Table 3. Comparison between some chemical constituents of slags and copper ores (percentage of original sample); cobalt and lead were not detected in the slags.

No.	Material	Cu	Fe	Mn	Cl	P_2O_5	CaO	MgO
136/55	Porous slag	1.74	35.6	2.71	0.1	0.72	4.17	1.04
137/55	Massive slag	1.55	35.3	2.74	0.06	1.05	4.68	1.11
348/55 through 352/55	Copper ores	15–23	0.4–17	0–0.07	0.1–0.8		0.8–7.8	0.1–0.4

Two kinds of black slag are found in the ash heaps of the acropolis, massive and porous. They are found in relatively small fragments, as a rule, in contrast to the large and irregular pieces of slag found at the foot of the acropolis, within an enclosure, and elsewhere in the area. It is not clear whether the slag in the acropolis was fragmented by man or by the natural agencies. If it was fragmented by man, the purpose of the operation is obscure. Melting points of both kinds of slag are the same, about 1250°C and higher—a remarkably high temperature. Their chemical composition is nearly the same (Table 3).

The discrepancy between the manganese content of the slags and of the copper ores is significant enough to make one doubt any relationship between the two materials, to doubt possibly the very supposition that it was copper that was melted in the acropolis, unless one could prove that manganiferous materials were used in the smelting flux (*8*). No such materials were found by us there, except a few rounded fragments of a manganese-quartz conglomerate. Studies now in progress may help clarify this and other problems posed by our preliminary findings.

Archeological-historical understanding of the ancient metallurgical skills is not possible without detailed chemical analysis and experiments in the laboratory and a full accounting in the field for all materials in the acropolis—that is, for the sources of ores, fluxes, and the out-of-place rock. Our interest is not in the scale of the operations but in their quality and kind, the more so since the acropolis seems to be unique among the smelting sites of southern Negev in regard to the materials it contains and the kind of operations their presence implies.

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References and Notes

1. Published by permission of the director, Machzavei Israel (Israel Mining and Industries).
2. A superficial description of this site is given by N. Glueck, in *The Other Side of Jordan* (American Schools of Oriental Studies, New Haven, Conn., 1940), p. 79.
3. The district may have been worked repeatedly, both before and after the reign of King Solomon.
4. The incipient white range; we are indebted to M. Chvalov of the Technion, Haifa, for these measurements.
5. According to Glueck, (*2*, p. 77) "Cupriferous sandstone protrudes all over the surface of the entire wadi." This is far from being the case. Outcrops of mineralized rock were not easy to find in Timnah, after extensive studies by a sequence of geologists. Some outcrops were found only recently and others remain inferred rather than proved. The wadi floors are chiefly alluvium, with only occasional fragments of concretionary copper ore of the kind that *was not* smelted by the ancients, despite its high copper content. The protrusions of cuprite and malachite mentioned by Glueck still remain to be found.
6. Not including the artifacts: a few blades of flint of a highly skilled workmanship; potsherds of different kinds, thicknesses, and modes of tempering and firing; grinding stones; mortar slabs; egg tray-like slabs of obscure origin or use; and so forth. Weathered fragments of large marine shells and bones of desert animals were found in bonfire residues, among other things.
7. We are indebted to A. Alon and Y. Mashal for the chemical data in this report, and to Nevies for analysis No. 78/52.
8. A. Dor and Y. Cohen, of the Machzavei Israel, succeeded in smelting a chrysocolla ore from Timnah using a charcoal, calcium carbonate flux.

26 September 1955

Cocarcinogens and Minimal Carcinogenic Doses

The concept of cocarcinogenesis originated in 1938, when it was reported that a coal tar distillate, the basic fraction of a creosote oil, was capable of enhancing the activity of 3,4-benzopyrene on mice even though alone it did not give rise to tumors after skin painting or subcutaneous injection (*1*). Since the fraction did not appear to be carcinogenic, it was termed a "cocarcinogen." Subsequent studies with croton oil, croton resin, ultraviolet light, ionizing radiation, trauma, heat, and burns established those agents as experimental cocarcinogens for the mouse and led to acceptance of the term to apply to physical or chemical agents that are noncarcinogenic but which enhance the effect of a carcinogen, especially when the carcinogen is weak or applied at too low a level to produce tumors (*2, 3*).

Recognized tumor-inducing agents also have been used experimentally as cocarcinogens on the assumption that they were applied at so-called "minimal" or "subminimal" levels. It was supposed that they could not both "initiate" and "promote" neoplastic changes at low dosages in normal cells; their action was interpreted to be only that of "promoting" the growth potential of cells already rendered neoplastic by some preceding mechanism.

With the recent demonstrations that almost all heretofore identified cocarcinogens are capable of both initiating and promoting the growth of tumors (*4*), it would appear that, with the possible exception of trauma, what have been termed cocarcinogens are probably tumor-inducing agents tested under conditions that did not disclose their potency as tumor initiators. It appears timely therefore to question what is meant by "minimal," "subminimal," "initiating," and "promoting" doses when a known tumor-inducing agent is involved.

A technique frequently employed in experiments on cocarcinogenicity involves the application of a single subminimal carcinogenic stimulus to a selected site of the experimental animal to initiate a neoplastic change; this is followed by repeated applications of a cocarcinogen to promote the development of a grossly visible tumor from the initiated, but latent neoplastic cells. An experiment (*5*) to study the individual effects of the initiating and promoting dose with the carcinogen 3,4-benzopyrene is illustrated in Table 1. In that experiment, one group of mice received on the shaved interscapular skin a 0.01-ml drop of 1.25-percent benzopyrene in benzene. This provided approximately 125 μg of the carcinogen as a single subminimal dose. To a second group of mice, an estimated total of 120 μg was applied as a promoting agent in a dosage form of approximately 1 μg of 3,4-benzopyrene in benzene three times weekly for 40 weeks. The absence of any interscapular tumors in the first group is in sharp contrast with tumor induction in 9 of 42 mice in the second group by the 40th week of the experiment. Thus, depending on dosage and duration of exposure, the total amount involved in a subminimal acute exposure was more than adequate for tumor induction when exposures involved fractions of the total dose administered repeatedly. These results, obtained with a percutaneously applied carcinogen, parallel the observation that repeated oral doses of CCl_4 produced hepatomas in mice, whereas an equal total amount given in one dose did not (*6*). The factors of dosage and

Table 1. Tumor induction following single and repeated exposures to equal amounts of 3,4-benzopyrene in benzene.

3,4-Benzopyrene (μg per application)	Applications (No.)	Tumors after 40 wk (%)
125	1	None
1	120*	20 (9/42)

* Applied three times per week to interscapular skin of C57/Bl male mice.

Table 2. Skin tumor induction following repeated exposures to approximately 1 μg of 3,4-benzopyrene that was applied percutaneously three times per week.

Mice		Weeks preceding tumor appearance												Mice with no tumors*
Strain	No.	30	35	40	45	50	55	60	65	70	75	80	85	
C57BL	13	1	2				1	1		2	1		4	1
DBA/2	13					1	1	1	1	1	1	1		6
CAF_1	12							1	1	1	1			6

* Nontumor deaths after the 30th week.

exposure time are essentials that have been omitted previously in proposed methods for assaying comparative carcinogenic potency (7). In the absence of experimental verification, the exposure level at which a carcinogen ceases to have "initiating potency" and retains only "promoting action" cannot be predicted at this time.

From the early studies in experimental carcinogenesis, there has been general acceptance of 0.3 percent as providing a standard low concentration of carcinogenic hydrocarbon dissolved in benzene for skin painting experiments (8). An indication that 0.3 percent is in fact a high concentration of carcinogen may be found as early as 1940, when, despite reference to the concentrations used as minimal doses of carcinogen, tumors were reported in 18 of 20 mice that had been painted with a 0.05-percent solution and in 14 of 20 mice that had been painted with a 0.02-percent solution of benzopyrene in benzene (9). In our laboratory, the tumor-inducing potency of even lower concentrations was demonstrated with the application of 1 μg or less of benzopyrene as a 0.01-percent solution in benzene three times weekly for the life span of the animal or until a tumor was induced (Table 2). Evidently, when solutions of 0.01-percent benzopyrene applied in microgram or lesser quantities induce tumors in 50 to 100 percent of exposed mice during their life span, such terms as *low standard concentration, minimal dose* of carcinogen, *initiator, promotor,* and *cocarcinogen* need to be redefined in quantitative terms.

It cannot be denied that cocarcinogens may exist, with roles in carcinogenesis comparable to that of pharmacologic adjuvants and physiologic or chemical catalysts. But their existence is yet to be conclusively demonstrated by the experimental oncologist.

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5. Supported by a grant from the Field Investigations and Demonstrations Branch of the National Cancer Institute and the Martha O. Freas Memorial Grant-in-Aid of the American Cancer Society.
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Preliminary Report on Biological Applications of Color Television

Electronic image processing (1) is the term we have used to describe a variety of electronic means for viewing objects or processes and picturing these in their original or in altered but meaningful forms. These techniques have been of particular interest to us when they permit visualization of biological phenomena that cannot otherwise be seen, or when the electronic systems employed bring out information that is concealed when the phenomena are viewed directly. Such systems are analogous to indicator systems used in morphological studies, such as stains.

Color television has been explored as one of these electronic image-processing techniques that can be applied to biological problems. Sixteen millimeter color kinescope (motion-picture) film records of a pilot experiment indicate that some theoretical advantages of this technique can be realized. An amphibian preparation (frog) was set up in the C.B.S. Studios in New York on 10 Apr. 1955, by Louise Warner of Georgetown University Medical School and Edward H. Bloch of the Western Reserve University School of Medicine; the quartz-rod illumination technique was employed. This preparation was selected because it is simple, the results are reproducible, and direct motion-picture records by this technique are familiar to investigators in the field of microscopic circulation as well as readily available for comparison by others. The C.B.S. color system was employed because it is a completely engineered system with inherent adaptability for these experimental purposes, and a fully developed kinescope recorder is available.

Microscopic circulation in frog mesentery and liver can be observed in normal color relationships at satisfactory magnifications and with good resolution. When lighting is reduced below levels for microcinematography, satisfactory films are obtained. Reductions in the Kelvin temperature of the light source can be compensated without sacrifice in the final picture. Thermal energy delivered to the tissue can be reduced to low levels, thus simplifying the problem of maintaining physiological conditions.

At will, the investigators could remove one or two colors from the picture and record the remaining color or colors. Gamma (the degree of contrast) could be varied independently for each color. "Crispening" circuits were employed to increase apparent contrast. Phase shifts between the camera color wheel and the monitor and recorder color wheels made it possible to record red subject matter as green or blue. The investigators could observe the exact picture that was being recorded on a monitor that was conveniently located near the subject material.

Examination of kinescope film made during this pilot experiment with unmodified equipment indicates that combinations of the afore-mentioned variables produce color motion-picture film that contains usable information that is not available by direct photography.

The extreme sensitivity to light that is an inherent property of such systems makes it conceivable that undisturbed human circulation can be observed and recorded at usefully high magnifications in the retina of man. With the substitution of appropriate filters for the color disks in the camera, chemical data could be correlated with living morphology in those instances in which dissociated light-transmission curves have chemical significance, as in the case of reduced and oxyhemoglobin.

The experimental film has been organized into a short motion-picture entitled, *Color Image Processing, Experiment 26, Joint Study of Electronic Image Processing.* It is one of 26 experiments conducted by the Special Devices Center, Office of Naval Research, U.S. Navy, and the National Institutes of Health, Department of Health, Education, and Welfare, in the course of the first part of a study of the usefulness of television and related techniques in the medical research environment.

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