NOTES ON WYNDER

November 4, 1956

1. Attitude

Wynder's first appearance in print, with Evarts Graham as second author, was in J.A.M.A., May 27, 1950, written before he received his M.D. as Graham's student. This paper reported Wynder's personal survey of smoking habits in 605 males and 25 females with bronchogenic carcinoma (adenocarcinoma excluded) plus data on 422 others collected at other hospitals (W. L. Watson later objected to distortion of Memorial Center data in this paper). "In the present paper the chief emphasis will be placed on our findings in regard to smoking," he said. "The data have clearly shown that the average patient with cancer of the lung smokes much more heavily than the average patient... with some other disease."

In Archives of Industrial Health for September 1951, Wynder & Graham said: "The data presented in this, as well as in other recent investigations, should lead research to concentrate its efforts in an attempt to identify and possibly isolate carcinogenic agents in tobacco smoke and in certain industrial substances with the hope that by their possible removal, or at least reduction, the incidence of primary cancer of the lungs may be decreased."

In Science for Nov. 14, 1952, Graham, Wynder & Croninger said: "We have obtained direct evidence that tar obtained from cigarette smoke will produce cancer experimentally when painted on the skin of mice over a period of about a year." The first published report on mice skin painting appeared a year later, in Cancer Research for November 1953. In 1954 Wynder said his experimental work began in 1949.

In other words, based on a statistical study which contains every known form of bias (hospital cases, hospital controls, interviewer bias, lumping cigarettes-cigars-tobacco, etc.), and before any experiments had been conducted, Wynder was making a case against tobacco and seeking removal or reduction of carcinogens as yet unidentified. In fact, arsenic was the first conjectured carcinogen he mentioned (March 1952). Everything he has done since was an effort to prove his case. Whenever his results did not jibe with theory, he would go on a new tack or explain away conflicting results as due to biological differences or unsuitability of the animals.

2. Extrapolation of Animal Results to Man

"The tumors that occur spontaneously in high lung-tumor strains of mice, such as strain A, are quite different histologically from the lung cancers that are encountered in man. On the other hand, human bronchogenic carcinomas which are usually of the epidermoid or undifferentiated types are histological types found very rarely in mice. It thus seems not justified to draw conclusions on the basis of a mouse strain with a high lung-tumor incidence if in fact we deal with a type of cancer that differs histologically as well as anatomically from that found in man." Arch. Indust. Health, March 1952 -- p. 224

"Finally, we must consider the possibility of species differences. It holds true for cancer as for many other diseases that a given etiologic agent for man may not elicit the illness in animals. Carcinogens may thus be species-specific. Among laboratory animals, such species differences have been established. How much greater, then, may be the difference between laboratory animals and humans." Arch. Indust. Health, March 1952 -- p. 225

"Animal data do not necessarily confirm or deny human data, although historically much of our present understanding of carcinogenesis is based on coronary studies between clinical and laboratory research.... In coal tar investigations experimental data confirmed the clinical data, and thus added import was given to both. A similar relationship now exists in the tobacco tar field.... It has been shown that a condensate of this smoke may induce epidermoid cancer of the skin in the experimental animal. The suspected human carcinogen has thus been proved to be a carcinogen for a laboratory animal." Cancer Research, Nov. 1953 -- p. 862

"When animal data coincides with human data, then, I believe, more significance may be attached to the meaning of the animal data. In this respect it must be emphasized again that the experimental tobacco tar studies were carried out because of the human experience already at hand. Without the human experience already available, the animal data would lose much of their significance. The present mouse data do not influence the proof at hand linking smoking to lung cancer in man. The mouse skin is not like the bronchial epithelium -- though they both represent epithelial tissue... At this time we can only assume, on the basis of the combined human and animal data, that these carcinogens are the same for man and for mice." Conn. State Med. J., April 1954 -- pp. 327-328

"It can only be assumed that the human and animal carcinogens are identical." From "The Biologic Effects of Tobacco," 1955 -- p. 127

"An animal experiment cannot significantly add and certainly cannot detract from these human observations (Hammond & Horn, Doll & Hill, Wynder 1954)." Cancer Research, Aug. 155 -- p. 448

"The significance of animal research in tobacco tar, to stress again, does not lie in the fact that they prove that smoking causes cancers in man. This proof rests entirely upon human clinical, statistical and pathological data. The significance of the animal experiment in this field is to help in the identification of specific carcinogens for a particular animal or strain of animal. In this respect the use of a susceptible animal is of great value... (as) one can observe results more quickly." Brit. J. of Cancer, Sept. 1956 -- p. 309

"If an agent is found to be carcinogenic to a variety of animals, and if the human epidemiological data are not inconsistent with this finding, then the burden of proof lies upon those who claim that these substances are not carcinogenic to man." Cancer, March-April 1957 -- p. 271

"In choosing the test site, one must be sure... to avoid one in which tumors cannot be produced even with very potent carcinogens.... The subcutaneous tissue of mice would be a less useful site because it does not yield epithelial tumors and also (is)... quite sensitive to a large variety of substances. On the other hand, the lungs of mice would not represent a good test organ.... The skin... is a satisfactory site... (because) similar to the epithelial tissue of the respiratory tract." Brit. Med. J., Feb. 7, 1959 -- p. 317

3. Species Differences

"The possibility remains that the CAF_1 strain of mice may be particularly susceptible to the carcinogenic effect of cigarette tars." Cancer Research, Nov. 1953 -- p. 862 (All mice painted with methylcholanthrene developed skin cancer; 44% of mice painted with cigarette smoke condensate developed skin cancer in about half their life-span.)

"It must also be considered that the strain of mice used might have been especially susceptible to skin cancer formation." Conn. State Med. J., April 1954 -- p. 327

"The Swiss mice tolerated the effect of the tobacco tar better than did the C57.... twelve out of 86 Swiss mice developed histologically proved cancer (14 per cent) compared with only two cancers among 89 C57 mice (2 per cent) by the 24th month.... C57BL mice have long been regarded as a strain relatively resistant to skin cancer as summarized by Berenblum, although Poel recently found it more susceptible to low doses of benzpyrene than either the Swiss or the CAF_1 strain.... The Swiss mouse, being genetically impure, can be regarded as a less reliable index of comparison for results of different investigators. The results.... clearly demonstrate that the C57 strain would be a poor strain to use for these studies." Cancer Research, August 1955 -- pp. 447-448

"In current experiments at this laboratory Swiss mice continue to develop tumors consistently earlier than the CAF_1 mice. It is for this reason that the Swiss mice prove valuable though because of the importance of the tobacco research program we have continued to use both strains." Brit. J. of Cancer, Sept. 1956 -- p. 509

"In general the survival rates were found to be higher for CAF_1 mice than for Swiss mice and the Swiss mice more susceptible." Cancer, March-April 1957 -- p. 260

"In general, the survival rates for the animals subjected to the various tars were similar once the nicotine had been removed. Occasional exceptions, such as the group of CAF_1 mice painted with neutral tar, are probably a reflection of an infection in a given cage of mice rather than a particular tar toxicity." Cancer, March-April 1957 -- p. 268

"In general, it may be concluded that tobacco has been shown to have a significant influence on the development of cancer of the upper alimentary tract in Swedish man but cannot account for the relatively high frequency of these cancers in Swedish women." Cancer, May-June 1957 -- p. 477

"No significant differences in tumor susceptibility were found between CAF_1, Swiss, and C57BL mice" (with benzpyrene tests). J. Nat. Cancer Inst., Sept. 1957 -- p. 370

"The animals painted for the duration of the experiment developed fewer cancers, at least in one experimental group (Group 2: 50 mice painted with 1:1 solution of tobacco "tar" in acetone thrice weekly for 22 months), than the group of mice on which tar application was stopped at twelve months (Group 10: 50 mice painted with 1:1 solution thrice weekly for 12 months). This could be the result of biological variation, as is suggested by the fact that in another experimental group of mice painted for their life span (Group 11: 40 mice painted with 1:1 solution thrice weekly for 20 months), the cancer yield was significantly higher than that in group 10 mice." Cancer, Nov.-Dec. 1957 -- p. 1198

"There is some variation in survival rates between the groups of mice painted with filtered-cigarette tar and those painted with unfiltered-cigarette tar, in both the Swiss and CAF_1 study group.... Although these results may be due to biological variations, they are more likely due to differences in the nicotine content of the tars." Cancer, Nov.-Dec. 1957 -- pp. 1201-1202

"For instance, we found Maryland-tobacco tar more active than Burley-tobacco tar in producing cancers in Swiss mice and less active than Burley-tobacco tar in producing cancers in CAF_1 mice.... These variations are probably a result of the biological variations that can be expected when a relatively small group of animals is studied." Cancer, Nov.-Dec. 1957:p. 1206 & 1208

"An apparent paradox has been the obvious fact that cancer of the oral cavity has not been increasing in men whereas a moderate increase has been noted among women." Cancer, Nov.-Dec. 1957 -- p. 1321

"The results show no significant differences in the carcinogenic activity of cigarette tar from... cigarettes smoked half way down or to the butt end. Differences such as those found in this particular study may be the result of biological variation alone." Cancer, Nov.-Dec. 1958 -- p. 1143

"The results (of mice and rabbit tests with cigar, pipe and all-tobacco cigarette "tar") suggest a somewhat higher degree of carcinogenic activity for cigar and pipe tars than for cigarette tar and a somewhat lesser activity for all-tobacco cigarette tar compared with standard cigarette tar. Some of the differences could be a result of differences in biological variation." Cancer Research, Dec. 1958 -- p. 1271

"One must realize, of course, that biological variation exists even when comparing the same type of tar in two different groups of mice of the same strain." Cancer Research, Dec. 1958 -- p. 1267

"The high frequency of carcinoma induction reported by Wynder et al. (1953) has not been achieved by other investigators, who reported that no more than 20% of animals, and usually considerably less, developed carcinoma of the skin." Cornfield, Haenszel, Hammond, Lilienfeld, Shinkin & Wynder, J.N.C.I., Jan. 1959 -- p. 189

"Considering the results of the present experiments, we conclude that though the carcinogenic activity of the condensate from extracted cigarettes is less in one group, it may still be within the limits of biological variation.... Our biological findings are somewhat equivocal in that in the experiment in which the cigarettes were first extracted and then smoked we observed a reduction in the biological activity of the smoke condensate.... It cannot be determined whether these differences... merely reflect the biological variations that may be expected from experiment to experiment." Cancer, Nov.-Dec. 1959 -- p. 1075 & p. 1076

"Since malignant neoplasms have been obtained in several strains of mice, and a few neoplasms have been produced in rabbits and rats, the issue of strain or species limitation to the reaction is more difficult to maintain. It is, of course, a fact that many agents shown to be carcinogenic to the skin of mice have not been proved carcinogenic to man. In most instances there is simply no experience with such agents in man, so that lack of proof really represents lack of data, pro and con." Cornfield, Haenszel, Hammond, Lilienfeld, Shimkin & Wynder, J.N.C.I., Jan. 1959 -- p. 189

4. Discounting Factors Other than Tobacco

"In the following ten paragraphs, points are outlined which, taken together, suggest tobacco as 'a' cause of lung cancer.... 10. No other explanation for the statistical relationship: We can suggest no other feasible explanation for the statistical association found." From 'The Biologic Effects of Tobacco," 1955 -- p. 109

"We can visualize no other plausible explanation for the statistical association found that tobacco is also a causative factor in lung cancer." Med. Clinics of North Am., May 1956 -- p. 933

"On the basis of statistical evidence... it may be said that between 80 and 90 per cent of all squamous and anaplastic lung cancer occurring in man today would not occur in the absence of smoking." Med. Clinics of North Am., May 1956 -- p. 635

"With the possible exception of a few isolated cities, such as Liverpool, air pollution is at best only a secondary factor. This belief is based on the fact that among non-smokers lung cancer occurs but rarely, that the incidence of lung cancer among women, who are also exposed to city air, is low, and that the age distribution.... is more compatible with an exogenous factor to which only the younger population group was exposed some 30 to 40 years ago rather than with air pollution, which would expose an entire population group at the same time." Testimony, Subcomm. of House, July 19, 1957

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5. Discrepancies in Results

The following examples of discrepancies between Wynder statements and Wynder results have been selected out of a number of studies conducted with mice and rabbits. In Cancer (Nov.-Dec. 1957:1193-1200) he argues that some of his mice died too soon to reflect higher dose responses. (All mice under A & B are of identical stock.)

A. Examine Table 1 herewith: The five-times-a-week mice (Group 1) all died sooner than the three-times-a-week mice (Group 2), it is true. But all two-times-a-week mice (Group 3) died before the others. Ergo, the argument of premature decease falls flat.

The true fact is that the three-a-week mice had three times as many cancers than the five-a-week mice from the 11th through the 15th months, a fact which Wynder has veiled by misdirecting the reader.

TABLE 1

TUMOR FORMATION BY FREQUENCY OF CIGARETTE-TAR APPLICATION*

No. mo.	Group 1			Group 2			Group 3			Group 4			Group 5			Group 6		
	No. sur.	% P	% C	No. sur.	% P	% C	No. sur.	% P	% C	No. sur.	% P	% C	No. sur.	% P	% C	No. sur.	% P	% C
1	50	0	0	50	0	0	40	0	0	40	0	0	40	0	0	40	0	0
2	42	0	0	50	0	0	40	0	0	40	0	0	40	0	0	39	0	0
3	34	0	0	49	0	0	37	0	0	40	0	0	37	0	0	38	0	0
4	32	2	0	48	0	0	37	0	0	39	0	0	37	0	0	38	0	0
5	28	2	0	47	0	0	35	0	0	36	0	0	35	0	0	35	0	0
6	27	4	0	45	4	0	33	0	0	36	0	0	33	0	0	35	0	0
7	22	6	0	39	6	0	32	0	0	36	0	0	27	0	0	27	0	0
8	19	6	0	36	12	2	22	3	0	31	0	0	23	0	0	25	0	0
9	18	6	0	36	12	2	20	5	0	29	0	0	23	0	0	19	0	0
10	13	8	2	36	20	2	19	5	0	25	0	0	23	0	0	19	0	0
11	11	8	2	31	20	6	18	8	0	24	0	0	22	0	0	18	3	0
12	9	10	2	30	26	6	15	8	0	24	0	0	20	0	0	17	3	0
13	8	10	4	26	28	12	13	8	0	21	0	0	17	3	0	15	8	0
14	6	10	4	21	30	12	10	10	3	18	0	0	15	5	0	13	15	0
15	6	12	4	17	36	12	7	10	3	15	3	0	11	5	0	7	15	0
16	6	12	8	11	36	12	4	10	3	12	3	0	8	5	0	7	15	0
17	5	12	8	9	36	12	0	10	3	11	3	0	1	5	0	2	15	0
18	0	12	8	7	36	14	...		...	7	3	0	1	5	0	1	15	0
19	.			5	36	14	...	.	.	3	3	0	0	5	0	0	15	0
20	...	.	.	3	38	16	...	.	.	3	3	0						
21	...	...	.	2	38	16	...	...	..	2	3	0						
22	...		.	0	38	16	...	...	.	2	6	0					...	...

*The mice were painted with a 1:1 tar acetone-solution for their life span, in the following frequencies: gp. 1, 5 times/wk., gp. 2, 3 times wk., gp. 3, 2 times/wk., gp. 4, 1 time wk., gp. 5, 3 times/wk. for alternating 2-wk. periods, and gp. 6, 3 times wk. for alternating 4-wk. periods.

5. Discrepancies (Cont'd)

B. Examine Table 2 herewith: This is intended to show that the longer mice painting continues, the more cancers are formed. It is true that mice painted thrice weekly for three and six months developed no cancers, and that such painting for 12 months produced more cancers than for nine months. However:

Point 1: The one-year mice already had begun to develop cancers in the 10th month, and already had twice the number of papillomas the nine-month mice. There must have been something other than tar-applications to account for this discrepancy, and also for the fact that the nine-month mice began to die off faster than the twelve-month mice from the second month on up! This is most suspicious.

Point 2: Now examine the Group 2 "life span" mice at the right: They didn't die as fast as the nine-month mice but were developing cancers earlier than any of the other groups shown -- at eight months. Did the mice know they were going to be painted for life? However that may be, only half as many of the "lifers" developed cancers as the one-year mice. These results, like all those tabulated, indicate wide variations in response.

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TABLE 2
TUMOR FORMATION BY CIGARETTE-TAR APPLICATION*

	Group 7			Group 8			Group 9			Group 10			Group 2 life span		
No. mo.	No. sur.	% P	% C	No. sur.	% P	% C	No. sur.	% P	% C	No. sur.	% P	% C	No. sur.	% P	% C
1	50	0	0	50	0	0	50	0	0	50	0	0	50	0	0
2	45	0	0	50	0	0	45	0	0	48	0	0	50	0	0
3	43	0	0	48	0	0	43	0	0	48	0	0	49	0	0
4	43	0	0	45	0	0	43	0	0	48	0	0	48	0	0
5	43	0	0	43	0	0	40	0	0	47	0	0	47	0	0
6	42	0	0	40	2	0	38	0	0	43	4	0	45	4	0
7	42	0	0	36	2	0	38	2	0	39	6	0	39	6	0
8	42	0	0	35	2	0	37	6	0	39	10	6	38	12	2
9	42	0	0	35	2	0	34	12	0	36	24	0	36	18	2
10	42	0	0	35	2	0	31	22	0	35	26	2	36	20	2
11	40	0	0	32	4	0	27	26	0	31	36	2	31	20	6
12	37	0	0	29	4	0	25	28	0	26	48	6	30	26	6
13	34	0	0	28	4	0	21	28	4	19	50	10	26	28	12
14	34	0	0	25	4	0	19	28	4	16	54	12	21	30	12
15	30	0	0	20	4	0	15	32	8	14	56	24	11	36	12
16	26	0	0	17	4	0	13	32	8	7	56	24	11	36	12
17	23	0	0	16	4	0	8	34	10	6	58	26	9	36	14
18	19	0	0	15	4	0	8	34	10	2	58	26	7	36	14
19	14	0	0	10	4	0	4	34	12	2	58	28	5	36	14
20	8	0	0	8	4	0	3	34	12	1	58	30	3	38	16
21	4	0	0	7	4	0	2	34	12	0	58	30	2	38	16
22	2	0	0	4	6	0	1	34	12	..	..		1	38	16

*The mice were painted with a 1:1 tar-acetone solution 3 times/wk. for the following durations: gp. 7, 3 mo., gp. 8, 6 mo., gp. 9, 9 mo., and gp. 10, 12 mo.

[illegible] KOTF ZIEGLER CANCER 10/1 1103-1200 NOV DEC 1957

C. The following Charts (Cancer Research, Dec. 1958:1263-1271) were prepared by Wynder to show the varying results of tests with the condensed smoke of cigarettes, all-tobacco cigarettes (with tobacco wrappers), cigars, and pipe tobacco on Swiss mice, all in 1:1 acetone solution applied thrice weekly. It shows that cigar smoke condensate got off to a fast start and headed the other tobacco forms both in cancers and in papillomas, both at 12 months and at 18 months. Not shown in this table is a faster mortality rate, which did not interfere with cancer production, as was alleged (wrongly) in example A above to explain lower tumor production.

Nonetheless, Wynder claims: "Current experiments are consistent with human epidemiological findings." He endeavors to explain this by an alleged "localization" of cigar and pipe smoke in the mouth, whereas cigarette smoke settles in the lungs. There is, however, no epidemiological evidence that oral, laryngeal cancer, etc are rising in frequency.

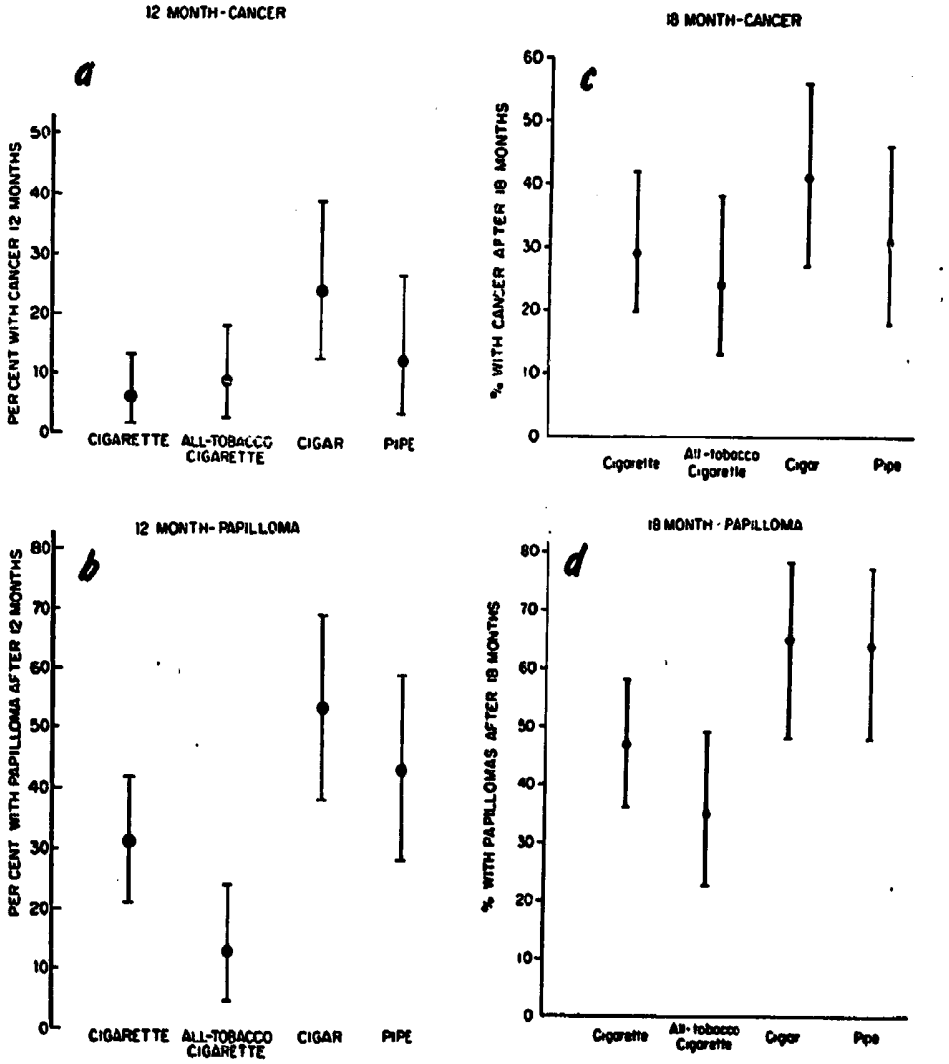

CHART 1a, 1b, 1c, and 1d.—Per cent of papillomas and cancers in Swiss mice, obtained by applying different tobacco tars, shown in confidence limits.

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5. Discrepancies (Cont'd)

D. In the same paper, Wynder has summarized his experimental statistics on Swiss and CAF_1 mice with various tobacco products. All data represent 1:1 acetone solutions of "tars" (except where 1:2 is shown), and thrice-weekly applications. It is not possible to tell from the Table which mice were Swiss and which CAF_1's, although Wynder repeatedly has reported different results with different strains.

"One must realize, of course, that biological variation exists even when comparing the same type of tar in two different groups of mice of the same strain," he says.... "The highest percentage of both papillomas and cancers obtained in this particular set of experiments was found in the group of Swiss mice painted with nicotine-free pipe and cigar tars..... In a 1:2 solution, among both Swiss and CAF_1 mice, no significant differences were found... between the two types of tars."

TABLE 6

SUMMARY OF EXPERIMENTAL STATISTICS ON SWISS AND CAF_1 MICE WITH VARIOUS TOBACCO PRODUCTS

Product	No. started	Date started	Months painted	Per cent pap.	In months: 1st pap. appearance	In months: Last pap. appearance	In months: Av. pap. appearance	Per cent ca.	In months: 1st ca. appearance	In months: Last ca. appearance	In months: Av. ca. appearance
Cigarette (fresh)	86	10/6/55	26	47	5	18	11.7	37	6	26	15.7
Cigarette (old)	92	10/21/55	25	53	5	20	11.5	36	9	24	15.0
Whole cigarette	40	3/1/56	24	15	13	18	15.6	20	15	24	20.1
All-tobacco cigarette	54	7/18/55	23	35	7	17	12.5	26	9	19	14.5
Whole all-tobacco cigarette	42	3/1/56	24	26	10	22	15.7	24	12	24	17.6
Nicotine-free cigar	46	4/20/56	19	65	5	18	9.8	41	9	15	11.7
Cigar (1:2)	78	6/3/55	26	33	6	25	14.3	19	11	26	17.5
Nicotine-free pipe	45	4/20/56	23	71	8	20	12.6	44	10	22	15.8
Nicotine-free pipe (1:2)	89	8/24/55	27	30	6	22	14.7	16	12	23	16.9
Whole nicotine-free pipe	40	3/1/56	24	35	5	21	15.2	20	11	23	19.0
Acetone	23	11/23/55	25	0				0			
Cigarette (fresh)	88	10/6/55	27	52	8	26	16.5	43	11	26	19.4
Cigarette (old)	87	11/9/55	26	48	10	23	17.1	44	14	26	20.1
All-tobacco cigarette	55	8/3/55	29	53	14	29	19.9	29	17	29	25.4
Cigar (1:2)	90	6/27/55	29	50	10	29	18.0	10	20	28	24.0
Nicotine-free pipe (1:2)	86	8/24/55	29	43	9	27	19.9	13	18	28	23.2
Acetone	24	11/23/55	30	0				0			
Untreated	50	11/23/54	32	0				0			