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FRANCE

ACUTE LEUKEMIA IN BENZENE POISONING. THE TOXIC ORIGIN OF CERTAIN ACUTE LEUKEMIAS AND THEIR RELATIONSHIP TO SEVERE ANEMIAS.

(Article by P. Delore and Borgomano: French; J. Med Lyon 9: 227-233, 1928)

Numerous observations have demonstrated that benzene poisoning produces severe anemia with hemorrhagic purpura. Leukopenia has been reported in clinical and experimental studies, and has lead to the use of benzene in the treatment of chronic leukemias.

We shall report the clinical history of a worker who was exposed for several years to the inhalation of small doses of benzene. The worker died from typical acute leukemia. One of his friends from the shop had died four years previously in the same hospital room from an "anemic syndrome" with purpura.

Benzene can induce opposite actions on leukopoiesis depending on its dose. Moreover, sensitivity tc the benzene compounds varies greatly among individuals. These two facts may explain the parodoxal development of acute leukemia induced by a compound that is used in the treatment of certain forms of leukemia.

Our clinical case report, which may seem unique until now, gives us the opportunity to discuss the relationships between leukemia and severe anemia and also the toxic etiology of certain acute leukemias. In addition to the fact that benzene, a coal tar derivative, my produce acute leukemia, a nev question arises regarding the relationship between certain forms of acute leukemia and sarcomatoses.

Because of its unusual nature and the consequent questions that arise, we shall report a clinical history of a worker who was exposed for several years to benzene inhalation and who died from typical acute leukemia. We believe that it is legitimate to include this case among the occupational accidents of benzene poisoning, even though we are accustomed to seeing only cases of severe anemia with leukopenia, and not cases of leukemia resulting from benzene exposure. We also should mention another very surprising fact. Four years previously, the patient's friend, employed in the very same shop, and who had also been repeatedly exposed to the inhalation of benzene vapors, died in the same hospital bed as our patient, from an acute anemia syndrome with purpura. The deceased's clinical history was reported in this same journal by CREMIEU (Ref. 1).

Before reporting our own clinical case and going into any discussion, we would like to review some classical concepts. The latter appear to us to be important before entering any discussion of the facts that we are going to present.

REVIEW OF CLASSICAL STUDIES

I. Chemical studies. Benzene, benzine and benzol.

According to KOHN-ABREST, ttic only distinction among these three chemical names. is a difference in purity. Benzene is a C_6H_6 hydrocarbon, the most simple compound of the aromatic hydrocarbon series and generally extracted from the light portion of coal tar.

[illegible] less impure commercial benzene. Benzol is real- unprocessed, nonrectifi c benzine. ;*rear compounds [illegible] tioned in increasing order of toxicity*.

In discussing the toxicology following the inhalation of benzene vapors. ttic distinction between benzol, pure benzine and unrefined benzinc or benzol should be made vhen ve are referring to massive doses. However, such a distinction is of no concern when we are referring to an atmosphere that is weakly or even moderately charged vith benzine. In such cases, ve hnvt learned from experience that the effects of the benzine impurities arc of a secondary nature. Thus. In discussing the toxicity of benzinè, we shall refer effectively to the toxicity of the pure C_6H_6 compound without taking into consideration the effect of any of the impurities that are found in benzols (KOHN-ABREST Ref., 2).

Therefore, benzine, benzene, and henzol hnvc vcrv similar chemical and toxicological properties. Many authors constantly confuse all three compounds. The cases of poisoning are always caused by benzene. Since SELLING, the clinicians have wrongly labeled the product that they use for the treatment of leukemias as benzol. The pharmacist supplies benzene, and it is wrong to call this compound by any other name (CREMIEU).

II. Experimental Studies. The importance of the dose.

Much experimental research has studied the effect of benzene on the blood.

In 1907, LANGLOIS and DESBOUIS (Ref. 3) reported that animals exposed to benzol vapors developed severe but transient hyperglobulia.

The same year, PAJAUD (Ref. 4) in studying slow and chronic toxicity, observed the following symptoms: anemia, a reduction in the hemoglobin

*In addition to benzene, benzol contains a large number nf impurties such as toluene, xylene, and a small amount of carbon sulfur. etc.

level, polynucleosis, and normoblasts in the blood.

In 1911, SELLING (Ref. 5) inspired by the clinical observations reported by Barker, administered subcutaneous injections of benzol to rabbits (mixed with an equal amount of olive oil) in a dose of 1 ml per kilogram of weight. The author observed considerable toxic effects on leukopoiesis.

PAPPENHEIM (Ref. 6) observed that if fairly low doses of benzol are used then primary leukocytoses develops. Using even lower doses, the leukocytoses is no longer followed by leukopenia and PAPPENHEIM concluded that benzol, when given in low doses, stimulates hematopoiesis and in high doses, ptoducc aplasia.

MASATOSHI TAHARA (Ref. 7) injected rabhits every day with 0.75 ml of pure benzine per kilogram of weight. The author observed a decrease in the red blood cell count, an increase in the number of white-blood cells, and then a progressive decrease in the number of leukocytes. HUTCHEN (Ref. 8) conducted experimental studies where benzol was injected subcutaneously and found that the compound produces marked stimulation of the bone marrow and affects the production of thrombocytes and leukocytes having polymorphous nuclei. However, in higher doses, benzol inhibits the bone marrow.

Based on the research that has been conducted, it seems that the effect of experimental benzene poisoning depends on the dose of the toxin administered. If the dose is high then there is a considerable and rapid decrease in the number of red blood cells. If the dose is moderate then primary leukocytoses and secondary leukopenta develop, and if the dose is lov then only leukocytoses occurs.

Generally, authors such as SELLING, in experimentally demonstrating the toxic effects of benzol on leukopoiesis, have administered what seem to be considerable doses to animals. This "leukotoxic" action was utilized in the treatment of chronic- leukemias. However, we should note that lov doses produce completely opposite results, not only in regards to the white blood cells but also red blood cells. In effect, benzol in high doses tends to destrov erythrocytes, while in low doses, it stimulates their formation (SELLING, LANGLOIS, and DESBOUIS). In therapy, we find many examples of physical agents or toxins that have different effects, depending entirely on their dose. This concept should always be kept in mtnd when interpreting the seemingly contradictory hematological findings of certain investigators. Also, the importance of the dose is a concept that shall be used in explaining the benzene etiology of the acute leukemia observed in our patient who vas exposed to benzine vapors for many years.

III. Therapeutic Findings.

In the field of therapeutics, we find many examples of how a compound's action differs depending on the dose. For example, in order for benzol to have a leukolytic action in the treatment of leukemia, it must be given in

high doses of 0.50 to 4 grams and even higher, per day, because conversely "low doses appear to stimulate leukopoiesis" (MANQUAT).

LECONTE (Ref. 9) reports that low doses stimulate leukopoiesis and, thus, increase the number of red blood cells. This increase is observed at the beginning in nearly all cases. In contrast, high doses produce an inhibition of leukopoiesis, and this is the therapeutic response sought in the treatment of leukemia.

IV. Clinical studies on benzene poisoning.

We shall only mention the most typical examples of benzene poisoning. One shall find that the effects are the same whether the poisoning is caused by benzine or benzol.

Accidents resulting from exposure to benzine and benzol have been reported for a long time in workshops with poor ventilation manufacturing these compounds, and in enterprises where the solvents are used for cleaning grease and as solvents for rubber.

In 1897, SANTESSON reported nine cases of chronic occupational poisoning. Four of the cases were fatal. The major symptom included anemia, hemorrhaging in the gingiva, and various viscera.

At the same time, LE NOIR and CLAUDE (Ref. 10) reported the case of a worker poisoned with benzine vapors. Thts worker developed hemorrhagic purpura and acute anemia. The patient died. Autopsy examination revealed a very large number of leukocytes filling the hepatic inter-trabecular capillaries. The leukocytes appeared to be more abundant than the red blood ccells. Careful examination of the blood was not made, but without counting. It was evident that the white blood cells were also more numerous in the blood than the erythrocytes.

In 1910, BARKER published the clinical histories of three young girls, two of whom died after having suffered from purpura nnd signs of aplastic ancmia for one month. These young girls had worked in a shop where benzol was used as a solvent.

In 1914, JULIEN and BONN (Ref. 12) reported the clinical history of a worker employed for two months in a factory where he spread a ruhbet solution dissolved in benzine onto canvas. The worker developed purpura with buccal hemorrhaging and gingivitis. He died after several days.

SOCQUET, KLINT., and KOHN-ABREST hnvc described cases of fatal poisoning where the following signs developed: fever, ancmia, purpura, jaundice, and gastrointcstinal disorders.

In 1922, FLANDIN and ROBERTI (Ref. 14) reported the observation of a woman who died of acute hemorrhagic purpura and high fever accompanied by severe anem a, leukopenia, and the near y complete disappearance of polynuclear ce ls. in fact, this was the ourth case of poisoning that

occurred in a workshop where benzine vapors vere being permanently discharged.

In a Saint-Etienne factory, CHAMBOVET (Ref. 15) found six women who had developed a syndrome characterized bv severr anemia and uterine hemorrhaging. Their gingiva had the appearance of scurvy.

In the observations published by OETTINGER (Ref. 16) and also by FAURE-BEAULIEU and LEVY-BRUHL (Ref. 17), cases of severe anemia with purpura and leukopenia were reported.

Finally, one of the most recent cases of poisoning has been reported by CREMIEU. The case was published in this journal in 1924. The worker observed by CREMIEU, had been employed in the same shop and worked under the same conditions as our own patient. Moreover, the patient's clinical course involved acute anemia with purpura. His clinical course vas very similar to the course of acute leukemia reported in our patient. Because of these reasons, we believe that it would be worthwhile to briefly review the clinical history reported. by CREMIEU. Thus. we shall better understand the matter when discussing the relationships between leukemia and anemia.

On February 7, 1923, a young 25 vear old man was admitted to Professor Roque's clinic. For half a day the patient hnd profuse epistaxis, refractory to treatment. The patient had the appearance of a bleeding, pale man who was close to death.

He reported that eight davs ago, when he was completely healthy, he noted the appearance of purpuric spots on his chest. At the same time, he developed a headache and fever. Next, gingival hemorrhaging occurred and finally, the day before his admission, he experienced a nasal hemorrhage that continued without stop for twelve hours.

Questioning failed to reveal anything remarkable in the patient's previous hereditary or personal history.

This man, who was in perfect health until the previous week, had been employed for the past five months in the manufacture of pharmaceutical products at the RHONE COMPANY. For the past six weeks, he was in charge of drying "pyramidon" - (aminophenazone--extraction of pyramidon by drying its solution in benzine). Moreover (and the fact was sufficiently remarkable so that the patient had no doubts about the source of his problems), the worker who had succeeded him at this task also had to quit because he developed repeated epistaxis.

Examination of the patient revealed acute, severe anemia, and epistaxis along with purpura, with a sphacelus on the mucous membranes of the lower lip, several hypertrophied ganglia in the axilla and groin. His temperature was between 39 and 40°. He had hemorrhagic retinitis.

The patient presented a blood dyscrasia. The source of this poisoning was being sought among the chemical substances that were used for drying the pyramidon. What vere these substances? According to the information supplied by the patient and subsequently completed by a medical-legal questionnaire, presented by Dr. Hazel. the operation in question consisted of filling a "centrifugal drier" with a semi-liquid mixture of pyramidon and benzine. His job was to start the drier, wat its operation, and then empty ft. During this operation, benzine vapors were released strongly but in moderate amounts. In contrast. during the cleaning of the equipment, the worker had to remove the lid of the drier and scrap off the paste that adhered to the walls for about 15 minutes. During this operation, he inhaled benzine vapors in large abundance, and since this task had to bc repeated four times during the day. he vas in all exposed for one hour to massive discharges of benzine vapors.

Thus, this was a case of benzine poisoning.

Examination of the potlent's blood revealed the following values:

Hematological examination:

Red blood cells	100,000
White blood cells	1,200
Hemoglobin	18%
Globular value	1

Leukocyte differential:

Polynuclear	27%
Lymphocytes	65%
Large mononuclears	3%
Average mononuclears	5%

No myelocytes. No reticulocytes. No nucleated red blood cells. The patient died on February 14 having retained consciousness until the end.

Thus, the victims of these observations underwent occupational poisoning with benzine or benzol. After a more or Less long dealy, they developed an acute anemic syndrome, purpura, accompanied by leukopenia vlth often a fatal outsome. FAURE-BEAULIEU (Ref. 17) hove differentiated between two forms of benzene induced anemia: a mild form characterized by an anemic syndrome and the appearance of scurvy and another more severe form characterized by a severe anemic syndrome and hemorrhagic purpura*.

An extraordinary fact is that nearly all of the observations mention gingival hemorrhaging with scorbutic changes in the gingiva. We know that this pseudo-scorbutis stomatitis is very common in cases of acute leukemia

*We are referring to severe cases of anemia and purpura of an arsenic-benzol etiology.

and we shall see later on that this symptom was of primary importance in our patient's clinical picture. The following is our patient's clinical history:

A case of acute typical leukemia during chronic benzene poisoning.

M... a 41 year old male, was admitted on July 14, 1927, to R. LEPINE'S department with a syndrome of hemorrhagic purpura, which he himself spontaneously attributed to a poisoning acquired during his employment in a pharmaceutical company In the Lyon area where he was employed.

The patient did not have any remarkable previous medical history. He was single and although he did not specify, he was a heavy drinker (two liters of wine daily).

For the past 15 years, he was employed in the same chemical company. For the past five years, he has been engaged in a department where pyramidon was dried with benzine. The work took place under conditions identical to those described previously by CREMIEU's patient. We shall not reiterate the working conditions. Our patient added that the work in this department was considered to be dangerous. His colleagues never spent more than one month on this job.

Apparently in good health, the patient experienced some epigastric pain about one month ago. He also had pain in the right hypochondrium and some bloody vomit. On July 1, he developed stomatitis and began to have a bloody cough. On July 5, subcutaneous hemorrhages appeared. On July 7, the patient became ill.

Upon admission, the patient was very pale, depressed; he had dyspnea. and a very extensive purpuric syndrome. The skin was covered by very many petechiae and ecchymoses. In addition. he had some hematomas, especially on the left forearm and infiltrating the subcutaneous tissues. His face was puffy and his chin covered by ecchymoses. the upper portion of his neck was deformed with a very large sub-angulo-maxillary adenopathy.

His mouth showed severe hemorrhages and ulcerative stomatitis. The lower gingiva were swollen, fungous ulcerated and bloody. The mucous membranes of the cheek and palatine area were ecchymotic. The patient constantly expectorated a bloody sputum. His breath was very fetid.

The lungs and heart were normal. The pulse rate was rapid at 108 beats and regular. The blood pressure was 11/8.

The liver exceeded the costal cage by three finger widths and was very painful. The lower pole of the spleen could be palpated.

The patient was very depressed and fatigued. He complained of a slight headache; he had no stiffness of the neck but a slight Kernig's sign. The tendon and cutaneous reflexes were normal.

Examination of the ganglia revealed numerous adenopathies in the form of small hard, painless ganglia without any periadenitis.

For the past three days, the patient's vision was impaired. His pupillary reactions were intact.

The large joints were slightly painful.

The urine was reduced in volume and very bloody.

His temperature was 37°.

Hemtological tests (Dr. VINCENT) were done as ooesible to diagnose the etiology of the purpura syndrome.

- The blood clotting time was delayed (20 minutes).
- The clot could not be retracted, no [illegible] 26 hours after drawing the blood.
- Hemoglobin level = 70%.

Blood count:

Red blood cells (per mm^3)	3,147,000
White blood cells (per mm^3)	542,500

Leukocyte differential:

Lymphoblasts	80%
Neutrophilic myelocytes	8%
Eosinophilis myelocytes	2%
Basophilic myelocytes	1%
Polynuclear neutrophils	6%
Lymphocytes	3%

Moreover, there were several nucleated erythrocytes that were mostly normoblasts.

Thus, there was no doubt that the diagnosis was acute leukemia. Furthermore, the clinical picture and especially the pseudo-scorbutic stomatitis were perfectly in agreement with this diagnosis.

- Lumbar puncture: the cerebrospinal fluid was clear, under pressure (Claude 35 in the supine position).
- Albumin: 0,20
  Cytology: 60 white elements per hand of Nageotte's cells.
- Blood culture: negative (Dr. VINCENT).

On the next day, thr patient's condition was considerably exacerbated. The purpuric eruption became more accentuated, the ecchymoses more numerous, and larger. On the inner surface of the right arm. the ecchymoses

extended broadly, two widths of the hand. The hematomas were also more numerous. They were localized on the limbs in the form of subcutaneous nodules the size of a hazel nut.

The condition of the patient's mouth was shocking. The gingiva vere fungous and hemorrhagic, containing some foci of sphacelus. The roof of the palate was violet in color and contained necrotic ulcerations. The base of the uvula was covered by a zone of sphacelus. The breath was fetid.

The patient became more and more fatigued. In moments, he was restless, anxious, despond. ent, thirsting for air as is seen after severe hemorrhages.

His abdomen was tender and painful. He had had no bowel movements since his admission.

The urine was the color of prune julce. The hematuria was nearly complete. The oliguria was 800 ml.

The patient died on the morning of July 17: his fever had risen to 39°. Autopsy. The lungs were very congested; there were no signs of tuberculosis. The heart was unremarkable except for numerous punctiform hemorrhages under the pericardial viscera. The inner vall of the aorta vas ecchymotic as a result of endarterial suffusions.. Slight peritoneal hemorrhagic effusions.

The liver was enlarged and had the appearance of a liver affected by toxins and infections. It was slate colored, the consistency of sand: a finger could be impressed without any difficulty. Upon sectioning, the parenchyma was discolored and clear yellow. This degenerated liver concafncd numerous necrotic foci.

The visceral peritoneum was congested.

The intestines were somewhat flatulent.

The kidneys were large, whitish, and edematous. They decapsulated easily. Upon sectioning, the middle was uniform yellowish color. It vas difficult to recognize the pyramids. The renal pelvis was filled with blood.

Upon opening rho cranium, the pia mater was very congested. The left frontal lobe was the site of a hemorrhage the size of an egg and showed hemorrhagic softening. The right occipital lobe contained softening of a yellowish color. The remaining two hemispheres contained very numerous disseminated hemorrhagic foci involving both the grey and the white matter. Some were ttic size of a hazel nut, others the size of a walnut.

DISCUSSION

Because of its etiology, this case was a very unusual one and perhaps even unique. We have, in effect, not been able to flnd in the litcrature any other case of acute leukemia resulting from benzene exposure.

One may well argue that the acute leukemia developed in our patient, independently of his former benzene poisoning, and that there is no etiological relationship between the benzene exposure and the subsequent leukemia. However. there arc numerous arguments in favor of Such a cause and effect relationship.

Recall that several accidents had already happened in the shop where our patient worked. One of his colleagues had repeated severe epistaxis. Another colleague died from a severe anemic syndrome with hemorrhagic purpura. The danger of benzene inhalation vas well-known in this shop, ana the workers who were employed there changed jobs at the end of the several weeks. We do not knov why our patlent remained there for five years.

However, there is more. At first glance. our case of acute leukemia a-pears to be the complete opposite of previous observations on benzene poisoning. where leukopenia was constantly observed. However, if we take into consideration the clinical fcatiires and not the hematological parameters, we may well be surprised by their similaritles. There are many analogies: the acute anemia, purpura, various hemorrhages, and especially the gingival hemorrhaged. with pseudo-scorbutic stomatitis, fever, and rapidly fatal course of the disease. In addition, in the case described by CREMIEU as well as in our patient, adenopathies were present. Overall. tlic post moretcm findings were similar in both cases. Therefore, our case differs from the other solely in regards to the blood picture. Our case is one of acute leukemia, while the other one involved pernicious anemia with leukopenia. Thus, we are Led to question if these opposite findings are so irreductible. We shall discuss the relationships betveen acute leukemia and pernicious anemia.

Such relationships are real. JOLY states that certain features of acute leukemias resemble that nf severe pernicious anemia. In JOLY's opinion, it may be that previously described rases of pernicious anemia were actually those of acute leukemia. This may be true of the case cited previously by LE NOIR and CLAUDE (Ref. 10). What complicates the question is that cases of acute leukemia without blood leukemia hnvc been described, for whom the term acute "aplastic leukemias" or better "leukopenic," has been proposed (CLERC). Thus. one may well ask if such forms of leukemia were not encountered in some of the previously reported rases of benzene poisoning, observations of acute anemia with purpura. where there was a disquieting frequency of the pseudo-scorbutic buccal lesions that arc fairly characteristic of acute leukemia.

The cases of "acute aplastic leukemia" or "leukopenic Leukemia" are very similar to cases of pernicious anemia. Moreover, despite the theoretical opposition that exists between the anemic and the leukemic processes, their association is not rare (RIEUX). Many cases of leukemia are accompanied by severe anemias. Some authors have proposed the term "Leucanemia" for the combination of leukemia and pernicious anemia. The question was raised and criticized in 1925 by CHALIER and CHEVALIER (Ref. 11) and by RIEUX (Ref. 13). In this respect, we would like to mention two fairly recent observations, one by NOBECOURT, GIRAUD and CH. RICHET Junior (Ref. 18) dealing with a clinical syndrome intermediate between acute pernicious anemia and acute leukemia. The other observation by CHAUFFARD and BERNARD (Ref. 19) involved a case of pernicious anemia that ended in acute myeloid leukemia.

Perhaps more suggestive are the observations reported by P. E. WEILL (Ref. '22). The studies demonstrated how radioactive substances may induce pernicious anemias as well as leukemias. Two individuals were exposed for nearly the same length of time to thorium radiation.' One developed pernicious anemia while the other had myelogenous leukemia.

Finally. it is known that the radiation therapy used to treat chronic leukemias. especially the myeloid leukcmias, may induce the appearance of a severe anemic syndrome ond acutc leukemia, that is, in effect, a "leukanemia" syndrome.

Consequently, pernicious ancmia and acute leukemia should not be considered to be two autnomous and independent diseases. In cases of benzene poisoning. we generally see a clinical picture of severe anemia vith leukopenia. However, our case indicates that benzene poisoning may also result In acute leukemia. The classical findings reporting acute anemia with leukopenia in cases of benzene poisoning do not exclude the possibility of acute Bcnzcne Induced leukemia. The two syndromes may be induced by the same poisoning.

The next question is, "Why is it that in certain cases, which are fndeed the more frcqucnt ones, does benzene poisoning lead to leukopenia?" And, "Why, In other cases, which until now uere infrequent, does benzene produce leukemia?" We may answer this question by referring to the effect of benzine on leukopoiesis. Benzine has opposite effects depending on the dose. We may also mention individual susceptibility which appears to play an important role in the benzene accidents, both in human clinical situations as well as in animal experimentation. POLICARD and BERNHEIM have demonstrated that animals have variable sensitivity to benzol (Ref. 23).

The fact of individual susceptibility also explains the high tolerance that our patient had towards benzine since acute leukemia developed only after the end of five years daily exposure. Such a tolerance among workers who suddenly fall victims to severe accidents after many years of chronic poisoning, has already been noted by BALTHAZARD (Ref. 20), as well as FAURE-BEAULIEU and LEVY-BRUHL (Ref. 17).

Our observation raises another question. This is the possible toxic etiology of certain acute leukemias. It to readily admissible that severe anemia with hemorrhagic purpura may be caused by the toxin in question here, namely benzine. Then, "why does not the same possibility hold ture €or acute leukemia?" Without denying that in some cases, the luekemia may be of an infectious etiology, it may be Cacluded that in other cases, che leukemia may *be of* a toxic orgin, the same as is true for pernicious anemia and purpura.

And going still further in our dtscussion. ve would like to discuss *some* of the neoplastic features of leukemia that develop, as Ln our case, after prolonged exposure to benzene. It is well-known that coal tar and several of its derivatives arc carcinogenic. At this point, we vould like to recall BARD's words who stated that leukemia is cancer of the blood, JOLY (Ref. 21) wrote.... "In certain acute leukemias, the blood leukocytes are considerable in number and are composed nearly exclusively of undifferentiated lymphoid cells, which are neither lymphocytes nor myelocytes, but which unquestionably resemble the cells of many invading lymphadenomas. These are neoplastic cells." We believe that our observation very definitely raises the question regarding the relationship bptveen certain acute Leukemias and sarcomatoses, because the toxic agent in question. benzene, is a coal tar derivative.

Theoretically, in animals, the leukemic syndrome can be produced by the administration of very low doses of benzene, doses that are much lover than the ones inducing leukopenia but given for a continuously length of time. We are currently attempting such experiments.

Finally. from the practical point of view. one may well ask if benzol' therapy is not sometimes capable of transforming chronic leukemia into acutc leukemia. This possibility is currently recognized in radiation therapy. We did not find any reports about leukemia being transformed into on acute stage following the administration *of* benzene. However, we should mention that the therapeutic doses of benzene are much higher than the doscr that, in our observations, are capable of increasing the number of white blood cells.

As we have already mentioned, different doscs of benzene can produce opposite effects.

Thus, such are the various problems that arise From our case of benzene poisoning uhere the acute leukemia did riot follow the classic course. As CHAUFFARD and BERNARD wrote (Ref. 19), "In hematology, the atypical case, comply poorly to our classifications vhirh are always too restrictive..... In fact, *these* arc the most interesting and the *most* worthwhile cases to study.. .*."

*This comment shall be discussed at length and in *more* detail in the next thesis written by one of us. The study will also include the results of current experimental studies where we are attempting to induce leukemia in animals by the administration of benzene.

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