

CIRC

November 11, 1974

MEMORANDUM

TO: W. T. Hoyt

CC: HHR  
WUG  
RCH  
WK

FROM: Leonard S. Zahn

SUBJECT: International Cancer Congress, Florence,  
Italy, Oct. 20-26, 1974

Even before the Congress opened, there was no doubt that tobacco would get considerable attention: on Saturday, Oct. 19, the first issue of the Daily Congress, a tabloid newspaper which appeared each day of the session, noted that "Smoking and Lung Cancer" would be one of five main topics "to be tackled." (The other four were virology, immunology, chemotherapy, and surgery. Oddly, environmental cancer as a major theme was omitted, odd because there were many papers on this subject and also because so many of the "experts" present continued the claim that about 80% or so of all human cancers are caused by environmental factors.)

"No smoking" signs were posted in all meeting rooms; a similar caveat appeared in the program. (Yet many scientists were seen smoking cigarettes outside the meeting rooms. At one session I attended, on cancer agency campaigns in different countries, an unidentified member of a UICC education committee was admonished from the platform for lighting up in the hall outside.) In addition to the symposium on cancer and smoking, there were many other sessions and papers at which smoking drew attention, either directly or indirectly.

An estimated 5000 persons registered as "full" members (there also were some 1,000 associate members) and the staff ran out of materials and closed registration in mid-week. The Congress itself had more than 2100 papers from 10 conferences, 45 symposia, 12 workshops, 81 panels, and 7 advanced courses. During the first two days, sessions were held in Florence and in five other cities reached by bus or train. In Florence itself the various sessions were held in three different areas.

Press attendance was about 175-200, most of them Italian print and broadcast media people. There were reporters from some other European countries, and a few from Asia (mostly Japan) and South America. U.S. press representation was surprisingly meager: Joann Rodgers of the Baltimore News-American was there for the Hearst newspapers; Medical Tribune assigned two European staffers, one of whom served as a correspondent for Associated Press; the National Enquirer sent two people from its London bureau; the St. Louis Post Dispatch had a writer there and so did Medical World News. If there were others there from the U.S., they spent little time in the two press rooms. All the press people with whom I talked were

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aware of, and expressed interest in, the many smoking papers.

As for the smoking reports, virtually all were anti, few, if any, were really new as far as substance was concerned, and most were repetitious, especially those given by such familiar persons as Wynder and Hammond.

Some highlights:

1. One "new" report came from Daniel Horn, ex-head of the National Clearinghouse on Smoking and Health (it officially was transferred during the Congress to Atlanta under the Center for Disease Control; Horn is staying in Washington with PHS in some as yet undetermined role). Interestingly, Horn divulged his information in an interview with Rodgers of the Hearst newspapers and mentioned it only slightly during a formal talk.

He told Rodgers that lung cancer death rates among U.S. males seemed to be on the decline for the first time in 20 years. Using 1971 statistics, the latest available, he has found a leveling off of the rate in most age groups with indications of a marked decrease in men under 40. The leveling off applies not only to lung cancer but also to what he called "cigarette-associated" tumors, such as those of the mouth, bladder, larynx and pancreas.

Horn said the decline is the result of widespread use of low tar-nicotine cigarettes since the Surgeon General's Report of 1964, efforts to change smoking behavior and public demand for self-protection. He said the 1973 mortality figures, when they are available, are certain to substantiate his findings and may provide an even more optimistic picture.

He said (but was not so quoted in Rodgers' story) that Doll in England has found a similar decline.

2. Major attention to smoking was the symposium on "Cancer and Smoking." Scheduled chairman Irving Selikoff of New York was absent (he reportedly was ill) and D.D. Reid of England replaced him. The session consisted of three panels, each with a moderator and two formal speakers. This was changed from what we saw months ago -- three speakers. Also changed was the panel on "Search for a less hazardous cigarette," originally described with Emerson Foote as chairman; actual chairman at the meeting was Wynder.

A. Reid opened by saying the smoking-lung cancer association is the most dramatic so far uncovered. We need to look at alcohol and tobacco in connection with cancer, as Hirayama has pointed out in regard to esophageal cancer. Tobacco may not be the main factor but may exert a synergistic effect. We have to search for possible interactions between habits and circumstances of early life, such as malnutrition, in regard to esophageal cancer. Even in lung cancer there's a possibility

of a relationship to childhood respiratory infection but this is slight. Makes one wonder if we can demonstrate effects of other factors in lung cancer. In some British cities it has been found that children who had bronchitis turn up with lung cancer at ages 45-64. The effect of the U.S. Surgeon General's Report and the Royal College of Physicians' report has been very disappointing.

B. "Changes in smoking patterns in the U.S." -- Daniel Horn. This was similar to the talk he gave last June at the AMA meeting in Chicago. Changes have been occurring in smoking habits since 1953 when studies first began to show smoking was related to lung cancer. The changes include cessation of smoking and increased demand for low tar-nicotine filter cigarettes. The changes are more evident in men in the upper socio-economic levels. He referred briefly to the data covered in his interview with Rodgers (see No. 1). ✓

C. "Changes in smoking patterns in the U.K." -- G.F. Todd, honorary research fellow, Dept. of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine. He said tar and nicotine contents of British cigarettes have declined continuously since 1965. Using a "standard tar index," adult male and female consumptions have been converted to what he called "constant tar cigarettes." In terms of such cigarettes, male consumption declined 33% between 1965 and 1973, female consumption fell by 18%. Regular cigarette smoking in Britain is starting at an increasingly younger age.

"Considerable publicity has been given in the U.K. to the possible mixing of synthetic smoking substances with tobacco in cigarettes. Figures have been quoted which suggest that the delivery of particulate matter and of some specific smoke constituents by future cigarettes could be substantially reduced. These changes could have major effects on the pattern of smoking habits in the coming years. This means that estimates of cigarette consumption in terms of constant tar cigarettes will become of increasing importance in the future."

Unpublished data show there is a close numerical association between the lung cancer death rates for different ages of starting to smoke and the duration of smoking raised to the fourth power. "Of course, it is not suggested that relationships in life are as simple as this numerical example might imply."

D. "Multiple interaction effects of cigarette smoking" -- E. Cuyler Hammond, New York. He gave background information about the one-million person ACS study and the asbestos insulation worker study he is doing with Selikoff. There is a strong relationship between asbestos exposure, lung cancer and cigarette smoking. Asbestos exposure in men who never smoked regularly produces little, if any, increase in the risk of lung cancer.

As of this date, very few human cancers are caused by exposure to a single factor. Possibly lung cancer is one type. Everything suggests multiple exposure, not just ✓

cigarette-related cases. Two factors could operate separately, or synergistically or additively. The best approach for cancer in general is to study multiple factors.

E. "Influence of age on susceptibility to carcinogens" -- F.J.C. Roc, England. Four groups of mice were painted with 3,4-benzpyrene in acetone, treatment starting at different ages for each group, to see whether it's the age or the dose that's responsible for skin tumors. There was no evidence that age influenced early or late appearing skin tumors. His findings are consistent with the aging hypothesis and inconsistent with the dose hypothesis. (N.B. Despite what abstract says, no association was found between BP application and subcutaneous tumors.) The mouse skin-BP model is pertinent to the cancer problem.

F. "Search for a less hazardous cigarette" -- Gio B. Gori, Bethesda, Md. Educational campaigns against smoking have fallen far short of desired goals. Should the PHS feel a responsibility to decrease the risk from smoking? Yes, and NCI is helping with a three-pronged approach: a) identification and modification of individuals at risk -- covering environmental, inborn host and behavioral characteristics; b) drug development to find a means to make it more difficult to smoke or less difficult to quit. Studies are underway to test the chronic effects of nicotine. c) modification of smoking products to find a less hazardous cigarette (LHC).

LHC could be based on the more undesirable precursors -- through agricultural process, dissolving in solution, sheet tobacco, dilution of smoke, additive to improve combustion. Use of filters to selectively remove certain components. Modification of the product will affect its desirability, but it's not that simple. Chemical analysis is not enough to determine if a cigarette is less hazardous. Biological and animal models will be needed. The first test is skin painting, the second is inhalation work.

Screening for LHC includes the tobacco itself. A cigarette that is developed will have to be acceptable to smokers. Lots of tests will be needed, including inhalation tests with dogs. Interpretation of the tests won't be easy. He has tested 100 different models (I assume he meant LHC models) with some consistent results: a correlation between nicotine content and mouse skin-painting tests (?); porosity of the paper and condensate; certain filters are useful in reducing amount of nitrous oxides; nicotine content and Ph of tobacco influence acceptability; degree of inhalation is related to "amount" of condensate.

In closing, he hoped for a valiant effort by the tobacco industry in connection with low tar and nicotine cigarettes. This would be less traumatic than governmental action (to force production of such cigarettes).

G. "Search for a less hazardous cigarette" -- W. Dontenwill, Hamburg, W. Germany. Described his previously published work. Fraction No. 5 he isolated was 17 times stronger than whole smoke condensate. Larynx cancers were induced in Golden Syrian hamsters exposed to smoke from different cigarettes. Sodium nitrite added to some cigarettes produced a lower response, biologically. No larynx tumors were induced in vapor phase experiments. The carcinogenic material is in the particulate phase.

With less condensate but a high carbon monoxide level in cigarettes, the risk may increase for damage to the cardiovascular system. ✓

H. "Towards reducing tobacco-related lung cancer" -- Wynder. He gave a formal address though he was moderator of the LHC panel. His talk was theatrically impassioned and similar to former presentations at other meetings. He opened with a comment that there has been too much emphasis recently on liver cancers from polyvinyl chloride -- only 19 cases -- and not enough on smoking-related cancers -- thousands. (Hammond later expressed mild resentment, noting the early smoking-lung cancer reports were similar to the current PVC-liver cancer work.) Today one must smoke more cigarettes to get lung cancer because they are less harmful than they were 20 years ago. He has never seen lung cancer in anyone who started on filter cigarettes. In the years to come, lung cancer will more and more become a disease of the lower income groups (because upper income people are smarter and are giving up the habit). Female lung cancer rates will never equal those of males because women started later and on filter cigarettes. ✓

With NCI support, an 8-city epidemiological study is under way: 2200 males, 750 females, covering tobacco-related cancers.

Concerning tobacco, alcohol and larynx cancer -- the heavier the alcohol consumption, the more likely it is that the drinker smokes non-filter cigarettes.

We should not and cannot prohibit tobacco but we need an answer that's practical. We need the cooperation of all parties, including the tobacco industry. Our greatest hope lies in the less harmful cigarette.

I. A Dr. Snyder (?), identified as a co-worker with Selikoff, said they are doing a CEA (carcinoembryonic antigen) study which so far involves over 100,000 CEA assays with these results: 97% of the nonsmokers are normal; smokers have high CEA levels; former smokers, who stopped at least one year before the test, have normal readings. Over 3-million subjects at high risk for cancer are being covered and the study is to be published.

3. "The American Cancer Society surveys and follow-up" -- L. Garfinkel, New York, who works with Hammond. At a symposium on the role of lay and medical volunteers, he summarized some of the results of the 1959-65 ACS study on mortality. Some 68,000 volunteers traced 1,780,000 people and findings related to smoking and health were: for all causes of death, 85% higher for cigarette smokers; 55% higher for smokers who combined cigarettes, cigars and pipes; 11% higher for pipe smokers; 17% higher for cigar smokers. Lung cancer rates were 20 times higher for smokers of two packs or more daily.

In 1971, after preliminary testing in five California counties proved that 95% of the subjects alive in 1965 could still be traced, the ACS began a project to find the original interviewers and the people they interviewed. They have compiled a list of about 120,000 deaths since 1965, a 93% return on their tracing effort. With 550,000 questionnaires completed, they are now analyzing the data to: find additional data; study ecological factors that may be related to cancer death rates; determine if death rates are lower for persons who switched to low tar-nicotine cigarettes. The last point is the most important of the study, Garfinkel said. ✓

4. "Transplacental chemical carcinogenesis" -- N.P. Napalkov, Leningrad, U.S.S.R. He undertook experiments with BP injections into pregnant mice to explore his theory about the possible protective role of the placental barrier against chemical carcinogens. Results indicated a protective effect exerted by the detoxifying mechanism of the placenta.

"There are still more questions and suppositions in the problem of transplacental carcinogenesis than answers and convincing proof. Therefore, further studies will be required to ascertain the degree to which the above experimental findings may be relevant to the control of environmental cancers in man. The data already obtained in experiments on transplacental carcinogenesis show that such experiments can lead to a better understanding of, at least, certain features of the tumor induction in prenatal life."

A copy of Napalkov's text was obtained and arrangements were made to have it published in full in the Congress' daily newspaper.

5. "Geo-epidemiological aspects of lung cancer in Europe" -- N. Kraus, Dusseldorf, Ger. Checking areas of high lung cancer mortality in the northern countries of Europe, he found the greatest density occurred in regions where certain species of birds and their migrations. He noted that birds are known carriers of viruses and more and more scientists are accepting the virus theory of cancer. He made comparisons with air pollutants, radiation, "nicotine consumption" and other factors -- "without any result." ✓

Kraus' paper was brought to the attention of the Associated Press correspondent who wrote a story on it.

6. "Enhancement of malignant transformation in hamster lung cultures after exposure to fresh cigarette smoke (Kentucky standard)" -- Cecile Leuchtenberg, Lausanne, Switzerland. Within 5-6 months after exposure to smoke, hamster cultures underwent malignant transformation. Injection of these cultures into nude mice induced fibrosarcomas. After hamster cultures were aged about 12 months, they were exposed to whole smoke and to the gas vapor phase with the same results. Some factor in the gas vapor phase may be involved in, or contribute to, the malignant transformation. Therefore, elimination of tar from cigarettes is no guarantee of safety for the smoker. ✓

7. "Cancer of the lung in New Zealand" -- J. Borrie, Dunedin. In 1971 lung cancer in New Zealand caused 28% of male cancer deaths and 7% of female cancer deaths. Maori women are extremely heavy smokers, beginning at school age. Of Maori cancer deaths, one in three males and one in six females die of lung cancer. Compared with whites (male and female), the Maori male has a 50% higher and the Maori female a 700% higher chance of death from lung cancer. The Maori woman thus has a higher likelihood of developing lung cancer than any other female race group in the world.

8. "Studies of lung cancer among migrants" -- D.D. Reid, London. Cigarette smoking is an obvious common factor in the etiology of deaths from lung cancer and from chronic non-specific lung disease among immigrants to the U.S. Cumulative consumption at the rates appropriate to the time period spent in both native and adopted country may be the most relevant index of risk associated with smoking -- this is being investigated in the current study of British and Norwegian migrants to the U.S. There are indications that exposure to the British environment may have an additional effect to that of smoking. Also, smoking and air pollution may act synergistically to increase the risk of death from lung cancer.

9. "(Tumors of the) Esophagus" -- Janez Kmet, IARC, Lyon, France. Esophageal cancer shows great variation in geographical distribution with a 200-fold difference in incidence between areas of highest and lowest risk. The disease is generally more common in males than in females, over 20 times in some regions, in others both sexes are equally affected or even females have a higher risk. Studies in the U.S., France, Puerto Rico and elsewhere show alcohol and tobacco to be of etiological significance but these factors can neither explain the peculiar world-wide distribution, the vagaries in sex ratio, the sharp borderlines between regions of varied incidence nor the recent rise in risk in some areas. ✓

10. "Apparent changes in cancer mortality in 1968 as a result of the introduction of the 8th revision, International Classification of Diseases" -- Constance Percy et al, Bethesda

and New York (L. Garfinkel of ACS was one of the authors). The average annual increase in lung cancer deaths in the U.S. between 1963 and 1967 was 5.7%. These data were based on coding death certificates according to the 7th Rev., ICD. In 1968, the 8th Rev., ICD was introduced and this rate jumped to 9.6%. As lung cancer deaths rose from 54,407 in 1967 to 59,656 in 1968, secondary cancer of thoracic organs fell 62% from 2,116 to 815 deaths and cancer of unspecified sites decreased 8% from 16,914 to 14,936 in the U.S. ✓

It was suspected that these differences might not be real but be caused by changes in classification or coding rules. This paper resulted from a study done to measure the effects of using the 8th Rev., ICD on each cancer site. One set of 2,752 death certificates was coded by both the 7th and 8th Rev., ICD and results showed that the marked change in lung cancer was not real. No significant changes were seen in other sites.

"From this study and previous international comparisons of coding death certificates, it is clear that the use of different ground rules seriously effects both national and international cancer mortality figures."

11. "Prospective studies on cancer epidemiology based on census population in Japan" -- Takeshi Hirayama, Tokyo. This is the latest report of a prospective study of selected risk factors, including cigarette smoking and alcohol drinking, under way in Japan since 1965. The subjects are 265,118 adults aged 40 and over, 91-99% of the census population in 29 health districts.

There were 21,167 deaths from major causes up to 1973. Cancer deaths totaled 5,560 and of these there were 423 male lung cancer deaths and 148 female. Contrasting the risk factors, a significant excess of lung cancer deaths was found in smokers vs. nonsmokers. Cigarette smoking was the most important risk factor in total cancer deaths -- 62% higher in smokers. The risk was higher if smoking was started by age 20. Also, the more one smoked daily, the higher the lung cancer mortality rate. ✓

Results were compared with the Hammond study -- it was seen that standard mortality ratio by age at the start of smoking was quite similar in both the U.S. and Japan. The U.S. "slope" for lung cancer was steeper than that in Japan; perhaps because of various environmental factors, later start of smoking in Japan, lower percentage of regular inhalers, etc.

12. "Carcinogens are mutagens: a simple method of detection" -- Bruce Ames, Berkeley. A test system has been developed for mutagen and carcinogen detection using a special set of bacterial tester strains combined with rat (or human) liver homogenate for carcinogen activation. The test can be used to



detect carcinogens in complex mixtures such as urine or cigarette smoke condensate fraction. Mutagenic activity can be detected in the tar from less than 1/100th of a cigarette. The system is inexpensive, sensitive and rapid. "We are living in a sea of chemicals that have not been tested by the usual methods."

13. "Cancer patterns in Australia -- 1950-70" -- Nigel Gray, East Melbourne. Cancer of the digestive system, in terms of incidence and mortality, is down; cancer of the lung is way up, especially in males -- from 15 per 100,000 in 1950 to 43.5 in 1970. Of male cancer mortality, 27% is lung cancer. However, there has been a real down trend in lung cancer in males aged 55-59 and 60-64. Among male smokers aged 60 and over, 39% have stopped; in the 50-59 group, 31%. The number of ex-smokers makes him believe the fall-off in lung cancer incidence is real.

14. "Localized submucosal bronchial injections of carcinogens in dogs" -- M. Okita, Arthur Cohen and John Benfield, Torrance, Cal. and Los Angeles. 3,4-benzo(a)pyrene in hematite or N-nitrosomethylurea were injected at weekly intervals in the same site in two sets of dogs. After three injections of 3,4-BP, three dogs had significant localized squamous metaplasia. This finding, plus others, led the authors to conclude they may be producing a canine lung cancer model.

15. "Experimental lung cancer in dogs produced by 20-methylcholanthrene and establishment of cell line (ELCD)" -- Y. Hayata et al, Tokyo. Lung cancer was successfully induced in six of seven dogs following administration of 20-MC via a vinyl tube pushed into the right lower lobe bronchus. Squamous cell carcinomas were induced in four dogs, adenocarcinoma in one and a mixed adeno-squamous cell carcinoma in another. There were metastases to the lymph nodes in all cases. A cell line was established from a metastatic lymph node, confirmed by transplantation to the cheek pouch of hamsters, and is now being tested for homotransplantability.

16. At a conference on public education, a number of speakers from various countries deplored the failure of anti-smoking campaigns. They urged stronger, more intensive campaigns, and it seems likely that this will occur in the years ahead under the sponsorship of UICC, WHO and other agencies.

Cliff Read, ex-American Cancer Society and still active as a consultant to ACS and others, said the news about smoking is "discouraging." However, he added, new materials are being issued, the media are interested and concerned, studies show that at least half of all cigarette smokers want to quit, and the ACS has plans to establish more clinics and programs to help smokers stop. "But the fact is that there is no evidence that a truly massive attack on cigarette smoking is planned or even possible."

17. The UICC's Public Education Committee met last spring in Monaco and recommended that the "highest priority" be given to research in cancer public education. Also recommended: "Public education against cigarettes and other environmental carcinogens should be pressed."

18. The UICC's Commission on Cancer Campaign and Organization is now preparing a "Handbook for Journalists." Its objective is "to be certain that journalists have the right kind of approach to the cancer problem and that they know whom they should contact to obtain specific information on a cancer subject."

19. A so-called advance course on lung cancer, for which participants paid an extra fee, was held the last day of the Congress. It was coordinated by R.J. Walton of Canada who noted in his opening that the smoking-lung cancer controversy was still being argued in some places.

A.J. Phillips of Canada discussed trends in lung cancer incidence in various countries, pointing out that Scotland leads the world in the incidence of both male and female lung cancer death rates.

A question about funds available for lung cancer research in different countries was answered by Wynder, who said the Tobacco Working Group in the U.S. had \$6-million this year.

Hammond spoke on "Environmental and occupational factors in etiology." This was a recount of data pertaining to the asbestos workers and other occupationally exposed groups.

He said the lungs of uranium miners who do not smoke look like lungs of light smokers. The greatest changes are seen in areas of the lung where radon concentrates. Auerbach is now doing the pathology on a small number of cases of lung cancer in uranium miners.

While benzpyrene "is all over the place," Hammond said, study of roofing workers shows this substance is not involved in lung cancer. BP in city air and in cigarette smoke is not an important factor, he said.

He also said his research involving occupational cancers and air pollution shows there is no relationship between the latter and lung cancer.

Wynder, speaking on "Smoking and lung cancer," said tobacco causes both lung cancer and coronary heart disease (and so does overeating). His data suggest smoking causes 40% of all male cancer deaths in the U.S. ✓

He and Dantenwill have induced larynx cancers in animals with smoke and he now using this particular animal model. There

is a major effort under way at his American Health Foundation to identify carcinogens in tobacco and to test various kinds of tobacco (cigarettes) in animals.

There are five full-time psychologists at the AHF's smoke cessation clinic where they have a 70% success rate -- but it's only 30% after one year.

With the cooperation of the tobacco industry and others, we hope we can report in 20 years that there is "no more scourge."

20. The 1978 Cancer Congress is scheduled to be held in Buenos Aires. ✓

21. An organizational meeting was held in Florence for something called "The International Association for Study of Lung Cancer." Prime mover for the group is Dr. O. Selawry of the Mayo Clinic, Rochester, Minn.; its purpose seems to be aimed primarily at treatment, but I'm not sure.

L.S.Z.

The following abstracts appeared in the program in Volume 1, on the pages indicated.

GRAYSON, Anti-Cancer Council of Victoria, East Melbourne, Australia

"Cancer patterns in Australia - 1950-1970." (p. 116)

"Until recently no attempt has been made to measure overall cancer incidence in Australia. Nevertheless, the trends may be discerned by analysis of death rates as determined by the hospital-based Victorian Cancer Registry, and of the alterations in survival patterns as evident from the same registry data.

"Impressive alterations have occurred in the pattern of digestive cancer and of lung cancer....

"A cohort analysis, based on relative incidence and death rates, will be presented for lung cancer as part of an effort to discover whether significant reductions in tar content of Australian cigarettes are yet reflected in death rates."

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