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time permitted to it to act in
digestion was not studied in
for it has long been recognised
eble in the stomach.
—Different preparations have
rding to their gastric evacua-
On studying the various con-
served that the reducing sub-
nach first, approximately half
other components. The order
reducing substances, other
n and then fats. The gastric
article was not directly pro-
position, e.g., emptying time
or milk and curd—having
sition was not equal.
m to be concerned in deter-
n from the stomach. After
cid peak the reducing sugars
he stomach indicating that
er the peak leading to some
c secretion. It appears that
s not the only determining
arian full meals the acidity
/10 acid per cent yet the
much longer than when
n, which brought about a
ion of 103 c.c. N/10 acid.
ices help to evacuate an
z evacuated the stomach
pauha from which the
Consistency of an article
mportant factor. Change
ed to commence soon.
liquefied within ½ hour.
chapati were aspirated
e after 2 hours and of
hours.
eached with usual meals
nged than what one is
esults of standard frac-
However, in the past
laid on the acid nature
mach and little atten-
ivity. When the food
is relaxed to accommo-
ncreasing the internal
ty stomach exhibits
ed rhythmic contrac-
conds—which are re-
ary to what is gene-
ty stomach is not a

gs, meat, cereals,
in 100 g. and also

stomachs.
evacuation time
analysis and fluoroscopy
gastric
ated.

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SPECIAL ARTICLE

HAEMATOLOGICAL REACTIONS TO DRUGS

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The highly specialised haemopoietic system is highly dynamic as well. The normal blood picture in the human system is maintained by two opposing forces of 'new' blood formation and 'old' blood destruction balancing each other in dynamic equilibrium. Under normal conditions approximately 40 ml. of 'old' blood is replaced daily by an equal amount of 'new' blood. Like many other essential organs, the bone marrow has got the potential capacity of working eight to ten times its routine work. This high reserve of bone marrow is essential to maintain normal blood picture against the manifold baneful influences of haemorrhages, infections, toxins, toxic drugs and various other haemotoxic agents to which the human system so often falls a prey. As long as the haemotoxic agent is mild and the period of exposure relatively short, the bone marrow rises

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to the occasion and overcomes the crisis without any significant deleterious effect. If, on the other hand, the haemotoxic agent is a severe one and the period of exposure fairly long, the resultant damage to the bone marrow is always considerable and in extreme cases may lead to irreversible aplasia. In between the two extreme forms of minimum and maximum damage there may be all gradations of haemodepression representing a spectrum of haematologic dyscrasia, characterised by various types of cytopenia.

During recent years there has been a considerable increase in these types of haematological reactions, a large number of which have been attributed to the various recently introduced drugs. The brilliant series of chemotherapeutic and antibiotic drugs that are now available for the control of infectious diseases have been a boon to mankind. One limitation of these specific drugs as also of other potent drugs is their undesirable side effects on blood and bone marrow. Chloramphenicol is an example in point. The possibility of serious haemopoietic depression reported to ensue from prolonged and repeated chloramphenicol therapy has compelled the cautious physician to restrict its use to a great extent. The cytopenias following the use of drugs like sulphonamide, aminopyrine, butazolidin, trimethadione and thiouracil have been very much discouraging to clinicians.

The first suggestion indicating the possibility of chemicals affecting the bone marrow appeared to have emerged from the use of benzene. Selling (1910) clearly demonstrated that in experimental animals benzene could induce varying degrees of bone marrow aplasia with proportionate peripheral cytopenia. Osler and subsequent workers sought to utilise this myelodepressant action of benzene in the treatment of leukaemia. The toxic reactions of benzene, however, far outweighed its possible usefulness. The disease, agranulocytic angina (Schultz, 1922), brought into bold relief the role of drugs in the causation of disease. Careful works of Kracke and Parker (1934), Madison and Squier (1934), Dameshek and Colmes (1936) and Plum (1937) demonstrated that agranulocytic angina was a manifestation of aminopyrine toxicity.

Influence of Drug Composition on Its Toxicity

Kracke and Parker (*loc. cit.*) were the first to point out that the chemical structure of a drug plays a significant role in determining its deleterious effect on blood and bone marrow. They asserted that the association of benzene ring with either N, NH or NH_2 group usually makes a drug toxic particularly to the leucopoietic tissue. Analysis of the chemical structure of a large series of drugs with known haemotoxic properties corroborated the view of Kracke and Parker (*loc. cit.*). Dameshek (1954) carefully reviewed the chemical structure of haemotoxic drugs and concluded that almost all of these drugs have a central benzene ring structure and a varying number of combinations with N, NH or NH_2 grouping. Chloramphenicol was introduced to the medical profession in 1949. In the same year Smadel pointed out the nitrobenzene radical in the drug and warned the profession of its possible haemotoxicity (Smadel, 1949 ; Dameshek, 1952). Numerous reports up-to-date indicate that chloramphenicol has a depressant action on the bone marrow. Agranulocytosis following the new drug chlorpromazine has similarly, been ascribed to the presence of nitrobenzene linkage in its structural formula (Yules and Baker, 1955). Dameshek (1954) pointed out that the highest toxicity is shown by drugs with the largest number of 'N' groupings in their structure such as aminopterin and triethylene melamine. The two anti-epileptic drugs, troxidonum and methoin have somewhat similar structures but the latter with two nitrogens is more toxic than the former with one nitrogen. Aminopyrine with three nitrogen atoms in its molecule is very toxic. It has been suggested that all drugs with a nitrobenzene radical are potentially myelotoxic. This is, however, not universally true and there are exceptions, notable among which is phenobarbitone.

Mechanism of Haemotoxicity

In general there are two ways in which drugs induce blood and bone marrow changes.

First is the direct destruction of the formative tissue in the bone marrow or of the formed elements in the peripheral blood. Benzene, nitrogen mustard, aminopterin, and chloramphenicol owe their toxicity to the direct destructive action they possess against the bone marrow. Under certain conditions bone marrow might be inhibited presenting a picture of maturation arrest. These drugs probably act by inhibiting enzyme systems which are indispensable for the growth and maturation of haemic cells or by biologically competing with nutritional factors needed for the same purpose. Megaloblastic anaemia may develop during therapy with folic acid antagonists due obviously to depletion of folic acid in the system. Megaloblastic anaemia that has been reported during therapy with the anti-epileptic drug, phenytoin sodium, may be explained on the basis of folic acid deficiency developing due either to absorption or utilisation defect (Israels and Sharp,

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1950; Badenoch, 1954; Hawkins and Meynell, 1954). Recently Girdwood and Laneman (1956) reported development of megalobastic anaemia in a patient while under treatment with primidone and phenobarbitone. There was no response to cyanocobalamin, but a good response to folic acid.

Many of the haemotoxic drugs like phenyl hydrazine, quinine and sulphonamides possess a direct haemolytic action on the red cells. In experimental animals a wide variety of drugs and chemicals have been employed to study the changes in erythrocytic morphology preceding haemolysis (Fertman and Fertman, 1955). Many of these haemolytic drugs produce characteristic intra-erythrocytic inclusion bodies variously designated as Heinz body, Heinz-Ehrlich body, inner body, innenkörperchen, innerkörpern. These inclusion bodies represent globules of haeme-containing protein denatured by the drugs. Demonstration of Heinz body in a case of anaemia constitutes a valuable sign in favour of the diagnosis of haemolytic anaemia. In addition, many of these toxic drugs also tend to produce methaemoglobinaemia or sulphhaemoglobinaemia. It has been suggested that methaemoglobin which precedes and accompanies the formation of Heinz bodies might catalyse the reaction of denatured haemoglobin. Another allied reaction to these drugs is porphyrinuria. The relevant literature on drug-induced porphyrinuria with the various noxious drugs including, sulphonal, barbiturate, sulphonamide, antipyretics, phosphorus, lead, arsenicals and alcohol has been reviewed by Dobriner and Rhoads (1940).

The second mechanism is mediated through specific antibodies which destroy the blood cells and/or inhibit their production in the bone marrow. Such antibodies against blood cells have, however, been demonstrated in cytopenic states independent of drugs (Harrington *et al*, 1953; Stefanini *et al*, 1953; Moeschlin *et al*, 1954). Grandjean (1948) was probably the first to show that a drug could cause thrombocytopenia on an immunologic basis. He demonstrated that plasma of a certain patient recovering from thrombocytopenia induced by quinine caused a decrease in the platelet count *in vitro* in the presence of quinine. Most convincing and unequivocal evidence was produced by Ackroyd (1949). He clearly showed that thrombocytopenia induced by allylisopropylacetyl carbamide was due to the development of a specific 'lytic' type of antibody which needed complement for its activation. Careful studies by Larson (1953), Plitman and Stefanini (1953), Bigelow and Desforges (1952) and Barkham and Tocantins (1954) indicated that thrombocytopenia due to quinidine was also mediated through the development of specific antibodies which were agglutinating and/or lytic in type.

Investigative works of Moeschlin and Wagner (1952) and of Dausset *et al* (1954) regarding the pathogenesis of agranulocytosis due to aminopyrine clearly suggest an immunologic basis. The sequence of events that lead to an immunologic disturbance may be as follows: The offending drug itself or one of its intermediate metabolic products possibly combines with a particular blood cell and the combination which may be further modified in the system acts as an auto-antigen. A highly specific auto-antibody develops which does not react with the blood cells directly but only in the presence of the offending drug. The reaction, in general, is active both *in vitro* and *in vivo*. Complement may be necessary for the activation of some of these reactions. The drug (partial antigen or hapten) is apparently needed to "couple" the agglutinating or lytic antibody with the specific blood cell against which sensitisation has developed.

The haemotoxicity appears to affect particularly some individuals who show a constitutional or hereditary susceptibility to a particular drug, a predisposition which is commonly attributed to allergy. Children who have comparatively unstable haemopoietic system are probably more susceptible to the various drugs. A list of the more commonly used drugs that have so far been reported for haemocytopenic reactions is appended in Schedules 1 and 2. The peripheral blood in all these cases showed cytopenia of varying grades and composition. The bone marrow pattern was, however, variable being either one of maturation arrest or of hypoplasia. The different categories of haematological reactions as reported with the various drugs are shown in Schedule 1—A to D.

Drugs and chemicals which are known to damage blood and blood forming organs may be also potentially leukaemogenic. Lignac (1932) produced various types of leucocytic proliferation in mice by prolonged administration of benzene. Mallory, Gall and Bricklay (1939) while critically reviewing all the available evidences could not exonerate benzene as a leukaemogenic agent. Hydrocarbons are certainly carcinogenic. Experiments of Law (1941) and of Shay *et al* (1952) show that hydrocarbons may induce leukaemia in experimental animals. A very strong presumptive evidence in favour of the speculation that myelotoxic drugs are potentially leukaemogenic is provided by the effect of irradiation on the bone marrow. Irradiation certainly tends to depress the normal haemopoietic tissue. Incidence of leukaemia in radiologists is at least eight times higher than that in a comparable group of physicians (March, 1944

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and 1950; Ulrich 1946). Haematological studies on the atom-bomb casualties show that while the incidence of aplastic anaemia was very high immediately after explosion, the incidence of leukaemia was thirteen times higher in the epicentre of the blasted area at Hiroshima than at the periphery (Amano, 1952). These evidences show that while immediate reaction to myelotoxic and haemotoxic drugs is essentially one of depression, the remote and cumulative effect of prolonged therapy may occasionally in a susceptible subject be manifested by a proliferative disorder.

It appears that the haemopoietic system is quite sensitive and sometimes selectively so, to many drugs and chemicals which are foreign to the human system. While the haemodepressive reactions to some of these may be minor and insignificant and while tolerance to some of these agents may be slowly acquired in course of time, there remain some to which tolerance is never acquired and to which the haemopoietic system will always react unfavourably. This brings into bold relief the necessity of ensuring the safety of any new drug by carefully investigating its immediate as well as remote effect on blood and bone marrow.

Prevention of Haemopoietic Depression

Drugs known to be potentially toxic to the blood and bone marrow elements should not be prescribed unless there are impelling indications for their use. Indiscriminate use of sulphonamides, antibiotics, analgesics, and sedatives cannot be too strongly condemned. Potent drugs should be withheld as long as the indications are equivocal and as long as safer therapeutic alternatives are available. Drugs with a 'benzamine' radical should be viewed with suspicion. New drugs awaiting full assessment of their therapeutic values and haemotoxic limitations should be used with particular caution. While under treatment with potentially toxic drugs the physician should be particularly vigilant for other side effects like, fever, skin rashes, arthralgia and gastro-intestinal symptoms. These side effects which may be overlooked as indefinite signs and symptoms may herald blood and bone marrow reaction. Periodic haematological check-up is also imperative when therapy is likely to be prolonged. Particular attention should be paid to the neutrophil which is not infrequently the first element to be affected. Timely withdrawal of these drugs can alone avert more serious crisis.

Ordinary skin tests for foretelling the drug sensitivity have not always proved useful. The employment of a test dose of the suspected drug and attempt to reproduce the blood dyscrasia are neither safe nor feasible. Pathogenicity and toxicity tests as ordinarily scheduled in experimental animals have not always proved adequate for the purpose. Only the test of time and the careful accumulation of statistically assessed observations can provide necessary data for proper appraisal of the safety or otherwise of a drug.

Management of Haemodepressive Reactions

The drug known or suspected to be the cause of mischief should be immediately withheld. The details of management will depend on the type of cell affected and degree of cellular depletion. The general principles may be enunciated here. When the symptomatology springs from rapidly developing haemolytic anaemia, blood transfusions are indicated. When neutropenia is the main problem, penicillin is the sheet anchor to sustain the patient against the infections which always tend to thrive in neutropenic states. When thrombocytopenia and consequent haemorrhagic manifestations are disturbing features, fresh blood transfusions especially in non-wettable containers, should be given. Steroid hormones have proved useful in the cytopenic states developing on an immunologic basis. In conditions of hypoplastic marrows, these hormones are worth giving a trial. Cobalt chloride in a dosage of 100 to 150 mg. daily has occasionally proved useful. The haematinics, iron, folic acid, vitamin B_{12}, and various other vitamins are usually of no use. Folic acid or folinic acid is indicated only in cases where the reactions are due to folic acid deficiency. Whole liver extract and pentanucleotides have sometimes proved useful in neutropenic states with 'maturation arrest' in the bone marrow. Provided there has been no irreversible damage to the bone marrow, most of the cases recover after a variable period. BAL may be useful in haemodepressive reactions following arsenicals, mercurials and gold salts. During the period of recovery as also in the immediate postrecovery period when the haemopoietic equilibrium has not been firm and stable, especial care should be taken to protect the bone marrow.

Summary

Haematological reactions, often of severe degree, may result from many of the common drugs. Drugs with a 'benzamin' linkage are particularly liable to cause these reactions. These drugs affect the circulating blood cells in the peripheral blood or their precursors in the bone marrow either directly or through the mediation of cellular antibodies developing on an immunologic basis. The peripheral blood shows cytopenias of varying grades and composition. The bone marrow picture is either cellular with maturation arrest or hypocellular. Preventive and curative aspects of drug-induced haematologic reactions are discussed.

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SCHEDULE 1

A. GRANULOCYTOPENIC DRUGS :

Amidopyrine†, Antithistaminics, Arsenicals†, Chloramphenicol†; Chlorpromazine, Dinitrophenol, Diethazine hydrochloride, Isoniazid, Methoin, Pamaquin, Pethidine, Phenylbutazone†, Procaine amide, Salicylates, Streptomycin, Sulphonamide†, Tapazole, Thiosemicarbazone, Thiouracil†, Troxidonum†.

B. THROMBOCYTOPENIC DRUGS :

Arsenicals†, Digitoxin, Gold salts, Hydantoins, Mercurial diuretics, Oestrogen, P-amino salicylic acid, Pertussis vaccine, Phenylbutazone, Procaine, Quinidine†, Quinine, Streptomycin, Sulphonamides, Thiouracil.

C. HAEMOLYTIC DRUGS :

Methoin, Mephanesin, Phenacetin†, Phenylbutazone, Phenylhydrazine†, Plasmochin†, Quinine†, Sulphonamide†.

D. PANCYTOPENIC DRUGS :

Antimitotic drugs†, Arsenicals†, Mepacrine, Chloramphenicol†, Gold salts, Hydantoin, Mercurials, P-aminosalicylic acid, Phenylbutazone, Radioactive isotopes, Streptomycin, Sulphonamides.

SCHEDULE 2

DRUGS LIABLE TO CAUSE HAEMATOLOGIC REACTIONS

(Letters—H, N, P, T, within parenthesis—to the left of the drugs refer respectively to haemolytic, neutropenic, pancytopenic and thrombocytopenic potentialities).

A. ANTIEPILEPTICS :

Oxazolidine—2, 4-diones : (P) Troxidonum (Trimethadione); (P) Paramethadione. *Hydantoin compounds* : (P, H) Methyl-phenyl-ethylhydantoin (methoin); (P) Diphenylhydantoin (phenytoin sodium); (N) 5, 5-phenyl ethyl hydantoin. *Others* : (N) Atrolactamide; (P) Phenacemide.

B. ANTIHISTAMINICS :

(N) Phenothiazine type; (N) Ethylenediamine type (tripelennamine hydrochloride); (H) Diphenhydramine hydrochloride.

C. ANTI-INFECTIVES (Chemotherapeutics and antibiotics) : (P) Arsenobenzols; (P) Chloramphenicol; (H, P) Sulphonamides; (H, P) Thiosemicarbazone; (P) Streptomycin; (N, P) P-aminosalicylic acid; (H, P) Isonicotinic acid hydrazide; (N) Glycobiarsol.

D. ANTIMITOTICS :

(P) Benzene; (P) Urethane; (P) Nitrogen mustard (Methyl bis-β chlor ethyl amine or HN_2); Triethylene melamine—TEM); (P) Folic acid antagonists; (P) Purin antagonists (6-Mercaptopurin); (P) Sulphonic acid ester.

† Reactions more frequent with these drugs.

E. ANTITHYROIDS :

(H) Thiouracil; (N) Methyl thiouracil; (H) Propyl thiouracil; (N) Methimazole.

F. ANTIMALARIALS :

(H, N) Quinine; (T) Quinidine; (H, N) Plasmochin; (N) Mepacrin (Quinacrine); (N) Amodiaquin [4-(3-diethylaminomethyl-4 hydroxyanilino)-7-chloroquinoline].

G. ANALGESICS AND SEDATIVES :

(T) Allylisopropylacetylurea; (N) Aminopyrin; (H) Phenacetin; (N) Chlorpromazine.

H. HORMONES :

(T, N) Oestrogens; (P) Corticotropin.

I. RADIOACTIVE ISOTOPES AND IONISING RADIATIONS :

These may cause pancytopenic and occasionally haemolytic reactions.

J. OTHERS :

(T) Ergot; (N, P) Gold preparations; (P, H) Phenylbutazone; (H) Phenylhydrazine; (T) Iodine and Potassium iodide; (N) Nitrophenols.

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CASE NOTE

PHENYLBUTAZONE IN HODGKIN'S DISEASE

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Phenylbutazone was synthesised in 1948. From its toxic action on cells and corticosteroid-like action, we thought that it might be used with advantage in leukaemia, carcinoma, and Hodgkin's disease where there are extensive tissue infiltrations. We were disappointed in the two former conditions but we met with great success, though temporary, in a case of Hodgkin's disease.

CASE REPORT

A male labourer, aged 35, was admitted in the Sassoon Hospitals under our care on the 4-4-54 with the history of fever fluctuating between 100°-102°F, anorexia, and enlargement of the glands in the neck, axilla and groin for 12 days. The liver and the spleen were palpable.

Laboratory examination: Hb. 80 per cent, R.B.C.—4·1 mill. per c.mm. W.B.C.—13,000 per c.mm. with polymorphs 68 per cent, lymphocytes 10 per cent, monocytes 14 per cent and eosinophils 8 per cent. Kahn test was negative. Heterophil antibody test and cold agglutination test were negative. Urine and stools were normal.

Blood examination 15 days later revealed: Hb. 68 per cent, R.B.C. 3·5 mill. per c.mm. W.B.C. 20,000 cells per c.mm., polymorphs 21 per cent, lymphocytes 11 per cent, monocytes 2 per cent and eosinophils 66 per cent.

A gland biopsy and bone marrow examination showed that the clinical condition under consideration was Hodgkin's disease. Before the diagnosis became clear, the patient had received penicillin, streptomycin and chloromycetin. Later on he was given liq. arsenicalis, nitrogen mustard and deep x-ray without much improvement. He went downhill inspite of the treatment, being kept up on repeated blood transfusions.

Cough and breathlessness developed later. A radiological examination showed the enlargement of the mediastinal glands which were perhaps pressing upon the trachea. At this stage he was put on phenylbutazone tablets, 200 mg. three times a day. From the third day of the treatment his temperature came down and remained normal, for the first time since his admission. His cough, breathlessness and glandular enlargement diminished very rapidly. His appetite returned. His colour improved. In three weeks' time he showed marked improvement, so much so that he demanded discharge. He discontinued the drug since his discharge on 7-9-54 and did not report for the next 11 months. Occasional inquiries revealed that he was doing well and earning his livelihood. He was re-admitted on 10-8-55 for breathlessness, swelling of the feet and enlargement of the abdomen, of about two weeks' duration. He was pale and emaciated. Inguinal, axillary, cervical and supraclavicular glands were markedly enlarged. Blood pressure was 105/75 mm. Hg. The spleen and the liver were enlarged 2 fingers below the costal arches.

Blood examination showed: Hb. 65 per cent, R.B.C. 2·91 mill. and W.B.C. 10,300 per c.mm.

This time phenylbutazone could not be procured for him. He was given repeated transfusion but he progressively became worse and died on 21-8-55. Autopsy examination could not be done.

COMMENTS

During the first admission of the patient there was a marked improvement in the clinical condition after the administration of phenylbutazone. The short treatment with the drug during his first stay in the hospital appears to have given him a fairly long remission during which he was able to earn for himself and his family. It is true that spontaneous remissions and intermissions are found during the course of Hodgkin's disease; but in this case the improvement was so dramatic after the use of the drug that it cannot be attributed to just a coincidence. A single case report is in no way conclusive but the experience definitely warrants a more extensive trial of the drug in Hodgkin's disease which has stubbornly eluded successful treatment so far.

Prof. J.B. Chatterjea
(1919-1972)

Dr. Jyoti Bhusan Chatterjea, Professor of Hematology and Director of the Calcutta School of Tropical Medicine was a renowned Indian hematologist, whois well known for his contribution in the field of hematology, notable among which is his research on Hemoglobin E/â-thalassaemia. [1]J. B. Chatterjea was born on 16 February 1919 in Kolkata, completed his graduation from Calcutta Medical College in 1942 and secured the degree of Doctor of Medicine from the same institution in 1949. He started his career as an assistant research officer under the ICMR at Calcutta School of Tropical Medicine and achieved the rank of a professor of hematology in 1956.[2] He was also appointed as the director of the institution in 1966.

Chatterjea's researches and contributions have played a significant role in understanding the hematological aspects of tropical diseases. His work on nutritional and iron deficiency anemia and biophysical, biochemical, genetics of Hemoglobin E in Bengali people established him as a stalwart and an international figure in hematology.[3] He was the honorable president of various medical organizations namely, Indian Society of Hematology, Indian Anthropological Society, Indian Public Health Association and at Indian Association of Pathologists and Microbiologists. His service as a counselor to international organizations such as International Society of Hematology, International Society of Blood Transfusion and the Reticuloendothelial Society has been remarkable.

His research has been acclaimed and applauded globally and he was awarded the Coates Medal of the University of Calcutta in 1958 and the Barclay Medal of the Asiatic Society in 1963.[4]

The ICMR honored him with the Basanti Devi Amir Chand Prize in 1964. He was elected as a fellow by the National Academy of Medical Sciences and received the Minto Medal in 1965.He was awarded Shanti Swarup Bhatnagar Prize by the Council of Scientific and Industrial Researchin 1966. He travelled worldwide to New York, New Jersey, Newcastle, Sydney to deliver lectures on his research.

On 29th February 1972, Prof. J.B. Chatterjea suffered a massive myocardial infarction and succumbed to death. His contributions and legacy in the field of hematology is indelible.

Comments of the Experts

Hematological Reaction to Drugs

Drug-induced hematological disorders may involve the entire spectrum of hematology, affecting red cells, white cells, platelets, and the coagulation system. Adverse effects of these drugs may be attributed to a direct toxic action of the drug or its metabolites on the bone marrow oron the circulating cells.Most drugs may act via an immunological mechanism. The drug may act as a hapten or maylead to the production of antibodies against the drug as well as autoantibodies.[5] Some drugs may act on erythrocytes with enzymatic pathway defects, e.g. glucose-6-phosphate dehydrogenase (G-6-PD) abnormalities, to produce hemolysis. However,in many cases, the mechanism of the adverse drug reaction is unknown.Early diagnosis and prompt treatment of drug-induced hematological dyscrasias are crucial to limit the seriousness of these disorders.

The common hematological reaction to drugs are formulated in Table 1.

Syndrome	Examples of associated drugs
Immunohemolytic anemia	Pencillins, cephaloporins, alpha-methyl-DOPA, oxaliplatin, fludarabine, anti-Rh D antiglobulin
Nonimmune hemolytic anemia	Ribavirin, phenazopyridine, chloroquine,
Methhemoglobinemia	Phenazopyridine, dapsone, benzocaine, prilocaine
Megaloblastic anemia	Rrimethoprim, pyrimethamine, diphenyhydantoin
Sideroblastic anemia	Isoniazid, chloramphenicol, linezolide
Aplastic anemia	Chloramphenical, gold, NSAIDs,
Pure red cell aplasia	Diphenylhydantoin, azathioprine, chlopropamide, isoniazid, erythropoietin
Immune thrombocytopenia	Quinine, quinidine, heparin, vancomycin, sulfas, pencillins, glycoprotein IIb-IIIa inhibitors
Thrombotic microangiopathy	Quinine, quinidine, clopidogrel, ticlopidine, cylosporine A, mitomycin-C, cisplatin
Platelet dysfunction	Pencillins, beta-lactam antibiotics, aspirin, NSAIDs
Hypercoagulability	Estrogens, tamoxifen, asparaginase, heparin, bevacizumab, thalidomide/lenalidomide, COX-2 inhibitors, erythropoietin
Circulating anticoagulants	Isoniazid, hydralazine, procainamide
Hypoprothrombinemia	Cephalosporins, pencillins, sulfas
Neutropenia	Antithyroid drugs, procainamide, sulfas, captopril, phenothiazines, diphenylhydantoin, rituximab
Neutrophilia	Glucocorticoids, lithium, G- and GM-CSF
Eosinophilia	Pencillins, sulfas, allopurinol, diphenylhydantoin
Polycythemia	Erythropoietin, anabolic steroids, diuretics
Acute leukemia/myelodyplasia	Alkylating agents, topoisomerase II inhibitors

Table 1 — Common hematological reaction to drugs.Source: David M. Mintzer, Shira N. Billet, Lauren Chmielewski, "Drug-Induced Hematologic Syndromes", Advances in Hematology, vol. 2009, Article ID 495863, 11 pages, 2009. https://doi.org/10.1155/2009/495863. Advances in Hematology / 2009 / Article / Tab 1

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