PRIMARY CANCER OF THE LIVER IN VIET NAM

Ton-That-Tung

(with the collaboration of Mrs. Trần Thi An,
Nguyễn Dãng Tâm, Pham Hoàng Phiêt, Nguyễn Nhu Bằng,
Tôn Thất Bách, Hoàng Văn Son and Dỗ Kim Son)

Translated from the French by the
Medical Documentation Service
College of Physicians
Philadelphia, Pennsylvania

Primary cancer of the liver has assumed considerable importance in the field of pathology in Viet Nam during recent years. From the etiological point of view, as well as from the diagnostic and therapeutic points of view, new problems are approached in this paper which seem to permit a better understanding of its pathogenesis and its behavior.

Etiology: The relating of cancer of the liver to a chemical cause was posed in Uganda (1, 2) where aflatoxin, a substance produced by Aspergillus flavus on the mildew peanut plant, was identified as the responsible agent. In Viet Nam, where primary cancer of the liver in humans has risen from eighth place to second place, experimental investigations emphasized the carcinogenic role of a chemical substance thus far known only as an impurity in defoliants. We are concerned here with 2,3,7,8-tetrachloro-dibenzo-p-dioxin, commonly called dioxin, which is a contamination of (2,4,5-trichlorophenoxy)acetic acid or 2,4,5-T, which was scattered in massive doses over Viet Nam.

Dioxin is a constant impurity of (2,4,5-trichlorophenoxy)-acetic acid, since it can be obtained directly from this acid by simple pyrolysis at 500-600° C (3). It is not soluble in water, it is only soluble in alcohol and fats; it cannot be destroyed at a temperature of 1,000° C (4) (according to Dow, it decomposes at 700° C). It is estimated that it amounts to 30 g per ton of 2,4,5-T and Westing thinks that the weight of dioxin scattered over South Viet Nam amounts to 550 kg, which is an enormous figure since the substance is active starting

with a few micrograms (1 microgram = $\frac{1}{10^6}$ g).

It is a very toxic substance: it causes hepatic necrosis by ingestion; by local application in animals, it provokes precancerous lesions: hyperplasia of the cutaneous epithelium and the suppression of the sebaceous glands (6).

The LD 50 lethal dose of dioxin for the guinea pig, which is the animal most susceptible to this product, is 0.6 micrograms/kg in the female guinea pig (7) and 0.5-1.0 micrograms/kg in the male guinea pig (8). Dioxin is teratogenic in the hamster between the sixth-tenth days of gestation at doses ranging between 0.5 micrograms/kg/day (5% fetal anomalies) and 9.1 micrograms/kg/day (82% anomalies) (9).

The carcinomimetic action of 2,3,7,8-tetrachlorodibenzo-p-dioxin was studied by Bửu Hội and his team (9).

Instead of relying on the technique of producing cancer directly in animals, which has been subjected to recent criticism by L. Goldbert (10), they used a chemical model based on two types of tests inspired by the study of chemical carcinogens (9).

1. Investigation of a modification in the proportion of two typical microsomal enzymes: zoxazolamine - hydroxylase and the hydroxylase deactivating phenobarbital.

2. Investigation of a possible effect on the biosynthesis of the hepatic arginase.

Zoxazolamine-hydroxylase test. This test is based on measuring the paralysis produced in the Wistar rat by a specific dose of zoxazolamine. The carcinogenic product administered

before zoxazolamine provokes the appearance of an enzyme of the hydroxylase which curtails this paralysis with respect to the control rats in direct proportion to the magnitude of its inductor power (11).

The inductor power of 2,3,7,8-tetrachlorodibenzo-p-dioxin is already manifested at a dose of 5 micrograms and proves to be at least 60 times more active than the classical benzo(a)pyrene carcinogen. Another interesting fact: alone, 2,3,7,8-tetrachlorodibenzo-p-dioxin is active while its other isomers (non-substituted form, 2-nitro, 1,6-dichloro, 2,7-dichloro, octachloro) are not.

Test with phenobarbital: on male Swiss mice, the dioxin test produces the appearance of a hydroxylase which curtails the sleep due to phenobarbital in a highly significant fashion.

Concentration of arginase in the liver: In Wistar rats, with dioxin, just as during chemical carcinogenesis of the liver, the hepatic arginase level decreases gradually in a significant fashion.

In conclusion, the results obtained show that 2,3,7,8-tetrachlorodibenzo-p-dioxin, even at very small doses, is capable of deeply disturbing the enzymatic equipment of the organism as is the case with typical carcinogenic substances such as benzo(a)pyrene and p-dimethylamino-azobenzene. These disturbances are probably due in part to the source of the extraordinary sustained-release toxicity of this substance.

These observations led Bưu Hội and his team to study the power of dioxin as an enzyme inductor (12), of the type in series, including an entire series of biochemical lesions.

It is in this way that adult Wistar rats receiving a simple 10 mg/kg dose by intraperitoneal injection in olive oil show an increase in their enzyme level ten days after the injection; the enzymes involved are SGOT, SGPT, lacticodehydrogenase, arylesterose, and cholinesterase.

The target organs of dioxin are first of all the liver (13), which displays centralobular stasis with dissociation of Remak's fibers, considerable alterations of the hepatocytes, and hyperplasia of the Kupffer cells, starting as early as the sixth day after intraperitoneal injection; next in order are the thymus gland, particularly in young animals, and finally the heart. These lesions are seen even at the small dosage of 1 mg/kg.

In summary, the investigations on animals show that 2,3,7,8-tetrachlorodibenzo-p-dioxin, alone out of all the isomers of this substance which were tested, is a powerful enzyme inductor which classifies it among the most powerful carcinogens known. The investigations also show that the hepatic gland is its main target.

Experimental observations led us to reinvestigate the frequency of primary cancer in Viet Nam as a function of the scattering of defoliants.

We used the year 1961 as a reference, the date of the first defoliant distributions, and we recorded the hepatic cancer figures for a period of six years before and after this date.

We recorded the following figures in Hanoi:

from 1955 to 1961: 159 cases out of 5,492 cancers

from 1962 to 1968: 791 cases out of 7,911 cancers

average number of cases for the first period: 26 cases per year

average number of cases for the second period: 144 cases per year.

$$Chi^2 = 164$$

$$p = 1.10^{-9}$$

(highly significant difference)

Primary cancer of the liver increased from 2.89% of the total number of cancers to 9.07% for these two periods before and after 1961, respectively.

We investigated other etiologies possibly responsible for this explosion of primary hepatic cancer, for example a currently "fashionable" viral source. However, systematic investigation of the Au antigen in the blood of our patients suffering from primary hepatic cancer only shows a very small positive value: 2.05%.

This recrudescence of primary hepatic cancer in North Viet Nam, although the defoliants were especially scattered throughout South Viet Nam, may be explained by the continual mixing of the populations between the two zones and perhaps - but this remains to be proved - by the long-distance conveying of the toxic product by the wind or animal vectors: mammals, birds, insects.

However, there is a missing link which, if found, will make it obvious that dioxin is an inductor chemical substance with respect to hepatic cancer in humans. This missing link is the positive proof of the presence of dioxin in the hepatic tissue of human cancers. However, at the present time, it is the most difficult type of investigation to carry out, even in the best laboratories in the world.

Matthew Meselson and Robert Baughman, of the Biochemistry and Molecular Biology Department of Harvard University, pointed out that even at the present time no method exists which is capable of proving the presence of dioxin in the body of an animal after the administration of a lethal dose. Thus for the guinea pig, the LD 50 lethal dose in the female was 0.6 micrograms/kg of weight. This means that if all the dioxin was retained in the dead animal, the entire dioxin concentration in its tissues would be on the order of less than 1.10^{-9} g, although the lowest limit of detection reported thus far has been 50.10^{-9} g. Mr. Meselson has just developed a technique for the titration of dioxin based on mass spectrography, the sensitivity of which would be on the order of 10^{-12} g (6). Mr. Meselson very kindly promised to help us in our investigation.

In summary, the stable dioxin substance forming a part of the 2,4,5-T as a constant impurity, appears to explain the residual effects of the dissemination of defoliants. A teratogenic substance, very probably mutagenic in humans (14), its role as a carcinogen is clearly suggested by its enzyme inductor properties, which put it in the category of the most powerful carcinogens known.

Experiments have proven that the target organ of its action is the liver, and the present explosion of primary hepatic cancer in Viet Nam may be related to the pollution of South Viet Nam by an enormous mass of 550 kgs of dioxin mixed with defoliants used by the American army. Still other studies seem necessary in order to confirm its action (detection of its presence in cancerous livers, for example).

Nevertheless, the results of the tests which we have compiled must draw the attention of the scientific world to this product, which was disseminated in massive doses on the rice fields and forrests of Viet Nam and whose deleterious effects on humans seem to exceed by far those of the known pollutants.

The Diagnosis of Hepatoma by Biological Methods.

1. Investigation of alpha 1 F.P. It is known that Abelew (1963) found in the serum of mice suffering from experimental hepatoma a protein that is ordinarily found in the embryo and that disappears rapidly at birth, designated by the name alpha 1-feto-protein (alpha 1 F.P.). This protein was investigated in our patients, according to the Ouchterlony technique. Out of 51 cases of hepatoma, the investigation was positive in only 28 cases, or a proportion of 54.90%.

This reaction is not specific to the hepatoma. In one case involving a patient suffering from a tumor on the right hypochondrium, with the presence of alpha 1 F.P.in the serum, we thought that a hepatoma was implicated. Upon operating, we found a malignant chorioepithelioma which had crept between the diaphragm and the posterior face of the liver, which was absolutely normal. The reaction became negative immediately after ablation of this tumor.

The above reaction seems to become increasingly less specific, to the extent that it is attempted to make it more sensitive. This is not the case with certain hepatic enzymes.

2. Titration of the hepatic enzymes. We wanted to verify the hypothesis of Schapira (15) (1963) that there is a loss of

specificity of the enzymatic constituents in primary hepatic cancer, which represents a veritable molecular lesion at the source of the cancer.

Enzyme of the urea cycle: It is known that this cycle requires five enzymes, three of which have been studied in experimental cancer by Chung Wu et al. (16): argininosuccinate synthetase, argininosuccinate lyase, and arginase.

Their activity is reduced in the experimental hepatomas of Novikoff and Morris 7787 and 7800. In hepatic cancer induced by chemical substances, other investigators, such as Sato (17) and Eliasson (18), showed that the hepatic arginase decreases gradually in a significant fashion.

We attempted to determine the arginase level of the hepatic tissue in the region of the cancer and at a distance from the cancer in primary hepatic cancer. The technique used is the modified method of Petrovic (19). Sampling was carried out after laparatomy, completed by a hepatectomy or an arterial ligature, always with a biopsy for the histological examination.

Here are the results expressed in international units per g of hepatic tissue.

Level of Hepatic Arginase Expressed in I.U. and per g of Tissue

Non-cancerous liver 110 I.U. 148, 128, 109

Hepatoma	Sampling near the tumor	Sampling at a distance from the tumor
	30 I.U.	(usually in the opposite lobe)
	7	
	7	
	25	38 I.U.
	70	100
	0	
	3	50
	44	68
	22	56
	25	62
	35	
	26	
	11	148
	63	156
	10	
	1.6	
	6.6	
	96.4	
	12	
	45	
	32	40
	12	
	46	
	30	
	106	
	1	
	23	83
	6	35
	28	66
	15	126
	13	81
	30	84
	8	
	8	
Cholangioma		
	70	100
	11	
	150	

In summary, the concentration of hepatic arginase in the hepatoma was less than or equal to 30 I.U. in 76.47% of the cases, while in the cholangioma, it was equal to or less than 30 I.U. in only 33.3% of the cases.

By taking as a normal concentration of hepatic arginase the figure 100 I.U. and as a pathological concentration the figure 30 I.U. of arginase per g of hepatic tissue, it may be said that it is possible to diagnose the hepatoma in at least 76% of the cases by means of the arginase test, which gives better results than with the alpha 1 F.P. investigation (only 54.90% of the cases).

In two cases, we investigated the hepatic arginase concentration in order to settle a delicate diagnosis: its value was undeniable.

1. Cancer of the liver taken for an abscess of the liver and drained. Rectification by investigation of the hepatic arginase level. Confirmation by selective arteriography. Ligature of the hepatic artery.

Phạm Thị Cu, 60 years old, admitted on 9/10/72 for pain in the right hypochondrium. Fever with shivering. No jaundice. Sign of agitation of the liver: positive. Sedimentation rate: 110 during the first hour. Bilirubinemia 10 mg/l, glycemia: 1.16 g/l, SGOT: 99, SGPT: 275. Prothrombin concentration: 75%. Teleradiograph: enlarged liver.

Puncture on the left lobe: chocolate-colored pus. Drainage on 10/11/72 after failure of the emetine treatment.

The liver remains large and hard. Mantoux: negative. Investigation of the alpha 1 F.P.: negative. Puncture, biopsy

with a Mengheni needle and investigation of the arginase concentration: 30 I.U./g of hepatic tissue. A selective arteriography shows a separation of the branches of the right hepatic artery with pools of blood in the medial segment. Laparatomy (12/4/72): large encephaloid tumor on the lower face of the medial segment having invaded both lobes. Puncture: emerging of cerebroid tissue. The tumor broke while being freed. Gauze plugging and ligature of the hepatic artery itself.

2. Retro-hepatic sympathicoblastoma taken for the primary hepatic cancer. Rectification of the diagnosis by investigating the hepatic arginase concentration. Confirmation of the diagnosis by exploration.

A young, 9-year-old boy, Nguyen Van Luyen, was admitted on 11/23/72 for a tumor on the right hypochondrium.

Tumor 2-months-old, with regular edges, extending from the right hypochondrium to the left hypochondrium, not indurated and accompanied by a slight splenomegaly. Sedimentation rate: 140 during the first hour, bilirubinemia: 6 mg/l, SGOT: 250, SGPT: 75, alpha 1 F.P.: negative. The diagnosis was: primary cancer of the left lobe. Puncture, biopsy, and investigation of the hepatic arginase concentration: 150 I.U. The diagnosis of hepatoma was eliminated.

Laparatomy: Retroperitoneal tumor, pushing the liver forward, adhering to the mesentery and to the spleen. Biopsy: sympathicoblastoma.

Other hepatic enzymes. It should be pointed out that other enzymes have been found to be altered in hepatic tissue afflicted

by hepatoma. F. Schapira et al. (15) reported that there is a predominance of aldolase F-1, 6-P with respect to aldolase F.1.P, i.e. that the ratio

$$\frac{\text{F-1, 6-P}}{\text{F.1.P}} = 3, \text{ instead of 1 (as in the normal liver)}$$

The above authors attribute this phenomenon to the fact that the normal hepatic aldolase is replaced by an embryonic aldolase, that is normally found in the muscular tissue. If we accept the hypothesis that the fetal aldolase is different from the adult aldolase, it may be suggested that the fetal aldolase exists in the adult but that its synthesis is repressed by a gene which only permits synthesis of the adult aldolase. In hepatoma, the adult aldolase is inhibited and the embryonic aldolase ceases to be repressed.

The return to the embryonic state of the enzymes was verified on the lacticodehydrogenases (LDH). It is known that there are five lacticodehydrogenases: LDH_1 is seen in the adult state and LDH_V is seen in the fetal state. When there is cellular differentiation due to cancer, LDH_V predominates over LDH_1.

Thus in cancer of the prostate, Oliver et al. (21) observed that the $\frac{LDH_V}{LDH_1}$ ratio is greater than 1, instead of being less than one as in the normal state. The same inclination towards LDH_5 was also observed by the Danish authors (22) in tissues from cancers of the uterus, colon, and lung. We titrated the LDH_5 and LDH_1 in the hepatic tissue of primary cancers, and this is what we found: in the normal hepatic tissue, the $\frac{LDH_5}{LDH_1}$ ratio is

approximately 2.3, while in tissue near the focus of the cancer, the $\frac{LDH_5}{LDH_1}$ ratio in seven patients suffering from hepatoma was 14.7, 17.6, 19, 19.7, 21, and 22, respectively; in two patients suffering from cholangioma, the ratio was 8, 9.2 - i.e., seven to ten times greater than normal for the hepatoma and three to four times greater than normal for the cholangioma.

It may thus be concluded that in hepatoma, by returning to the embryonic state, there are serious biological disturbances which it has been possible to use or which must be used for diagnosing the disease. The investigation of the alpha 1 F.P. in the serum has already been put into practice. But it is still necessary to investigate the decrease in the hepatic arginase concentration or to titrate the aldolases and the lacticodehydrogenases of the hepatic tissue and to examine the ratios:

$$\frac{F - 1 . 6 - P}{F.1.P.} \quad \text{and} \quad \frac{LDH_V}{LDH_1}$$

in order to confirm the diagnosis of primary hepatic cancer.

The clinical behavior of primary hepatic cancer in Viet Nam.

The average age is relatively young: 45 years (United States (23): 53.3 years; France (24): 60-69 years). There is a difference between the two sexes: 75% for men and 25% for women.

The duration of the cancer is approximately 6 months (Paris (23): 6 months, Hiroshima and Naganaki (25): 5 months, Dakar (26): less than 6 months). The average is three months between the appearance of the first symptom and hospitalization.

The tumoral form is the usual form. It is perhaps for this reason that diagnosis has usually been easy. It is very often associated with dull pains, which worry the patient. We have the impression that the cancer is always accompanied by a clinically enlarged liver. If it is not possible to palpate it below the costal area, it is possible to detect an elevation of the right diaphragmatic hemicupula by means of teleradiography. Very often the tumor is preceded by pain, fever, and shivering. Without puncture, it was often impossible for us to differentiate between a primary hepatic cancer and an abcess of the liver, and we observed that an abcess may precede the appearance of a primary cancer. The usual biological signs have no diagnostic value. The laparoscopy in our hands is sometimes less affirmative than the clinical investigation. Selective arteriography, carried out in a makeshift manner on a serioradiogram, sometimes supplied us with definite pictures: separation and overhanging of the arterial branches, hypervascularization, with the presence of pools of blood.

Hepatoma exists in a proportion of 94.25% as against 5.75% for cholangioma. The hepatoma is associated with cirrhosis in 52.40% of the cases. The ganglionic metastases in the hepatoma only appear in 1/5 of the cases and the pulmonary metastases in 15.0%. Portal thrombosis was recognized upon autopsy in less than 5% of the cases.

The Mantoux reaction was negative in 58.70% of the primary hepatic cancer cases. The Au antigen investigation was positive in 2.05% of the cases.

Hepatectomy in primary cancer of the liver. 119 resections were carried out between 1962 and 1972 in our clinic:

48	total right lobectomies or hepatectomies with	14 deaths
37	left hepatectomies with	7 deaths
24	left lobectomies with	6 deaths
10	segmentectomies or sub-segmentectomies with	1 death
or 119	hepatectomies with	

a total mortality of 23.53%.

Actually, the mortality was lower during the past six years. From 1/1/66 to 11/28/72, the following operations were carried out:

14	right hepatectomies with	2 deaths
1	right hepatectomy with colectomy with	1 death
1	total right lobectomy	
17	left hepatectomies with	2 deaths
10	left lobectomies	
3	medial segmentectomies, extended to the sub-segments V and VI	
	1 with transverse colectomy	
	1 with resection of the biliary tripod and immediate restorative or plastic operation	
or 46	hepatectomies with	5 deaths

which gives us a mortality of 10.86%, quite comparable to the figures established by other authors (Moreaux and Hepp (27): 10% out of 10 resections; Lin (28): 11.9% out of 41 resections).

As far as hepatectomy was concerned, we proceeded as follows: in those cancers that had already invaded the neighboring organs or the hepatic pedicle, limited resection, combined with resections

of the invaded organs and sometimes with ligature of the hepatic artery. The duration of survival does not seem to us to be related to the extent of the exeresis.

The hepatectomy was always carried out according to our technique which, in order to be fast and effective, requires strict adherence to the following rules: locating of the vena cava inferior, of the caudal process, and of the bed of the gall bladder. Cut well into the capsule in order to aid the digital separation, which may not be possible in cirrhosis. In such cases, we used a flat clamp which dilacerates the hepatic tissue without injurying the vessels. This permits the finger to finish the work begun by the clamp. In recent years, we have always used abdominal incision without thoracic incision, with the costal ridge lifted up forceably by means of a sub-pubic valve. A perfect knowledge of the intrahepatic anatomy is the only condition for success.

Ligature of the hepatic artery and dearterialization of the liver. We used ligature of the hepatic artery alone in most cases and sometimes, in more than one-third of the cases, in combination with a dearterialization which was usually lobar; total dearterialization of the liver was carried out only rarely in the treatment of primary hepatic cancers generalized to both lobes (usually the hepatoma is verified by a broad biopsy on the tumor). These are thus cases which exceed the present surgical possibilities.

We performed 110 ligatures of the hepatic artery, usually the hepatic artery proper (the common hepatic artery is only used

in cases of massive infiltration of the pedicle by ganglions) combined with 23 left lobar dearterializations, total dearterializations of the liver, and 8 hepatectomies .

Total dearterialization consists of sectioning the suspensory ligament, along with the entire omentum minus, including sectioning of the accessory hepatic artery coming from the cardiac stomach arch, and of the coronary ligaments. Lobar dearterialization is only concerned with a single cardiac ligament. In the associated hepatectomy, it is usually a question of a sub-segmentectomy and of a left lobectomy or a left hepatectomy.

There are 10 cholangiomas and 100 hepatomas out of 110 ligatures and dearterializations.

There were 11 deaths: the operatory mortality is thus 10%. This figure could have been lower if it had been possible for us to choose our patients at the beginning. At present, we do not operate on patients having a high bilirubinemia (approximately 20 mg/l), high transaminases (greater than 100), a prothrombin concentration less than 70%, or patients with ascites. During the first six months of 1972, we only had one death out of 34 ligatures, mortality: 2.94%.

The immediate results of the ligature can be followed by means of the following criteria: (1) disappearance of the pain; (2) resumption of appetite; (3) regression of the tumor; (4) drop in the alpha 1 F.P.; (5) increase in weight. Criteria (1), (2), (4) and (5) are fairly frequent, while criterion (3) is often lacking.

It was possible to study the effect of ligature of the hepatic artery or lobar dearterialization on the autopsy pieces from subjects who died in the first five days. On the tumor

itself, coagulation necrosis of the ischemic type predominates characterized by cellular destruction with preservation of the hepatic fibers, while the non-cancerous liver is the site in particular of less extensive anoxic necrosis lesions, characterized by the disintegration of the cellular fibers. Dearterialization entails ischemic necrosis lesions extended throughout the tumoral zone, but anoxic necrosis is also extensive on the non-cancerous parenchyma. The ligature of the hepatic artery produces central necrosis of the tumor, but it seems that the periphery remains unharmed. On the other hand, lesions of the non-cancerous liver are less extensively disseminated and are usually localized around the centrolobular zone. It is thus the quality of the remaining hepatic parenchyma which regulates the prognosis.

In summary, lobar dearterialization seems to sterilize the cancerous focus more completely, but causes necrotic lesions that are more extensive in the healthy parenchyma. Ligature of the hepatic artery causes central necrosis of the tumor in particular, but the necrosis is not as extensive as in the healthy parenchyma. Nevertheless, relapse at some time in the distant future is the rule with both dearterialization and ligature. This is why we think that a medical treatment with stimulating adjuvants should be combined with the surgical treatment.

Treatment with stimulating adjuvants. Treatment with stimulating adjuvants was brought to our attention by Professor Halpern of the Broussais Hospital. This treatment seems to be all the more indicated since the Mantoux reaction was negative

on our patients in 54.90% of the cases.

We did not use chemotherapy on our patients.

At the beginning we used BSG attenuated at 70° C, injecting it intradermally in the arm or at the level of the tumor once a week. Since these injections caused the appearance of small fistulas, we replaced the BSG by an activating substance prepared by our friend Ng. D. Tam (Gif sur Yvette) and tested at Villejuif, which we designated by the name LH.1. We injected this substance intradermally (3/10 of an mg of LH_1 + lidocaine) once a week for the patients with a positive Mantoux and twice a week for the patients with a negative Mantoux. We did not observe any toxic effects and the long-term results have been promising.

Long-term results. Here is the rule that we established in order to judge the value of the survival. Since the patient always arrives around the third month after the first symptom appears, and since the total duration of the disease is six months, we rarely saw a patient getting past the third-month point after exploratory laparatomy, before the use of arterial ligatures. Thus when one of our patients happens to exceed the sixth month after the operation, we attribute the prolonged survival to the effect of the therapy used. The six-month survival model thus permits us to measure the effectiveness of the treatment.

a) Hepatectomies (without treatment with stimulating adjuvants): 19 patients were seen again after the operation; 7 lived for more than six months afterward. The survival rate of more than 6 months is therefore 37.21%. Only a single one of these 19 patients was able to get beyond more than four years.

b) Ligature and dearterialization along with treatment by stimulating adjuvants: 25 out of 110 patients were seen again and 7 patients passed the six-month peak. The survival rate for more than six months is therefore 28%. Secondary death in our patients seems to be due to three main causes: hepatic insufficiency, hemorrhage due to rupturing of varices, and hematobilia. Treatment with stimulating adjuvants seems to fix the evolution of the tumor. Thus one patient, seen again during the eighth month after his ligature, maintained the same radiological appearance of the liver and the same rounded image of pulmonary metastasis on the left, eight months after the operation. Only a single patient reached the third year after selective ligature of the right hepatic artery and preservation of the left hepatic artery, exposed and left alone. A control arteriography shows that there is always a tumor characterized by an overhanging image with pools of blood in the region of the right hepatic artery, obliterated in the pedicular portion. The Mantoux reaction, which was negative at first, becomes positive after intradermal injections of LH_1.

It may thus be said that although not providing a true cure, the method of arterial ligatures with associated treatment by means of stimulating adjuvants has been able to prolong survival in the patients in one-third of the cases - a survival which appears to be fairly comfortable since the patient attends to his usual activities and even works as he did before he became sick.

We feel that new observations are still necessary in order to make a conclusion as to the therapeutic value of this method. Nevertheless, under the present conditions, this method seems

to be that which has least disappointed us, and we believe that dearterialization does not seem to give better results than simple ligature.

CONCLUSIONS

Primary cancer of the liver has increased to an abnormal extent in Viet Nam and the authors attribute this increase to the probable carcinogenic action of a chemical impurity, 2,3,7,8-tetrachlorodibenzo-p-dioxin, mixed with the defoliant 2,4,5-T, which was massively distributed over Viet Nam. Diagnosis via the biological method seems to be the most certain means of diagnosis and perhaps the fastest: titration of the alpha 1 F.P. in the serum; titration of the arginase, the aldolases, and the lacticodehydrogenases in the liver. The enzymatic disorder seems to be the molecular lesion, having as its basis primary cancer of the liver. An early hepatectomy which should be combined with a treatment by means of stimulating adjuvants, might improve the survival. In bilateralized cancers, vascular interruptions (ligature of the hepatic artery, dearterialization) combined with a treatment by means of stimulating adjuvants, seem to prolong the survival of one-third of the patients, who continue to live in a comfortable manner.

ACKNOWLEDGEMENTS

We sincerely thank Professor M. Meselson (Harvard) for having read over the chapter on dioxin and Drs. Henrik Ekberg (Lund) and Yvonne Capdeville (Faculty of Orsay) for having helped us physically in this report.

REFERENCES

1. Alpert M.E., M.S.R. Hutt & C.S. Davidson, Lancet 1968, i:1265
2. Korobkin P.M. & E.H. Williams, Yale J. Biol. Med. 1968, 41:69
3. Buu Hôi, G. Saint Ruf, P. Bigot & M. Mangane, C.R. Seances de l'Acad. Sc. 1971, 273 :708
4. Buu Hôi, personal commun., 1970
5. Westing A.H., Science Today 1972, 6: 46
6. Jones E.L & H.J.Krizek, J. Swest. Derm. 1962, 39 : 511
7. Meselson M. & Robert Baughman, An improved analysis for 2,3,7, 8-tetrachloro-dibenzo-p-dioxin, Amer. med. Soc. 162 nd Nat. meet, Washington D.C., 17 sept. 1971.
8. FDA studies, cited by Dr S.S. Epstein, US Senate 91 & Congress Washington, 1970, Second session on Effects of 2,3,5T on Man and the Environment, p.410.
9. Buu Hôi, D.P. Hien, G. Saint Ruf & Mmem Servoin-Sidoine, CR. des seances de l'Acad. Sc. 1971, 272 :1447
10. Goldberg L.,, cited by Ravina, Presse méd. 1971, 79 : 492
11. Conney A.H. & Buu Hôi, J. biol. chem. 1954, 209 : 211
12. Buu Hôi, P.H. Chanh, G. Sesqué, Mme Azum. Celade & G. Saint-Ruf. Die Naturwissenchaften 1972, 58 :173
13. Buu Hôi, P.H. Chanh, G. Sesqué, Mme Azum Gelade & G. Saint-Ruf, Die Naturwissenchaften 1972, 58 : 174
14. Tôn Thất Tùng et coll. Clinical effects of the continuous use of defoliants on civilian population, Reunion int. de scientifiques sur la guerre chimique au Viet Nam, E. Lederer, 91 - Orsay, 12 Dec. 1970
15. Schapira F., J.C. Dreyfus & G. Schapira, Nature, 1963, 200:99
16. Chung Wu et coll. Cancer Res. 1967, 27 : 956
17. Sato S. Tohoku Igaku Zasshi 1963, 67 : 597
18. Eliasson, E.E., Cancer Res. 1967, 27 : 955
19. Petrovic J. & D. Kanazir, Archiv Biloskih Naaka 1966, 18:1
20. Hers H.G. & J. Joassin, Enzymol. biol. clin. 1971, 1 : 4

21. Oliver J. et coll. Cancer , 1970 , 25 : 863

22. Kieler J., person. communication 1972

23. Curucher H.P. et coll. Surgery 1971 , 70 : 467

24. Lambling et coll. Arch. fr. App. dig. 1970 , 59 : 113

25. Schreiber W.M. et coll. Cancer 1970 , 26 : 69

26. Sankalé M. et coll. Arch. fr. Mal. dig. 1971 , 60 : 616

27. Moreaux J.M. Veyrières & J. Hepp, Nouv. Presse méd. 1972, 1: 1139

28. Lin R.Y. Surg. Gyn. Obst. 1966, 123 : 289