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L & M - A PERSPECTIVE REVIEW

1. There are biologically active materials present in cigarette tobacco.

   These are:
   a) cancer causing
   b) cancer promoting
   c) poisonous
   d) stimulating, pleasurable, and flavorful.

2. There is no reason why the poisonous group, CO, HCN, NO_2, etc., cannot be reduced, even though they are not seen as a primary health hazard. Methods for removal are:
   a) filtration (treated carbon, etc.)
   b) treatment for removing precursors, CN elimination
   c) addition as a reactant (urea for NO_2).

3. Cancer promoting materials, esters, phenols, amines, can possibly be reduced by some treatment, extraction, etc.

4. The cancer-causing materials apparently are in many substances that are pyrolyzed but seem to be associated with tobacco in greater concentration than for primarily cellulose.

5. There appear to be variations in radically different methods for preparing tobacco in the biological measurements.

6. There are many forces which continue to emphasize that L & M is in the tobacco business, not the pleasure business. Any shift from being in the tobacco business will have to be accomplished by avoiding these major pressures. A means is emerging. Is it correct? Can it be accelerated?

7. The use of C.T.I. not as a product but as a concept opens a way of having a "tobacco" cigarette and at the same time exploring a great deal about the "causative factors" in cigarettes and at the same time not having to face major opposition for not using tobacco.

8. Perhaps one of the reasons that an emphasis on the little poisonous molecules was avoided was that filtering them out seemed a major threat to the other gas phase materials that are added as flavoring agents.

   We know that gaseous molecules can be preferentially removed compared to aerosol particles. The use of filters to remove all gases may remove odor and flavor components. From this there is some evidence that the cigarette is becoming more a flavor principle than a truly tobacco product alone.

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9. What the "causative precursors in tobacco are is not well known. The low-temperatu pyrolytic demonstration of long term biological activity suggests precursors that are molecularly sizable and different from the little-molecule-polymerization view which is amply demonstrated by the enhanced P.N.A.H. found at high temperature pyrolysis fractions now on long term test.

   So there is the suggestion of two mechanisms for causative agent products:

   1) low temperature formation
   2) high temperature polymerization,

   but what good is this? We've known it for several years--so what?

10. The non-tobacco exploration has indicated that the specific activity can be less--but no one wants a hemp cigarette.

    The use of solka floc in the <u>C.T.S. process</u> has produced a product of markedly lower activity--but it isn't tobacco in taste-flavor.

11. The C.T.S. variations even with tobacco suggest that we are not yet getting the controlling concepts. Are they in part physical? Some pressure bomb work is planne but it has been slow to date.

    Are the effects from chemical precursors?

12. The naturally occurring class of tobacco phenols are possible precursors, e.g., chlorogenic acid, rutin, and caffeic acid.

13. By extraction of tobacco fractions with solvents, etc., we should be able to take ou many "tobacco" materials and recombine them in the <u>C.T.S. process</u> onto solka floc to give an acceptable "tobacco" cigarette whose short and long term effects can be tested.

    A.D.L. can do the same adding the extracted components to Kleenex to make cigarettes for short term testing.

14. The promoting materials, e.g., esters, small phenols,ie, in Kleenex or C.T.S. cigarettes, etc., should be looked at in the same manner, but the short term tests may be harder to interpret.

15. Chemical treatments have not been too successful on tobacco. Perhaps the acid treatments are a help. Others are doubtful.

16. The chemical reagent additives to tobacco have been without marked effect except for the nitrates. The nitrates act at the time of decomposition probably in the condense phase, but certainly prior to the formation of the aerosol of smoke. The nitrates do not cut down activity by the action of the oxides of nitrogen in spite of the fact that these oxides do react with the smoke condensate.

17. Other reagents including cobalt compounds are essentially without major interesting effect.

18. Nitrates added to tobacco are not commercially attractive.

19. The making of a C.T.S. cigarette is commercially acceptable and perhaps economically competitive with normal tobacco.

20. Are we not on the march to a "disassembled" tobacco cigarette that we "reassemble" via the C.T.S. process to minimize the biological effect. If this is true, what abo the patent situation? A.M.F. has the strongest position. L & M has a position with C.T.S. if it is with tobacco and with their own "loop-hole" binders.

But what about C.T.S. with only fractions of tobacco and with a base of cellulose, e.g., solka floc? Are we not already late in the concept sense?

There are two patent emphases:

1) patent a C.T.S. assembling process where the assembling has the entire range of freedom and where the concept is controlled,

2.) patent ways of doing it, of getting in binders, making binders in the process of treatments, e.g. pressure, explosion, etc., and all the little details that hold an entre but may not make it exclusive.

21. What are the flavor problems if a C.T.S. assembly process is possible that reduces biological activity?

22. Can't this approach be introduced as a part composition with normal tobacco as well? Like, 50% regular C.T.S. and 50% solka floc C.T.S. with "safe" additive to be equivalent to the nitrate added product currently experimental long term?

23. What about 22. but nitrating the regular tobacco only to give ED_{50}'s in the range of 40-60 in comparison to the current controls of 15? The 1/3 to 1/4 activity would be a good claim!

24. Is it possible that the above reduces the activity of all but the high-temperature little-molecule effects? What do nitrate cigarettes do long term when the smoke condensate is obtained from the Durham 700°C-1000°C pyrolysis?

25. Isn't the above the most optimistic view of the possibilities for this product since 1954?

26. How can we plan to "push" at an accelerated rate to tie down these concepts?