stitute, who had demonstrated ... these compounds produced hy... keratosis in cattle, were withou... fect in the chick edema test. We ... tested a long list of chlorinated ... pounds including aldrin, dieldrin, dane, DDT, DDE, BHC, chlor... toxaphene, methoxychlor, and a s... of Halowaxes, without any defin... positive indication. Further... these have all been heated with ... acid at 250° C. for long periods ... then fed to chicks, with negativ... sults. Also, on the theory that ... may sometimes be bleached wit... tive chlorine materials which ... chlorinate a sterol nucleus, we ... chlorinated cholesterol, squale... tone and equilenin with negativ... sults. To test the theory ...

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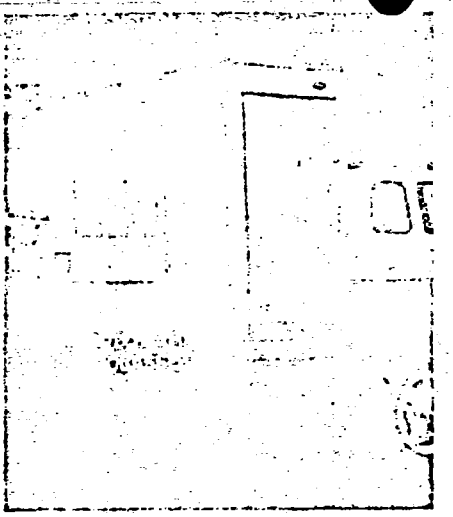

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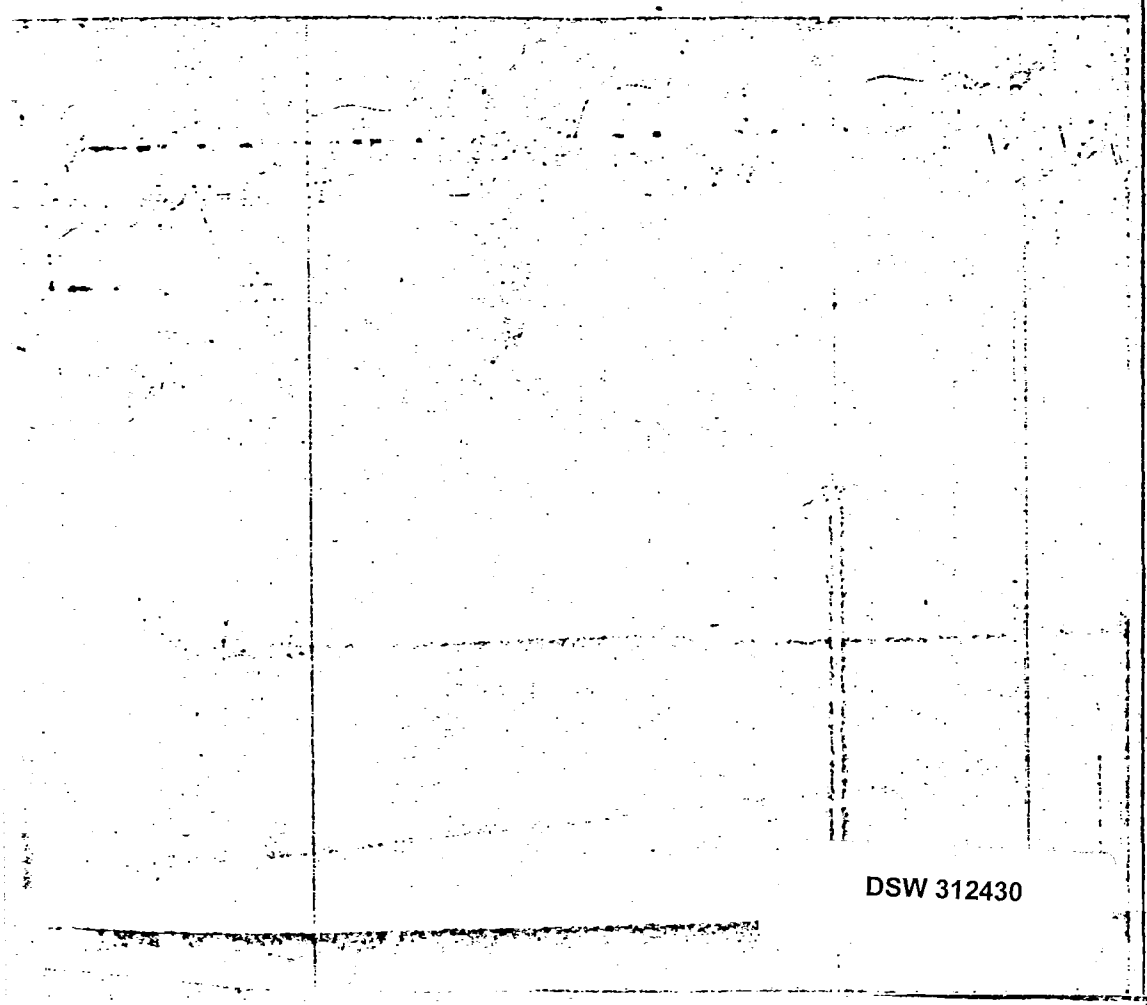

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CHICK EDEMA

(Continued from page 21)

toxic substance is a metabolite o chlorinated insecticide we have large doses of chlordane, metho chlor, heptachlor, aldrin and dield to rats for a month and are feed the unsaponifiable extract of the carcass in the chick test. The resu to date show that chlordane and m thoxychlor produce no response.

Industrial Experiments

Similar experiments have been c ried out and are still in progress at least two industrial laborator under conditions of fatty acid prod tion. The results so far have be largely negative or at best only s gestive but not clear cut. Dr. Artin has reported that chlorination naphthalene and phenanthrene substitution reactions has produc CEF active products. The chlorinat phenanthrene is particularly prom ing, since preliminary fractionati experiments indicated the possibil that a highly toxic compound w produced.

Dr. Boyd O'Dell and colleagues the University of Missouri observ hydro ricardium and other sym toms of chick edema disease in chic housed in freshly painted cages. Th traced the responsible agent down one of the paint ingredients, a chlo nated biphenyl sold under the nar Arochlor. We have tested seve Arochlors of different chlorine co tent. Some were not toxic; others pr duce the disease but only at rel tively high feeding levels, e.g., 2 ppm. It may be that an impurity these compounds is the toxic ager or that they are innately toxic at t high levels fed. Of interest is the u of one of these Arochlors in some i secticide formulations. At the prese time there has been no real eviden developed to implicate any produ or compound. However, the circum stantial evidence is stimulating co siderable speculation and activity.

The feed industry has managed i careful control of ingredients to avo a recurrence of the 1957 epidemi The color test developed by Brew, e al., at Purina has been very usefu in screening out toxic fats. This te is not specific but is useful since th presence of large amounts of steroid compounds that give this test usual indicates still residues that may b toxic. It is useless, however, for fat acids and other products such as tri lein, monogylcerides, etc., that gi no response in this test; but whi sometimes are quite toxic.

Georgia Outbreak

Last year, at this time, an outbre of the chick edema disease occurr in Georgia. Although considera chlordane residues were found in t feed, we do not believe they were sponsible for the symptoms obser Furthermore, the best inform

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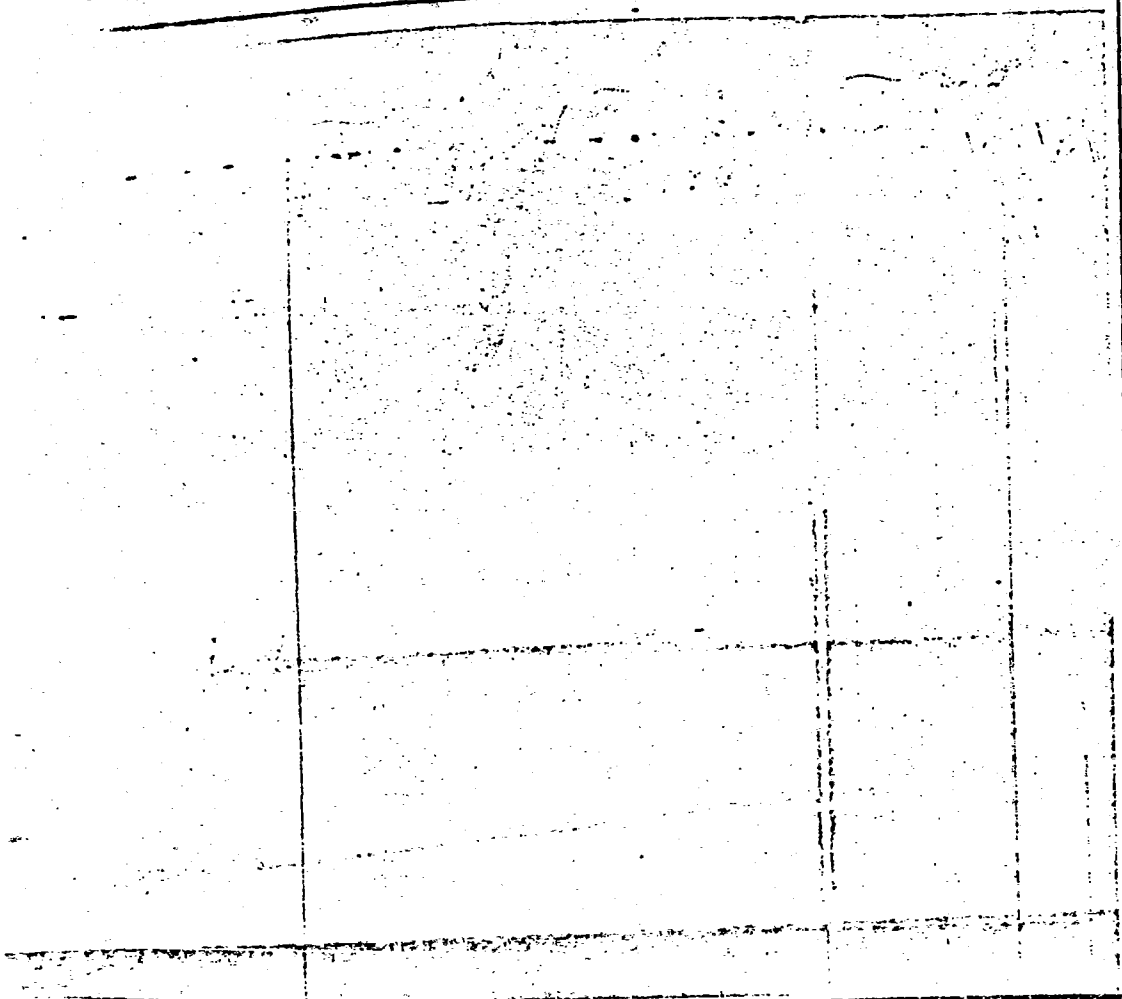
... compartment-type ... which is a completely enclosed alumi- | No. 7903 on the coupon ...



experiments indicated the ... that a highly toxic compound ... produced.

Dr. Boyd O'Dell and colleagues ... the University of Missouri observed hydro-pericardium and other symptoms of chick edema disease in chicks housed in freshly painted cages. They traced the responsible agent down to one of the paint ingredients, a chlorinated biphenyl sold under the name Arochlor. We have tested several Arochlors of different chlorine content. Some were not toxic; others produce the disease but only at relatively high feeding levels, e.g., 20 ppm. It may be that an impurity in these compounds is the toxic agent or that they are innately toxic at the high levels fed. Of interest is the use of one of these Arochlors in some insecticide formulations. At the present time there has been no real evidence developed to implicate any product or compound. However, the circumstantial evidence is stimulating considerable speculation and activity.

The feed industry has managed by careful control of ingredients to avoid a recurrence of the 1957 epidemic. The color test developed by Brew, et al., at Purina has been very useful in screening out toxic fats. This test is not specific but is useful since the presence of large amounts of steroidal compounds that give this test usually indicates still residues that may be toxic. It is useless, however, for fatty acids and other products such as triolein, monogylcerides, etc., that give no response in this test, but which sometimes are quite toxic.

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Georgia Outbreak

Last year, at this time, on outbreak of the chick edema disease occurred in Georgia. Although considerable chlordane residues were found in the feed, we do not believe they were responsible for the symptoms observed. Furthermore, the best information we have indicates that only rendered fat was used in this feed and no product of the fatty acid industry was involved. With each new development the scope of the problem increases. First we were concerned only with still residues, then also with fatty acid distillates and their derivatives. For a long time it was felt that even the fat derived from animals was involved. Recent evidence from sources in the fatty acid industry and our own studies indicates that some vegetable fat sources may yield fatty acids contaminated with CEF.

Still another development has occurred to further complicate the picture. Early this year in the course of our regulatory activities, we examined a sample of oleic acid. All test chicks died by the end of the second week, with symptoms of severely stunted growth, ascites, jaundice and pathology of the liver and other organs, but with no hydropericardium. This sample had been tested by the manufacturer last year before the adoption of the present A... test procedure. The testing laboratory had used the procedure we ours...

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had used in our earlier work, and had found the sample negative for chick edema. Repeat of the test in both laboratories by both procedures confirmed both findings. The sample is free of chick edema disease factor when tested on a diet of natural ingredients, and the chicks survive in apparent good health. On the casein-sucrose diet of the AOAC chick edema test, the chicks fail to grow and die early with the described symptoms but no hydropericardium. Furthermore, the dose response curve for this effect is very steep, since the ratio of the dose that gives a maximum effect to the dose that produces a minimum effect is less than two, as compared to a ratio of four to five for chick edema factor. Evidence from preliminary fractionation studies also indicates that this is an entirely different substance. There is no other information as to its characteristics at this time. There is evidence that this toxic contamination has occurred in different places from time to time and in a variety of fatty acid samples and may occasionally occur together with CEF. Here again we must anticipate that this material may occur elsewhere independently of the fatty acid industry.

For whatever comfort we may derive, it should be noted that chick edema disease has been observed in England. In a letter to the editor of the Veterinary Record of June 10, 1961, C. C. Wannop of the Houghton Poultry Research Station draws attention to a condition apparently identical with that reported by Sanger, et al., and Schmittle, et al., in 1958, that has appeared in several broiler flocks. In a personal note dated Sept. 29, he says that the condition has disappeared for the time in his country.

At the present time fatty acids can be used in the manufacture of foods or food ingredients only if they are free from CEF. This requirement made necessary the development of a bioassay which has been accomplished by collaborative work and is now being adopted as official by the AOAC.

I have tried to review the history of this troublesome problem, what little is known of its toxicology and its physiological aspects, the speculations as to the origin of the contamination, and attempts to track down its sources. I have sketched quickly our own attempts at isolation and identification of the toxic factor and have alluded to the most recent developments along this line that were reported at the AOAC Section of Fats and Oils by Dr. Artman.

* * *

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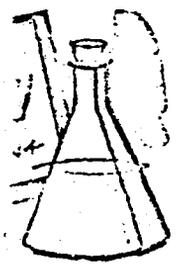

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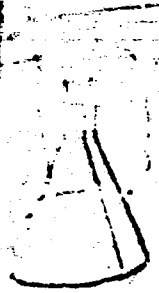

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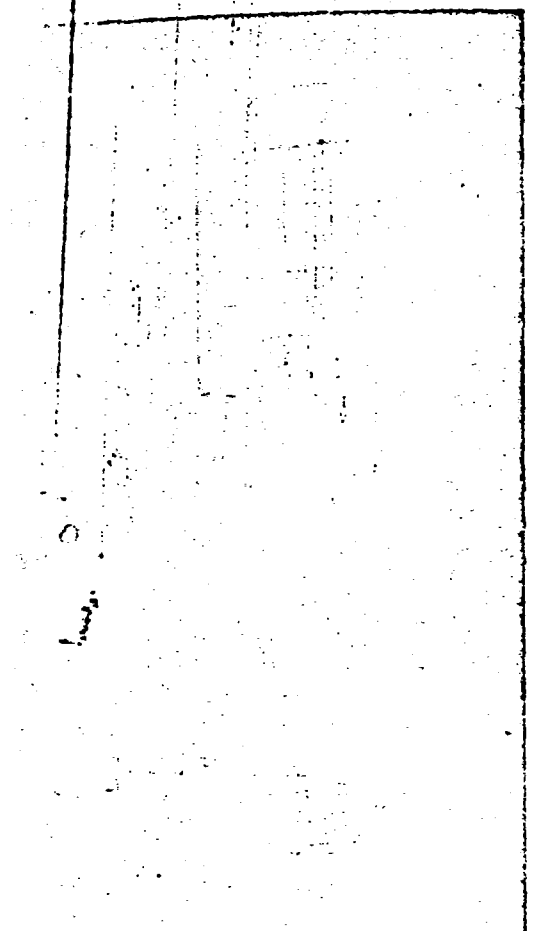

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I have tried to review the hi... of this troublesome problem, w... little is known of its toxicology a... its physiological aspects, the spec... lations as to the origin of the co... tamination, and attempts to trac... down its sources. I have sketche... quickly our own attempts at isolatio... and identification of the toxic fact... and have alluded to the most rece... developments along this line... were reported at the AOAC Sec... of Fats and Oils by Dr. Ar...n.

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