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CLINICAL EVIDENCE FOR THE LATENT AND ADDITIVE ACTION OF BENZOL WITH OTHER TOXIC INSULTS: REPORT OF TWO CASES**

Two cases have been presented in support of following concept.

First, benzol and perhaps other toxic insults may cause a long latent disturbance in functioning capacity insufficient to produce manifest disease.

Second, a second toxic insult of similar or dissimilar behavior may by additive or synergistic action produce disease, in these instances blood dyscrasia.

Third, non-occupational factors such as chronic hemorrhage, ingestion of drugs may be in part responsible for the clinical end picture.

It is not an original idea that more than one toxic insult may be operating to produce a clinical syndrome and definite pathology. In the first place the synergistic action of carbon tetrachloride and alcohol is well known. Dr. ALICE HAMILTON describes the effect of alcohol when combined with industrial exposure to, among other chemicals, $CaCN_2$, lead, carbon disulphide, mercury, sulphuric ether. FOULGER has also pointed out the importance of two toxic agents acting separately in the same individual. A second factor of importance in the mechanism of production of job-related illness may be excess function of a system vulnerable to the particular toxic material to which the patient is exposed. A clear example of such pathogenesis is the development of aplastic anemia in young women exposed to benzol. Because of menstrual or pregnancy-related blood loss, the hematopoietic system is

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under constant functional stress prior to or during benzol exposure with possible resultant damage. Also since certain drugs produce disturbance in bone marrow function, it seems possible that the current practice of considerable drug administration may be relevant to the development of blood dyscrasias with the added effect of industrial toxic exposure.

Two cases are presented which suggest that certain blood dyscrasias may be the result of a combination of insults to the hematopoietic system.

This report is presented with the intention of arousing attention to the relationship of etiology and pathogenesis of certain blood dyscrasias to early and repeated insults. It is here suggested that the insults may be of dissimilar character and may each produce damage insufficient to result in disease but acting additively or synergistically may in time cause irreversible pathology.

Case I

W. C. was 73 years old at the time of his admission to the hospital in 1950. The patient complained of being dizzy and unsteady in walking for the two months prior to his hospitalization. He also noticed that he was short of breath on exertion. Swelling of his legs had appeared at the end of a day's work for the previous month. This was so bothersome that W. C. stopped working and the swelling disappeared.

This patient had been well up until the present time except for chronic and frequent but not disabling attacks of asthma. W. C. had typhoid fever at the age of 35 years and a short bout of renal colic when he was 53 years old. More recently he had noticed nocturia. During the year prior to admission he had herpes zoster.

The occupational history shows that up until 1941, W. C. worked as a cook, a baker, a farmer, a laundryman. a policeman, a carpenter, and an odd job man. From 1941 to 1945 the patient worked in a munitions factory. For two of these years he worked as a carpenter and came in contact with fairly heavy exposures of tetryl and trinitrotoluene in repairing jobs. During 1943 and 1944 W. C. worked with bars of magnesium, an operation that generated a fair amount of dust. The last year of his work in this factory was spent in disposing of trinitrotoluene and tetryl. It seems fair to conclude from this story that W. C. was freely exposed to the usual chemicals involved in explosive manufacture and probably heavily exposed at intervals to TNT and tetryl. From 1946–1948 the patient worked as a caretaker of a large house. He used a paint remover known to contain benzol off and on in the course of his repair work during this period. W. C. also took a drug to reduce his weight at one time (the composition of this medication is unknown but thought to be benzedrine sulfate). All his life W. C. has taken salicylates and proprietary drugs known to contain coal tar products.

Hospital study revealed this man to have a marked anemia. There was no disturbance in liver function and the spleen not enlarged. Hemorrhages and edema of the retina were discovered. The peripheral blood count on admission to the hospital showed a hemoglobin of 3.5 grams, white blood cell count of 4,400, polymorphonuclear leucocytes of 33 per cent, lymphocyte count of 53 per cent, monocyte count of 7 per cent. Biopsy of the bone marrow showed hypoplasia of all the cellular elements. Transfusions were given at frequent intervals and brought the hemoglobin to 10 grams. The white blood cell count ranged from 2600 to 4700. The bleeding time was 3 to 5½ minutes; the clotting time 3¼ to 4 minutes. With frequent transfusions W. C. is reasonably comfortable, able to drive his automobile and do light work as carpenter. The hemoglobin is maintained at about 8 grams (October, 1951). The diagnosis is considered to be aplastic anemia of chemical origin.

The question of benzol exposure in W. C.'s work in the munition plant was raised. Inquiry has revealed that in America the explosive industry uses toluol rather than benzol. Since trinitrotoluene is established as a bone marrow depressant, it is believed that this received a definite insulting dose during his years in the munition plant 5 to 8 years prior to his hospital admission. The intermittent exposure to benzol during 1946–1948, it is suggested, was large enough to produce an additive effect with the trinitrotoluene ending in clinically evident aplastic anemia. One can speculate that W. C.'s practice of taking drugs freely may have played some part in the depression of the hematopoietic system.

Case II

G. J. was 49 years old at the time of the onset of his illness. He complained of pallor, weakness, dyspnea and loss of appetite. Because these symptoms were not relieved by liver injections, his family physician sent him to this hospital for study and care. At entrance G. J. showed pallor, slight dyspnea even at rest, and scattered petechiae in the left axilla. There were a few persistent fine râles heard at the right lung base. Liver and spleen were not felt and no lymphadenopathy was discovered. The examination of the central nervous system revealed no abnormalities. Urinalysis was normal and the stool guaic test was negative. X-ray study of long bones, chest, upper and lower gastrointestinal tract showed no evidence of malignancy. The hemoglobin value was 6 grams; the red blood cell count 2,730,000, the white blood cell count 3,600 with 23 per cent polymorphonuclears, 70 per cent lymphocytes, 4 per cent monocytes, and a reticulocyte count of 0.1 per cent. The anemia was studied by sternal marrow biopsy after attempted aspiration of iliac crest and sternal marrow failed, suggesting fibrosis of the marrow. The biopsy showed an overall decrease in the number of cellular elements, few cells of the myeloid series, many normoblasts

and unidentifiable immature large cells with foci of fibrosis, a picture which made the diagnosis of aplastic anemia.

Transfusions made the patient feel much better. During his hospital stay he showed some tendency to bleed into the subcutaneous tissues, the gums, and once from the rectum. He also began to run an elevation in temperature not controlled by antibiotics. All blood cultures were negative. After seven transfusions of 500 cc. of whole blood, G. J. was sent home with a hemoglobin of 12.5 gm., feeling much stronger.

G. J.'s past medical history brought out no tuberculosis, diabetes, anemia, malignancy, heart or renal disease in relatives. The patient was born in Greece and came to the United States of America 38 years ago when he was 12 years old. At 18 years of age this man went to work for five years as a weaver in a local textile mill. Then he worked for five years cutting soles and heels in a nearby rubber heel factory. It is of interest that in this particular plant benzol was used in quantity. During the 22 years prior to his death G. J. worked in a rubber manufacturing company and for 16 of these years he was in the press room probably exposed to no toxic chemicals. During the war years 1943–1945 he worked at the manufacture of self-sealing tanks for airplanes. Methyl-ethyl ketane and ethylene dichloride were used in the dope to paint these tanks which were then dried with lamps. The patient and other workers were bothered with headache, nausea and sometimes vomiting, considered due to the methyl-ethyl ketane and suggesting volatilization of the ethylene dichloride as well. Studies made by the Massachusets Division of Occupational Hygiene of this operation show that the concentrations of ethylene dichloride in the worker's breathing zone varied from 75 to 220 parts per million parts of air. The permissible level of steady exposure to ethylene dichloride used by Massachusetts is 35 parts per million parts of air.

G. J. pushed a small truck carrying supplies to various parts of the factory for the three years after the war. When his illness began to manifest itself he could no longer do the physical work involved in the trucking job and was given light maintenance work until his admission to the hospital.

Following his discharge from the hospital he was seen in the Anemia Clinic at frequent intervals. It was necessary to give G. J. repeated 500 cc. whole blood transfusions to combat his symptoms and restore his hemoglobin which fell rapidly between transfusions. For instance, in one month after six transfusions had raised his hemoglobin to 11.5 gm. it fell to 5.4 gm. The blood smears continued to show pancytopenia in spite of forty-seven pints of blood, liver extract, testosterone.

Ten months after G. J.'s original visit to the hospital enlargement of the spleen and lymph nodes was noted and the white blood cell count had risen to 13,000 to 14,100 but with a persistently low polymorphonuclear leukocyte count of between 6 to 19 per cent. Biopsy of the lymph node suggested myeloid metaplasia. Because of sepsis of the left

cervical region with great weakness, vomiting and increased bleeding tendency, the patient was readmitted to the hospital where he died within three weeks. Autopsy revealed leukemia involving ribs, pleura, pericardium, heart, paratracheal, mediastinal, and retroperitoneal lymph nodes and spleen. There was hematopoiesis of the spleen but not of the liver.

We cannot prove definitely how much benzol exposure G. J. had when he worked for five years in a rubber heel factory more than twenty years before his death because his work records are no longer available. However, because of illness and deaths in this plant it seems fair to infer that this patient was exposed to benzol. We suggest that he may have had benzol effect without suffering enough insult to his bone marrow to develop evidence of disease. Then for two years within five to seven years of his death this worker was exposed to a second insult, the inhalation of a chlorinated hydrocarbon, ethylene dichloride. There is little knowledge of human exposure to this material but it is considered similar to carbon tetrachloride in its toxic action. G. J. kept steadily at the job involving ethylene dichloride and methyl-ethyl ketane exposure in spite of some symptoms, which caused his fellow workers to leave after much shorter periods of exposure. We want to propose here that the benzene exposure presumed from earlier years produced real bone marrow disturbance insufficient to produce symptoms - a latent effect perhaps like certain ionizing radiation insults - until the further insult of ethylene dichloride acted either directly or through damage to the liver to disturb the hematopoietic system causing apparent aplastic anemia and subsequent terminal leukemia. When this case was being discussed at the Massachusetts General Hospital, Dr. TRACY MALLORY when asked about this consept from the standpoint of animal experimental work reported the following analogy. He said that it is possible to paint the skin of a rabbit with a carcinogenic tar for a short period of time during which either no tumor is produced or, if one should start, the skin will revert to normal on cessation of the painting. Then months later if the skin is painted with a simple irritant like turpentine a tumor is produced. Dr. MALLORY argued that in this instance the carcinogenic agent had made a real but invisible change in the skin which would allow a non-carcinogenic agent to produce a tumor at a later date. Therefore, in the case of G. J. one might suggest the working hypothesis that the early benzol effect was the carcinogen and the ethylene dichloride was the precipitating non-carcinogen.

Conclusion

Two cases have been presented in support of the following concept. First, benzol and perhaps other toxic insults may cause a long latent disturbance in functioning capacity insufficient to produce manifest disease.

Second, a second toxic insult of similar or dissimilar behavior may by additive or synergistic action produce disease, in these instances blood dyscrasia.

Third, non-occupational factors such as chronic hemorrhage, ingestion of drugs may be in part responsible for the clinical end picture.

It is hoped that this type of report may interest others to produce supporting evidence, if such exists, as useful in understanding the etiology and pathogenesis of certain chemical intoxications and perhaps preventing their occurrence.

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SADRŽAJ

Prikazana su dva slučaja u prilog slijedećoj tezi:

Prvo: benzol, a eventualno i druge toksičke tvari možda uzrokuju dugotrajne latentne funkcionalne smetnje, koje nisu dosta velike da uzrokuju manifestnu bolest.

Drugo: toksička tvar, koja izaziva iste ili slične posljedice, može aditivnom ili sinergetskom akcijom izazvati bolest, u ovom slučaju diskraziju krvi.

Treće: neprofesionalni faktori kao na pr. kronična hemoragija ili uzimanje lijekova mogu djelomično utjecati na konačnu kliničku sliku.

Autor se nada, da bi ova vrsta referata mogla zainteresirati druge i ponukati ih da iznesu dokazni materijal, koliko ga ima, koji bi bio isto tako koristan za razumijevanje etiologije i patogeneze izvjesnih kemijskih otrovanja, a možda i za to, da spriječi njihovo nastajanje.

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