DISEASES OF MEDICAL PROGRESS*

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The truly amazing advance of therapeutic procedures and the discovery of more and more specific remedies in the treatment of disease over the past 30 or 40 years has created a new, exciting, and often highly satisfying climate in which to practice medicine. We now have large numbers of remedies which work their cures almost miraculously. As evidence of this we are faced with most interesting and radical changes in the treatment of many diseases. Thus tuberculosis sanatoria all over the world have closed down or will close down, because modern antituberculous therapy is so effective that institutions are seldom necessary now for the treatment of tuberculosis. Pneumonias are more often than not treated at home because of modern effective therapy, so that few cases need to be treated in hospital. Gone are the days of the laborious long-drawn out wash-outs for gonorrhoea, and the prolonged and hazardous therapy for syphilis. Instead we have the rapidly effective penicillin, the antibiotics, the steroids, etc. These are powerful remedies indeed.

However, we are faced with new dangers and responsibilities when using these potent remedies, so much so that in modern therapeutics a definite rule should be laid down: No-one is entitled to prescribe a medicament who knows only the specific effect claimed for the remedy. It behoves him equally well to know the complications which may result from the therapy.

Certain complications that occurred in the old days during the course of drug treatment of diseases were usually ascribed to toxic reactions to the drug used, due either to overdosage or impurity in the drug, or else to hypersensitivity or idiosyncracy on the part of the patient. In modern therapy a variety of mechanisms are operative in this respect. Some of these mechanisms are biochemical or metabolic, possibly through enzymatic action. The implication of this knowledge naturally is that we shall be able to predict the action of certain drugs, and so avoid dangerous and even disastrous reactions and effects. It is for instance well known that allergic reactions to penicillin may be more than a nuisance—they may be fatal.

In many cases we are on the threshold of discovering the exact mechanism or mode of action of the newer drugs. One example is that of certain blood dyscrasias which have been shown to be due to enzymic deficiencies in the recipient's cells and which are produced as so-called toxic effects of certain drugs.

Some reactions are physiological. When we give the diabetic too much insulin or the rheumatoid arthritic full doses of steroid, we reproduce what the naturally occurring hormones bring about when they are produced in excess. Even here we do not understand why we may produce peptic ulcers by steroid therapy, because the naturally occurring cases of Cushing's disease do not have this lesion.

When we give patients a broad-spectrum antibiotic it is common

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for them to develop diarrhoea. Usually it is no more than an inconvenience. We believe, probably correctly, that this is due to the altered ecology of the intestinal flora. But this self-same alteration of the intestinal flora may be the cause of a staphylococcal colitis resulting from—so we believe—our having upset the balance of nature. This condition may be rapidly fatal unless diagnosed and treated. Through a similar mechanism we may produce fungus infections, and it is not always easy to be sure whether this has not become a systemic infection and not merely the easily treated local infection in the mouth. Many reactions are hardly understood at all. For instance how is drug fever produced?

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Dr. Landau

We seem to have learned how to avoid deafness and vertigo from streptomycin and dihydrostreptomycin. When the virologists have isolated the virus of infective hepatitis we shall be able to give transfusions without fear of giving the patient homologous serum jaundice.

We are therefore now faced with a situation where, during the course of therapy, and often sound therapy, new disorders appear in patients whom we are trying to cure of their original diseases. These disorders may be drug induced and have been labelled 'diseases of medical progress'.

The list of these disorders grows apace, and it may be of some use if I attempt to classify them as follows:

1. METABOLIC DISEASES

(i) *Secondary Gout and Uric-acid Calculi*

It is well known that gout occasionally occurs as a result of the breakdown of leucocytes in the natural course of leukaemias and primary polycythaemia. With the introduction of the newer antifolic-acid compounds (amethopterin and aminopterin) and the newer purine analogues (6 mercaptopurine, etc.) there is rapid breakdown of large numbers of cells and sudden release of large amounts of nucleoprotein, which in turn leads to rapid rise in purine and blood uric-acid concentration. This may be associated with acute arthritis and the formation of uric-acid calculi during the course of therapy. Similar effects have been observed occasionally after the use of radio-active phosphorus, nitrogen mustard, tri-ethylene-melamine (TEM) and the uricosuric agent probenecid (benemid).

(ii) *Low Sodium (Salt) Syndromes and Resistance to Mercurials*

While many patients have their lives prolonged by the use of mercurial diuretics, and more recently by chlorothiazide, in some cases a stage is reached when the response to the diuretic used becomes less and less effective. At this stage the serum sodium is often found to be markedly decreased. The patient complains of painful muscle cramps, anorexia, nausea, weakness and drowsiness. There is persistent oliguria due to diminution in renal blood flow and nitrogen retention, and a diminished blood volume. The low serum sodium in some patients may not be an index of sodium depletion but of escape of sodium into tissue cells, and some such patients have been found to retain administered potassium, sometimes with definite clinical improvement. Another cause of loss of response to mercurials is the development of hypochloraemic alkalosis, demonstrable by a low plasma chloride and raised alkali reserve. This is amenable to treatment with ammonium chloride, and a further period of good response to mercurials may be obtained.

(iii) *Hypopotassaemia*

The appearance of potassium depletion is similar to the above problem and is found in many cases subjected to diuretic therapy, particularly when the newer diuretics chlorothiazide and dichlorothiazide, hydol, esidrex, etc. are used. Diminished potassium intake is a contributory factor. As a therapeutic problem it is also seen in cases under the influence of adrenocortical steroids. A fall in the serum potassium can be associated with weakness and paralysis of voluntary and respiratory muscle, and characteristic ECG changes, e.g. a prolonged QT interval and T-wave inversion.

(iv) *Potassium Excess*

The administration of excessive potassium, e.g. when potassium citrate is used in treating urinary infections, or in correcting potassium depletion, may cause serious symptoms to appear as the potassium plasma level rises to 8 - 10 mEq/l. Cardiac arrhythmia occurs with changes in the ECG—peaking of T-wave, then widening of the QRS segment and loss of P waves tending towards a biphasic tracing and ultimately cardiac arrest. The other notable manifestation of hyperkalaemia is muscular paralysis, sometimes of an ascending Landry type, associated with paraesthesiae.

Similar problems are encountered during the correction of electrolyte disturbance in cases of renal failure treated by dialysis in the artificial kidney, and also in the treatment of uraemia, diabetic coma, etc.

(v) *Hypervitaminosis A*

The intake of vitamin A in excess of requirement results in a toxic syndrome known as hypervitaminosis A. All the reported cases in children have occurred after the twelfth month of life and have been associated with vitamin-A intakes ranging from 75,000 to 500,000 units per day, usually from overzealous prophylactic vitamin therapy. The most conspicuous sign of hypervitaminosis A is the appearance of subcutaneous swellings in the forearms, legs and feet. The swellings are deep with the overlying skin freely movable over them and attached to bone. They are tender and painful. On X-ray examination bone lesions appear as multiple areas of hyperostoses, usually in the ulnas, clavicles, and metatarsals. Dry excoriated skin, coarse hair, bleeding fissures at the corners of the mouth, and scaly lips are other signs which may appear. In adults an acute form of presumed vitamin-A poisoning has been reported after ingestion of certain fish livers, polar-bear liver, and whale liver. The syndrome is associated with drowsiness and toxicity, headache and vomiting, and rapid generalized peeling of the skin.

(vi) *Hypervitaminosis D*

The prolonged administration of excessive amounts of vitamin D leads to a serious disorder of calcium metabolism known as hypervitaminosis D. Clinically most cases are seen in adults who have received large doses for the treatment of conditions unassociated with vitamin-D deficiency, but which are supposed to be benefited by vitamin-D therapy, notably rheumatoid arthritis. The metabolic derangement which leads to the toxic syndrome is probably the mobilization of calcium from bone, with the production of metastatic calcification in soft tissue, e.g. nephrocalcinosis.

The initial signs and symptoms are those associated with hypercalcaemia and consist of weakness, lassitude, fatigue, headache, nausea, vomiting, and diarrhoea. Later there is impaired renal function with polyuria, nocturia, polydipsia and albuminuria, and even some hypertension. The blood shows an elevated serum calcium and non-protein nitrogen. Calcification occurs in the kidney, myocardium, blood vessels, lungs, and skin.

2. COLLAGEN DISORDERS

(i) *Periarteritis Nodosa*

Since the introduction of sulfonamides in 1936 there has been a notable increase in the number of cases of periarteritis nodosa. Rich attributed this to a non-specific sensitivity reaction to sulfonamides, with the production of a type of 'hypersensitivity angiitis', but Zeek and his associates believe that hypersensitivity angiitis is an entity distinct from periarteritis nodosa, both aetiologically and pathologically.

(ii) *The Lupus-erythematosus Syndrome*

Hydralazine (apresoline) was at one time, and in fact is still, used extensively in the treatment of hypertension, either by itself or together with other hypertensive agents like reserpine (serpasil). However, in quite a few such cases treated with hydralazine, a new syndrome appeared resembling very closely a mild form of rheumatoid arthritis with polyarthralgia and myalgia. Later there followed polyarthritis with symmetrical involvement of the proximal interphalangeal joints. If therapy is stopped at this stage the condition usually clears up fairly rapidly. If therapy is resumed the same sequence of events may occur, and even progress to a lupus-

erythematosus phase with fever, skin rashes very like solar dermatitis or lupus-type rashes, synovial pleural or pericardial effusions, chills, pneumonitis, splenomegaly, and lymphadenopathy. Blood examination may reveal increase of the serum globulin (especially the alpha and gamma fractions) with reduction in the serum albumin, as well as anaemia, leucopenia, raised sedimentation rate, and even the appearance of LE cells in both blood and bone-marrow. Interestingly enough, haematuria and albuminuria are not features of this syndrome to any extent.

(iii) *Interstitial Pulmonary Fibrosis*

This syndrome resembles the Hamman-Rich syndrome and has been described with prolonged administration of the antihypertensive drug hexamethonium. It is characterized by increasing and disabling dyspnoea from pulmonary fibrosis and results in death from pulmonary failure of cor pulmonale within a month or two of the onset of the syndrome.

3. STEROID-INDUCED DISEASES

(i) *Cushing's Disease (or Cushingoid Disorders)*

Everyone is familiar with the appearance of the Cushingoid features of patients receiving long-term steroid therapy in cases of rheumatoid arthritis, DLE, asthma, etc. The condition usually appears quite insidiously with the development of moon face, mental torpor, general weakness, buffalo hump, acne, and hirsutism. Hypertension and/or hyperglycaemia with glycosuria may appear together with sodium retention and potassium loss, and even a negative nitrogen balance with muscle wasting and osteoporosis.

(ii) *Adrenal-exhaustion Syndrome*

This syndrome is also well known in patients receiving steroid therapy, e.g. cortisone or ACTH. It has been shown conclusively that when stressful situations such as surgical operations, accidents, burns, and even parturition arise, patients previously treated with steroids run a definite risk of succumbing to 'adrenal exhaustion' from adreno-cortical atrophy induced by the steroids. It has therefore become the rule that any patient who has received cortisone or ACTH within 3–6 months before a contemplated operation should again receive treatment with steroids as a prophylactic for fear of adrenal unresponsiveness to the stressful situation. In such cases many surgeons administer hydrocortisone before and after operation and carefully watch their patients for signs of adrenal exhaustion in the first 12 hours after operation.

(iii) *Steroid-withdrawal Syndrome*

In patients who have been on prolonged steroid therapy the sudden withdrawal of the drug may lead to unpleasant symptoms usually occurring within 24 hours. The patients complain of headache, nausea, vomiting, joint and muscle pain, and general restlessness. These symptoms usually subside in a few days.

(iv) *Peptic Ulcer and Perforation in Ulcerative Colitis*

Steroids may lead to the appearance of peptic ulceration with haemorrhage and perforation in patients receiving therapy. There may or may not have been a history of previous peptic ulceration. Hence steroids should be given with great caution in patients with a history of peptic ulcer.

Steroids are also used extensively in the management of ulcerative colitis, but it is as well to remember that a significant incidence of bowel perforation has been reported in such cases.

(v) *Tuberculosis*

A well-known hazard with steroid therapy is the reactivation of latent tuberculosis, pulmonary or systemic. The presence of tuberculosis may have been known, but active tuberculosis often appears during steroid therapy without there being a previous history of this disease. If the patient is known to have had tuberculosis previously, or if healed lesions are seen on X-ray films, then the concomitant use of steroids and antituberculous drugs may have to be considered should there be adequate and cogent reasons for giving the patient steroids.

4. NEUROLOGICAL DISEASES

(i) *Parkinsonism and Epilepsy*

Reserpine, the active principle of *Rauwolfia serpentina*, is used extensively in the treatment of hypertension and in mental disorders, and there are now numerous reports of the occurrence of a syndrome suggestive of Parkinsonism or of convulsive seizures in cases receiving this therapy.

Parkinsonism also occurs not infrequently in patients receiving trifluoperazine (stelazine) for depressive states and when used as a 'tranquillizer' for mild mental and emotional disturbances.

(ii) *Psychoses*

One of the well-known dangers of the use of steroids is the precipitation of toxic psychoses with maniacal symptoms. Similarly, the rauwolfia derivatives may cause severe depression and even lead to suicide. Many other drugs have been implicated in the precipitation of toxic psychoses.

(iii) *Peripheral Neuropathy*

Many drugs used therapeutically have been known to cause peripheral neuritis. Common examples are the arsenicals and mercurials, and more recently isonicotinic acid hydrazide (INH) used in the treatment of tuberculosis, and even streptomycin. Stilbamidine, used to combat fungal infections, may cause hyperaesthesias and even facial palsy. Also many varieties of sera may cause neuritis as part of the serum-sickness reaction.

5. HEPATIC DISEASES

(i) *Jaundice*

(*a*) *Toxic hepatitis.* This disease has been known for a long time to be the result of treatment with many of the older drugs including arsenobenzol compounds in the treatment of syphilis, gold compounds in the treatment of tuberculosis and rheumatoid arthritis, and sulfonamides. Some of the newer drugs which may cause toxic hepatitis when used therapeutically are phenylbutazone (butazolidin), INH, phenylacetyl urea (phenurone—an anti-epileptic), and iproniazid (marsilid) used in the treatment of mental disorder and angina pectoris. In fact the hepatitis which occurs with the use of marsilid is usually severe and fatal in its outcome.

(*b*) *Jaundice from intrahepatic obstruction.* This is usually a benign form of drug-induced jaundice, though the jaundice may last for weeks or even months. There is evidently little parenchymal damage in these cases, and the jaundice is due to plugging of the centrilobular biliary canaliculi by inspissation and viscous biliary secretions. In its behaviour and serological reactions this type of jaundice is distinguished with great difficulty from the common infectious or homologous-serum hepatitis. Some of the common drugs known to cause this disease are chlorpromazine (largactil), thiouracil, methimazole (tapazole), methyltestosterone, atophan-cincophen, and arsphenamine.

(ii) *Hepatic Coma*

Patients suffering from multilobular Laennec's cirrhosis are at times precipitated into hepatic failure and coma by the injudicious use of a high-protein diet or intravenous protein hydrolysate in an attempt to correct a low serum protein. Similarly when oedema is present in such cases the use of ammonium chloride as a diuretic may have disastrous results. The liver in such cases is apparently unable to detoxify ammonia, and the raised ammonia levels are responsible for the cerebral manifestations of hepatic coma.

6. HAEMATOLOGICAL DISEASES

(i) *Haemotoxic Drug Reactions*

Dameshek divides these reactions into three or four categories:

(*a*) *Antigranulocytic reactors.* In this group the granulocytic elements of the bone marrow are depressed by drugs containing a benzene ring in combination with an amino or NH group, with the resultant production of potentially serious agranulocytosis.

Examples in this group are dinitrophenol, which was at one time used for weight reduction, sulfapyridine, sulfadiazine and sulfisoxazole, antithyroid drugs such as thiouracil, propylthiouracil and methimazole and phenylbutazone (butazolidin) used in the treatment of gout and rheumatoid arthritis. Further examples are certain antihistaminics such as pyribenzamine and antergan. Lastly, the broad-spectrum antibiotic chloramphenicol (chloromycetin) used so effectively in the treatment of typhoid and typhus, and in combination with other antibiotics against gram-negative organisms, may occasionally produce a serious granulopenia.

(*b*) *Anti-erythrocyte reactors.* In this reaction serious anaemia may be produced either by direct depression of erythropoiesis, causing aplastic anaemia, or by haemolysis. Examples of drugs producing this reaction are sulfanilamide, acetanilid (pyramidon) and phenyl hydrazine—drugs which were not so very long ago used extensively in therapeutics. Megaloblastic anaemia has also resulted from treatment with the anti-epileptic drug epanutin.

(c) *Antiplatelet reactors.* In this reaction there may be direct depression of megakaryocytes in the bone marrow, or auto-immunization of circulating platelets. Examples that may be quoted in this group are quinidine, used in the treatment of cardiac arrhythmias; sedormid, a sedative hypnotic; and even phenyl-butazone (butazolidin). In these cases a syndrome clinically almost identical with thrombocytopenic purpura is produced.

(d) *Total bone-marrow reactors.* The above mechanisms may be combined in certain cases when haemotoxic drugs are employed, or the therapeutic agents used may cause total unselective depression of all the bone-marrow elements. Well-known examples of drugs in this category are amphetamine (benzedrine); the anti-epileptic drugs tridione, dilantin and mesantoin; the antimalarial drug quinacrine (atabrine); phenyl-butazone, and hydralazine.

(ii) *Surgical Anaemias*

(a) *Iron-deficiency anaemias* have been reported following gastrectomy.

(b) *Megaloblastic anaemia* may develop as late as 2 - 5 years after total gastrectomy, either because a very small amount of cardia is left which may supply sufficient intrinsic factor to permit normal utilization of vitamin B12 for several years, or because the liver stores of erythrocyte-maturation factor may not become depleted for several years. Furthermore, almost every post-gastrectomy patient receives some multi-vitamin preparation for some time after the operation. These preparations usually contain sufficient folic acid to prevent the emergence of megaloblastic anaemia for some considerable time. However, the absence of any source of intrinsic factor prevents extrinsic factor from being absorbed, and so a megaloblastic anaemia ultimately appears. Megaloblastic anaemia may also occur in cases that have been subjected to gastro-enterostomy.

7. ANTIBIOTIC-INDUCED DISEASES

These diseases are probably among the most important and numerous of the disorders induced by modern therapy. In most of these the antibiotic used upsets the normal ecologic balance of the gastro-intestinal tract by destroying susceptible organisms and thus allowing overgrowth of resistant organisms, and allowing the latter to assume virulent properties.

(i) *Diseases caused by Resistant Staphylococci*

Treatment of many diseases by antibiotics may result in the appearance of staphylococcal septicaemia in the manner described above and may even cause acute staphylococcal septicaemia. Furthermore, we often meet cases of antibiotic-induced entero-colitis, particularly in cases of surgical resection of portions of the bowel followed by therapy with the tetracyclines. In these cases the enteritis produced may be severe with the passage of blood and pus in the diarrhoeic stools, and severe toxaemia is an associated complication. Lastly in this group is the increased incidence of staphylococcal pneumonia and multiple lung abscesses following on the treatment of pneumonias, usually pneumococcal, with broad-spectrum antibiotics.

(ii) *The Ano-rectal Syndrome*

This very annoying and unpleasant disorder, with the production of anal pruritus and even pain, is one of the well-known hazards of broad-spectrum antibiotic therapy, and may be very troublesome and persist for months after cessation of therapy with the offending agent.

(iii) *Monilia Infections*

The appearance of fungal infections with the production of ulcers in the mouth and tongue, pneumonia, diarrhoea, and even pyelocystitis are well known, and are good examples of how antibiotic therapy may upset the normal ecologic balance.

(iv) *Bacteraemia with Gram-negative Organisms*

Here again the normal ecology is upset by antibiotic therapy and allows of the development and appearance of bacteraemia due to *E. coli*, *Aerobacter aerogenes*, paracolon organisms and *Proteus vulgaris*.

(v) *Deficiency of Vitamin K and B Complex*

Colon bacilli are sometimes destroyed by prolonged antibiotic therapy. This may interfere with the synthesis of Vitamin K and B Complex.

(vi) *Neurological Disturbances*

Streptomycin, polymixin and neomycin therapy may lead to the development of paraesthesiae of the tongue, the circumoral region, and the hands. Furthermore, these antibiotics sometimes cause a severe peripheral neuritis. Streptomycin may also produce vestibular dysfunction by acting on the 8th cranial nerve, and dihydrostreptomycin may cause deafness.

(vii) *Serum-sickness Reaction*

As a result of the extensive use of penicillin, often without any good indication, there has been a corresponding increase in the number of cases of serum-sickness reactions and, what is more tragic, numbers of cases of anaphylactic reactions, many of them fatal, have been reported from all over the world as the result of penicillin therapy. Also on the increase are other sensitivity reactions with the development of penicillin-induced urticaria, angioneurotic oedema, and even arthritis.

8. CARDIAC DISEASES

(i) *Arrhythmias*

Overdosage with digitalis may produce many cardiac arrhythmias such as ventricular and auricular extrasystoles, coupled beats, paroxysmal auricular tachycardia, varying grades of block, and even ventricular tachycardia. It is important in such cases to recognize that the appearance of these arrhythmias may be due to digitalis therapy and not to the underlying heart disease. Potassium loss may be the mechanism in these cases. Quinidine used in the treatment of auricular fibrillation may cause sudden and serious increases in ventricular rate, and has been known to cause ventricular tachycardia; this condition may also be precipitated by the use of procaine amide (pronestyl) when used in the treatment of some ectopic rhythm.

(ii) *Haemorrhagic Pericardial Effusion*

Cases of haemorrhagic pericardial effusion have often been reported in cases of acute myocardial infarction following on the use of anticoagulant drugs.

9. PULMONARY DISEASES

(i) *Lipoid Pneumonia*

The use of mineral oil as a throat lubricant or as a vehicle for nose drops or as a laxative can cause chronic pulmonary lesions and lipoid pneumonia.

(ii) *Paraffinoma*

This lesion, which roentgenologically resembles a neoplasm, may also follow on the use of mineral oil inhalations. The inhaled oil, being insoluble, acts as a foreign body in the pulmonary tissues and stimulates the proliferation of granulomatous tissue and giant-cell systems.

(iii) *Radiofibrosis*

This condition of the lungs may follow X-ray therapy for malignancy especially after radical mastectomy.

10. RENAL DISEASES

(i) *Acute Renal Shut-down*

Renal failure may occur quite acutely following on therapy with sulfonamides, especially if there is inadequate concurrent hydration and alkalinization. Incompatible blood transfusions too may lead to acute renal shut-down (lower-nephron nephrosis, acute tubular necrosis).

(ii) *Nephroses*

Following on the use of tridione, and intravenous infusions of hypertonic glucose, sucrose, urea, and acacia a nephrotic-like syndrome may appear.

11. DERMATITIS

Drug-produced dermatitis is always being described; the number of offending drugs is legion and they have been known for a long time. Among the more modern potential offenders may be cited the sulfonamides and penicillin, the latter often causing a very resistant type of urticaria.

CONCLUSIONS

There can therefore be no doubt that we must continually be alert to the possibility of the toxic and potentially harmful effects of modern therapy. It is important to realize that an onus and

responsibility is placed upon the doctor ordering treatment. He must recognize that many of the newer drugs used may cause serious disorders in already ill patients or even in patients not so ill, and weigh the implications of these reactions against the natural history and prognosis of the disease which he is attempting to treat. He must answer the question: 'Is the treatment which I am ordering potentially harmful, is the risk justified, and is the treatment going to be worse in its effects than the disease treated?'

There are other problems in modern therapy which I shall not attempt to discuss but which may be briefly mentioned. There are for instance numerous iatrogenic or doctor-induced disorders and neuroses, not due to any medication used. Modern surgery too may, as the result of the operative procedure used, lead to interesting and even serious new disorders.

Most times, of course, the therapeutic procedure is sound, and the emergence of a new syndrome as a result of therapy is to be regarded as a justifiable risk which, fortunately, if recognized early, is reversible in most cases, simply by withdrawal or even reduction in the dose of the drug. In many cases the patient himself makes the decision—he refuses to continue with the specific drug prescribed.

It has been suggested by one author that today the multiplicity of effective therapeutic agents available suggests a modification of the ancient injunction, *primum non nocere* perhaps to 'first run no therapeutic risk greater than that of the disease'.